Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 3, 2023

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Pharmacy and Therapeutics (P&T) Committee

Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to ensure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug List but will require a prior authorization (PA). Clinical criteria must be met in order to be approved.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are preferred with clinical criteria, in non-preferred status, or if they required PA prior to the PDL.

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maximum Unit/Max Cost Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Anti-infective Agents

Preferred Agents

- Requests for preferred agents in the HCV anti-infective class must meet certain clinical criteria, please see Form 415 Criteria instruction booklet.

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed two treatment trials of no less than three-days each, with at least two prescribed and preferred anti-infectives, either generic, OTC, or brand, for the above diagnosis within the past 30 days or have a documented allergy or contraindication to all preferred agents for the diagnosis submitted.

- For the HCV anti-infectives, please see separate PA forms for specific information.

Stable Therapy

- Patients on anti-infective therapy while institutionalized once discharged or transferred to another setting or patients having a 60 day consecutive stable therapy may continue on that therapy with supportive medical justification or documentation.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested. Approval may also be given, with medical justification, if the medication requested is indicated for first line therapy when there are no other indicated preferred agents available or if indicated by susceptibility testing or evidence of resistance to all preferred agents.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Not Applicable.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Cerebral Stimulants/Agents Used for ADHD

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- For agents with an FDA-approved indication of narcolepsy, the patient must have an appropriate diagnosis supported by documentation in the patient record of appropriate diagnostic testing.

Prior Therapy

- If the request is for a *short- or intermediate-acting* cerebral stimulant/agent used to treat ADHD, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred short- or intermediate-acting cerebral stimulants/agents used for ADHD, either generic, OTC, or brand, within the past 6 months.

- If the request is for a *long-acting* cerebral stimulant/agent used for ADHD, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred long-acting cerebral stimulants/agents used for ADHD, either generic, OTC, or brand within the past 6 months.

- In lieu of prior usage requirements, approval may be given if there is a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Cerebral Stimulant/Agent Used for ADHD agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Wakefulness Promoting Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- For agents with an FDA-approved indication of idiopathic hypersomnia in children 18 and under, narcolepsy, obstructive sleep apnea, or shift work sleep disorder, the patient must have an appropriate diagnosis supported by documentation in the patient record of appropriate diagnostic testing.

Prior Therapy

- The patient must have also failed 30-day treatment trials with at least two prescribed and preferred wakefulness promoting agents, either generic, OTC, or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Wakefulness Promoting are not included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

May 3, 2023
1:00 p.m. – 3:00 pm

1. Opening remarks…….....….....….Chair
2. Approval of February 8, 2023 P&T Committee Meeting minutes……..…….....…Chair
3. Pharmacy program update…….…...…….....….....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews…….....……..UMass Clinical Pharmacy Services
    - Anthelmintics - AHFS 080800
    - Aminoglycosides - AHFS 081202
    - Cephalosporins - AHFS 081206
    - Miscellaneous β-Lactam Antibiotics - AHFS 081207
    - Chloramphenicol - AHFS 081208
    - Macrolides - AHFS 081212
    - Penicillins - AHFS 081216
    - Quinolones - AHFS 081218
    - Sulfonamides - AHFS 081220
    - Tetracyclines - AHFS 081224
    - Antibacterials, Miscellaneous - AHFS 081228
    - Cerebral Stimulants/Agents Used for ADHD
        - Central Alpha-Agonists – AHFS 240816 (current brands to be included: Kapvay®)
        - Amphetamine Derivatives – AHFS 282004 (current brands to be included: Adderall®, Adderall XR®, Adzenys XR-ODT®, Desoxyn®, Dexedrine®, Dyanavel XR®, Evekeo®, Mydayis ER®, ProCentra®, Vyvanse®, Xelstrym®, & Zenzedi® only)
        - Respiratory and CNS Stimulants – AHFS 282032 (current brands to be included: Adhansia® XR, Aptensio XR®, Azstarys®, Concerta®, Cotempla XR-ODT®, Daytrana®, Focalin®, Focalin XR®, Jornay PM®, Methylin®, QuilliChew ER®, Quillivant XR®, Relexxii ER®, Ritalin®, & Ritalin LA® only)
        - Central Nervous System Agents, Miscellaneous – AHFS 289200 (current brands to be included: Intuniv®, Strattera®, & Qelbree ER® only)
    - Wakefulness Promoting Agents – AHFS 282080 (current brands to be included: Nuvigil®, Provigil®, Sunosi®, Wakix®, Xyrem®, & Xywav® only)
6. Results of voting announced……..…….....…….Chair
7. New business
    - 2023 P&T Meeting Dates:
        - August 2, 2023
        - November 8, 2023
8. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anthelmintics
AHFS Class 080800
May 3, 2023

I. Overview

The anthelmintics are approved for the treatment of cestode, nematode, and trematode infections.[1-7] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[8] Helminths that parasitize humans are classified into cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes).[8,9] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the United States, followed by *Ascaris lumbricoides*.[10]

Helminths vary with respect to life cycle, bodily structure, localization within the host, epidemiology, and susceptibility to chemotherapy.[9] The population density of the worm burden is an important factor in determining the pathogenicity of the infection.[11] Most infected persons harbor few worms and are asymptomatic or exhibit minimal signs or symptoms of disease.[8] However, persons with large numbers of worms are at risk for severe disease. Children infected with helminths are at risk of malnutrition, impaired growth, and impaired intellectual development. The diagnosis of helminthic infections is based primarily on microscopic examination of stool, urine, blood, other body fluids, and/or tissues.

The anthelmintics act locally to expel worms from the gastrointestinal tract. They also act systemically to eradicate adult helminths or developmental forms that invade organs and tissues.[9] Most human infections, caused by either flukes or intestinal helminths, may be cured or controlled by the available anthelmintic agents. Systemic infections caused by tissue-dwelling helminths may only partially respond to currently available drugs. Acquired resistance to anthelmintics in humans has yet to become a major factor limiting clinical efficacy.

The anthelmintic agents differ with regards to their mechanism of action. Albendazole exhibits inhibitory effects on tubulin polymerization, which results in the loss of cytoplasmic microtubules. Ivermectin binds to glutamate-gated chloride ion channels leading to hyperpolarization of the nerve or muscle cell, which results in paralysis and death of the parasite. Mebendazole irreversibly blocks glucose uptake and other nutrients in susceptible adult intestine-dwelling helminths. Praziquantel induces a rapid contraction of schistosomes by affecting the permeability of the cell membrane, which causes vacuolization and disintegration of the schistosome tegument. Triclabendazole inhibits tubulin function as well as protein and enzyme synthesis. These metabolic disturbances are associated with inhibition of motility and disruption of the surface and ultrastructure that includes inhibition of spermatogenesis and vitelline cells.[1-7]

The anthelmintics that are included in this review are listed in Table 1. This review encompasses all oral dosage forms and strengths. This class was last reviewed in May 2021.

Table 1. Anthelmintics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Albendazole	tablet	Albenza®*	albendazole
Ivermectin	tablet	Stromectol®*	ivermectin
Mebendazole	chewable tablet	Emverm®	none
Praziquantel	tablet	Biltricide®*	praziquantel
Triclabendazole	tablet	Egaten®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

The anthelmintics have been shown to be active against the strains of organisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the anthelmintics that are noted in Table 4. These agents may also have been found to show activity to other organisms in vitro; however, the clinical significance of this is unknown since their safety

and efficacy in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials. Although empiric antiparasitic therapy may be initiated before diagnostic test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Anthelmintics[1-7]

Organism	Albendazole	Ivermectin	Mebendazole	Praziquantel	Triclabendazole
Cestodes (Tapeworms)					
Echinococcus granulosus	✔				
Taenia solium	✔				
Nematodes (Roundworms)					
Ancylostoma duodenale			✔		
Ascaris lumbricoides			✔		
Enterobius vermicularis			✔		
Necator americanus			✔		
Onchocerca volvulus		✔			
Strongyloides stercoralis		✔			
Trichuris trichiura			✔		
Trematodes (Flukes)					
Clonorchis sinensis				✔	
Fasciola gigantica					✔
Fasciola hepatica					✔
Opisthorchis viverrini				✔	
Schistosoma haematobium				✔	
Schistosoma japonicum				✔	
Schistosoma mansoni				✔	
Schistosoma mekongi				✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the anthelmintics are summarized in Table 3.

Table 3. Treatment Guidelines Using the Anthelmintics

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[12]** **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended.

Clinical Guideline	Recommendation(s)
	Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
Center for International Blood and Marrow Transplant Research/ National Marrow Donor Program/ European Blood and Marrow Transplant Group/American Society of Blood and Marrow Transplantation/ Canadian Blood and Marrow Transplant Group/ Infectious Diseases Society of America/Society for	• Hematopoietic stem cell transplant candidates with pretransplant screening tests positive for *Strongyloides* species, or those with an unexplained eosinophilia and a travel or residence history indicative of exposure to *Strongyloides stercoralis*, should be empirically treated before transplantation. • The preferred prophylactic treatment is ivermectin 200 µg/kg/day orally for two consecutive days; this regimen is repeated after two weeks. • The alternative prophylactic treatment is albendazole 400 mg orally twice daily for seven days or thiabendazole 25 mg/kg orally twice daily for two days. • Some clinicians advocate preemptive treatment for patients from endemic areas who have no symptoms, no eosinophilia, and negative screening test results. • Indications for empiric treatment for strongyloidiasis before hematopoietic stem cell transplant are the same among children or adults, except for children weighing <15 kg, for whom the preferred drug is thiabendazole.

Clinical Guideline	Recommendation(s)
Healthcare Epidemiology of America/Association of Medical Microbiology and Infectious Diseases Canada/Centers for Disease Control and Prevention: **Guidelines for Preventing Infectious Complications Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective (2009)**[13]	

III. Indications

The Food and Drug Administration (FDA)-approved indications for the anthelmintics are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Anthelmintics[1-7]

Indication	Albendazole	Ivermectin	Mebendazole	Praziquantel	Triclabendazole
Cestodes (Tapeworms)					
Cystic hydatid disease of the liver, lung, and peritoneum	✔				
Parenchymal neurocysticercosis due to active lesions	✔				
Nematodes (Roundworms)					
Onchocerciasis		✔			
Strongyloidiasis of the intestinal tract		✔			
Ascariasis (*Ascaris lumbricoides*)			✔		
Hookworm (*Ancylostoma duodenale* and *Necator americanus*)			✔		
Pinworm (*Enterobiasis vermicularis*)			✔		
Whipworm (*Trichuriasis trichiura*)			✔		
Trematodes (Flukes)					
Clonorchiasis (liver flukes)				✔	
Fascioliasis					✔
Opisthorchiasis (liver flukes)				✔	
Schistosomiasis, all species				✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the anthelmintics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Anthelmintics[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Albendazole	<5	70	Liver	Renal (<1)	8 to 12
Ivermectin	Well absorbed	>99	Liver	Renal (<1); Feces	18
Mebendazole	5 to 10	90 to 95	Liver	Renal (2); Feces (98)	1 to 12
Praziquantel	80	80	Liver	Renal (80)	0.8 to 3.0
Triclabendazole	Not reported	97	Liver	Not reported	8

V. Drug Interactions

Major drug interactions with the anthelmintics are listed in Table 6.

Table 6. Major Drug Interactions with the Anthelmintics[2]

Generic Name(s)	Interaction	Mechanism
Mebendazole	Metronidazole	Concurrent use of mebendazole and metronidazole may result in increased risk of Stevens-Johnson syndrome and/or toxic epidermal necrolysis.
Praziquantel	Carbamazepine	Concurrent use of carbamazepine and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Dexamethasone	Concurrent use of dexamethasone and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Phenobarbital	Concurrent use of phenobarbital and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Phenytoin	Concurrent use of phenytoin and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Rifampin	Rifampin may increase the hepatic metabolism of praziquantel, resulting in reduced plasma levels and possibly producing a loss in therapeutic effect.
Triclabendazole	CYP2C19 Substrates	Concurrent use of triclabendazole and CYP2C19 substrates may result in increased exposure to CYP2C19 substrate.
Triclabendazole	QT interval prolonging drugs	Concurrent use of triclabendazole and QT prolonging drugs may result in increased risk of QT interval prolongation.

VI. Adverse Drug Events

The most common adverse drug events reported with the anthelmintics are listed in Table 7. At recommended dosages, the anthelmintics are generally well tolerated. Some adverse effects may be secondary to the parasitic infection being treated and/or to dead and dying parasites rather than to the drug itself. Such effects may be more frequent and/or severe in patients with a heavy worm burden. Cutaneous and/or systemic reactions of varying severity (Mazzotti reaction) and ocular effects may occur in patients with onchocerciasis receiving macrofilaricidal drugs, such as ivermectin. Patients with onchocerciasis who are also heavily infected with *Loa loa* may develop serious or fatal neurologic events (e.g., encephalopathy and coma) either spontaneously or following rapid killing of microfilariae with macrofilaricidal agents.

Table 7. Adverse Drug Events (%) Reported with the Anthelmintics[1]

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Triclabendazole
Cardiovascular					
Arrhythmia	-	-	-	✔	-
Chest discomfort	-	<1	-	-	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Triclabendazole
Dyspnea	-	<1	-	-	-
Facial edema	-	1	-	-	-
Hypotension	-	<1	-	-	-
Orthostatic hypotension	-	1	-	-	-
Peripheral edema	-	✔	-	-	-
Tachycardia	-	4	-	-	-
Central Nervous System					
Asthenia	-	<1	-	✔	-
Coma	-	✔	-	-	-
Confusion	-	✔	-	-	-
Dizziness	1	3	✔	✔	-
Drowsiness	-	✔	✔	-	-
Fatigue	-	<1	-	-	-
Fever	1	-	-	✔	-
Headache	1 to 11	<1	✔	✔	14
Increased intracranial pressure	0 to 2	-	-	-	-
Insomnia	-	-	-	-	-
Lethargy	-	✔	-	-	-
Malaise	-	-	-	✔	-
Meningeal signs	1	-	-	-	-
Mental status changes	-	✔	-	-	-
Seizures	-	✔	✔	✔	-
Somnolence	-	<1	-	✔	-
Stupor	-	✔	-	-	-
Tremor	-	✔	-	-	-
Vertigo	1	<1	-	✔	-
Dermatological					
Alopecia	<1 to 2	-	✔	-	-
Erythema multiforme	✔	-	-	-	-
Hyperhidrosis	-	-	-	-	25
Pruritus	-	3	✔	✔	4
Rash	<1	<1	✔	-	-
Stevens-Johnson syndrome	✔	✔	✔	-	-
Toxic epidermal necrolysis	-	✔	✔	-	-
Urticaria	<1	<1	✔	✔	11
Gastrointestinal					
Abdominal pain	0 to 6	<1	✔	✔	93
Anorexia	-	<1	-	✔	-
Appetite decreased	-	-	-	-	18
Constipation	-	<1	-	-	-
Diarrhea	-	2	✔	✔	7
Fecal incontinence	-	✔	-	-	-
Nausea	4 to 6	2	-	-	18
Vomiting	4 to 6	<1	✔	✔	7
Genitourinary					
Acute renal failure	✔	-	-	-	-
Glomerulonephritis	-	-	✔	-	-
Hematuria	-	-	✔	-	-
Urinary incontinence	-	✔	-	-	-
Hematologic					
Anemia	-	✔	-	-	-
Agranulocytosis	<1	-	✔	-	-
Aplastic anemia	✔	-	-	-	-
Bone marrow suppression	✔	-	-	-	-
Eosinophilia	-	3	✔	✔	-
Hemoglobin decreased	-	-	✔	-	-
Hemoglobin increased	-	1	-	-	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel	Triclabendazole
Granulocytopenia	<1	-	-	-	-
Leukopenia	<1	✔	✔	-	-
Neutropenia	✔	-	✔	-	-
Pancytopenia	<1	-	-	-	-
Thrombocytopenia	<1	-	-	-	-
Hepatic					
Abnormal liver function tests	1 to 16	2	✔	-	3 to 5
Acute liver failure	✔	-	-	-	-
Hepatitis	✔	-	✔	-	-
Hyperbilirubinemia	-	✔	-	-	7
Musculoskeletal					
Back pain	-	✔	-	-	-
Musculoskeletal chest pain	-	-	-	-	4
Myalgia	-	<1	-	✔	-
Neck pain	-	✔	-	-	-
Weakness	-	-	-	-	-
Special Senses					
Abnormal eye sensation	-	✔	-	-	-
Anterior uveitis	-	✔	-	-	-
Chorioretinitis	-	✔	-	-	-
Choroiditis	-	✔	-	-	-
Conjunctival hemorrhage	-	✔	-	-	-
Conjunctivitis	-	✔	-	-	-
Eyelid edema	-	✔	-	-	-
Keratitis	-	✔	-	-	-
Ocular limbitis	-	4 to 6	-	-	-
Ocular punctate opacity	-	✔	-	-	-
Red eye	-	✔	-	-	-
Other					
Angioedema	-	1	✔	-	-
Asthma exacerbation	-	✔	-	-	-
Hypersensitivity reaction	<1	-	✔	✔	-
Mazzotti-type reaction	-	>10	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the anthelmintics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Anthelmintics[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Albendazole	Cystic hydatid disease of the liver, lung, and peritoneum: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles); ≥60 kg, 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles)	Cystic hydatid disease of the liver, lung, and peritoneum: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles); ≥60 kg, 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles)	Tablet: 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Parenchymal neurocysticercosis due to active lesions: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for eight to 30 days; ≥60 kg, 400 mg twice daily with meals for eight to 30 days	Parenchymal neurocysticercosis due to active lesions: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for eight to 30 days; ≥60 kg, 400 mg twice daily with meals for eight to 30 days	
Ivermectin	Onchocerciasis: Tablet: A single oral dose designed to provide approximately 150 µg of ivermectin per kg of body weight; retreatment may be considered at intervals as short as three months Strongyloidiasis of the intestinal tract: Tablet: A single oral dose designed to provide approximately 200 µg of ivermectin per kg of body weight; in general, additional doses are not necessary	Onchocerciasis: Tablet: ≥15 kg, A single oral dose designed to provide approximately 150 µg of ivermectin per kg of body weight; retreatment may be considered at intervals as short as three months Strongyloidiasis of the intestinal tract: Tablet: ≥15 kg, A single oral dose designed to provide approximately 200 µg of ivermectin per kg of body weight; in general, additional doses are not necessary	Tablet: 3 mg
Mebendazole	Hookworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Pinworm: Tablet: 100 mg once; repeat in three weeks if necessary Roundworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Whipworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary	Hookworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Pinworm: ≥2 years of age: Tablet: 100 mg once; repeat in three weeks if necessary Roundworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Whipworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary	Chewable tablet: 100 mg
Praziquantel	Clonorchiasis, opisthorchiasis: Tablet: 25 mg/kg three times per day as a one-day treatment Schistosomiasis, all species: Tablet: 20 mg/kg three times per day as a one-day treatment	Clonorchiasis, opisthorchiasis: Tablet: ≥4 years of age, 25 mg/kg three times per day as a one-day treatment Schistosomiasis, all specifies: Tablet: ≥4 years of age: 20 mg/kg three times per day as a one-day treatment	Tablet: 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Triclabendazole	Fascioliasis: Tablet: Two doses of 10 mg/kg given 12 hours apart	Fascioliasis: Tablet: ≥6 years of age, two doses of 10 mg/kg given 12 hours apart	Tablet: 250 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the anthelmintics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Anthelmintics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cestodes (Tapeworms)				
Chaurasia et al.[14] (2010) Albendazole 15 mg/kg/day for three days vs placebo	DB, PC, RCT Patients with new onset seizures and solitary cysticercus granuloma (neurocysticercosis)	N=67 6 months	Primary: Resolution of lesion on computed tomography scan, seizure control at six months Secondary: Not reported	Primary: Complete resolution of lesions in the albendazole group was 84.8% compared to 41.2% in the placebo group (P=0.001). Partial resolution of lesions occurred in 6% of albendazole patients compared to 11.8% of placebo patients (P=0.06). Seizures occurred in 9.1% of albendazole patients and 2.9% of placebo treated patients (P=0.239). Secondary: Not reported
Carpio et al.[15] (2008) Albendazole 400 mg every 12 hours (>50 kg) or 15 mg/kg/day (<50 kg) for eight days vs placebo All patients received prednisone; anticonvulsants were allowed for patients with	DB, PC, RCT Patients of any age or gender with new onset of symptoms associated with neurocysticercosis and active and/or transitional neurocysticercosis cysts (Ecuador)	N=178 1 year	Primary: Disappearance of active cysts by 12 months of follow-up Secondary: Disappearance of transitional or calcified cysts at one, six and 12 months, change in number of cysts in a specific phase, time to seizure recurrence, and adverse events	Primary: Active cysts were identified in 69% of the albendazole treatment group and 66% of the placebo group. By 12 months following treatment, 38% of those with 12 month scans were free of active cysts in the treatment group compared to 20% in the placebo group (P=0.048). Secondary: The difference in cyst disappearance by treatment was greatest at one month of follow-up, with 31% of those in the albendazole group being free of active cysts at month one of follow-up compared to 7% of those in the placebo group (P=0.001). Of those patients followed and scanned at six months, 35% were free of active cysts in the albendazole treatment arm compared to 12% in the placebo group (P=0.006). The mean number of active cysts decreased between baseline and month

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
newly occurring seizures.				one for the albendazole (mean number at baseline 3.88 and at one month 1.86) group but not for the placebo group (mean at baseline 2.67 and at one month 2.69). Those taking albendazole had a significant decrease in the number of active cysts between baseline and month one compared to those in the placebo group (P=0.001). There was no difference by treatment group in the change in the number of active cysts between month one and month six (P=0.797) or month six and month 12 of follow-up (P=0.938). The change in the number of transitional cysts and inactive calcifications between baseline and month one of follow-up did not differ by treatment group (transitional cysts; P=0.234, calcifications; P=0.456). The mean time seizure free was 8.86 months in the albendazole group vs 7.67 months in the placebo group (P=0.274). The three most common symptoms reported during treatment, and the first month following treatment, were headache, seizures, and stomach problems. During the eight days of treatment, three patients developed intracranial hypertension, all in the placebo group.
Bildik et al.[16] (2007) Albendazole 10 mg/kg twice daily prior to surgery (group I=one month; group II=two months; group III=three months) vs	RCT Patients with isolated hydatid cysts of the liver	N=84 3 months	Primary: Clinical signs of disease Secondary: Not reported	Primary: Thirty-five percent of the patients showed no clinical signs of the disease. Sixty-two percent had tenderness in the right hypochondrium, 34.5% had hepatomegaly, and 30.0% had palpable mass. Following treatment with albendazole, scoleces were alive in 47.6% of patients in group I, 33.3% of patients in group II, and 0.9% of patients in group III. In the control group, 80% of patients' scoleces were intact. When group III was compared to the control group, a significant difference was observed (P<0.05). There was a significant difference between the groups when groups I and II were compared to group III.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no preoperative therapy				Secondary: Not reported
Wen et al.[17] (1994) Albendazole 15 to 20 mg/kg/day orally, for 30 days with intervals of 10 days between treatments for three to six courses (12 to 18 courses for multi-organ cystic echinococcosis and alveolar echinococcosis) vs albendazole and surgery vs surgery	OL Patients with cystic echinococcosis or alveolar echinococcosis in China	N=178 3 to 7 years	Primary: Endocyst collapse rate, proscolex viability, cyst wall pathology, clinical symptoms and signs Secondary: Side effects	Primary: Twenty-seven of 34 cysts (79.4%) in patients treated with albendazole and surgery showed increased necrotic changes and decreased viability of the cysts compared to the surgery group (P<0.001). However, 10 of 84 (11.9%) cysts in the surgery group showed spontaneous evidence of necrosis at surgery. Albendazole treatment alone was successful in 14 (24.1%) patients, resulted in improvement in 29 (50%) patients and had no effect in 15 (25.9%) patients. Seven of the alveolar echinococcosis patients treated with albendazole and surgery showed improvement, with hydatid masses diminished or disappeared, jaundice subsided, and appetite and energy regained. Of the remaining seven patients who continued to receive albendazole for six to 15 more courses, four stabilized, and three deteriorated of which two died. Of the five alveolar echinococcosis patients receiving albendazole alone, one improved, two stabilized, and two deteriorated of which one died. Secondary: Side effects were reported in 18.4% of patients receiving albendazole and were primarily gastrointestinal symptoms (diarrhea, nausea, abdominal pain and vomiting) and transient elevation of serum transaminase levels. Albendazole was withdrawn in one patient after one week of therapy due to intolerable itch.
Kaur et al.[18] (2009) Albendazole 15 mg/kg/day in three divided doses for seven days, plus prednisolone 2 mg/kg/day for	DB, PC, RCT Children one to 13 years of age with seizures due to neurocysticercosis	N=112 1 year	Primary: Recurrence of seizure and resolution of lesions on CT Secondary: Not reported	Primary: Resolution of lesions at one, three, and six months was higher in the praziquantel group (35, 60, and 72%, respectively) compared to those receiving placebo (25, 42, and 52%, respectively), but this did not reach statistical significance. Non-resolution and calcification at one, three, and six months were numerically lower in the praziquantel group compared to placebo; however, this was not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
five days, plus praziquantel 75 mg/kg/day in three divided doses for one day vs albendazole 15 mg/kg/day in three divided doses for seven days, plus prednisolone 2 mg/kg/day for five days, plus placebo				Recurrence of seizures within six months of therapy was reported in three children in each treatment group. There were no signs of elevated intracranial pressure. Secondary: Not reported
Del Brutto et al.[19] (2006) Albendazole vs praziquantel vs placebo vs no therapy	MA Patients with neurocysticercosis	N=942 (11 trials) Variable duration	Primary: Resolution of cystic lesions, risk of seizure recurrence, frequency of seizures Secondary: Effect of corticosteroids on cysticidal drug efficacy, adverse events	Primary: Cysticidal drug therapy was associated with complete resolution of cystic lesions (44 vs 19%; P=0.025). Trials on enhancing lesions showed a trend toward lesion resolution favoring the use of cysticidal drugs (72 vs 63%; P=0.38) that became statistically significant when an outlier trial was excluded from the analysis (69 vs 55%; P=0.006). Risk for seizure recurrence was lower after cysticidal treatment in patients with enhancing lesions (14 vs 37%; P<0.001). The single trial evaluating the frequency of seizures in patients with cystic lesions showed a 67% reduction in the rate of generalized seizures with treatment (P=0.006). This MA did not further analyze and compare the efficacy or safety of albendazole to praziquantel. Secondary: Only one study compared the efficacy of cysticidal drugs alone or in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				combination with corticosteroids, showing that albendazole plus dexamethasone was not better than albendazole alone in terms of lesion resolution (74 vs 76%) or risk of seizure recurrence during follow-up (12 vs 14%). Data from the trials did not allow an evaluation of the exact number of patients developing adverse events, but these manifestations generally were mild and resolved with analgesics or other symptomatic medications in a few days. The occurrence of adverse events did not differ between albendazole or praziquantel, or whether the patient received routine corticosteroids.
Das et al.[20] (2007) Group A Albendazole 15 mg/kg/day for 14 days plus dexamethasone 2 mg every eight hours for 14 days, plus antiepileptic drugs vs Group B antiepileptic drugs plus placebo	RCT Patients with newly diagnosed neurocysticercosis with more than one lesion detected on contrast head computed tomography imaging	N=300 8 years	Primary: Recurrence of seizures, encephalopathy, need for subsequent hospital admission, death, resolution of lesions on follow-up computed tomography Secondary: Not reported	Primary: During the first year of treatment the incidences of seizure, encephalopathy, and readmission were greater for group A than group B (group A: 95% CI, 0.20 to 0.34; group B: 95% CI, 0.10 to 0.22; P=0.05). Two patients in group A died from intractable seizures and encephalopathy in the first three months of treatment. For every follow-up point after one year of treatment, the incidences of seizure and need for readmission were also marginally higher in group A, but the differences were not statistically significant. Over the entire study period, the proportion of patients with complete resolution of lesions was greater in group B than in group A (group A: 95% CI, 0.56 to 0.57; group B: 95% CI, 0.72 to 0.74; P=0.05), but the proportion of patients with calcification of lesions was greater in group A than in group B (group A: 95% CI, 0.33 to 0.34; group B: 95% CI, 0.22 to 0.23; P=0.05). Secondary: Not reported
Nematodes (Roundworms)				
Issaka-Tinorgah et al.[21] (1994) Ivermectin 150	PC, RCT, SB Patients over 18 years of age from a Ghana village	N=385 15 months	Primary: Emergence and migration of guinea worms, adverse events	Primary: There was no significant difference in the proportion of persons with emergent guinea worms between the two treatment groups. Overall, 54 of the 385 participants who were followed for 15 months developed a total of 69 emergent guinea worms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/kg as a single dose vs placebo	highly endemic for guinea worm infections		Secondary: Not reported	Migration of guinea worms in the tissues was not affected by ivermectin, with 80% of emergent guinea worms located below the knee. There was no difference in the patterns of adverse events between the ivermectin and placebo groups. Secondary: Not reported
Fobi et al.[22] (2005) Gardon et al.[23] (2002) Kamgno et al.[24] (2004) Ivermectin 150 µg/kg annually (reference group) vs ivermectin 150 µg/kg every three months vs ivermectin 400 µg/kg then 800 µg/kg annually vs ivermectin 400 then 800 µg/kg every three months	DB, RCT Men 18 to 60 years of age with *Onchocerca volvulus* infections (Cameroon)	N=657 3 years	Primary: Vital status of female worms[35], adverse events[36], ophthalmological exam[34], ocular and visual symptoms[34] Secondary [35]: Fertility of female worms, skin microfilariae, number of non-fertile female and male worms	Primary and Secondary: After three years, more female worms had died in the groups treated every three months than in the reference group (150 µg/kg dose: OR, 1.84; 95% CI, 1.23 to 2.75; P=0.003 and 400 to 800 µg/kg dose: OR, 2.17; 95% CI, 1.42 to 3.31; P<0.001). Female worms were also less fertile in these groups than in the reference group (OR, 0.24; 95% CI, 0.14 to 0.43; P<0.0001 and OR, 0.14; 95% CI, 0.06 to 0.29; P<0.0001, respectively). No difference was recorded between groups treated yearly (P=0.83 for the proportion of dead females). More than 90% of patients on yearly treatment had microfilariae in their skin snips (difference, 1.9%; 95% CI, 3.9 to 7.8; P=0.52), compared to 40 and 26%, respectively, in the groups treated every three months at 150 µg/kg and at high doses (difference, 13.8%; 95% CI, 2.5 to 25.1; P=0.0180). The mean numbers of skin microfilariae did not differ between the two groups treated yearly (P=0.45). High doses (400 to 800 µg/kg) administered annually produced little marginal parasitological benefit compared to 150 µg/kg. After the first dose, dosing every three months was associated with a reduced risk of reactions, especially edematous swellings, pruritus, and back pain. Edematous swellings and subjective ocular troubles were found to be associated with high doses of ivermectin. Transitory subjective visual problems were reported more frequently in the two groups receiving the high ivermectin doses than in the reference group (P<0.03 and P<0.001 for the ivermectin 800 µg/kg annual and every three

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Every patient was given a clearing dose of 150 µg/kg ivermectin prior to the start of the study.				month regimens, respectively). In the ophthalmological examinations, the only differences recorded between the groups were a lower prevalence and mean number of microfilariae in the anterior chamber in the groups treated every three months, and, at the first examination round, a higher prevalence of early lesions of the iris in the group treated at high doses annually. Results of the ophthalmological exam did not show the cause of the transitory ocular complaints, nor explain why they were more frequent in the groups treated with higher doses.
Awadzi et al.[25] (1999) Ivermectin 150 µg/kg as a single dose vs ivermectin 150 µg/kg or placebo, then 400 µg/kg vs ivermectin 150 µg/kg or placebo, then 600 µg/kg vs ivermectin 150 µg/kg or placebo, then 800 µg/kg vs ivermectin 800 µg/kg for two	DB, PC, RCT Males infected with *Onchocerca volvulus* (Ghana)	N=100 21 months	Primary: Nodule characteristics, adult worm viability, reproductive activity, skin and ocular microfilariae Secondary: Not reported	Primary: There were no significant trends among the dosage regimens regarding the number of live worms per nodule, the male: female ratio or in the number of nodules with live microfilariae (P>0.05). There was however a significant trend to a reduction in the number of nodules without male worms with increasing doses of ivermectin (P=0.02). There was no significant trend in mortality among female and male worms in the treated groups (P>0.05). Increasing doses of ivermectin had no marked effect on embryogenesis. There was a significant trend towards an increase in the number of female worms with nearly empty uteri (P=0.04), and a reduction in the proportion of female worms with young embryos (P=0.015) and coiled microfilariae (P=0.004) with increasing doses. There was no significant trend with dose in the proportion of worms with young oocytes only, with stretched microfilariae, or with degenerate stretched microfilariae. Between 95% and 100% of live male worms contained intact spermatozoa with no differences between groups. At days 30 and 180, the higher dose groups had a greater suppression of skin microfilariae (P<0.05), but the effect was minor (maximum differences were 1.6%) and transient. By one year, the mean skin microfilariae densities were again similar in all groups. The clearance of ocular microfilariae was also similar in all groups. There was no significant difference in ocular mf between the treatment groups. Overall, the treatment groups maintained at one year a 96% reduction on initial counts for both skin and ocular microfilariae. Total doses of ivermectin (≤1,600 µg/kg) were not more effective than 150

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses				µg/kg. They did not reproduce the marked inhibitory effects of the repeat standard-dose regimens on embryogenesis, or the modest effect on adult worm viability, at comparable total doses.
Olsen et al.[26] (2009) Albendazole: Albendazole 400 mg as a single dose Mebendazole 1: Mebendazole 100 mg twice daily for 3 days (study 1) Mebendazole 2: Mebendazole 100 mg twice daily for 5 days (study 2)	OL School-age children infected with *Trichuris trichiura*	Albendazole: N=70 14 days Mebendazole 1: N=34 3 days Mebendazole 2: N=35 7 days	Primary: Albendazole: Cure and egg reduction rates Mebendazole 1/2: Recovery of adult *Trichuris trichiura* worms Secondary: Not reported	Primary: Albendazole study: At day seven, the cure rate (negative for eggs in stool sample) was 8% and the geometric egg reduction rate was 89% (P<0.001). At day 14, all children were egg-positive, and the egg count was 57% higher than baseline (P<0.001). Mebendazole 1 study: With the three-day course of mebendazole, four adult worms were obtained at days three to five after the start of treatment from two of the 34 children delivering 24 hour stool samples. Mebendazole 2 study: With the five-day course of mebendazole, 10 of 21 infected children expelled a total of 27 worms. Secondary: Not reported
Critchley et al.[27] (2005) Albendazole vs placebo, ivermectin, diethyl-carbamazine	MA Patients with lymphatic filariasis	N=6,997 (7 trials) Up to 2 years	Primary: Microfilariae prevalence, microfilariae density, antigenemia prevalence or density, adult worms Secondary: Acute filariasis, appearance or disappearance of hydrocele or	Primary and Secondary: A comparison of albendazole to placebo detected no effect on microfilariae prevalence after three to 12 months (N=920 participants, three trials). One trial (N=499) reported a significantly greater reduction in microfilariae density at six months in the albendazole group compared to placebo (34.7 vs 10.3% reduction, respectively; P<0.05). There were no statistically significant differences in the prevalence of circulating filarial antigen positivity from two trials after six to 12 months (N=1,090). One trial reported no statistically significant difference in the development of acute filariasis, leg lymphedema, and hydrocele, or improvement of hydrocele and leg lymphedema; however, the trials lacked power so clinically important differences cannot be ruled out. One trial reported no statistically significant difference in systemic adverse events between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			change in size, adverse events	albendazole and placebo. Another trial reported statistically significant reductions in myalgias and cough for albendazole compared to placebo, but no statistically significant differences in headache, fever or mean treatment impact score. Albendazole performed slightly worse than ivermectin in two trials (N=436). Albendazole was slightly poorer in clearing microfilariae, but this only just reached statistical significance (RR, 0.84; 95% CI, 0.72 to 0.9; N=198). There was no statistically significant difference in the number of patients positive for circulating filarial antigen after 12 months for those treated with albendazole or ivermectin. Ivermectin produced higher reductions in microfilariae and antigen densities than albendazole (statistical tests were only applied in one comparison where P=0.02). One trial reported no statistically significant differences in the risk of developing hydrocele, or improvements in lymphedema or hydrocele, but sample sizes were small and CIs wide. There was no statistically significant difference in the number of systemic adverse events between albendazole and ivermectin. When albendazole was added to ivermectin, microfilariae prevalence and density were statistically significantly lower with the combination compared to ivermectin alone in two of three trials (N=649). There were no significant differences in the remainder of the primary and secondary end points. Compared to diethylcarbamazine, two small trials (N=56) found little difference in microfilariae prevalence over an extended follow-up. One larger trial (N=502) found a statistically significant effect for diethylcarbamazine at six months (RR, 1.74; 95% CI, 1.05 to 2.88), but not at three months. Microfilariae density appeared to fall faster with diethylcarbamazine compared to albendazole; however, there were no statistically significant differences in percentage reductions at any time points. Antigen density was reduced by 17% in the diethylcarbamazine group compared to 3.2% in the albendazole group (P<0.05). The mean score of adverse reaction intensity was lower for albendazole compared to diethylcarbamazine (P<0.05), but the validity and clinical significance of this scoring system was uncertain. There were no significant differences in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the remainder of the primary and secondary end points. Two trials compared albendazole plus diethylcarbamazine with diethylcarbamazine alone and found no statistically significant difference in microfilariae prevalence, though one trial favored the combination at six months (RR, 0.62; 95% CI, 0.32 to 1.21; N=491). This trial also found a significant reduction in microfilariae density with the combination arm vs albendazole (80.4 vs 50.4%, respectively; P<0.05). There were no significant differences in the remainder of the primary and secondary end points.
Datry et al.[28] (1994) Albendazole 400 mg/day for three days vs ivermectin 150 to 200 µg/kg as a single dose	OL, RCT Patients with *Strongyloides stercoralis* of the intestinal tract (France)	N=60 90 days	Primary: Parasitological cure, adverse events Secondary: Not reported	Primary: Ivermectin was significantly more effective in producing parasitological cure than albendazole (83 vs 38%; P<0.01). Clinical and biological adverse reactions were negligible in both treatment groups. The 20 patients who failed therapy were given a second treatment course with ivermectin in a single dose or on two consecutive days. Sixteen patients were cured and the other four had only incomplete follow-up. Secondary: Not reported
Wen et al.[29] (2008) Ivermectin 0.1 mg/kg as a single dose (*Ascaris* infection) vs ivermectin 0.2 mg/kg as a single dose (*Trichuris* or *Enterobius*	DB, MC, PC, RCT Fecal egg-positive farmers and children over six years of age from rural areas with confirmed intestinal nematode infections	N=816 Single dose	Primary: Cure rates and egg reduction rates Secondary: Adverse events	Primary: The cure rates of ivermectin against *Ascaris* (100%) and *Trichuris* (66.7%) infections were similar to albendazole against *Ascaris* (99.0%; P=1.000) and *Trichuris* (67.7%; P=0.881). Ivermectin was less effective against hookworm (33.3%) and *Enterobius* (52.9%) than albendazole (69.6%; P<0.0001). The percentages of the worms expelled were 41.9, 48.6, 9.6, 0 and 0% in a total of 681worms released on days one through five after ivermectin treatment, respectively. The percentages of the worms expelled with albendazole were 0.1, 24.3, 52.6, 22.9 and 0.1% in a total of 744 worms released on days one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
infection) vs albendazole 6.7 mg/kg as a single dose				through five post-treatment, respectively. Expulsion of worms reached a peak on day three after albendazole treatment. Secondary: For ivermectin, adverse events included dizziness, abdominal pain, and tiredness, which were mild and transient. For albendazole, a total of 2.21% of patients experienced adverse events, including dizziness, vomiting, and diarrhea. No significant difference between the two treatments in terms of adverse events was shown (P=0.806).
Suputtamongkol et al.[30] (2011) Ivermectin 200 µg/kg as a single dose vs ivermectin 200 mg/kg as a single dose given two weeks apart vs albendazole 400 mg twice daily for seven days	OL, PRO, RCT Patients ≥18 years of age with *Strongyloides stercoralis* larvae on microscopy (chronic strongyloidiasis)	N=90 19 to 36 weeks	Primary: Cure (clinical improvement and absence of larvae in stool at day 14 of treatment and through follow up), failure (presence of larvae two weeks after initiation of treatment or reappearance of larvae during follow-up) Secondary: Not reported	Primary: Parasite elimination occurred in 63.3% of albendazole patients, in 96.8% of patients receiving a single dose of ivermectin, and in 93.1% of patients receiving two doses of ivermectin (P=0.006). Patients receiving albendazole had 14.7 times (95% CI, 1.8 to 111.9) and 5.7 times (95% CI, 1.3 to 25.7) higher risk for reinfection/relapse of strongyloidiasis compared to patients receiving single-dose or double-dose ivermectin therapy, respectively. Overall, albendazole and ivermectin were well tolerated. Secondary: Not reported
Muchiri et al.[31] (2001) Albendazole 600 mg at 6 month	DB, RCT Children ages 4 to 19 years of age with *Ascaris*	N=1,186 1 year	Primary: Cure rate, egg reduction Secondary:	Primary: The cure rates for albendazole were 92.4% for hookworm infection, 83.5% for *Ascaris lumbricoides*, and 67.8% for *Trichuris trichiura*. Mebendazole given either two or three times in a year had cure rates of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intervals vs mebendazole 600 mg at 4 or 6 month intervals	*lumbricoides*, *Trichuris trichiura* and/or hookworm infections in West Kenya		Not reported	50.0 and 55.0%, respectively, for hookworm, 79.6 and 97.5% for *Ascaris lumbricoides*, and 60.6 and 68.3% for *Trichuris trichiura* infection. Albendazole was significantly more effective than either regimen of mebendazole for treating hookworm infections (P<0.0001). Three doses of mebendazole were more effective against *Ascaris lumbricoides* than two doses of albendazole (P<0.0001). The cure rate for *Trichuris trichiura* by mebendazole given at four-month intervals was higher than the six-month regimen (P=0.035), but comparable to albendazole given at six-month intervals. The geometric mean intensity of hookworm eggs per gram of stool decreased by 96.7% after albendazole treatment compared to 66.3 and 85.1%, respectively, for second or third doses of mebendazole (P<0.05) over the same period. Reductions in eggs per gram for *Ascaris lumbricoides* and *Trichuris trichiura* were comparable for both drugs. Secondary: Not reported
Legesse et al.[32] (2002) Albendazole 400 mg as a single dose vs mebendazole 100 mg two times a day for 3 days	RCT Patients with single or mixed *Ascaris lumbricoides* and/or *Trichuris trichiura* infections	N=not specified 3 days	Primary: Cure rate, egg reduction, adverse effects Secondary: Not reported	Primary: Both drugs were found to be highly effective against *Ascaris lumbricoides* infection, with cure rates >96.0% and egg reduction rates >99.8%. The efficacy of the two drugs against *Trichuris trichiura* infection was low. Mebendazole exhibited a cure rate of 34.7% and egg reduction of 92.3%, as opposed to 13.9 and 63.4%, respectively, for albendazole. More complaints were reported by individuals treated with albendazole than with mebendazole. Secondary: Not reported
Legesse et al.[33] (2004) Albendazole 400 mg as a single dose	RCT Children 6 to 19 years of age with *Ascaris*	N=534 21 days	Primary: Cure and egg reduction rates Secondary:	Primary: The cure rate and egg reduction rates obtained with albendazole and mebendazole from the three brands were not significantly different in the treatment of ascariasis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mebendazole 100 mg two times a day for 3 days	*lumbricoides* and/or *Trichuris trichiura* infections (Ethiopia)		Not reported	Significant differences were found among the percentage cure and egg reduction rates of the four groups in the treatment of trichuriasis. The highest cure rate (89.8%) and egg reduction rate (99.1%) were observed with Janssen mebendazole (Vermox®), followed by Unibios (India) mebendazole (53.3 cure and 96.5% egg reduction rates), and then East African mebendazole (27.9 cure and 88.5% egg reduction rates) with P<0.05 between the three brands. The lowest cure (17.1%) and egg reduction (69.8%) rates were seen in the albendazole-treated group (P<0.05 compared to the mebendazole brands). Secondary: Not reported
Flohr et al.[34] (2007) Study 1 Mebendazole 500 mg once vs placebo Study 2 Mebendazole 500 mg daily for 3 days vs albendazole 400 mg once vs albendazole 400 mg daily for 3 days	RCT Study 1 6- to 11-year-old children attending school in Khanh Hoa province, central Vietnam Study 2 Adults 16 years of age and older living in one village in Khanh Hoa province, central Vietnam	N=271 (Study 1) N=209 (Study 2) 2 weeks	Primary: Hookworm intensity as measured by percent decline in arithmetic mean eggs per gram after treatment Secondary: Cure from hookworm infection	Primary: Study 1 Efficacy in terms of percentage reduction in arithmetic mean eggs per gram feces relative to placebo was not significantly different between the mebendazole treatment group and the placebo group (31%, 95% CI −9 to 56). Study 2 The estimated reduction in arithmetic mean eggs per gram of feces relative to placebo was 63% (95% CI, 30 to 81), 75% (95% CI, 47 to 88), and 88% (95% CI, 58 to 97) for triple dose mebendazole, single dose albendazole, and triple dose albendazole, respectively. Secondary: Study 1 There was no significant difference between treatments in the proportion of infected children cured at two weeks: 33% in the placebo group and 38% in the mebendazole group. Study 2 The cure rates were 26% for three dose mebendazole, 45% for single dose albendazole, 79% for three dose albendazole, and 35% for placebo. Only the triple dose albendazole course was significantly superior to placebo in terms of cure (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Sacko et al.[35] (1999) Albendazole 400 mg as a single dose vs mebendazole 500 mg as a single dose vs pyrantel pamoate 12.5 mg/kg as a single dose vs placebo	PC, RCT, SB Patients 3 to 70 years of age with hookworm infections (Mali, West Africa)	N=145 10 days	Primary: Efficacy (evaluated by seven procedures which included cure rate) Secondary: Not reported	Primary: Cure rates were reported in 83.8% of patients receiving albendazole, 51.4% of patients receiving mebendazole, 37.8% of patients receiving pyrantel pamoate and 16.7% of patients receiving placebo. Using other efficacy measurements, albendazole was the most effective showing efficacies in the range of 92.1 to 99.5%, depending on the method of evaluation and the particular subset of the treatment group. Neither mebendazole nor pyrantel pamoate was as effective, with efficacies ranging from 60.9 to 89.9%, and 4.8 to 89.7%, respectively. Secondary: Not reported
Simonsen et al.[36] (2004) Ivermectin 150 to 200 µg/kg vs ivermectin 150 to 200 µg/kg and albendazole 400 mg	DB, RCT Children infected with *Wuchereria bancrofti* (Tanzania)	N=1,829 Duration not specified	Primary: Prevalence and intensities of *Wuchereria bancrofti* microfilariae and circulating filarial antigen Secondary: Not reported	Primary: The overall prevalence of *Wuchereria bancrofti* microfilariae and circulating filarial antigen was 17.3 and 43.7%, respectively. Both treatment regimens resulted in a considerable decrease in mean microfilariae intensities, with overall reductions being slightly but statistically significantly higher for the combination than for ivermectin alone. The difference in effect between the two regimens was most pronounced at six months, whereas it was minor at 12 months after treatment. The relative effect of treatment on mean circulating filarial antigen units was less pronounced than on microfilariae.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For both treatment regimens, reductions in circulating filarial antigen intensity appeared to be higher in children who were both circulating filarial antigen and microfilariae positive before treatment, which may suggest that treatment mainly affected the survival and/or production of microfilariae, rather than the survival of adult worms. Adverse reactions were few and mild in both groups, and mainly reported from pretreatment microfilariae and circulating filarial antigen positive children. Secondary: Not reported
Awadzi et al.[37] (2003) Albendazole 400 mg plus placebo vs ivermectin 200 µg/kg as a single dose plus placebo vs albendazole 400 mg plus ivermectin 200 µg/kg as a single dose vs no treatment	DB, PC, RCT Male patients 19 to 54 years of age with moderate to heavy *Onchocerca volvulus* microfiladermia and palpable onchocercal nodules (Ghana)	N=42 1 year	Primary: Viability and reproductive activity of adult worms determined by histopathology and noted by two independent readers, macrofilaricidal efficacy (measured by reductions in microfilariae skin counts), pharmacokinetic parameters, adverse events Secondary: Not reported	Primary: No difference in the viability of the adult worms between the ivermectin groups was reported. The combination was not consistently more effective than ivermectin alone in the effects on reproductive activity. There was no difference between albendazole and no treatment in the effect on adult-worm reproductive activity. There was no difference between the ivermectin groups in the rate at which microfilariae were killed or in the macrofilaricidal efficacy. Both groups reduced microfilariae skin counts by 99% at day 30. The overall reduction of microfilariae skin counts with albendazole was 22% at day 30. There was no significant pharmacokinetic interaction when albendazole was administered with ivermectin. The co-administration of albendazole with ivermectin did not produce more severe adverse effects than ivermectin alone. Secondary: Not reported
Knopp et al.[38] (2010)	DB, PC, PRO, RCT	N=610	Primary: Cure rate	Primary: The highest cure rate was 55% in the mebendazole-ivermectin group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albendazole 400 mg as a single dose vs albendazole 400 mg plus ivermectin 200 µg/kg as a single dose vs mebendazole 500 mg as a single dose vs mebendazole 500 mg plus ivermectin 200 µg/kg as a single dose	Children in grades one through seven with *Trichuris trichiura* positive stool smears in Tanzania	Median 29 days	(percentage of children excreting eggs before treatment who became negative), egg reduction rate Secondary: Adverse events	followed by a 38% cure rate in the albendazole-ivermectin group. Mebendazole cured significantly more *Trichuris trichiura* compared to albendazole (OR, 2.05; 95% CI, 1.38 to 3.04). Ivermectin cured significantly more *Trichuris trichiura* compared to placebo (OR, 5.4; 95% CI, 3.55 to 8.22). The addition of Ivermectin increased cure rate from 14 to 47% compared to placebo. The highest egg reduction rate was seen in the mebendazole-ivermectin group (97%), which was significantly greater than in the albendazole-ivermectin group (91%). The lowest egg reduction rates were observed in the monotherapy groups. Albendazole treated groups had significantly greater reductions in hookworm infections compared to other groups. Secondary: Abdominal cramps were reported in 13% of children, headache, fatigue and nausea were reported in 5% of children and 3% of children experienced diarrhea and vertigo.
Belizario et al.[39] (2003) Albendazole 400 mg as a single dose vs ivermectin 200 µg/kg as a single dose vs diethylcarbamazin	PC, RCT, SB Children in an elementary school in the Philippines infected with *Ascaris lumbricoides* and/or *Trichuris trichiura*	N=784 1 year	Primary: Cure and infection rates, egg counts Secondary: Not reported	Primary: Albendazole, ivermectin, and the drug combinations gave significantly higher cure and egg reduction rates for ascariasis than diethylcarbamazine (P<0.001). Infection rates were significantly higher at day 180 with diethylcarbamazine (P<0.001); however, there were no significant differences between treatments on day 360. Albendazole, ivermectin, and albendazole plus ivermectin produced cure rates of 69.7, 78.4, and 78.1%, respectively. For trichuriasis, albendazole plus ivermectin produced significantly higher cure rates (P<0.001) and egg reduction rates (P<0.001) than other treatments. Albendazole plus ivermectin produced the lowest infection rates on days 180 and 360 (P<0.001). Albendazole, ivermectin, and albendazole plus ivermectin produced cure rates of 31.5, 35.1, and 65.1%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
e 150 mg as a single dose vs albendazole 400 mg and diethylcarbamazine 150 mg as a single dose vs albendazole 400 mg and ivermectin 200 µg/kg as a single dose				Secondary: Not reported
Makunde et al.[40] (2004) <u>Co-infections:</u> Albendazole 400 mg and ivermectin 150 µg/kg as a single dose or placebo; 5 days later the treatment regimen was reversed <u>Single infections:</u> Albendazole 400 mg and ivermectin 150 µg/kg as a single dose or albendazole 400 mg as a single dose	RCT (Co-infections: DB, PC, XO; single infections: OL) Patients 15 to 55 years of age co-infected with *Onchocerca volvulus* and *Wuchereria bancrofti* or single infections with *Wuchereria bancrofti* (Tanzania)	N=40 1 year	Primary: Microfilariae intensity, microfilariae prevalence, adverse reactions Secondary: Not reported	Primary: The treatment of co-infections with albendazole and ivermectin resulted in a rapid reduction of microfilariae intensity that was sustained throughout the 12 months of follow-up. Microfilariae prevalence was reduced to 13 and 6% for *Onchocerca volvulus* and *Wuchereria bancrofti*, respectively, at 14 days posttreatment but increased throughout the rest of the follow-up ranging from 33 to 53% for *Onchocerca volvulus* and 40 to 67% for *Wuchereria bancrofti*. Treatment of single *Wuchereria bancrofti* infection with albendazole resulted in a sustained reduction of microfilariae intensity throughout the follow-up period, and the addition of ivermectin significantly improved efficacy at all time points ($P<0.05$). Treatment with albendazole alone resulted in a 15 to 38% reduction in mf prevalence, compared to reductions of 73 to 100% in the combination group. There was no significant difference between single and co-infected individuals in the geometric mean mf intensity of *Wuchereria bancrofti* during albendazole and ivermectin treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The frequency of adverse events in co-infected individuals was 63 and 57% in the combination and placebo groups, respectively, and of mild or moderate intensity. The frequency of adverse events in patients with single infections was 50 and 38% in the combination and albendazole monotherapy groups, respectively, and was of similar intensity to those experienced by patients with co-infections. There were no differences in adverse events between treatment groups. Secondary: Not reported
Dembele et al.[41] (2010) Albendazole 400 mg plus ivermectin 150 µg/kg administered annually for two years (low dose) vs albendazole 800 mg plus ivermectin 400 µg/kg administered bi-annually for two years (high dose)	RCT Patients14 to 65 years of age with *Wuchereria bancrofti* microfilariae	N=42 24 months	Primary: Difference in *Wuchereria bancrofti* levels at 12 months Secondary: Circulating antigen levels, presence of eosinophilia	Primary: Microfilarial levels were significantly decreased in the high dose group at 12 months (P<0.001), 18 months (P<0.019), and 24 months (P<0.044) compared to standard dose groups. Complete clearance was significantly more common in the high dose group (zero patients with microfilariae at 12, 18, and 24 months) compared to standard dose group (12, six and five patients with microfilaria at 12, 18, and 24 months, respectively; P<0.001, P=0.02, and P=0.02, respectively). Secondary: Circulating antigen levels decreased over 24 months, with differences that were not significant between the treatment groups. Eosinophilia (>500 cells/mm^3) decreased in both groups, with the most significant change occurring after six months.
Bregani et al.[42] (2006) Ivermectin 200 µg/kg biweekly for three subsequent administrations vs	OL Patients 9 to 90 years of age with *Mansonella perstans* infections (Chad)	N=165 15 months	Primary: Microfilariae density, median eosinophil percentage, recovery (full recovery defined as the number of patients with	Primary: In the diethylcarbamazine group, microfilariae density significantly decreased (P<0.01), while median eosinophil percentage increased both after the first (P<0.01) and second course of treatment (P=NS). However, the second course of treatment further improved the full recovery (complete elimination of microfilariae) from 3.8 to 15.0%. In the mebendazole group, a significant decrease in microfilariae was observed (P<0.01), while median eosinophil percentage did not change

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diethylcarbamazine 200 mg twice daily for 21 days, course repeated if full response not achieved vs mebendazole 100 mg twice daily for 28 days vs praziquantel 40 mg/kg as a single dose vs thiabendazole 50 mg/kg for children or 3 g for adults as a single dose or in double administration on the first and eighth days vs diethylcarbamazine 200 mg twice daily for 21 days plus mebendazole			complete clearance of blood microfilaria and partial recovery defined as number of patients with reduction of blood microfilaria without complete clearance), adverse events Secondary: Not reported	(P=NS). A full recovery and overall response were observed in 21.7% and 87.0% of patients, respectively. In the thiabendazole group, a statistically significant decrease in microfilariae was reached only after the second therapeutic step (-33.3%; P<0.04). Full response was achieved in one case (6.7% of patients), and an overall response of 73.0% was observed in the group who received two consecutive treatments. Thiabendazole was significantly less effective both on microfilariae reduction and on full response than diethylcarbamazine and mebendazole. In the diethylcarbamazine plus mebendazole treatment group, a highly significant fall in microfilariae was seen (P<0.01), while median eosinophil percentage values showed the same trend towards an increase as in the diethylcarbamazine group. No significant difference was observed in microfilariae reduction among the three treatment regimens using the combination of diethylcarbamazine and mebendazole. The combination of diethylcarbamazine and mebendazole produced full and overall recovery rates of 37 and 96%, respectively. There were no significant changes in microfilariae density in the groups receiving ivermectin, praziquantel or no treatment. Full and overall recovery was reported in 0 and 44.4% of patients, respectively, who received no treatment. All treatments were well tolerated, and no adverse effects were observed. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg for 21 days or 100 mg twice daily for 14 or 21 days				
Tarr et al.[43] (2003) Ivermectin rectal enema 200 µg/kg/day for seven days (prepared from tablets) in combination with nasogastric albendazole and ivermectin for 14 days, an additional five days of oral ivermectin were given two weeks after hospital discharge	Case report 55-year-old female renal transplant recipient with *Strongyloides stercoralis* hyperinfection syndrome and progressive ileus unresponsive to nasogastric albendazole and ivermectin	N=1 19 months	Primary: Clinical symptoms, presence of larvae, adverse events Secondary: Not reported	Primary: The patient improved markedly within approximately 72 hours and recovered fully. Stool studies, done periodically and, in the absence of symptoms, were negative for *Strongyloides stercoralis.* The ivermectin enemas were well tolerated, diarrhea was not induced. Nausea, abdominal pain, and shortness of breath resolved, and oxygen requirements as well as amounts of larvae in nasogastric aspirate samples decreased. At 19 months, the patient had no gastrointestinal symptoms. Secondary: Not reported
Albonico et al.[44] (2003) Mebendazole 500 mg vs levamisole 40 mg or 80 mg vs mebendazole 500	PC, RCT Children with *Ascaris lumbricoides*, hookworm and/or *Trichuris trichiura* infections (Pemba Island, Zanzibar)	N=904 21 days	Primary: Egg counts, cure rates, reductions in prevalence and egg reduction rates Secondary: Not reported	Primary: Follow-up egg counts, cure rates, reductions in prevalence and egg reduction rates for the three nematode infections were statistically significantly better with all of the drug regimens compared with those of baseline, except for cure rates for hookworm infections with mebendazole and for *T trichiura* infections with levamisole (although in both cases the mean egg counts were reduced substantially). Compared with placebo, all drug treatments produced significantly higher cure rates and egg reduction rates, and lower prevalence at follow-up, except for the egg reduction rate for levamisole in *T trichiura* infections. Both drugs had very high efficacy (98.5% and 99.1% egg reduction rates for levamisole and mebendazole, respectively) against *A lumbricoides*. Mebendazole alone and in combination with levamisole had better

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg plus levamisole 40 mg vs placebo				efficacy than levamisole alone for *T trichiura* infection (81% and 85% vs 41.5% egg reduction rates, P<0.001). Levamisole treatment produced a marginally significant reduction in prevalence of hookworm infection, which was greater than the reduction seen with mebendazole (8.9% vs 3.6%, P<0.05); the combination had better efficacy in reducing prevalence than either drug alone (23.6%, P<0.001). The egg reduction rate for hookworm infection was 88.7% for the combined treatment, but significantly less for either drug alone (61.3% for levamisole and 52.1% for mebendazole, P<0.001). No difference in mebendazole efficacy was found in children who had been treated repeatedly compared with those who had not been treated previously. Secondary: Not reported
Cleary et al.[45] (2007) Mebendazole 100 mg as a single treatment every 3 months vs mebendazole 100 mg as a single treatment every 12 months	CC Persons living along Amazon tributaries in Northeastern Peru	N=126 (stool samples) 2 years	Primary: Cure rates Secondary: Not reported	Primary: At 12 months and 24 months, 91.0% and 92.5% of the treatment group, respectively, had negative stool samples for *A. lumbricoides*. Changes in growth were evaluated based upon the quantity of individuals who were less than the 3rd percentile value for weight. A 12% improvement in those subjects below the 3rd percentile was observed over the villagers living in remote locations (control villages). Secondary: Not reported
Trematodes (Flukes)				
Kjetland et al.[46] (2006) Praziquantel 40 mg/kg as a single dose or 60 mg/kg	OL Women 20 to 49 years of age infected with *Schistosoma*	N=527 12 months	Primary: Cure rate, ova, change in shape and size of lesions, detection of sexually	Primary: *Schistosoma haematobium* ova were found in 39% of women at baseline, which decreased to 7 and 5% at three and 12 months, respectively. At baseline, 46% of the women had “sandy patches” (areas of granulomatous lesions containing schistosome ova), 44% had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in two divided doses (five hours apart)	*haematobium* (Zimbabwe)		transmitted diseases Secondary: Not reported	neovascularization, and 23% had contact bleeding. Although urinary ova excretion decreased following treatment (OR, 10.3; 95% CI, 3.8 to 27.8; P<0.001), praziquantel treatment was not associated with a significant reduction in genital lesions or contact bleeding (P=0.31 to P=0.94). There was no influence of human immunodeficiency virus seropositivity on the effect of treatment. There was no significant association between the sexually transmitted diseases and sandy patches, neovascularization or contact bleeding. Secondary: Not reported
Li et al.[47] (2002) Praziquantel 40 mg/kg given at least three times over a five-year period	OL Patients nine to 65 years of age infected with *Schistosoma japonicum* were selected for the five-year longitudinal study, all egg-positive subjects were cured at the start of the study with praziquantel (China)	N=120 5 years	Primary: Prevalence, intensity of infection (defined as geometric mean eggs per gram), ultrasound changes Secondary: Not reported	Primary: Prevalence of schistosome infection fell by 43% and intensity of infection declined by 80% over the five-year study. However, transmission persisted at 13% per year for re-infection or new infection in the cohort. The prevalence of left-lobe enlargement and dilated portal vein fell significantly (P<0.01) to about half, although a few patients progressed during the study. At study endpoint, infection was nearly twice as common if the portal vein was dilated (23 vs 13%, respectively), but this association was not statistically significant (P>0.05). However, end point infection was even more strongly associated with left-lobe enlargement (57 vs 15%; P<0.01). The proportions of subjects with improved parenchymal and periportal fibrosis were much higher than the proportions of subjects that progressed (P<0.05). Reduction of prevalence and intensity of infection and improvement of subclinical morbidity were benefits of repeated treatments. Secondary: Not reported
Kabatereine et al.[48] (2003)	OL Patients five to 54	N=482 12 weeks	Primary: Cure rate, reduction in	Primary: The cure rate following the first and second treatments was 41.9 and 69.1%, respectively. The cure rate was higher in adults than in children,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Praziquantel 40 mg/kg as a single dose, repeated six weeks later	years of age infected with *Schistosoma mansoni* (Uganda)		intensity of infection, adverse reactions Secondary: Not reported	irrespective of intensity of infection. In addition, the cure rate declined markedly with increasing intensity of infection. The reduction in intensity of infection was marked, being 97.7 and 99.6% after the first and second treatments, respectively. A pre- and post-treatment symptom questionnaire revealed a broad range of side effects, including abdominal pain and diarrhea. However, no serious or long-lasting complications affecting compliance were observed. Secondary: Not reported
Raso et al.[49] (2004) Praziquantel 40 mg/kg as a single dose	OL Patients five days to 91 years of age infected with *Schistosoma mansoni* (Côte d'Ivoire)	N=200 6 weeks	Primary: Cure rate, egg reduction rate, adverse reaction Secondary: Not reported	Primary: The overall cure rate, assessed six weeks posttreatment, was 60.9%. The overall cure rates among individuals who had light, moderate, or heavy infections pretreatment were 70.3, 50.0, and 33.3%, respectively. The total egg count reduction was 61.4%. Among the 200 treated patients, 25 (12.5%) reported one or more side effects within 24 hours post-treatment. The most frequent side effects were abdominal pain, dizziness, and diarrhea. Secondary: Not reported
Picquet et al.[50] (1998) Praziquantel 40 mg/kg as a single dose repeated in 40 days	OL Adults and children infected with *Schistosoma mansoni* (Senegal)	N=113 153 days	Primary: Cure rate, egg counts, intensity reduction rate Secondary: Not reported	Primary: The overall cure rate after the first treatment was 42.5 and was 76.1% after the second treatment. The greatest increase in cure rate between the two treatments was in those individuals who were initially the most heavily infected (>1,000 eggs/gram of feces). The overall intensity reduction rate after the first and second treatments were 70.7 and 88.1%, respectively. There was no apparent difference in cure rate between younger (<20 years) and older individuals (>20 years). There was no evidence for the existence of a praziquantel tolerant strain of *Schistosoma mansoni*.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Degu et al.[51] (2002) Praziquantel 40 mg/kg as a single dose	OL All children 10 to 14 years of age attending the primary school in Gorgora, Amhara (Ethiopia)	N=325 6 weeks	Primary: Prevalence of *Schistosoma mansoni*, fecal eggs, egg reduction rate, evidence of resistance Secondary: Not reported	Primary: Of the 325 children examined, 50.8% had *Schistosoma mansoni* eggs in the first fecal sample. Six weeks after treatment, 94% of the children had no detectable *Schistosoma mansoni* eggs, and the average egg reduction rate was 97%. Sixty-seven of the children reported that they had previously been diagnosed with schistosomiasis and had been treated with praziquantel. Of these, 32 (47.8%) were found to be excreting eggs, a proportion not significantly different from the prevalence among children who did not report previous infection (52.2%). No evidence of praziquantel resistance was detected. Secondary: Not reported
Hou et al.[52] (2008) Praziquantel 60 mg/kg plus 6 mg/kg artemether (group A) vs praziquantel 60 mg/kg (group B) vs praziquantel 120 mg/kg plus 6 mg/kg artemether	DB, PC, RCT, Patients ten to 60 years of age weighing over 25 kg and diagnosed with acute *Schistosoma japonicum*	N=205 45 days	Primary: Human infection status Secondary: Hemoglobin and alanine aminotransferase levels over time	Primary: All groups had similarly high treatment efficacies ranging from 95.7% (group D) to 98.0% (group A). Comparisons of group A with group B and group C with group D for the determination of the additive effect of artemether showed that there were no significant difference in treatment efficacies in the regimens that included artemether (P=0.947). The two different dosages of praziquantel provided the same level of efficacy. Fever subsided in 3.9, 5.1, 6.4, and 5.2 days post-artemether treatment in groups A, B, C, and D, respectively (P=0.027). Combined artemether and praziquantel (60 mg/kg) treatment was the most effective for fever clearance. Patients in groups A , B, C, and D remained in hospital on average 6.4, 8.0, 9.4, and 8.9 days, respectively; the hospital stay of patients in group A was significantly shorter than in the other groups (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(group C) vs praziquantel 120 mg/kg (group D)				Secondary: Little change in hemoglobin levels of patients was observed over the course of the trial and there were no significant differences between the groups both pre- and post-treatment. In total, 34 cases had an elevated alanine aminotransferase level before treatment, of which 24 returned to normal at day 20 post-artemether treatment. There were no statistically significant differences between the groups, and the mean levels of alanine aminotransferase at 20 days post-artemether treatment dropped to normal levels.
Martins-Leite et al.[53] (2008) Praziquantel 50 mg/kg once and repeated after two months if necessary	OL Patients presenting with an infection with *Schistosoma mansoni* (Brazil)	N=91 1 year	Primary: Immune response and reversal of Symmers' fibrosis Secondary: Not reported	Primary: A significant reduction in the mean values for longitudinal and anteroposterior measurements of liver (left and right lobes), as well as the diameters of portal and splenic veins was observed. In contrast, the spleen measurements were augmented significantly. The numbers of individuals with non-detectable fibrosis and those with incipient fibrosis increased. One year after treatment with praziquantel, 29% of individuals reverted to a lower degree of fibrosis, 4% experienced an increase in fibrosis, and 67% did not experience any change. The proportion of individuals with pathology (grade 2 or 3) decreased from 24% prior to treatment to 4% after treatment ($P<0.001$). Nine (9.9%) participants remained positive for the presence of eggs of *Schistosoma mansoni*, and their infection levels ranged from four to 184 eggs/gram. When distributed according to the degree of hepatic fibrosis (classified into three groups as determined by posttreatment ultrasound measurements), no statistically significant differences in levels of cytokines could be detected. However, when the levels of these cytokines were categorized as low or high (on the basis of the median value of each cytokine titer for 91 patients) for individuals not presenting (group 0) or presenting (groups 1 and 2) with fibrosis, the proportion of subjects with a high level of IL-13 was significantly larger in the latter two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Koukounari et al.[54] (2007) Praziquantel and albendazole Large-scale administration of the agents against soil-transmitted helminths by the national Burkinabe´ helminth control program.	EPI Burkinabe´ children six to 14 years of age	N=1,727 12 months	Primary: Parasitological and morbidity data Secondary: Not reported	Primary: During the 12 months between examinations, the overall prevalences of *Schistosoma haematobium, Schistosoma mansoni,* and hookworm infections decreased significantly (P<0.001). For both years examined, *Ascaris lumbricoides* infection was absent, and the prevalence of *Trichuris trichiura* infection was estimated to be 1.1% at baseline and totally absent one year later. A significant increase in mean hemoglobin concentration (P<0.001) and a significant decrease in the prevalence of anemia (P=0.021) were also observed. The unadjusted observed changes in both recent and chronic undernutrition from baseline to follow-up were not significant (P=0.135 and P=0.093, respectively). Secondary: Not reported
Maco et al.[55] (2015) Triclabendazole 2 dosages of 7.5mg/kg each with a 12-h interval (Group I) vs Triclabendazole single 10-mg/kg dose (Group II)	MC, OL, RCT Peruvian children 2 to 16 years of age with *Fasciola hepatica* eggs in their stools	N=84 60 days	Primary: Presence (parasitological failure) or absence (parasitological cure) of eggs compatible with *F . hepatica* 60 days post-treatment Secondary: Tolerability	Primary: A parasitological cure was obtained in 100% of individuals from Group I and 95% of individuals from Group II. Secondary: The most common adverse event was biliary colic.
Miscellaneous Infections				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Namwanje et al.[56] (2011) <u>Schistosomiasis alone:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs praziquantel 40 mg/kg as a single dose <u>Schistosomiasis alone:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose <u>Lymphatic</u>	RCT Children five to 18 years of age with lymphatic filariasis alone; schistosomiasis alone; soil-transmitted helminthiasis alone; lymphatic filariasis + schistosomiasis and lymphatic filariasis + schistosomiasis + soil-transmitted helminthiasis	N=235 5 weeks	Primary: Adverse drug events with triple therapy Secondary: Efficacy (mean percentage reduction in egg counts)	Primary: There were no significant differences in adverse drug events in the treatment group compared to the control group. A total of 22.2% of the test group (triple therapy) reported an adverse drug event compared to 66.7% of the control group. The most frequent adverse drug events reported were abdominal pain and headache. Secondary: The overall mean reduction in schistosomiasis eggs for the test group and control group was 99%. There was no significant difference among the treatment groups. The overall mean reduction in soil-transmitted helminthiasis eggs for the test group was 94 and 93% for control group. There was no significant difference among the treatment groups. The overall mean reduction in lymphatic filariasis microfilariae was 92% in the test group and 99% in the control group. There was no significant difference among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>filariasis alone:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose <u>Lymphatic filariasis + schistosomiasis:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose followed by				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
praziquantel 40 mg/kg as a single dose after one week <u>Lymphatic filariasis + schistosomiasis + soil-transmitted helminthiasis:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose followed by praziquantel 40 mg/kg as a single dose after one week				

Study abbreviations: CC=case control, CI=confidence interval, DB=double-blind, EPI=epidemiologic study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, OR=odds ratio, RCT=randomized-controlled trial, RR=relative risk, SB=single-blind, XO=crossover.

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Anthelmintics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Albendazole	tablet	Albenza®*	$$$$$	$$$
Ivermectin	tablet	Stromectol®*	$$	$
Mebendazole	chewable tablet	Emverm®	$$$$$	N/A
Praziquantel	tablet	Biltricide®*	$$$$	$$$$
Triclabendazole	tablet	Egaten®	N/A	N/A

*Generic available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The anthelmintics are approved for the treatment of cestode, nematode, and trematode infections.[1-7] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[8] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the United States, followed by *Ascaris lumbricoides*.[10]

Albendazole is approved for the treatment of cestode infections, including cystic hydatid disease (liver, lung, and peritoneum) and parenchymal neurocysticercosis. Clinical trials have demonstrated successful treatment of cystic hydatid disease and parenchymal neurocysticercosis with this agent.[14-19]

Ivermectin is approved for the treatment of nematode infections, including onchocerciasis and strongyloidiasis of the intestinal tract. Clinical trials have demonstrated successful treatment of onchocerciasis and strongyloidiasis with this agent.[22-25,28,37]

Mebendazole is approved for the treatment of nematode infections, including ascariasis, hookworms, pinworms, and whipworms. Clinical trials have demonstrated successful treatment of helminthic infections with mebendazole.[31-33,35,44,45]

Praziquantel is approved for the treatment of trematode infections, including clonorchiasis, opisthorchiasis, and schistosomiasis. Several clinical trials have demonstrated successful treatment of schistosomiasis with praziquantel.[46-54]

Triclabendazole is approved for the treatment of fascioliasis in patients six years of age and older. Clinical trials have demonstrated successful treatment of fascioliasis with triclabendazole.[7,55]

Albendazole, ivermectin, mebendazole, praziquantel, and triclabendazole are considered first-line therapy for some parasitic diseases that are not commonly seen in the United States. Therefore, patients with a diagnosis of one of these uncommon helminthic infections should be allowed approval for a brand anthelmintic through the medical justification portion of the prior authorization process.

Therefore, all brand anthelmintic products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand anthelmintic product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Aminoglycosides
AHFS Class 081202
May 3, 2023

I. Overview

The parenteral aminoglycosides are used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated urinary tract infections.[1-3] Once susceptibility tests are available and a pathogen has been identified, the aminoglycosides are often discontinued so that treatment with a less toxic agent can be initiated.[3] Neomycin is administered orally as adjunctive therapy to suppress the normal bacterial flora of the bowel to prepare the gastrointestinal tract for surgery. It is also used as an adjunctive agent for the treatment of hepatic coma to reduce the ammonia-forming bacteria in the intestinal tract.[1-4] Tobramycin inhalation solution and inhalation powder are approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[6-9]

Currently, there are five inhaled tobramycin agents available on the market. TOBI® (tobramycin solution for inhalation) was the first available agent in 1997, followed by Bethkis® (tobramycin solution for inhalation) in early 2013, TOBI® Podhaler (tobramycin inhalation powder) in June 2013, generic tobramycin inhalation solution in November 2013, and lastly Kitabis® Pak (tobramycin solution for inhalation), in December 2014. All of these products have the same FDA-approved indication of management of cystic fibrosis adults and pediatric patients six years of age and older with *Pseudomonas aeruginosa*.[6-9] The most recently approved agent, Kitabis® Pak (tobramycin solution for inhalation), was FDA approved using the same clinical trial data as TOBI® (tobramycin solution for inhalation). This is the only agent that co-packages the generic tobramycin inhalation solution with a reusable nebulizer (PARI LC Plus™).[9] There are several minor differences between each of these agents, the most notable being that the TOBI® Podhaler (tobramycin inhalation powder) does not require a nebulizer and does not need to be stored in a refrigerator. In addition, the time to administer these agents does vary between products from two to seven minutes for the TOBI® Podhaler (tobramycin inhalation powder) and approximately 15 minutes for the remainder of the tobramycin agents.[2,6-9]

The antibacterial properties of aminoglycosides result from both the inhibition of bacterial protein synthesis and the creation of fissures in the outer membrane of the bacterial cell membrane. Irreversible binding to bacterial ribosomes and disruption of the cell membrane results in leakage of intracellular contents and accounts for most of the bactericidal activity.[3,10,11] The aminoglycosides display concentration-dependent bactericidal activity and a prolonged post-antibiotic effect. They act synergistically when administered with other antibacterial agents.[11] Resistance to the aminoglycosides has been reported infrequently. Amikacin has the broadest spectrum of activity and may be used to treat infections caused by gentamicin- and tobramycin-resistant organisms.[3,12]

The aminoglycosides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the aminoglycosides are available in a generic formulation, with the exception of amikacin inhalation suspension, plazomicin, and tobramycin inhalation powder. This class was last reviewed in May 2021.

Table 1. Aminoglycosides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amikacin	inhalation suspension, injection	Arikayce®	amikacin
Gentamicin	injection	N/A	gentamicin
Neomycin	tablet	N/A	neomycin
Plazomicin	injection	Zemdri®	none
Streptomycin	injection	N/A	streptomycin
Tobramycin	inhalation solution, inhalation powder, injection	Bethkis®*, Kitabis®*, TOBI®*, TOBI Podhaler®	Bethkis®*, Kitabis®*, tobramycin§

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.
§ Injection and inhalation solution (generic TOBI) are preferred.

The aminoglycosides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the aminoglycosides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Aminoglycosides[1-9]

Organism	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin
Gram-Positive Bacteria						
Enterococcus faecalis					✔	
Staphylococcus species	✔	✔				
Staphylococcus aureus						✔
Streptococcus viridans					✔	
Gram-Negative Bacteria						
Acinetobacter species	✔					
Aerobacter aerogenes					✔	
Brucella species					✔	
Citrobacter species		✔				✔
Enterobacter species	✔	✔	✔	✔		✔
Escherichia coli	✔	✔	✔	✔	✔	✔
Francisella tularensis					✔	
Haemophilus ducreyi					✔	
Haemophilus influenzae					✔	
Klebsiella species	✔	✔	✔			✔
Klebsiella granulomatis					✔	
Klebsiella pneumoniae				✔	✔	
Morganella morganii						✔
Proteus species	✔	✔		✔	✔	✔
Providencia species	✔					✔
Pseudomonas species	✔					
Pseudomonas aeruginosa		✔				✔
Serratia species	✔	✔				✔
Yersinia pestis					✔	
Miscellaneous Organisms						
Mycobacterium tuberculosis					✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the aminoglycosides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Aminoglycosides

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[13]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for four weeks (in β-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients).

Clinical Guideline	Recommendation(s)
	○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[14]	<u>Secondary prevention of rheumatic fever</u> • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. <u>Endocarditis prophylaxis</u> • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: ○ Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. ○ Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. ○ Previous infective endocarditis. ○ Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. ○ Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. <u>Recommendations for medical therapy for infective endocarditis</u> • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective

Clinical Guideline	Recommendation(s)
	endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered. • Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[15]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is

Clinical Guideline	Recommendation(s)
	recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or

Clinical Guideline	Recommendation(s)
	moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[16]** **(Was reviewed and deemed current as of July 2011)**	<u>Empirical therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended.

Clinical Guideline	Recommendation(s)
	Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[17]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem.

Clinical Guideline	Recommendation(s)

	• *Staphylococcal* species:
	  o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected.
	  o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.
	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem.
	• Pseudomonal meningitis:
	  o Meropenem±gentamicin.

Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[18]	<u>Empiric Therapy</u>
	• Empiric therapy should be used when infection is suspected but cultures are not yet available.
	• Vancomycin plus an anti-pseudomonal β-lactam (e.g., cefepime, ceftazidime, or meropenem) is recommended.
	• Choice of anti-pseudomonal β-lactam should be based on local resistance patterns.
	• In seriously ill adult patients, vancomycin troughs should be maintained at 15 to 20 µg/mL.
	• For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin.
	• Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens.
	
	<u>Pathogen Specific Therapy</u>
	• Methicillin-susceptible *S. aureus*
	  o Recommended treatment includes nafcillin or oxacillin
	  o In patients who cannot receive β-lactams, vancomycin is recommended
	• Methicillin-resistant *S. aureus*
	  o Recommended treatment includes vancomycin
	• *P. acnes*
	  o Recommended treatment includes penicillin G
	• *Pseudomonas* species
	  o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone
	• Gram-negative bacilli
	  o Recommended treatment includes ceftriaxone or cefotaxime
	• Extended-spectrum β-lactamase–producing gram-negative bacilli
	  o Recommended treatment includes meropenem
	• *Acinetobacter* species
	  o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B
	• *Candida* species
	  o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine
	• *Aspergillus* or *Exserohilum*
	  o Recommended treatment includes voriconazole
	• In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain
	  o Use of rifampin as part of combination therapy is recommended
	
	<u>Duration of Therapy</u>

Clinical Guideline	Recommendation(s)

	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms
	  o Duration is recommended to be 10 days
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features
	  o Duration is recommended to be 10 to 14 days
	• Infections caused by *S. aureus* or gram-negative bacilli
	  o Duration is recommended to be 10 to 14 days
	• Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy
	  o It is recommended that therapy be continued for 10 to 14 days after the last positive culture

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)[19]**	<u>Impetigo and ecthyma</u>
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When methicillin-resistant *S. aureus* (MRSA) is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	<u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u>
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	<u>Recurrent skin abscesses</u>
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.

Clinical Guideline	Recommendation(s)
	• Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. <u>Erysipelas and cellulitis</u> • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. <u>Necrotizing fasciitis</u> • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-

Clinical Guideline	Recommendation(s)
	acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. <u>Pyomyositis</u> • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. <u>Clostridial gas gangrene or myonecrosis</u> • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. <u>Animal bites</u> • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure.

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	Bacillary angiomatosis and cat scratch disease
	• Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol:
	  ○ Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days.
	  ○ Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days.
	• Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis.
	
	Erysipeloid
	• Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid.
	
	Glanders
	• Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility.
	
	Bubonic plague
	• Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin.
	
	Tularemia
	• Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every eight hours intravenously) is recommended for treatment of severe cases of tularemia.
	• Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[20]	Genital herpes
	• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management.
	• Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy.
	• Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued.
	• Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes.
	• Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability.
	• Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged.
	• Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.
	• Recommended regimens for first episodes of genital herpes:
	  ○ acyclovir 400 mg orally three times daily for seven to 10 days
	  ○ famciclovir 250 mg orally three times daily for seven to 10 days

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	○ valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: ○ acyclovir 400 mg orally twice daily ○ famciclovir 250 mg orally twice daily ○ valacyclovir 500 mg orally once daily ○ valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: ○ acyclovir 800 mg orally twice daily for five days ○ acyclovir 800 mg orally three times daily for two days ○ famciclovir 1,000 mg orally twice daily for one day ○ famciclovir 500 mg orally once; followed by 250 mg orally twice

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	daily for two days ○ famciclovir 125 mg orally twice daily for five days ○ valacyclovir 500 mg orally twice daily for three days ○ valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: ○ acyclovir 400 to 800 mg orally two to three times daily ○ famciclovir 500 mg orally twice daily ○ valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: ○ acyclovir 400 mg orally three times daily for five to 10 days ○ famciclovir 500 mg orally twice daily for five to 10 days ○ valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical

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	resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. <u>Pediculosis pubis (pubic lice infestation)</u> • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off. o Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. <u>Scabies</u> • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. o Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.

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	• Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. <u>Bacterial vaginosis</u> • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence.

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	• BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. Uncomplicated vulvovaginal candidiasis • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.

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	Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution

Clinical Guideline	Recommendation(s)
	Vaginal warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal Intra-anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)**[21] Reviewed and deemed current as of 07/2013	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute pyelonephritis • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance

Clinical Guideline	Recommendation(s)
	to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)[22]** Reaffirmed 2016	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days. o Trimethoprim 100 mg twice daily for three days. o Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days. o Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days. o Fosfomycin tromethamine, 3 g dose (powder) single dose.
American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in Women: Guideline (2022)[23]**	Evaluation • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women.

Clinical Guideline	Recommendation(s)
	• Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy.
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[24]	Aerosolized antibiotics • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. Anti-inflammatory agents • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or

Clinical Guideline	Recommendation(s)
	allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with a forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. • For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. <u>Bronchodilators</u> • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. <u>Hypertonic saline</u> • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. <u>Ivacaftor</u> • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. <u>Macrolide antibiotics</u>

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	• For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. <u>Recombinant human DNase</u> • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)[25]** Reviewed and deemed current as of 04/2013	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia</u>

Clinical Guideline	Recommendation(s)
Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-acquired Pneumonia (2019)[26]**	(CAP) in adults in outpatient setting: • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid. • Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-**	Empiric Therapy • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in

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associated Pneumonia: 2016 Clinical Practice Guidelines (2016)[27]	patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known o Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available <u>Pathogen-Specific Therapy</u> • MRSA o Vancomycin or linezolid are recommended treatments • *P. aeruginosa* o It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy o In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli o Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species o Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens o If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin <u>Duration of therapy</u> • Seven day course of treatment
World Health Organization: **Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017)[28]**	<u>Treatment of drug-susceptible tuberculosis (TB)</u> • In patients with drug-susceptible pulmonary TB, four-month fluoroquinolone-containing regimens should not be used and the six-month rifampicin-based regimen 2HRZE/4HR (two months of H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol and four months of H = isoniazid, R = rifampicin) remains the recommended regimen. • The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB. • In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing (i.e., intermittent dosing) is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency. • Initiation of antiretroviral treatment (ART) in TB patients living with HIV:

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	o ART should be started in all TB patients living with HIV regardless of their CD4 cell count. o TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of treatment. HIV-positive patients with profound immunosuppression (e.g., CD4 counts <50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment. • In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a six-month standard treatment regimen is recommended over an extended treatment for eight months or more. • The use of adjuvant steroids in the treatment of extrapulmonary TB disease: o In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over six to eight weeks should be used. o In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. • In patients who require TB retreatment, the category II regimen should no longer be empirically prescribed, and drug-susceptibility testing should be conducted to inform the choice of treatment regimen. <u>Patient care and support</u> • Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions: o Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. o A package of treatment adherence intervention may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option. o One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: ▪ tracers (communication with the patient including via SMS, telephone (voice) calls, or home visit) or digital medication monitor; ▪ material support to patient; ▪ psychological support to patient; ▪ staff education. o The following treatment administration options may be offered to patients on TB treatment: ▪ Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment; ▪ DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment; ▪ Video observed treatment (VOT) can replace DOT when the video communication technology is available and can be appropriately organized and operated by health-care providers and patients. Summary of changes in the new guidelines 2017 and policy recommendations on treatment of drug-susceptible TB and patient care in other existing WHO guidelines that remain valid

Guidelines for treatment of tuberculosis, 2010	Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update
Duration of rifampicin in new TB patients	
New patients with pulmonary TB should	Remains valid

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	receive a regimen containing 6 months of rifampicin: 2HRZE/4HR	
	The 2HRZE/6HE treatment regimen should be phased out	Remains valid
	Effectiveness of shortened fluoroquinolone-containing regimens	
	No existing specific recommendation	UPDATED: In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen
	Use of fixed-dose combination formulations or separate drug formulations	
	No existing specific recommendation	The use of FDC tablets is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB
	Dosing frequency of TB treatment in new TB patients	
	Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy	Remains valid
	New patients with pulmonary TB may receive a daily intensive phase followed by a three-times-weekly continuation phase [2HRZE/4(HR)], provided that each dose is directly observed	UPDATED: In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency
	Three-times-weekly dosing throughout therapy [2(HRZE)/4(HR)] may be used as another alternative, provided that every dose is directly observed, and the patient is NOT living with HIV or living in an HIV-prevalent setting	
	New patients with TB should not receive twice-weekly dosing for the full course of treatment unless this is done in the context of formal research	Remains valid
	Dosing frequency of TB treatment in persons living with HIV	
	TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of rifampicin-containing treatment regimen. The optimal dosing frequency is daily during the intensive and continuation phases.	Remains valid
	Duration of TB treatment for TB patients living with HIV	
	It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients	Remains valid
	In TB patients who are living with HIV and receiving antiretroviral therapy during TB treatment, is there a need to prolong duration of TB treatment longer than 6 months? No existing specific recommendation	UPDATED: In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-months standard treatment regimen is recommended over an extended treatment for 8 months or longer
	Initial regimen in countries with high levels of isoniazid resistance	
	In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR	Remains valid
	Treatment extension in new pulmonary TB patients	

Clinical Guideline	Recommendation(s)	
	In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended	Remains valid
	The use of steroids in the treatment regimen of tuberculous meningitis and tuberculous pericarditis	
	No existing specific recommendation	UPDATED: In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over six to eight weeks should be used. In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used.
	Treatment of previously treated TB patients	
	Specimens for culture and drug-susceptibility testing should be obtained from all previously treated TB patients at or before the start of treatment. Drug-susceptibility testing should be performed for at least isoniazid and rifampicin	Remains valid
	In settings where rapid molecular-based drug-susceptibility testing is available, the results should guide the choice of regimen	Remains valid
	In settings where rapid molecular-based drug-susceptibility testing results are not routinely available to guide the management of individual patients, TB patients whose treatment has failed or other patient groups with high likelihood of MDRTB should be started on an empirical MDR regimen	Remains valid
	In settings where rapid molecular-based drug-susceptibility testing results are not routinely available to guide the management of individual patients, TB patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are unavailable	UPDATED: In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen
	In settings where drug-susceptibility testing results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment	Remains valid
	National TB control programmes should obtain and use their country-specific drug resistance data on failure, relapse and loss to follow-up of patient groups to determine the levels of MDR-TB.	Remains valid
	Patient care and support: treatment supervision (e.g., DOT, VOT), social support and digital health interventions: No existing specific recommendation	UPDATED: 1. Health education about the disease and counselling on treatment adherence should be provided to patients on TB treatment 2. A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option 3. One or more of the

Clinical Guideline	Recommendation(s)
	following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracer or digital medication monitor b) material support to patient; c) psychological support to patient; d) staff education. 4. The following treatment administration options may be offered to patients on TB treatment: a) Community or home-based DOT is recommended over health facility-based DOT or unsupervised treatment; b) DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment; c) Video observed treatment (VOT) can replace DOT when the video communication technology is available and it can be appropriately organized and operated by health care providers and patients.
The American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America: **Treatment of Drug-Resistant Tuberculosis (2019)**[29]	<u>Recommendations for the selection of an effective multidrug-resistant (MDR)-TB treatment regimen and duration of MDR-TB treatment</u> • Use at least five drugs in the intensive phase of treatment and four drugs in the continuation phase of treatment (conditional recommendation, very low certainty in the evidence). • Use an intensive-phase duration of treatment of between 5 and 7 months after culture conversion (conditional recommendation, very low certainty in the evidence). • A total treatment duration of between 15 and 21 months after culture conversion is suggested (conditional recommendations, very low certainty in the evidence). • In patients with pre extensively drug-resistant (XDR)-TB and XDR-TB, which are both subsets of MDR-TB, a total treatment duration of between 15 and 24 months after culture conversion is suggested (conditional recommendations, very low certainty in the evidence). <u>Recommendations for the selection of oral drugs for MDR-TB treatment (in order of strength of recommendation)</u> • Including a later-generation fluoroquinolone is recommended (levofloxacin or moxifloxacin) (strong recommendation, low certainty of evidence). • Including bedaquiline is recommended (strong recommendation, very low certainty in the evidence). • Including linezolid is recommended (conditional recommendation, very low certainty in the evidence). • Including clofazimine is recommended (conditional recommendation, very low certainty of evidence). • Including cycloserine is recommended (conditional recommendation, very low certainty in the evidence). • Including ethambutol is suggested only when other more effective drugs cannot be assembled to achieve a total of five drugs in the regimen (conditional recommendation, very low certainty in the evidence). • Including pyrazinamide in a regimen for treatment of patients with MDR-TB or with isoniazid-resistant TB is suggested when the *M. tuberculosis* isolate has not been found resistant to pyrazinamide (conditional recommendation, very low certainty in the evidence). • A clinical recommendation for or against delamanid could not be made

Clinical Guideline	Recommendation(s)
	because of the absence of data. Until additional data are available, the guideline panel concurs with the conditional recommendation of the 2019 WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment that delamanid may be included in the treatment of patients with MDR/rifampin-resistant (RR)-TB aged ≥3 years on longer regimens. <u>Recommendations for selected oral drugs previously included in regimens for the treatment of MDR-TB</u> • Including amoxicillin–clavulanate is NOT recommended, with the exception of when the patient is receiving a carbapenem wherein the inclusion of clavulanate is necessary (strong recommendation, very low certainty in the evidence). • Including the macrolides azithromycin and clarithromycin is NOT recommended (strong recommendation, very low certainty in the evidence). • including ethionamide/prothionamide if more effective drugs are available to construct a regimen with at least five effective drugs is NOT suggested (conditional recommendation, very low certainty in the evidence). • including *p*-aminosalicylic acid in a regimen is NOT suggested if more effective drugs are available to construct a regimen with at least five effective drugs (conditional recommendation, very low certainty in the evidence). <u>Recommendations for the selection of drugs administered through injection when needed to compose an effective treatment regimen for MDR-TB</u> • Including amikacin or streptomycin is suggested when susceptibility to these drugs is confirmed (conditional recommendation, very low certainty of evidence). • Including a carbapenem is suggested (always to be used with amoxicillin-clavulanic acid) (conditional recommendation, very low certainty of evidence). • Including kanamycin or capreomycin is NOT suggested (conditional recommendation, very low certainty in the evidence). <u>Recommendations for the use of the WHO-recommended standardized shorter-course 9- to 12-month regimen for MDR-TB</u> • The shorter-course regimen is standardized with the use of kanamycin (which the committee recommends against using) and includes drugs for which there is documented or high likelihood of resistance (e.g., isoniazid, ethionamide, pyrazinamide). • The guideline committee cannot make a recommendation either for or against this standardized shorter-course regimen, compared with longer individualized all-oral regimens that can be composed in accordance with the recommendations in this practice guideline. <u>Recommendations for the treatment of isoniazid-resistant TB</u> • Adding a later-generation fluoroquinolone to a six-month regimen of daily rifampin, ethambutol, and pyrazinamide is suggested for patients with isoniazid-resistant TB (conditional recommendation, very low certainty in the evidence). • In patients with isoniazid-resistant TB treated with a daily regimen of a later-generation fluoroquinolone, rifampin, ethambutol, and pyrazinamide, the duration of pyrazinamide can be shortened to two months in selected situations (i.e., noncavitary and lower burden disease or toxicity from pyrazinamide) (conditional recommendation, very low certainty in the evidence).

Clinical Guideline	Recommendation(s)
	Recommendations for the management of contacts to patients with MDR-TB • Offering treatment for latent TB infection (LTBI) for contacts to patients with MDR-TB is suggested versus following with observation alone (conditional recommendation, very low certainty in the evidence). Six to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug is suggested, on the basis of drug susceptibility of the source-case *M. tuberculosis* isolate. On the basis of evidence of increased toxicity, adverse events, and discontinuations, pyrazinamide should not be routinely used as the second drug.
World Health Organization: **Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment (2019)**[30]	Regimens for isoniazid-resistant tuberculosis (Hr-TB) • In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. • In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. The composition of longer MDR-TB regimens • In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. • Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens. • Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. • Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged six to 17 years. • Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. • Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. • Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. • Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. • Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. • Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. • Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. • Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible. • p-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or

Clinical Guideline	Recommendation(s)
	delamanid are not used or if better options to compose a regimen are not possible. • Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. <u>The duration of longer MDR-TB regimens</u> • In MDR/RR-TB patients on longer regimens, a total treatment duration of 18 to 20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. • In MDR/RR-TB patients on longer regimens, a treatment duration of 15 to 17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. • In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of six to seven months is suggested for most patients; the duration may be modified according to the patient's response to therapy. <u>Use of the standardized, shorter MDR-TB regimen</u> • In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of nine to 12 months may be used instead of the longer regimens. <u>Monitoring patient response to MDR-TB treatment using culture</u> • In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. <u>Start of antiretroviral therapy in patients on second-line antituberculosis regimens</u> • Antiretroviral therapy is recommended for all patients with HIV and DR-TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of antituberculosis treatment. <u>Surgery for patients on MDR-TB treatment</u> • In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. <u>Care and support for patients with MDR/RR-TB</u> • Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment. • A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option. • One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: o tracers and/or digital medication monitor; o material support to the patient; o psychological support to the patient; o staff education. • The following treatment administration options may be offered to patients

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	on TB treatment: o Community- or home-based directly-observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment. o DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment. o Video-observed treatment (VOT) may replace DOT when video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients. • Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization. • A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment. Note: H=isoniazid, R=rifampicin, Z=pyrazinamide and E=ethambutol Note: Group A = levofloxacin/moxifloxacin, bedaquiline, linezolid; Group B = clofazimine, cycloserine/terizidone; Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid
World Health Organization: **Consolidated Guidelines on Tuberculosis: Prevention: Tuberculosis Preventive Treatment (2020)[31]**	<u>TB preventive treatment options</u> • The following options are recommended for the treatment of latent tuberculosis infection (LTBI) regardless of HIV status: six or nine months of daily isoniazid, or a three-month regimen of weekly rifapentine plus isoniazid, or a three-month regimen of daily isoniazid plus rifampicin. A one-month regimen of daily rifapentine plus isoniazid or four months of daily rifampicin alone may also be offered as alternatives. • In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.
American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: **Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis (2016)[32]**	<u>Recommended treatment regimens</u> • The preferred regimen for treating adults with tuberculosis caused by organisms that are not known or suspected to be drug resistant is a regimen consisting of an intensive phase of two months of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by a continuation phase of four months of INH and RIF. • The intensive phase of treatment consists of four drugs (INH, RIF, PZA, EMB) because of the current proportion of new tuberculosis cases worldwide caused by organisms that are resistant to INH; however, if therapy is being initiated after drug susceptibility test results are known and the patient's isolate is susceptible to both INH and RIF, EMB is not necessary, and the intensive phase can consist of INH, RIF, and PZA only. EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF. • Pyridoxine (vitamin B6) is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons infected with human immunodeficiency virus [HIV]; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age). • With respect to administration schedule, the preferred frequency is once daily for both the intensive and continuation phases. <u>Practical aspects of treatment</u> • Mild adverse effects usually can be managed with treatment directed at

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	controlling the symptoms; severe effects usually require the offending drug(s) to be discontinued and may require expert consultation on management. • If a drug is permanently discontinued, then a replacement drug, typically from a different drug class, is included in the regimen. • Patients with severe tuberculosis often require the initiation of an alternate regimen during the time the offending drug(s) are held. • In general, for complicated diagnostic or management situations, consultation with local and state health departments is advised. <u>Special populations</u> • For HIV-infected patients receiving antiretroviral therapy (ART), using the standard six-month daily regimen consisting of an intensive phase of two months of INH, RIF, PZA, and EMB followed by a continuation phase of four months of INH and RIF is suggested for the treatment of drug-susceptible pulmonary tuberculosis. In the uncommon situation in which an HIV-infected patient does not receive ART during tuberculosis treatment, extending the continuation phase with INH and RIF for an additional three months (i.e., a continuation phase of 7 months in duration, corresponding to a total of nine months of therapy) is suggested for treatment of drug-susceptible pulmonary tuberculosis. • As is noted for drug-susceptible pulmonary tuberculosis in patients without HIV coinfection, the continuation phase is extended in specific situations that are known to increase risk for relapse, as well as for selected extrapulmonary sites of disease, namely tuberculous meningitis, and bone, joint, and spinal tuberculosis. • Adjunctive corticosteroids are not suggested to be used routinely in the treatment of patients with pericardial tuberculosis. However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction. • Chemotherapy for tuberculous meningitis is initiated with INH, RIF, PZA, and EMB in an initial two-month phase. After two months of four-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional seven to 10 months, although the optimal duration of chemotherapy is not defined. Based on expert opinion, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy. • In children with tuberculous meningitis, the American Academy of Pediatrics (AAP) lists an initial four-drug regimen composed of INH, RIF, PZA, and ethionamide, if possible, or an aminoglycoside, followed by seven to 10 months of INH and RIF as the preferred regimen. There are no data from controlled trials to guide the selection of EMB vs an injectable or ethionamide as the fourth drug for tuberculosis meningitis. Most societies and experts recommend the use of either an injectable or EMB. For adults, based on expert opinion, this guideline prefers using EMB as the fourth drug in the regimen for tuberculous meningitis.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children (2010)**[33]	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity.

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	• Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health care-associated infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage,

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	multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[34]	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is

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	recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve) • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. Management of methicillin-resistant *Staphylococcus aureus* pneumonia • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an

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	additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression (2018)**[35]	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir). • Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household

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	contacts and health care providers.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)**[36]	Low infection risk prophylaxis
	• Antimicrobial prophylaxis is not recommended in patients with low infection risk.
	
	Intermediate infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis during neutropenia.
	• Additional prophylaxis may be necessary.
	
	High infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis during neutropenia.
	• Additional prophylaxis may be necessary.
	
	Pneumocystis jirovecii prophylaxis
	• Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria.
	• Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim.
	• Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.
	
	Pneumococcal infection prophylaxis
	• Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant.
	• In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis.
	
	Initial empiric antibiotic therapy
	• Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection.
	• Intravenous antibiotic monotherapy for uncomplicated infections (choose one):
	  ○ Cefepime.
	  ○ Imipenem-cilastatin.
	  ○ Meropenem.
	  ○ Piperacillin-tazobactam.
	  ○ Ceftazidime.
	• Oral antibiotic combination therapy for low-risk patients with uncomplicated infections:
	  ○ Ciprofloxacin plus amoxicillin-clavulanate.
	  ○ Moxifloxacin.
	  ○ Levofloxacin.
	  ○ Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used.
	• Complicated infections (choose based on local antibiotic susceptibility patterns):
	  ○ Intravenous antibiotic monotherapy is preferred.
	  ○ Intravenous combination therapy could be considered especially in cases of resistance.
	
	Antibacterial agents: empiric gram-positive activity

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	• Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. o Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. o Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime o Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. o Empiric therapy for neutropenic fever. o Data are limited, but it is expected that doripenem, like meropenem, would be efficacious. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and

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	anaerobic organisms. o Use for suspected intra-abdominal source. o Not recommended for meningitis. o Empiric therapy for neutropenic fever. <u>Antibacterial agents: other</u> • Aminoglycosides o Activity primarily against gram-negative organisms. o Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes. o Oral combination therapy in low-risk patients. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. o Increasing Gram-negative resistance in many centers. o Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms. o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. o Interactions with methotrexate.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)**[37]	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole. • For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides

Clinical Guideline	Recommendation(s)
	(amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[38]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or

Clinical Guideline	Recommendation(s)
	vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. <u>Biliary tract procedures</u> • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. <u>Appendectomy procedures</u> • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Small intestine procedures</u> • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Hernia repair procedures</u> • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. <u>Colorectal procedures</u> • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation. • Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole

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	plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	Neurosurgery procedures
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	Cesarean delivery procedures
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.
	
	Hysterectomy procedures
	• The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin.
	• Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone.
	
	Ophthalmic procedures
	• Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis.
	• As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species.
	
	Orthopedic procedures
	• Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials.
	• Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin.
	• The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be

Clinical Guideline	Recommendation(s)
	reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. <u>Urologic procedures</u> • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or urinary tract infection should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. <u>Vascular procedures</u> • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. <u>Heart, lung, heart-lung, liver, pancreas, and kidney transplantation</u> • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. <u>Plastic surgery and breast procedures</u> • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.
American Association for the Study of Liver Diseases/ European Association for the Study of the Liver: **Practice Guideline: Hepatic Encephalopathy in Chronic Liver**	• Identify and treat precipitating factors for hepatic encephalopathy. • Lactulose is the first choice for treatment of episodic overt hepatic encephalopathy. • Rifaximin is an effective add-on therapy to lactulose for prevention of overt hepatic encephalopathy recurrence. • Oral branched-chain amino acids can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy. • Intravenous L-ornithine L-aspartate can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy.

Clinical Guideline	Recommendation(s)
Disease (2014)[39]	• Neomycin is an alternative choice for treatment of overt hepatic encephalopathy. • Metronidazole is an alternative choice for treatment of overt hepatic encephalopathy. • Lactulose is recommended for prevention of recurrent episodes of hepatic encephalopathy after the initial episode. • Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of hepatic encephalopathy after the second episode. • Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-transjugular intrahepatic portosystemic shunt (TIPS) hepatic encephalopathy. • Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued. • Treatment of minimal hepatic encephalopathy and covert hepatic encephalopathy is not routinely recommended apart from a case-by-case basis. • Daily energy intakes should be 35 to 40 kcal/kg ideal body weight. • Daily protein intake should be 1.2 to 1.5 g/kg/day. • Small meals or liquid nutritional supplements evenly distributed throughout the day and a late-night snack should be offered. • Oral branched-chain amino acid supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the aminoglycosides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Aminoglycosides[1-8]

Indication	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin
Central Nervous System Infections						
Adjunctive therapy in hepatic coma			✔			
Central nervous system infections	✔	✔			✔	✔ *
Dermatological Infections						
Burns	✔	✔				
Skin and skin-structure infections	✔	✔				✔ *
Gastrointestinal Infections						
Gastrointestinal tract infections		✔				
Suppression of the normal bacterial flora of the bowel			✔			
Genitourinary Infections						
Chancroid					✔	
Granuloma inguinale					✔	
Urinary tract infections	✔	✔		✔	✔	✔ *
Respiratory Infections						
Management of cystic fibrosis patients with *Pseudomonas aeruginosa*						✔ †
Mycobacterium avium complex lung disease	✔ ^					
Pneumonia					✔	
Respiratory tract infections	✔	✔			✔	✔ *
Tuberculosis					✔	
Miscellaneous Infections						
Bacteremia					✔	
Bone and/or joint infections	✔	✔				✔ *
Brucellosis					✔	
Endocarditis					✔	
Intra-abdominal infections	✔					✔ *
Plague					✔	
Postoperative infections	✔					
Septicemia	✔	✔				✔ *
Serious infections caused by susceptible microorganisms	✔	✔			✔	
Tularemia					✔	

*Injection formulation.
†Inhalation formulation.

^Inhalation formulation. This indication is for adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of six consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.

IV. Pharmacokinetics

The pharmacokinetic parameters for the aminoglycosides are summarized in Table 5.

Table 5. Pharmacokinetic Parameters of the Aminoglycosides[2]

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amikacin	4 to 11	Not significant	Renal (90 to 98)	2
Gentamicin	0 to 30	Not reported	Renal (65 to 100)	1.5 to 4.0
Neomycin	0 to 88	Not reported	Renal (30 to 50) Feces (97)	3
Plazomicin	20	Not significant	Renal (97.5) Feces (<0.2)	3.5
Streptomycin	34 to 35	Not significant	Renal (65)	2.5
Tobramycin	0 to 30	Not reported	Renal (60 to 85)	1.6 to 3.0

V. Drug Interactions

Major drug interactions with the aminoglycosides are listed in Table 6.

Table 6. Major Drug Interactions with the Aminoglycosides[2]

Generic Name(s)	Interaction	Mechanism
Aminoglycosides (amikacin, gentamicin, streptomycin, tobramycin)	Ataluren	Concurrent use of ataluren and intravenous aminoglycosides may result in decreased ataluren activity and increased risk of aminoglycoside-associated nephrotoxicity.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Nondepolarizing muscle relaxants	Aminoglycosides may increase the neuromuscular blocking effects of non-depolarizing muscle relaxants. Prolonged respiratory depression and apnea may occur.
Aminoglycosides (amikacin, gentamicin, streptomycin, tobramycin)	Succinylcholine	Neuromuscular blocking effects of succinylcholine may be increased by aminoglycosides. Prolonged respiratory depression with extended periods of apnea may occur.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Furosemide	Concurrent use of aminoglycosides and furosemide may result in increased amikacin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.
Aminoglycosides (amikacin, gentamicin, tobramycin)	Vancomycin	Concurrent use of aminoglycosides and vancomycin may result in additive ototoxicity and/or nephrotoxicity.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Colistimethate	Concurrent use of colistimethate sodium and aminoglycosides may result in respiratory depression.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Ethacrynic acid	Concurrent use of aminoglycosides and ethacrynic acid may result in increased amikacin plasma and tissue concentrations and additive ototoxicity.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Cidofovir	Concurrent use of aminoglycosides and cidofovir may result in nephrotoxicity.
Aminoglycosides (neomycin)	Sorafenib	Concurrent use of neomycin and sorafenib may result in decreased sorafenib exposure.
Aminoglycosides	Mannitol	Concurrent use of mannitol and tobramycin may result in

Generic Name(s)	Interaction	Mechanism
(tobramycin)		increased tobramycin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the aminoglycosides are listed in Table 7. The boxed warnings for the aminoglycosides are listed in Tables 8 through 10. Ototoxicity and nephrotoxicity are the most serious adverse effects with the aminoglycosides and are most frequently reported in geriatric or dehydrated patients, patients with renal impairment, patients who are receiving high doses or for long periods, those who are also receiving or have received other ototoxic and/or nephrotoxic drugs, and in patients with preexisting tinnitus, vertigo, or hearing loss.[1] Additionally, cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrially encoded 12S rRNA gene (MT-RNR1), particularly the m.1555A>G variant.[4-9]

Table 7. Adverse Drug Events (%) Reported with the Aminoglycosides[1-9]

Adverse Events	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Cardiovascular							
Chest pain	-	-	-	-	-	26*	-
Hypertension	-	✔	-	2	-	-	-
Hypotension	✔	✔	-	1	-	-	-
Central Nervous System							
Acute organic brain syndrome	-	✔	-	-	-	-	-
Confusion	-	✔	-	-	-	-	✔
Convulsions	-	✔	-	-	-	-	-
Depression	-	✔	-	-	-	-	-
Disorientation	-	-	-	-	-	-	✔
Dizziness	-	✔	-	✔	-	6*	✔
Encephalopathy	-	✔	-	-	-	-	-
Fever	✔	✔	-	-	✔	33*	✔
Headache	✔	✔	-	1	-	11 to 27	✔
Lethargy	-	✔	-	-	-	6*	✔
Malaise	-	-	-	-	-	6*	-
Myasthenia gravis-like syndrome	-	✔	-	-	-	-	-
Neuromuscular blockade	✔	-	✔	-	-	-	-
Neurotoxicity	✔	✔	✔	-	✔	-	✔
Paresthesia	✔	✔	-	-	✔	-	-
Peripheral neuropathy	-	✔	-	-	-	-	-
Pseudotumor cerebri	-	✔	-	-	-	-	-
Pyrexia	-	-	-	-	-	16†	-
Vertigo	-	✔	-	-	✔	-	✔
Dermatological							
Alopecia	-	✔	-	-	-	-	-
Burning	-	✔	-	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Exfoliative dermatitis	-	-	-	-	✔	-	✔
Itching	-	✔	-	-	-	-	✔
Rash	✔	✔	-	-	✔	2 to 5	✔
Skin tingling	-	✔	-	-	-	-	-
Urticaria	-	✔	-	-	✔	-	✔
Gastrointestinal							
Abdominal pain	-	-	-	-	-	13*	-
Anorexia	-	-	-	-	-	19*	-
Appetite decreased	-	✔	-	-	-	-	-
Constipation	-	-	-	✔	-	-	-
Diarrhea	-	-	-	2	-	2 to 6*	✔
Dysgeusia	-	-	-	-	-	4†	-
Gastritis	-	-	-	✔	-	-	-
Hemoptysis	-	-	-	-	-	13 to 19	-
Malabsorption syndrome	-	-	✔	-	-	-	-
Nausea	✔	✔	✔	1	✔	8 to 11	✔
Salivation increased	-	✔	-	-	-	-	-
Sputum discoloration	-	-	-	-	-	21*	-
Sputum increased	-	-	-	-	-	38*	-
Stomatitis	-	✔	-	-	-	-	-
Taste perversion	-	-	-	-	-	7*	-
Vomiting	✔	✔	✔	1	✔	6 to 14	✔
Weight loss	-	✔	-	-	-	10*	-
Genitourinary							
Azotemia	✔	-	-	-	✔	-	-
Cylindruria	✔	✔	-	-	-	-	✔
Hematuria	✔	-	-	✔	-	-	-
Nephrotoxicity	-	-	✔	4	-	-	-
Oliguria	✔	✔	-	-	-	-	✔
Proteinuria	✔	✔	-	-	-	-	✔
Pyuria	✔	-	-	-	-	-	-
Hematologic							
Agranulocytosis	-	✔	-	-	-	-	-
Anemia	✔	✔	-	-	-	-	✔
Eosinophilia	✔	✔	-	-	✔	2*	✔
Granulocytopenia	-	✔	-	-	-	-	✔
Hemolytic anemia	-	-	-	-	✔	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Leukocytosis	-	-	-	-	-	-	✔
Leukopenia	-	✔	-	-	✔	-	✔
Pancytopenia	-	-	-	-	✔	-	-
Red blood cell sedimentation rate increased	-	-	-	-	-	8*	-
Reticulocytes decreased	-	✔	-	-	-	-	-
Reticulocytes increased	-	✔	-	-	-	-	-
Thrombocytopenia	-	✔	-	-	✔	-	✔
Laboratory Test Abnormalities							
Aspartate aminotransferase increased	-	✔	-	-	-	-	✔
Alanine transaminase increased	-	✔	-	✔	-	-	✔
Bilirubin increased	-	✔	-	-	-	-	✔
Blood glucose increased	-	-	-	-	-	3†	-
Blood urea nitrogen increased	-	✔	-	-	-	-	✔
Calcium decreased	-	✔	-	-	-	-	✔
Immunoglobulins increased	-	-	-	-	-	2*	-
Lactate dehydrogenase increased	-	✔	-	-	-	-	✔
Magnesium decreased	-	✔	-	-	-	-	✔
Potassium decreased	-	✔	-	-	-	-	✔
Pulmonary function test decreased	-	-	-	-	-	7†	-
Serum creatinine increased	✔	✔	-	4	-	3*	✔
Sodium decreased	-	✔	-	-	-	-	✔
Musculoskeletal							
Arthralgia	✔	-	-	-	-	-	-
Asthenia	-	-	-	-	-	36*	-
Back pain	-	-	-	-	-	7*	-
Joint pain	-	✔	-	-	-	-	-
Muscle twitching	-	✔	-	-	-	-	-
Musculoskeletal chest pain	-	-	-	-	-	5†	-
Tremor	✔	-	-	-	-	-	-
Weakness	-	-	-	-	✔	-	-
Respiratory							
Apnea	-	-	-	-	-	-	✔

Adverse Events	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Asthma	-	-	-	-	-	16*	-
Bronchitis	-	-	-	-	-	3*	-
Chest discomfort	-	-	-	-	-	7†	-
Cough	-	-	-	-	-	48†	-
Cough increased	-	-	-	-	-	46*	-
Dyspnea	-	-	-	✔	-	16 to 34	-
Hyperventilation	-	-	-	-	-	5*	-
Forced expiratory volume decreased	-	-	-	-	-	4 to 31	-
Lower respiratory tract infection	-	-	-	-	-	6*	-
Lung disorder	-	-	-	-	-	16 to 34	-
Nasal congestion	-	-	-	-	-	8†	-
Productive cough	-	-	-	-	-	18†	-
Pulmonary fibrosis	-	✔	-	-	-	-	-
Rales	-	-	-	-	-	7 to 19	-
Respiratory depression	-	✔	-	-	-	-	-
Rhinitis	-	-	-	-	-	35*	-
Sinusitis	-	-	-	-	-	8*	-
Throat irritation	-	-	-	-	-	5†	-
Wheezing	-	-	-	-	-	5 to 7	-
Special Senses							
Amblyopia	-	-	-	-	✔	-	-
Dysphonia	-	-	-	-	-	6 to 14	-
Ear pain	-	-	-	-	-	7*	-
Hearing loss	-	✔	-	-	✔	✔	✔
Ototoxicity	✔	✔	✔	2	✔	-	✔
Tinnitus	-	✔	-	-	-	3*	✔
Visual disturbances	-	✔	-	-	-	-	-
Other							
Acute renal failure	-	-	-	≤4			
Anaphylaxis/anaphylactoid reaction	-	✔	-	-	✔	-	-
Angioneurotic edema	-	-	-	-	✔	-	-
Ear and labyrinth disorders	-	-	-	-	-	10†	-
Epistaxis	-	-	-	-	-	3 to 7	-
Hepatomegaly/splenomegaly	-	✔	-	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Plazomicin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Laryngeal edema	-	✔	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	-	14†	-
Pain	-	-	-	-	-	8*	-
Pain at injection site	-	✔	-	-	-	-	✔
Pharyngitis	-	-	-	-	-	38*	-
Pharyngolaryngeal pain	-	-	-	-	-	3*	-
Purpura	-	✔	-	-	-	-	-
Tonsillitis	-	-	-	-	-	2*	-
Upper respiratory tract infection	-	-	-	-	-	7†	-
Voice alterations	-	-	-	-	-	13*	-

✔ Percent not specified.
- Event not reported or incidence <1%.
* Inhalation solution only.
† Inhalation powder only.

Table 8. Boxed Warning for Parenteral Aminoglycosides[1]

WARNING
Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established. **Ototoxicity:** Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible. **Nephrotoxicity:** Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy. **Neuromuscular blockade:** Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary. **Monitoring:** Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 µg/mL. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. Blood urea nitrogen, serum creatinine, or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment. **Concurrent therapy:** Concurrent and/or sequential systemic, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration. The concurrent use of amikacin with potent diuretics (ethacrynic acid, or furosemide) should be avoided because diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. **Pregnancy:** Aminoglycosides can cause fetal harm when administered to a pregnant woman.

Table 9. Boxed Warning for Amikacin Liposome Inhalation Suspension[1]

WARNING
Arikayce has been associated with an increased risk of respiratory adverse reactions including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.

Table 10. Boxed Warning for Neomycin[1]

WARNING
Toxicity: Systemic absorption of neomycin occurs following oral administration, and toxic reactions may occur. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with the use of neomycin. Neurotoxicity (including ototoxicity) and nephrotoxicity following the oral use of neomycin sulfate have been reported, even when used in recommended doses. The potential for nephrotoxicity, permanent bilateral auditory ototoxicity, and sometimes vestibular toxicity, is present in patients with healthy renal function when treated with higher doses of neomycin or for longer periods than recommended. Serial, vestibular and audiometric tests, as well as tests of renal function, should be performed (especially in high-risk patients). The risk of nephrotoxicity and ototoxicity is greater in patients with impaired renal function. Ototoxicity is often delayed in onset, and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction, and total or partial deafness may occur long after neomycin has been discontinued. Other factors which increase the risk of toxicity are advanced age and dehydration. **Neuromuscular blockage:** Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuromuscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics; neuromuscular-blocking agents such as tubocurarine, succinylcholine, decamethonium; or massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary. **Concurrent therapy:** Concurrent or sequential systemic, oral or topical use of other aminoglycosides, including paromomycin and other potentially nephrotoxic or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin and viomycin, should be avoided because the toxicity may be additive. The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenous, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.

VII. Dosing and Administration

The usual dosing regimens for the aminoglycosides are listed in Table 11.

Table 11. Usual Dosing Regimens for the Aminoglycosides[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amikacin	*Mycobacterium avium* complex (MAC) lung disease: Inhalation: Once daily inhalation of the contents of one vial (590 mg of amikacin) using the Lamira Nebulizer System Unspecified infections: Injection: 7.5 mg/kg every 12 hours or 5 mg/kg every eight hours IM or IV; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients) Urinary tract infections (Uncomplicated): Injection: 250 mg IM or IV twice daily	Unspecified infections: Injection: Newborns, 10 mg/kg loading dose, followed by 7.5 mg/kg every 12 hours; total daily dose should not exceed 15 mg/kg/day; children and older infants, 15 mg/kg/day IM or IV, divided into two or three equal doses, administered at equally divided intervals; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients)	Inhalation: 590 mg/8.4 mL Injection: 500 mg/2 mL 1,000 mg/4 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	may be used		
Gentamicin	Life-threatening infections: Injection: Up to 5 mg/kg/day IV or IM may be administered in three or four equal doses; the dose should be reduced to 3 mg/kg/day as soon as clinically indicated Serious infections: Injection: 3 mg/kg/day IV or IM in three equal doses every eight hours	Unspecified infections: Injection: Children, 6 to 7.5 mg/kg/day IV or IM (2 to 2.5 mg/kg every eight hours); infants and neonates, 7.5 mg/kg/day IV or IM (2.5 mg/kg every eight hours); premature or full-term neonates one week of age or younger, 5 mg/kg/day IV or IM (2.5 mg/kg every 12 hours)	Injection: 20 mg/2 mL 40 mg/mL
Neomycin	Adjunctive therapy in hepatic coma: Tablet: 4 to 12 g/day in divided doses for five to six days; treatment for periods longer than two weeks is not recommended Suppression of the normal bacterial flora of the bowel: Tablet: Initial, 1 g orally 19, 18, and nine hours prior to surgery with oral erythromycin or metronidazole as an adjunct to mechanical cleansing of bowel	Safety and efficacy in children have not been established.	Tablet: 500 mg
Plazomicin	Complicated Urinary Tract Infections (cUTI) including Pyelonephritis: Injection: 15 mg/kg administered every 24 hours by IV infusion over 30 minutes	Safety and efficacy in children have not been established.	Injection: 500 mg/10 mL
Streptomycin	Endocarditis (Streptococcal infections): Injection: 1 g twice daily IM for the first week, and 500 mg twice daily IM for the second week in combination with penicillin Endocarditis (Enterococcal infections): Injection: 1 g twice daily IM for two weeks and 500 mg twice daily IM for an additional four weeks in combination with penicillin Plague: Injection: 2 g/day IM in two divided doses for a minimum of 10 days Tuberculosis: Injection: 15 mg/kg IM once daily, 25 to 30 mg/kg IM twice weekly, or 25 to 30 mg/kg IM three times weekly Tularemia: Injection: 1 to 2 g daily IM in two divided doses for seven to 14 days until the patient is afebrile for five to seven	Unspecified infections: Injection: 20 to 40 mg/kg/day in divided doses every six to 12 hours Tuberculosis: Injection: 20 to 40 mg/kg IM once daily, 25 to 30 mg/kg IM twice weekly, or 25 to 30 mg/kg IM three times weekly	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days Unspecified infections: Injection: 1 to 2 g IM in divided doses every six to 12 hours for moderate to severe infections; maximum, 2 g/day		
Tobramycin	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*: Inhalation solution: 300 mg administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Life-threatening infections: Injection: Up to 5 mg/kg/day IV or IM may be administered in three or four equal doses; the dosage should be reduced to 3 mg/kg/day as soon as clinically indicated Serious infections: Injection: 3 mg/kg/day IV or IM divided in three equal doses every eight hours	Management of cystic fibrosis patients with *Pseudomonas aeruginosa* in patients ≥6 years of age: Inhalation solution: 300 mg administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules twice daily for 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Septicemia in patients ≤1 week of age: Injection: Up to 4 mg/kg/day IV or IM may be administered in two equal doses every 12 hours Septicemia in patients >1 week of age: Injection: 6 to 7.5 mg/kg/day IV or IM in three or four equally divided doses (2 to 2.5 mg/kg every eight hours or 1.5 to 1.89 mg/kg every six hours)	Inhalation solution: 300 mg/4 mL 300 mg/5 mL Inhalation powder: 28 mg Injection: 10 mg/mL 40 mg/mL 1.2 g

Abbreviations: IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the aminoglycosides are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Aminoglycosides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cystic Fibrosis				
Ramsey et al.[40] (1999) Tobramycin inhalation solution 300 mg BID for three cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	DB, MC, PC Patients at least six years of age with cystic fibrosis, a respiratory tract culture positive for *Pseudomonas aeruginosa,* ability to perform pulmonary function tests, and FEV_1 25 to 75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *Pseudomonas aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with IV antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 $\log_{10}$ colony forming unit per gram of sputum, as compared to the value at zero weeks, whereas the density in the placebo group had increased by 0.3 $\log_{10}$ colony forming unit per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics.
Murphy et al.[41] (2004) Tobramycin inhalation solution 300 mg BID for seven cycles (each cycle consisting of 28 days during which the medication was administered and 28	MC, OL, PG, RCT Patients six to 10 years of age with cystic fibrosis and chronic *Pseudomonas aeruginosa,* FEV_1 $\geq$70% and $\leq$110% of predicted value; patients 11 to 15 years of age with	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer tobramycin inhalation solution patients were hospitalized for worsening of respiratory symptoms (11.0 vs 25.6%; P<0.011), and fewer tobramycin inhalation solution patients were hospitalized overall (16.5 vs 27.8%; P<0.065). Fewer tobramycin inhalation solution patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days during which it was not administered) vs placebo	cystic fibrosis and FEV_1 >70% and <90% of predicted value			received oral antibiotics (76.9 vs 91.1%; P<0.009). Secondary: Not reported
Quittner et al.[42] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	RETRO Patients greater than six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 25 to 75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005). Secondary: Not reported
Moss et al.[43] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *Pseudomonas aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain Secondary: Not reported	Primary: Patients originally randomized to tobramycin inhalation solution and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5 and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *Pseudomonas aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. Secondary: Not reported
Ratjen et al.[44] (2019) EARLY	DB, MC, RCT, XO Patients 3 months	N=51 12 months	Primary: Proportion of patients having throat	Primary: On Day 29, 84.6% patients in the TOBI versus 24.0% in the placebo group were *Pseudomonas aeruginosa*-free (P<0.001). At the end of the cross-over period, 76.0% patients receiving TOBI in the initial 28 days were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tobramycin inhalation solution (TOBI®) 300 mg/5 mL twice daily vs placebo	to <7 years of age with cystic fibrosis who had an early infection with *Pseudomonas aeruginosa*		swabs/sputum free of *Pseudomonas aeruginosa* on Day 29 Secondary: Safety	*Pseudomonas aeruginosa*-free compared to 47.8% receiving placebo initially. Secondary: Adverse events were consistent with the TOBI safety profile with no differences between TOBI and placebo.
Bowman[45] (2002) Tobramycin inhalation solution 300 mg BID for nine cycles (each cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	OL Patients at least six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=396 48 weeks	Primary: Pulmonary function and antibiotic use Secondary: Not reported	Primary: At the start of the OL study period, the patients who had been receiving tobramycin inhalation solution continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over from placebo to OL tobramycin inhalation solution had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with tobramycin inhalation solution in the initial, DB phase. By the end of the 12th treatment cycle, the mean FEV_1 in the tobramycin inhalation solution-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo-tobramycin inhalation solution XO group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with tobramycin inhalation solution had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving tobramycin inhalation solution (both the randomized and the OL portions of the trial, regardless of initial study group assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13 to 17 years. The adolescent patients treated with tobramycin inhalation solution from the beginning had a marked

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued tobramycin inhalation solution maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of tobramycin inhalation solution. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive tobramycin inhalation solution in the OL phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on tobramycin inhalation solution in the DB study. The mean FEV_1 values of this XO group after nine cycles (72 weeks) of tobramycin inhalation solution were maintained at levels above those at the start of the OL part of the study. Secondary: Not reported
Briesacher et al.[46] (2011) Tobramycin inhalation solution	RETRO Patients with cystic fibrosis with at least one claim for tobramycin inhalation solution	N=804 Variable duration	Primary: Adherence and hospitalization Secondary: Not reported	Primary: Chronic use of tobramycin inhalation solution was low in patients with *Pseudomonas aeruginosa* as only 6% were dispensed four or more cycles per year. Tobramycin inhalation solution usage was similar for patients with and without the diagnosis of *Pseudomonas aeruginosa*. In comparison to patients with high utilization of tobramycin inhalation solution, those using less than four cycles a year were more likely to be hospitalized. High use of tobramycin inhalation solution was associated with a decreased risk of hospitalization relative to low use (AOR, 0.40; 95% CI, 0.19 to 0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20 to 10.90), a coded diagnosis of *Pseudomonas aeruginosa* (AOR, 3.0; 95% CI, 2.13 to 4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09 to 7.14) were all independently associated with an increased risk of hospitalization.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
O'Sullivan et al.[47] (2011) Tobramycin inhalation solution	RETRO Patients at least six years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization Secondary: Not reported	Primary: A higher percentage of children had at least one cystic fibrosis-related office visit (P=0.0046), cystic fibrosis-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and cystic fibrosis-related emergency room visit (P=0.0159) compared to adults. Adults with cystic fibrosis averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more cystic fibrosis-related outpatient hospital visits (P=0.004) as well as prescriptions for than tobramycin inhalation solution (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than tobramycin inhalation solution and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03). Secondary: Not reported
Ratjen et al.[48] (2010) Tobramycin inhalation solution for an additional 28 days vs discontinuation of tobramycin	MC, OL, RCT Patients at least six months with cystic fibrosis and early *Pseudomonas aeruginosa* infection who had already received 28 days of treatment with tobramycin	N=123 56 days	Primary: Median time to recurrence of any strain of *Pseudomonas aeruginosa* Secondary: Proportion of patients free of *Pseudomonas aeruginosa* one	Primary: The median time to recurrence of *Pseudomonas aeruginosa* was 26.12 and 25.82 months following than tobramycin inhalation solution for 28 and 56 days, respectively (P=0.593). At the time of each patient's final study visit, 66% of patients remained free of *Pseudomonas aeruginosa* in the 28-day than tobramycin inhalation solution group and 69% remained free of *Pseudomonas aeruginosa* in the 56-day than tobramycin inhalation solution group. Secondary: The proportion of patients free of *Pseudomonas aeruginosa* at day 28 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	inhalation solution		month after the end of treatment; time to recurrence of any strain of *Pseudomonas aeruginosa*; number of patients with the same genotype of *Pseudomonas aeruginosa* at baseline and recurrence or a new genotype at recurrence; proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status; number and length of hospital admissions for respiratory indications	one month after the end of treatment was comparable in both groups. The proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day than tobramycin inhalation solution group were hospitalized on one occasion, each for a pulmonary exacerbation during the study. No major short- or long-term changes in spirometric parameters were observed during the study period.
Hodson et al.[49] (2002) Tobramycin	RCT Patients older than six years of age	N=115 4 weeks	Primary: Mean change from baseline to week four in FEV_1	Primary: Tobramycin inhalation solution produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalation solution 300 mg BID vs colistin nebulized solution 80 mg inhaled BID	with cystic fibrosis, FEV_1>25%; *Pseudomonas aeruginosa* positive sputum culture		percent predicted Secondary: Change in sputum *Pseudomonas aeruginosa* density, tobramycin/colistin MICs, and safety assessment	Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum *Pseudomonas aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Berlana et al.[50] (2011) Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	OBS, PRO Adult patients with cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *Pseudomonas aeruginosa* bronchial colonization, a history of chronic *Pseudomonas aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or chronic obstructive pulmonary disease, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy	N=81 4 years	Primary: Frequency and duration of hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *Pseudomonas aeruginosa* eradication in the airways, mortality, safety, and changes in respiratory function	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *Pseudomonas aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *Pseudomonas aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received. No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 12 patients (14.8%) died during the study, all for respiratory causes. There were no significant differences in mortality between the study groups, and FEV_1 percent was linked to mortality (HR, 0.93; 95% CI, 0.86 to 0.98).
Smyth et al.[51] (2005) Tobramycin 10 mg/kg/day IV administered TID for 14 days plus ceftazidime vs tobramycin 10 mg/kg/day IV once daily for 14 days plus ceftazidime IV	DB, RCT Patients older than five years of age with cystic fibrosis who had a pulmonary exacerbation	N=244 14 days	Primary: Change in FEV_1 over 14 days of treatment, mean change in baseline FEV_1 Secondary: Change in serum creatinine	Primary: The mean change in FEV_1 (percent predicted) over 14 days was similar between the two regimens (10.4% [once daily] vs 10.0% [TID] (adjusted mean difference, 0.4%; 95% CI, –3.3 to 4.1). Mean % change in FEV_1 from baseline was also similar in both treatments (21.9 vs 22.1%; –0.1%; –8.0 to 7.9). Secondary: There was no significant difference in percent change in creatinine from baseline (–1.5% [once daily] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean percent change in creatine, –4.5% [once daily] vs 3.7% [TID] (adjusted mean difference, –8.0%; 95% CI, –15.7 to –0.4; P=0.04).
Konstan et al.[52] (2011) Tobramycin inhalation powder 112 µg via T-326 inhaler BID for three treatment cycles (28 days on-drug, 28 days off-drug) vs tobramycin inhalation solution 300 mg/5 mL via PARI LC PLUS	OL, RCT Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥25 to ≤75% predicted	N=553 24 weeks	Primary: Safety assessments; relative chance in FEV_1 percent predicted from baseline, change in sputum *Pseudomonas aeruginosa* density, tobramycin susceptibility to *Pseudomonas aeruginosa* using MIC, antipseudomonal antibiotic use,	Primary: More patients in the tobramycin inhalation powder group reported adverse events compared to tobramycin inhalation solution group (90.3 vs 84.2%; P<0.05). The percentage of adverse events was highest in cycle 1, 77.9% with tobramycin inhalation powder group and 66.5% with tobramycin inhalation solution group and decreased with cycles 2 and 3 (cycle 2: 67.0 vs 66.3%; cycle 3: 65.8 vs 58.5%, respectively). The most frequently reported adverse event was cough during the study period (tobramycin inhalation powder: 48.4% vs tobramycin inhalation solution: 31.1%). The rate of cough suspected to be study drug related was higher in tobramycin inhalation powder group (25.3 vs 4.3%). Twelve out of 308 (4%) tobramycin inhalation powder-treated patients discontinued due to cough vs 1% (2/209) of tobramycin inhalation solution-treated patients. Dysphonia (13.6 vs 3.8%) and dysgeusia (3.9 vs 0.5%) were also more commonly reported in the tobramycin inhalation powder group. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nebulizer BID for three treatment cycles (28 days on-drug, 28 days off-drug)			respiratory-related hospitalizations Secondary: Not reported	incidence of serious adverse events was similar in both groups. Both treatment groups had similar increases in FEV_1 percent predicted from baseline to day 28 of cycle 3 (least squares mean difference, 1.1% relative change [standard error, 1.75]). On day 28 of cycle 3, 11.6% tobramycin inhalation powder-treated patients and 9.9% tobramycin inhalation solution-treated patients had negative *Pseudomonas aeruginosa* cultures. The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with tobramycin inhalation powder group (64.9 vs 54.5%; P=0.0148). The number of patients hospitalized for respiratory-related events was similar in the tobramycin inhalation powder group vs tobramycin inhalation solution group (24.4 vs 22.0%). Administration time was significantly less for tobramycin inhalation powder compared to the solution formulation (mean, 5.6 vs 19.7 minutes; P<0.0001). Secondary: Not reported
Mazurek et al.[53] (2014) Tobramycin nebulization solution 300 mg/4 mL (28 days on-drug, 28 days off-drug) vs tobramycin nebulization solution 300 mg/5 mL (28 days on-drug, 28 days off-	MC, OL, RCT (core phase) SA (extension phase) Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥40 and ≤80% predicted	N=321 (N=321: core phase; N=209: extension phase) 56 weeks (8 weeks: core phase; 48 weeks: extension phase)	Primary: Core phase: absolute change in FEV_1 percent predicted from baseline to week four; extension phase: long term safety of tobramycin nebulization solution 300 mg/4 mL; both phases: microbiological assessments, adverse events, and audiometry	Primary: In the core phase, FEV_1 percent predicted increased similarly from baseline (absolute change) following a single on-treatment cycle for both groups: tobramycin nebulization solution 300 mg/4 mL, 7.0% vs tobramycin nebulization solution 300 mg/5 mL, 7.5% (difference between treatments, -0.5; 95% CI, -2.6 to 1.6). The baseline- and country-adjusted mean of absolute change from baseline to week four in FEV_1 percent predicted was 4.7 and 5.2% for 4 and 5 mL solution, respectively, with a significant (P<0.001) improvement vs baseline for both groups. These improvements were maintained throughout the extension phase. *Pseudomonas aeruginosa* sputum count reductions ranged between 0.6 (95% CI, 0.2 to 0.9) to 2.3 (95% CI, 2.0 to 2.6) log_{10} colony forming unit/g throughout the 56 weeks. No remarkable safety issues were identified throughout both study phases, with similar percentages of patients reporting adverse events in the two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
drug) Subset of patients continued receiving tobramycin nebulization solution 300 mg/4 mL only.			findings Secondary: Not reported	treatment groups during the core phase (4 mL, 31.4%; 5 mL, 28.0%; P=0.579). The adverse events that were judged to be related to the drug were also similar between the two groups (4 mL, 6.4%; 5 mL, 6.0%; P=1.000). Cough, rhinitis, pharyngitis, and pulmonary exacerbations were the most commonly reported adverse events, proportionally similar between the two groups. Serious adverse events occurred in six (3.8%) and two (1.2%) of patients treated with 4 and 5 mL solution, respectively (Fisher's test, P=0.161). During the extension phase, adverse events were reported by 148 patients (70.8%). Similar to the core phase, the most commonly reported adverse events included pulmonary exacerbation (24.9%), rhinitis (12.4%), cough (11%), pyrexia (7.7%), and bronchitis (7.2%). Bronchospasm and death was not reported in either core or extension phase. Secondary: Not reported
Galeva et al.[54] (2013) Tobramycin inhalation powder 112 µg, as capsules administered via dry powder inhaler, BID vs placebo	DB, MC, PC, Phase 3, RCT Patients six to 21 years of age with cystic fibrosis with FEV_1 ≥25 and ≤80% and a positive sputum or throat culture for *Pseudomonas aeruginosa* within six months of screening and a positive sputum culture for *Pseudomonas aeruginosa* at the screening visit	N=62 Duration not specified	Primary: Relative change in FEV_1 percent predicted from baseline to day 29 Secondary: Relative change in forced vital capacity percent predicted and forced expiratory flow 25 to 75% predicted from baseline to day 29; change from baseline in sputum density of *Pseudomonas aeruginosa*; rates	Primary: Mean treatment difference was 5.9% (95% CI, -2.2 to 14.0; P=0.148) for relative change in FEV_1 percent predicted. Secondary: Mean treatment difference was 4.4% (95% CI, 0.0 to 8.8; P<0.05) for absolute change in FEV_1 percent predicted. Tobramycin inhalation powder significantly reduced sputum *Pseudomonas aeruginosa* density by -1.2 log_{10} colony forming unit (P=0.002). The tobramycin group had higher clearance rate for *Pseudomonas aeruginosa* compared to placebo (41.4 vs 0% at day 29). Antipseudomonal antibiotic use was reported to be used in three patients in each of the treatment groups. Hospitalization due to respiratory events occurred in one patient in the placebo group. Adverse events were mild to moderate in severity and they occurred in 26.7% patients in the tobramycin group compared to 34.4% patients in the placebo group. Drug-related adverse events occurred in five (16.7%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of antipseudomonal antibiotic use and hospitalizations due to respiratory events; safety assessments: the incidence and severity of all adverse events and serious adverse events and regular monitoring of hematology, blood chemistry and urine protein, vital signs, physical condition, and bodyweight	tobramycin-treated patients compared to two (6.3%) patients in the placebo group; the difference was due to adverse event of cough that was reported in three patients in the tobramycin group to be drug-related. There was no difference between the groups in serious adverse events. There were no major differences that were observed between the groups in any hematology, renal or biochemistry variables, or acuity.
Chuchalin et al.[55] [abstract] (2007) Tobramycin inhalation solution 300 mg/4 mL vs placebo Four-week treatment periods ('on' cycles) were followed by four-week periods without treatment	DB, MC, PC Patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection	N=247 24 weeks Endpoint time assessment was at week 20	Primary: FEV_1 percent predicted normal Secondary: Forced vital capacity, forced expiratory flow at 25 to 75% of forced vital capacity, *Pseudomonas aeruginosa* susceptibility, MIC required to inhibit 90% of strains, rates of *Pseudomonas*	Primary: FEV_1 was significantly increased in the tobramycin group and the adjusted mean difference between groups in the intention-to-treat population was statistically significant (P<0.001). Secondary: Tobramycin group had clinically relevant improvements in forced vital capacity (P=0.022) and forced expiratory flow at 25 to 75% of forced vital capacity (P=0.001). The microbiologic outcomes at the end of the last 'on' cycle period were better in the tobramycin group than the placebo group (P=0.024). There was a concomitant trend toward an increase in the minimum concentration required to inhibit 90% of strains of isolated *Pseudomonas aeruginosa* strains. Tobramycin group had a lower percentage of patients hospitalized (P=0.002) and had a lower need for parenteral antipseudomonal antibiotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
('off' cycles)			*aeruginosa* - negative culture, *P. aeruginosa* persistence and superinfection, need for hospitalization and parenteral antipseudomonal antibiotics, loss of school/working days due to the disease, and nutritional status (bodyweight and body mass index); safety parameters including adverse events, audiometry, and renal function	(P=0.009) compared to the placebo group. Tobramycin group patients had fewer lost school/working days due to the disease (P<0.001). Compared to placebo, there was a favorable effect of tobramycin in terms of an increase in bodyweight and body mass index at all time points (P<0.01 and P<0.001, respectively). There were no significant changes in serum creatinine and auditory function. The proportion of patients with drug-related adverse events was 15% in both treatment groups.
Lenoir et al.[56] (2007) Tobramycin inhalation solution 300 mg/4 mL BID for four weeks vs placebo BID	DB, MC, PC, PG, PRO, RCT Patients six years of age and older with cystic fibrosis with a FEV_1 ≥40 and ≤80% of predicted normal with *Pseudomonas aeruginosa* infection	N=59 8 weeks	Primary: Pulmonary function as measured by FEV_1, forced vital capacity, and forced expiratory flow at the midportion of vital capacity, *Pseudomonas aeruginosa* susceptibility, microbiologic results, and in vitro	Primary: The tobramycin group had a significant increase in FEV_1 from baseline compared to the placebo group: the absolute difference between groups (intent-to-treat population) of predicted normal was 13.2% at week two (95% CI, 4.88 to 21.54; P=0.002) and 13.3% at week four (95% CI, 4.74 to 21.81; P=0.003). The forced vital capacity and forced expiratory flow at the midportion of vital capacity also increased in the tobramycin group compared to the placebo group: the estimated differences at week four visit were 10.65% (95% CI, 1.94 to 19.37; P=0.017) and 15.78% (95% CI, 5.24 to 26.32; P=0.004) for the two variables, respectively. There were no significant effects in terms of maintenance of *Pseudomonas aeruginosa* negative cultures at the end of the run-out phase in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			MIC for 90% of strains; safety as monitored by the recording of adverse events, audiometry (bone conduction at 250 to 8,000 Hz frequency), laboratory tests, physical examination, and general health condition Secondary: Not reported	tobramycin group (P=0.202 between-group comparison). There were no differences between treatments in the mean changes from baseline of MIC for 90% at the end of week four in patients with persistent *Pseudomonas aeruginosa* (P=0.780). There was no difference between the treatment groups in terms of drug-related adverse events (P=0.184). Results of audiometric tests did not show statistically significant differences between groups. There were no differences between treatment groups in increase in serum creatinine levels (P=0.850). There were no clinically significant changes in heart rate and blood pressure in either group at any time. Secondary: Not reported
Miscellaneous Infections				
Evans et al.[57] (1986) Amikacin vs gentamicin vs netilmicin vs sisomicin vs	MA, RCT Patients with urinary tract infections, obstetric gynecologic infections, major gram-negative infections, and serious systemic infections	42 trials Variable duration	Primary: Efficacy (bacteriologic or clinical response), nephrotoxicity, auditory toxicity Secondary: Not reported	Primary: Efficacy was an end point in 33 trials. A statistically significant difference was found in only two of the 44 aminoglycoside comparisons. These two studies noted that sisomicin had greater efficacy than gentamicin. Nephrotoxicity was an end point in all 42 trials. Statistically significant differences were only found for four of the 53 aminoglycoside comparisons. Two studies noted a greater risk of nephrotoxicity among patients receiving gentamicin than those receiving amikacin (specific details including statistical analyses were not available). Another study noted that patients receiving gentamicin had a higher risk of nephrotoxicity than those receiving tobramycin. A fourth study noted a higher risk of nephrotoxicity among patients receiving tobramycin than among those receiving netilmicin. Auditory toxicity was an end point in 23 trials. Statistically significant results were found for only one of the 32 aminoglycoside comparisons. That study noted a greater risk of auditory toxicity in patients receiving tobramycin than in those receiving netilmicin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tobramycin				Secondary: Not reported
Contopoulos-Ioannidis et al.[58] (2004) Amikacin vs gentamicin vs tobramycin vs netilmicin Multiple-daily dosing and once-daily dosing for the aminoglycoside classes were compared.	MA Patients receiving aminoglycosides in different clinical settings (neonatal intensive care unit, cystic fibrosis, cancer, urinary tract infections, diverse infections, pediatric intensive care units)	N=995 (24 trials) Variable duration	Primary: Clinical failure rates, microbiologic failure rate and combined clinical or microbiologic failure rates Secondary: Safety endpoints of nephrotoxicity and ototoxicity	Primary: No significant difference between once-daily dosing and multiple-daily dosing in the clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored once-daily dosing consistently. A statistically significant benefit was seen with once-daily dosing over multiple-daily dosing in trials using amikacin, whereas no statistical difference was seen in trials using other antibiotics. Secondary: There was no significant difference between once-daily dosing and multiple-daily dosing in the primary nephrotoxicity outcomes. Secondary nephrotoxicity outcomes were significantly better with once-daily dosing. There was no significant difference between once-daily dosing and multiple-daily dosing in the primary ototoxicity outcomes. Studies noting only the clinical impression of hearing impairment also failed to identify any toxicity (once-daily dosing: 114 cases; multiple-daily dosing: 114 cases).
King et al.[59] (1992) Amikacin vs tobramycin vs	OBS, PRO All gram-negative bacilli isolates from any patient source during study period	N=11,641 resistant isolates 64 months	Primary: Resistance, bacteremic episodes, and bacteremia-associated deaths before and after institution of amikacin as the sole preferred	Primary: Resistance rates to gentamicin, tobramycin, and amikacin among aerobic and facultative gram-negative bacterial isolates were 12.8, 10.8, and 5.9%, respectively, before amikacin was adopted as the sole formulary aminoglycoside. After amikacin was adopted as the sole formulary aminoglycoside, over the next 30 months the rates of resistance to gentamicin, tobramycin, and amikacin were 6.3, 5.0, and 3.3%, respectively. (P=0.02)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gentamicin			aminoglycoside Secondary: Not reported	During the 30 months when amikacin had preferred status, the incidence of bacteremia-associated death decreased from 18.6 to 11.5% (P=0.003). Secondary: Not reported
Gerding et al.[60] (1991) Amikacin vs tobramycin vs gentamicin	PRO All gram-negative bacilli isolates in a single hospital setting	N=25,000 aerobic and gram-negative bacillary isolates 10 years	Primary: Resistance rates Secondary: Not reported	Primary: Introduction of amikacin at a high level of usage in the 1980's was associated with a significant reduction in resistance to gentamicin and tobramycin among gram-negative bacilli. Gentamicin resistance decreased from 12.0 to 6.4% (P<0.001), tobramycin resistance decreased from 9.5 to 4.8% (P<0.001). Rapid introduction of gentamicin usage in 1982 after the use of amikacin was associated with a significant and rapid increase in gentamicin and tobramycin resistance. Gentamicin resistance increased from 6.4 to 9.2% (P<0.001) and tobramycin resistance increased from 4.8 to 6.0% (P<0.05). However, in 1986, gentamicin was again reintroduced to the institution and the usage of gentamicin was gradually increased over a 15-month period without significant change in resistance to gentamicin, tobramycin, or amikacin. Gentamicin resistance decreased from 5.8 to 5.7%, and tobramycin increased from 4.0 to 4.2% (P=not statistically significant). Secondary: Not reported
Griffith et al.[61] (2018) CONVERT Amikacin liposome inhalation suspension (ALIS) once daily added to guideline-based therapy (GBT)	OL, R Adults with amikacin-susceptible *Mycobacterium avium* complex (MAC) lung disease and MAC-positive sputum cultures despite at	N=336 16 months	Primary: Culture conversion, defined as three consecutive monthly MAC-negative sputum cultures by month six Secondary:	Primary: Sputum culture conversion by month six was achieved by significantly more patients in the ALIS + GBT arm than in the GBT-alone arm (29.0% vs 8.9%, respectively; adjusted OR, 4.22; 95% CI, 2.08 to 8.57; P<0.001). Patients treated with ALIS + GBT were nearly four times as likely to achieve culture conversion compared with GBT alone (HR, 3.90; 95% CI, 2.00 to 7.60). Secondary: Respiratory adverse events (primarily dysphonia, cough, and dyspnea) were reported in 87.4% of patients receiving ALIS + GBT and 50.0%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs GBT	least 6 months of stable GBT		Adverse events	receiving GBT alone; serious treatment-emergent adverse events occurred in 20.2% and 17.9% of patients, respectively.
Sexton et al.[62] (1998) Gentamicin 3 mg/kg once daily plus ceftriaxone 2 g IV once daily for two weeks vs ceftriaxone 2 g IV once daily for four weeks	MC, OL, RCT Patients ≥18 years of age with endocarditis who had received <72 hours of parenteral antibiotic therapy	N=51 4 years	Primary: Clinical cure Secondary: Not reported	Primary: Clinical cure was observed for patients both at termination of therapy and at the three-month follow-up: 25 (96.2%) of the monotherapy patients and 24 (96%) of combination therapy patients were considered clinically cured. Ceftriaxone 2 g once daily for four weeks and ceftriaxone 2 g once daily plus gentamicin 3 mg/kg once daily for two weeks were both judged effective for treatment of streptococcal endocarditis. Secondary: Not reported
Mithani et al.[63] (1996) Gentamicin or tobramycin 1.5 to 2 mg/kg every eight hours vs gentamicin or tobramycin 6 mg/kg every 24 hours	RETRO All patients who received once-daily aminoglycoside therapy	N=200 1 year	Primary: Rates of clinical response, failure and relapse Secondary: Toxicity	Primary: Eighty-nine patients were cured or improved with once-daily administration vs 90 patients with conventional administration. Secondary: One patient in each group developed definite aminoglycoside-induced renal toxicity.
Song et al.[64] (1998) Gentamicin plus metronidazole vs	MA Patients scheduled to undergo elective surgery of the colon	147 trials 12 years	Primary: Rate of surgical wound infections Secondary: Not reported	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy				A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR, 1.17; 95% CI, 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR, 1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported
Mwengee et al.[65] (2006) Gentamicin 2.5 mg/kg IM every 12 hours for seven days vs doxycycline 100 mg (adults) or 2.2 mg/kg (children) orally every 12 hours for seven days	OL, RCT Adults and children with symptoms of bubonic, septicemic, or pneumonic plague lasting less than or equal to three days	N=65 2 weeks	Primary: Efficacy Secondary: Not reported	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin (95% CI, 81.1 to 99.0) and 97% for doxycycline (95% CI, 83.4 to 99.8). *Yersinia pestis* isolates obtained from 30 patients belonged to biotype *antiqua* and were susceptible to gentamicin and doxycycline, which had MICs of 0.13 mg/L and 0.25 to 0.5 mg/L, respectively. Serum concentrations of antibiotics were within therapeutic ranges, and adverse events were infrequent. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.05). Both gentamicin and doxycycline were effective therapies for adult and pediatric plague, with high rates of favorable responses and low rates of adverse events. Secondary: Not reported
Roushan et al.[66] (2010) Gentamicin 5 mg/kg once daily for five days plus doxycycline 100 mg BID for eight weeks (gentamicin-doxycycline group) vs streptomycin 1 g IM for two weeks plus doxycycline 100 mg BID for 45 days (streptomycin-doxycycline group)	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin-doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).
Lewis[67] (2002) Neomycin 2 g orally vs amikacin 1 g IV vs	MA Patients scheduled to undergo elective surgery of the colon	N=215 3 years	Primary: Wound infections Secondary: Not reported	Primary: Wound infections occurred in five patients in the combined group (oral and systemic antibiotics) but in 17 of the systemic antibiotic-only group (RR, 0.29; 95% CI, 0.11 to 0.75; P<0.01). Bacteria isolated from wound infections and wound fat were more frequent in the colon in the systemic group (P<0.001) and occurred in wound fat in the systemic group twice as often as in the combined group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 2 g orally vs metronidazole 1 g IV vs placebo				The summary weighted risk difference in surgical site infections between groups and the summary RR both favored combined prophylaxis (risk difference, 0.56; 95% CI, 0.26 to 0.86) (RR, 0.51; 95% CI, 0.24 to 0.78; P<0.001). Secondary: Not reported
Boulanger et al.[68] (2004) Streptomycin vs gentamicin vs tetracycline vs gentamicin plus tetracycline	RETRO Patients with plague whose cases were reported in New Mexico during 1985 to 1999	N=75 Duration varied	Primary: Mean number of hospital days, fever days, complications, and deaths Secondary: Not reported	Primary: The mean number of fever days after the initiation of antimicrobial treatment was 3.5 days for the streptomycin group, 2.6 days for the gentamicin group, 1.9 days for the gentamicin-tetracycline group and 2.6 days for the tetracycline group (P=0.23). The mean duration of hospital days was 6.2 days in the streptomycin group, 7.2 days in the gentamicin group, and 6.0 days in the gentamicin-tetracycline group (P=0.57). There were no deaths among the 50 patients in the four treatment groups. The mean numbers of fever days, hospital days, and complications and the number of deaths did not differ between patients treated with streptomycin and those treated with gentamicin. Secondary: Not reported
Mwengee et al.[69] (2006) Doxycycline 100 mg (adults) and 2.2 mg/kg (children) by mouth BID for	OL, RCT Adults and children with symptoms of bubonic, septicemic, or	N=65 2 weeks	Primary: Efficacy (resolution of fever, bubo swelling, and all other plague symptoms)	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
seven days vs gentamicin 2.5 mg/kg IM BID for seven days	pneumonic plague		Secondary: Not reported	All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin and 97% for doxycycline. Secondary: Not reported
Smith et al.[70] (2021) SCAMP Ampicillin, gentamicin, and metronidazole (group 1) vs ampicillin, gentamicin, and clindamycin (group 2) vs piperacillin-tazobactam and gentamicin (group 3) Doses stratified by postmenstrual age; Additional gram-positive therapy (e.g., vancomycin, nafcillin, oxacillin, linezolid) was	MC, OL, RCT Infants ≤33 weeks gestational age at birth with a postnatal age <121 days, who demonstrated physical, radiologic, and/or bacteriologic findings consistent with complicated intra-abdominal infection (cIAI) Due to slow enrollment, a protocol amendment allowed eligible infants already receiving study regimens to enroll without randomization	N=180 (128 randomized [R], 52 non-randomized [NR]) 30 days	Primary: Mortality within 30 days of study drug completion Secondary: Adverse events, outcomes of special interest, and therapeutic success (absence of death, negative cultures, and clinical cure score >4) 30 days after study drug completion	Primary: Twenty-nine (16%) infants were transferred or discharged before the 30-day safety and overall therapeutic success evaluations. Thirty-day mortality was 8%, 7%, and 9% in groups 1, 2, and 3, respectively. Secondary: There were no differences in safety outcomes between antibiotic regimens. After adjusting for treatment group and gestational age, mortality rates through end of follow-up were 4.22 (95% CI, 1.39 to 12.13), 4.53 (95% CI, 1.21 to 15.50), and 4.07 (95% CI, 1.22 to 12.70) for groups 1, 2, and 3, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
permitted at the discretion of the treating physician				
Festi et al.[71] (1993) Study 1 Rifaximin 1,200 mg/day for 21 days Study 2 Rifaximin 1,200 mg/day for 21 days vs neomycin 3,000 mg/day for 21 days Study 3 Rifaximin 1,200 mg/day for 21 days vs lactulose 40 g/day for 21 days	OL (Study 1), RCT (Study 2 and 3) Patients 40 to 75 years of age with clinical and biochemical signs of mild hepatic encephalopathy and liver cirrhosis	N=136 21 days	Primary: Neurological signs, electro-encephalographic abnormalities, ammonia levels Secondary: Not reported	Primary: Study 1 Rifaximin significantly reduced the frequency of neurologic signs. After five days of treatment, the percentage of patients who exhibited asterixis was significantly lower than at baseline; after 15 days of treatment, no patients showed this neurologic sign. After seven days, a significantly lower percentage of patients exhibited electroencephalography abnormalities. Blood ammonia levels were significantly improved with rifaximin after five days. Blood ammonia concentrations reached normal values and remained within the normal range throughout the study. Study 2 Both rifaximin and neomycin reduced the neurologic signs of hepatic encephalopathy, but at different rates. Treatment with rifaximin led to a significant reduction in the frequency of asterixis after three days compared to five days with neomycin. A significantly lower percentage of patients exhibited electro-encephalographic abnormalities with rifaximin and neomycin compared to baseline ($P<0.001$). Ammonia levels were significantly reduced by rifaximin and neomycin. Normal values were achieved after seven days of treatment. Study 3 Both rifaximin and lactulose reduced the neurologic signs of hepatic encephalopathy compared to baseline ($P<0.05$). Electro-encephalographic abnormalities significantly decreased in frequency with rifaximin and lactulose compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Ammonia levels were significantly decreased with both treatments (P<0.01). Secondary: Not reported
Miglio et al.[72] (1997) Rifaximin 400 mg TID for 14 days each month vs neomycin 1 g TID for 14 days each month	DB, RCT Patients with cirrhosis and chronic hepatic encephalopathy of grade 1 or 2	N=60 6 months	Primary: Improvement of at least one grade of hepatic encephalopathy, neurological signs, Reitan test, ammonia levels, liver function tests Secondary: Not reported	Primary: There was a progressive reduction in hepatic encephalopathy grade with rifaximin and neomycin. There was no significant difference between the two treatment groups. The improvement in hepatic encephalopathy was significant after 30 days (P<0.001 for each group). In both groups, the disturbances in speech, memory, behavior and mood, gait, asterixis, writing, serial subtraction of 7s and five-pointed star tests showed the highest improvement (P<0.001). The Reitan test only showed a significant improvement in the rifaximin group (P<0.02). Blood ammonia levels were decreased from 210.2 to 88.9 µg/100 mL in the rifaximin group (P<0.001) and from 202.1 to 86.2 µg/100 mL in the neomycin group (P<0.001). There was no significant difference between the treatment groups. There were significant decreases in aspartate aminotransferase (P<0.02) and alanine transaminase (P<0.01 in the rifaximin group and P<0.03 in the neomycin group). Secondary: Not reported
Wagenlehner et al.[73] (2019) EPIC Plazomicin (15 mg/kg of body weight once daily IV) vs	DB, MC, RCT Patients ≥18 years of age with complicated urinary tract infections (UTIs), including acute pyelonephritis	N=609 32 days	Primary: Noninferiority of plazomicin to meropenem (Composite cure at day 5 and test of cure defined as resolution or improvement of clinical cUTI	Primary: Plazomicin was noninferior to meropenem with respect to the primary efficacy end points. Secondary: At day five, composite cure was observed in 88.0% of the patients in the plazomicin group and in 91.4% in the meropenem group (difference, –3.4 percentage points; 95% CI, –10.0 to 3.1). At the test-of-cure visit, composite cure was observed in 81.7% and 70.1%, respectively (difference, 11.6 percentage points; 95% CI, 2.7 to 20.3).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
meropenem (1 g every 8 hours IV) option for oral step-down therapy after a minimum of 4 days of IV therapy, for a total of 7 to 10 days of therapy (levofloxacin was the preferred oral agent)			symptoms and a microbiological outcome of eradication) Secondary: Composite cure (clinical cure and microbiologic eradication) at day 5 and at the test-of-cure visit (15 to 19 days after initiation of therapy) in the microbiologic modified intention-to-treat population	

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, TID=three times daily.
Study abbreviations: AOR=adjusted odds ratio, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo- controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SA=single arm, SEM=standard error of the mean.
Miscellaneous abbreviations: FEV_1=forced expiratory volume in one second, MIC=minimum inhibitory concentration.

Additional Evidence

Dose Simplification
Once-daily dosing of aminoglycosides is possible due to their rapid concentration-dependent killing and post-antibiotic effect. There was no significant difference between once-daily dosing and multiple daily dosing regimens with regards to clinical failure rates, microbiologic failure rates, or the combined clinical/microbiologic failure rates. Studies have demonstrated that once-daily dosing regimens are as safe as multiple daily dosing regimens with similar efficacy.[8,35-36]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 13. Relative Cost of the Aminoglycosides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amikacin	inhalation suspension, injection	Arikayce®	$$$$$	$$$$$
Gentamicin	injection	N/A	N/A	$$$$
Neomycin	tablet	N/A	N/A	$
Plazomicin	injection	Zemdri®	$$$$$	N/A
Streptomycin	injection	N/A	N/A	$$$$$
Tobramycin	inhalation solution, inhalation powder, injection	Bethkis®*, Kitabis®*, TOBI®*, TOBI Podhaler®	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The parenteral aminoglycosides are often used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated

urinary tract infections. All of the aminoglycosides are available in a generic formulation, with the exception of amikacin inhalation suspension, plazomicin, and tobramycin inhalation powder.

There are many guidelines that define the appropriate place in therapy for the oral/parenteral aminoglycosides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the aminoglycoside. The parenteral aminoglycosides are recommended as an initial empiric treatment option for serious infections, including acute pyelonephritis, community-acquired pneumonia, nosocomial pneumonia, and febrile neutropenia.[21,26,27,35] They are also recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, pelvic inflammatory disease, and plague.[13,14,15-18,26,30,31,34,37] The aminoglycosides are recommended as an alternative treatment option for skin and soft-tissue infections, granuloma inguinale, tuberculosis, and for surgical prophylaxis.[19,20,30-32,38] Neomycin is recommended for the treatment of hepatic encephalopathy, as well as for the prophylaxis for colorectal surgery.[38,39] Clinical trials have demonstrated comparable efficacy when the oral/parenteral aminoglycosides have been compared to each other, as well as to antibacterial agents in other classes.[57,58,63-66]

The chronic use of inhaled tobramycin is recommended for patients six years of age and older with cystic fibrosis colonized with *Pseudomonas aeruginosa* regardless of the severity of lung disease.[24] Treatment with tobramycin has been associated with improvements in pulmonary function, improved quality of life, decreased requirement for intravenous anti-pseudomonal antibiotics, and a decrease in hospitalizations compared to placebo.[40-46] Open-label studies following patients for up to two years have also demonstrated continued benefit over time.[43,45] Tobramycin inhalation powder provides a dosing option with decreased medication administration time, compared to the tobramycin inhalation solution.[6,7] However, there is no clinical evidence of differences in efficacy with the various inhaled tobramycin formulations.[52-56]

Arikayce® (amikacin inhalation suspension) is indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of six consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for Arikayce® are currently available, reserve for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.[4] Study results from CONVERT highlighted that Arikayce® was safe for patients with limited or no treatment options for MAC lung disease and that there was a statistically significant improvement in culture conversion, which may prevent further lung structure damage, for those who had this agent added on to guideline-based therapy.[61]

Zemdri® (plazomicin) is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Enterobacter cloacae*. As only limited clinical safety and efficacy data are currently available, reserve plazomicin for use in cUTI patients who have limited or no alternative treatment options.[5] In the phase III EPIC study, plazomicin demonstrated noninferiority to meropenem with respect to primary endpoints of composite cure (microbiological eradication and clinical cure) in adult patients with cUTI/pyelonephritis at Day 5 and test of cure.[73]

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity, nephrotoxicity, and neurotoxicity associated with their use.[1] Safety for treatment periods which are longer than 14 days has not been established.

Therefore, all brand aminoglycosides products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Tobramycin inhalation solution and inhalation powder has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4-9,52-56] Therefore, these patients should be allowed approval for inhalation solution and inhalation powder through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand aminoglycosides product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cephalosporins
AHFS Class 081206
May 3, 2023

I. Overview

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-9] They exert their bactericidal action by binding to penicillin-binding proteins, which leads to inhibition of cell-wall synthesis.

The cephalosporins have been shown to be active against a wide range of gram-positive and gram-negative organisms.[1-10] They are frequently grouped into generations based on their spectrum of activity. The first generation cephalosporins (cefadroxil, cefazolin, and cephalexin) are most active against gram-positive aerobes with limited activity against gram-negative aerobes. The second generation cephalosporins (cefaclor, cefprozil, and cefuroxime) have a greater gram-negative spectrum than first generation agents while retaining some activity against gram-positive cocci. They are also more resistant to β-lactamases. The third generation cephalosporins (cefdinir, cefixime, cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) have a broad spectrum of activity and enhanced activity against gram-negative organisms. Cefepime is a fourth-generation cephalosporin, which is an extended-spectrum agent with similar activity against gram-positive organisms as first generation cephalosporins. It also has a greater resistance to β-lactamases than the third generation cephalosporins. Ceftaroline is a fifth-generation cephalosporin with a spectrum of activity similar to ceftriaxone. It has greater activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-intermediate *Staphylococcus aureus*. Although the concept of "generations" was initially helpful, differences in antimicrobial spectra and pharmacokinetic properties within each generation exist. Additionally, there is an overlap in the spectra between generations. Cefiderocol is a siderophore cephalosporin with activity against multidrug-resistant gram-negative bacteria, including extended-spectrum beta-lactamase- or carbapenemase-producing organisms.[3-9]

Zerbaxa® (ceftolozane-tazobactam) and Avycaz® (ceftazidime-avibactam) are both combination products FDA-approved for the indications of complicated intra-abdominal infections when used in combination with metronidazole, complicated urinary tract infections including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia .[2,8,9] Ceftolozane-tazobactam has demonstrated activity against gram-negative and gram-positive microorganisms, including *Pseudomonas aeruginosa*. Tazobactam and avibactam are β-lactamase inhibitors. β-lactamase inhibitors have a high, irreversible binding affinity for the β-lactamase enzyme and prevent hydrolysis of the β-lactam ring. They also bind to the penicillin-binding proteins of the bacteria, increasing the effectiveness of certain cephalosporins. However, they have little clinically relevant in vitro activity against bacteria themselves.[1-3,7,8]

The cephalosporins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the cephalosporins are available in a generic formulation with the exception of ceftaroline and the combination products. This class was last reviewed in May 2021.

Table 1. Cephalosporins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Cefaclor	capsule, extended-release tablet, suspension	N/A	cefaclor
Cefadroxil	capsule, suspension, tablet	N/A	cefadroxil
Cefazolin	injection	N/A	cefazolin
Cefdinir	capsule, suspension	N/A	cefdinir
Cefepime	injection	N/A	cefepime
Cefiderocol	injection	Fetroja®	none
Cefixime	capsule, chewable tablet, suspension	Suprax®*	cefixime

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cefotaxime	injection	Claforan®*	cefotaxime
Cefpodoxime	suspension, tablet	N/A	cefpodoxime
Cefprozil	suspension, tablet	N/A	cefprozil
Ceftaroline	injection	Teflaro®	none
Ceftazidime	injection	Tazicef®*	ceftazidime
Ceftriaxone	injection	N/A	ceftriaxone
Cefuroxime	injection, tablet	N/A	cefuroxime
Cephalexin	capsule, suspension, tablet	N/A	cephalexin
Combination Products			
Ceftazidime and Avibactam	injection	Avycaz®	none
Ceftolozane and Tazobactam	injection	Zerbaxa®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

The cephalosporins have been shown to be active against the strains of microorganisms indicated in Tables 2 and 3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the cephalosporins that are noted in Table 5. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Cephalosporins[1-8]

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefiderocol	Cefixime	Cefotaxime	Cefpodoxime
Gram-Positive Aerobes									
Enterococcus species								✔	
Staphylococci	✔	✔							
Staphylococcus aureus	✔		✔	✔	✔			✔	✔
Staphylococcus epidermidis			✔					✔	
Staphylococcus saprophyticus									✔
Streptococci		✔	✔		✔			✔	
Streptococcus agalactiae			✔						
Streptococcus pneumoniae	✔	✔	✔	✔	✔		✔	✔	✔
Streptococcus pyogenes	✔	✔	✔	✔	✔		✔	✔	✔
Gram-Negative Aerobes									
Acinetobacter baumannii complex						✔			
Acinetobacter species								✔	
Citrobacter species								✔	
Enterobacter cloacae complex						✔			
Enterobacter species					✔			✔	
Enterococci			✔						
Escherichia coli	✔	✔	✔		✔	✔	✔	✔	✔
Haemophilus influenzae	✔		✔	✔			✔	✔	✔
Haemophilus parainfluenzae				✔				✔	
Klebsiella species	✔	✔	✔					✔	
Klebsiella pneumoniae					✔	✔			✔
Moraxella catarrhalis	✔	✔		✔			✔		✔
Morganella morganii								✔	
Neisseria gonorrhoeae							✔	✔	✔
Neisseria meningitidis								✔	

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefiderocol	Cefixime	Cefotaxime	Cefpodoxime
Proteus species								✔	
Proteus mirabilis	✔	✔	✔		✔	✔	✔	✔	✔
Proteus vulgaris								✔	
Providencia rettgeri								✔	
Providencia stuartii								✔	
Pseudomonas species								✔	
Pseudomonas aeruginosa					✔	✔		✔	
Serratia marcescens						✔		✔	
Anaerobes									
Bacteroides species								✔	
Bacteroides fragilis					✔				
Clostridium species								✔	
Fusobacterium species								✔	
Peptococcus species								✔	
Peptostreptococcus species								✔	

Table 3. Microorganisms Susceptible to the Cephalosporins (cont.)[1-8]

Organism	Cefprozil	Ceftaroline	Ceftazidime	Ceftolozane	Ceftriaxone	Cefuroxime	Cephalexin
Gram-Positive Aerobes							
Staphylococcus aureus	✔		✔		✔	✔	✔
Staphylococcus aureus (including methicillin-resistant isolates)		✔					
Staphylococcus epidermidis					✔		
Staphylococcus saprophyticus							
Streptococci					✔		
Streptococcus anginosus				✔			
Streptococcus agalactiae		✔	✔				
Streptococcus constellatus				✔			
Streptococcus pneumoniae	✔		✔		✔	✔	✔
Streptococcus pyogenes	✔	✔	✔		✔	✔	✔
Streptococcus salivarius				✔			
Gram-Negative Aerobes							
Acinetobacter calcoaceticus					✔		
Citrobacter species			✔				
Enterobacter species			✔		✔		
Enterobacter aerogenes					✔		
Enterobacter cloacae				✔	✔		
Escherichia coli		✔	✔	✔	✔	✔	✔

Organism	Cefprozil	Ceftaroline	Ceftazidime	Ceftolozane	Ceftriaxone	Cefuroxime	Cephalexin
Haemophilus influenzae	✔	✔	✔		✔	✔	✔
Haemophilus parainfluenzae					✔	✔	
Klebsiella species			✔				
Klebsiella oxytoca		✔		✔	✔		
Klebsiella pneumoniae		✔		✔	✔	✔	✔
Moraxella catarrhalis	✔				✔	✔	✔
Morganella morganii					✔		
Neisseria gonorrhoeae					✔	✔	
Neisseria meningitidis			✔		✔		
Proteus species			✔				
Proteus mirabilis			✔	✔	✔		✔
Proteus vulgaris			✔		✔		
Pseudomonas species			✔				
Pseudomonas aeruginosa			✔	✔	✔		
Serratia species			✔				
Serratia marcescens					✔		
Anaerobes							
Bacteroides species			✔				
Bacteroides fragilis				✔	✔		
Clostridium species					✔		
Peptostreptococcus species					✔		
Spirochete							
Borrelia burgdorferi						✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cephalosporins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Cephalosporins

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[10]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for four weeks (in β-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o β-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial

Clinical Guideline	Recommendation(s)
	healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[11]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered.

Clinical Guideline	Recommendation(s)
	• Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[12]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of

Clinical Guideline	Recommendation(s)
	therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable.

Clinical Guideline	Recommendation(s)
	○ For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. ○ For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. ○ If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[13] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole

Clinical Guideline	Recommendation(s)
	or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[14]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.

Clinical Guideline	Recommendation(s)

	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem.
	• Pseudomonal meningitis:
	  o Meropenem±gentamicin.

Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[15]	<u>Empiric Therapy</u>
	• Empiric therapy should be used when infection is suspected but cultures are not yet available.
	• Vancomycin plus an anti-pseudomonal β-lactam (e.g., cefepime, ceftazidime, or meropenem) is recommended.
	• Choice of anti-pseudomonal β-lactam should be based on local resistance patterns.
	• In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 µg/mL
	• For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin
	• Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens
	<u>Pathogen Specific Therapy</u>
	• Methicillin-susceptible *S. aureus*
	  o Recommended treatment includes nafcillin or oxacillin
	  o In patients who cannot receive β-lactams, vancomycin is recommended
	• Methicillin-resistant *S. aureus*
	  o Recommended treatment includes vancomycin
	• *P. acnes*
	  o Recommended treatment includes penicillin G
	• *Pseudomonas* species
	  o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone
	• Gram-negative bacilli
	  o Recommended treatment includes ceftriaxone or cefotaxime
	• Extended-spectrum β-lactamase–producing gram-negative bacilli
	  o Recommended treatment includes meropenem
	• *Acinetobacter* species
	  o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B
	• *Candida* species
	  o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine
	• *Aspergillus* or *Exserohilum*
	  o Recommended treatment includes voriconazole
	• In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain
	  o Use of rifampin as part of combination therapy is recommended
	<u>Duration of Therapy</u>
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms
	  o Duration is recommended to be 10 days
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features
	  o Duration is recommended to be 10 to 14 days
	• Infections caused by *S. aureus* or gram-negative bacilli

Clinical Guideline	Recommendation(s)
	○ Duration is recommended to be 10 to 14 days • Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy • It is recommended that therapy be continued for 10 to 14 days after the last positive culture
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[16]	<u>Impetigo and ecthyma</u> • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. ○ Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. ○ Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. <u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u> • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. <u>Recurrent skin abscesses</u> • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood.

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	Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is

Clinical Guideline	Recommendation(s)
	recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. <u>Clostridial gas gangrene or myonecrosis</u> • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. <u>Animal bites</u> • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. <u>Bacillary angiomatosis and cat scratch disease</u> • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis.

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	Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)**[17]	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended.
	• Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost.
	• A course of antibiotic therapy of one to two weeks is usually adequate for most mild and moderate infections.
	  o For more serious skin and soft tissue infections, three weeks is usually sufficient.
	  o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed.
	• Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding.
	• For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity.
	• For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection.
	• For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.

World Gastroenterology Organization:	General considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is

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Acute Diarrhea (2012)[18]	known. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)[19]**	<u>Epidemiology</u> • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. <u>Diagnosis</u> • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. <u>Treatment of acute disease</u> • The usage of balanced electrolyte rehydration over other oral rehydration options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness.

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	• In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. <u>Evaluation of persisting symptoms</u> • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. <u>Prevention</u> • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.

Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)[20]**	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more.
	• Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures.
	• Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified.
	• Recommended antimicrobial agents by pathogen:
	  ○ *Campylobacter*
	  ▪ First choice: Azithromycin
	  ▪ Alternative: Ciprofloxacin
	  ○ *Clostridium difficile*
	  ▪ First choice: Oral vancomycin

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	▪ Alternative: Fidaxomicin ▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). o Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, sulfamethoxazole-trimethoprim, or amoxicillin. o *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or sulfamethoxazole-trimethoprim or azithromycin o *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: sulfamethoxazole-trimethoprim or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. o *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone o Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside o *Yersinia enterocolitica* ▪ First choice: sulfamethoxazole-trimethoprim ▪ Alternative: Cefotaxime or ciprofloxacin o *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response o *Cyclospora cayetanensis* ▪ First choice: sulfamethoxazole-trimethoprim ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer durations of sulfamethoxazole-trimethoprim treatment o *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3

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	years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. o *Cystoisospora belli* ▪ First choice: sulfamethoxazole-trimethoprim ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide o *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole ▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[21]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2

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	recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis,

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	disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants

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	treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. Pediculosis pubis (pubic lice infestation) • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off. o Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. o Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases.

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	Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. Uncomplicated vulvovaginal candidiasis • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days.

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	○ Miconazole 1,200 mg vaginal suppository one suppository for one day. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved

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	substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
	
	<u>Cervical warts</u>
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	<u>Vaginal warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	<u>Urethral meatus warts</u>
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	<u>Intra-anal warts</u>
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

Infectious Diseases Society of America/European Society for Microbiology and	<u>Acute uncomplicated bacterial cystitis</u> • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an

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Infectious Diseases: **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)**[22] Reviewed and deemed current as of 07/2013	appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute pyelonephritis</u> • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days. o Trimethoprim 100 mg twice daily for three days.

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Infections in Nonpregnant Women (2008)[23] Reaffirmed 2016	○ Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days. ○ Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days. ○ Fosfomycin tromethamine, 3 g dose (powder) single dose.
American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in Women: Guideline (2022)[24]**	Evaluation • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. • Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no

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	contraindication to estrogen therapy.
American Academy of Pediatrics/ American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[25] Reaffirmed 2019	Observation option • Observation without use of antibacterial agents in a child with unilateral acute otitis media is an option for selected children based on age, illness severity, and assurance of follow-up after joint decision-making with the parent(s)/caregiver. The "observation option" for acute otitis media refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children six months and older without severe symptoms at presentation. Antibacterial options - temperature <39°C without severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial options - temperature ≥39°C and/or severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for three days.
American Academy of Pediatrics: **Red Book – Group A streptococcal infections (2021)**[26]	• Penicillin V is the drug of choice for Group A *Streptococci* pharyngitis. Prompt administration of penicillin shortens the clinical course, decreases risk of transmission and suppurative sequelae, and prevents acute rheumatic fever, even when administered up to nine days after illness onset. All patients with acute rheumatic fever should receive a complete course of penicillin or another appropriate antimicrobial agent for Group A *Streptococci* pharyngitis, even if group A streptococci are not recovered from the throat. • Amoxicillin, orally as a single daily dose (50 mg/kg; maximum, 1000 to 1200 mg) for 10 days, is as effective as penicillin V or amoxicillin administered orally multiple times per day for 10 days and is a more palatable suspension than penicillin V. This regimen is endorsed by the American Heart Association and the Infectious Disease Society of America in its guidelines for the treatment of Group A *Streptococci* pharyngitis and the prevention of acute rheumatic fever. Adherence is particularly important for once-daily dosing regimens. • The dose of oral penicillin V is 400 000 U (250 mg), 2 to 3 times per day, for 10 days for children weighing <27 kg and 800 000 U (500 mg), 2 to 3 times per day, for those weighing ≥27 kg, including adolescents and adults. To prevent acute rheumatic fever, oral penicillin or amoxicillin should be taken for 10 full days, regardless of promptness of clinical recovery. Treatment failures occur more often with oral penicillin than with intramuscular penicillin G benzathine because of inadequate adherence. Notably, short-course treatment (<10 days) for Group A *Streptococci* pharyngitis, particularly with penicillin V, is associated with inferior bacteriologic eradication rates. • Intramuscular penicillin G benzathine is appropriate therapy, ensuring adequate blood concentrations and avoiding adherence issues, but administration may be painful. Discomfort is decreased if the preparation of penicillin G benzathine is brought to room temperature before intramuscular injection. Mixtures containing shorter-acting penicillins (e.g., penicillin G procaine) in addition to penicillin G benzathine are not more effective than penicillin G benzathine alone but are less painful. Although supporting data are limited, the combination of 900 000 U (562.5

Clinical Guideline	Recommendation(s)
	mg) of penicillin G benzathine and 300 000 U (187.5 mg) of penicillin G procaine is satisfactory for most children; however, the efficacy of this combination for heavier patients has not been documented. • For patients who have a history of nonanaphylactic allergy to penicillin, a 10-day course of a narrow-spectrum (first-generation) oral cephalosporin (e.g., cephalexin) is indicated. Patients with immediate (anaphylactic) or type I hypersensitivity to penicillin should receive oral clindamycin (20 mg/kg per day in three divided doses; maximum, 900 mg/day for 10 days) rather than a cephalosporin. • An oral macrolide (e.g., erythromycin, azithromycin, or clarithromycin) also is acceptable for penicillin-allergic patients. This should not be used in patients who can take a beta-lactam agent. Therapy for 10 days is indicated, except for azithromycin, which is given for five days. Group A *Streptococci* strains resistant to macrolides have been highly prevalent in some countries and have resulted in treatment failures. In some areas in the United States, macrolide resistance rates of more than 20% have been reported. Testing for macrolide resistance may help to decide the best antimicrobial agent for specific penicillin-allergic patients. • Tetracyclines, sulfonamides, and fluoroquinolones should not be used for treating Group A *Streptococci* pharyngitis. • Children with recurrent Group A *Streptococci* pharyngitis shortly after a full course of a recommended oral agent can be retreated with the same antimicrobial agent (if it is a beta-lactam), an alternative beta-lactam oral drug (such as cephalexin or amoxicillin-clavulanate), or an intramuscular dose of penicillin G benzathine. Susceptibility testing should be performed when considering a macrolide or clindamycin.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[27]	<u>Symptomatic relief of viral rhinosinusitis</u> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. <u>Symptomatic relief of acute bacterial rhinosinusitis</u> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. <u>Initial management of acute bacterial rhinosinusitis</u>

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	• Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. <u>Choice of antibiotic for acute bacterial rhinosinusitis</u> • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. <u>Treatment failure for acute bacterial rhinosinusitis</u> • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)[28]**	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)[29]**	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided

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	doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[30]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[31] Reviewed and deemed current as of 04/2013	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not

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	fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-Acquired Pneumonia (2019)**[32]	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) <u>Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting</u>: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. <u>Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting</u>: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with

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	CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid. • Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)[33]**	<u>Empiric Therapy</u> • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known o Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available <u>Pathogen-Specific Therapy</u> • MRSA o Vancomycin or linezolid are recommended treatments • *P. aeruginosa* o It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy o In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli o Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species o Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens o If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin <u>Duration of therapy</u> • Seven day course of treatment
Infectious Diseases Society of America:	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and

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Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children (2010)[34]	facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or

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	ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health care-associated infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[35]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response.

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	• For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include

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	the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression (2018)[36]**	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir).

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	• Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)**[37]	Low infection risk prophylaxis
	• Antimicrobial prophylaxis is not recommended in patients with low infection risk.
	
	Intermediate infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis during neutropenia.
	• Additional prophylaxis may be necessary.
	
	High infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis during neutropenia.
	• Additional prophylaxis may be necessary.
	
	Pneumocystis jirovecii prophylaxis
	• Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria.
	• Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim.
	• Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.
	
	Pneumococcal infection prophylaxis
	• Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant.
	• In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis.
	
	Initial empiric antibiotic therapy
	• Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection.
	• Intravenous antibiotic monotherapy for uncomplicated infections (choose one):
	  ○ Cefepime.
	  ○ Imipenem-cilastatin.
	  ○ Meropenem.
	  ○ Piperacillin-tazobactam.
	  ○ Ceftazidime.
	• Oral antibiotic combination therapy for low-risk patients with uncomplicated infections:
	  ○ Ciprofloxacin plus amoxicillin-clavulanate.
	  ○ Moxifloxacin.
	  ○ Levofloxacin.
	  ○ Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used.
	• Complicated infections (choose based on local antibiotic susceptibility patterns):
	  ○ Intravenous antibiotic monotherapy is preferred.

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	○ Intravenous combination therapy could be considered especially in cases of resistance. Antibacterial agents: empiric gram-positive activity • Vancomycin ○ Gram-positive organisms with the exception of VRE and a number of rare organisms. ○ Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. ○ Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin ○ Has in vitro activity against VRE but is not FDA-approved for this indication. ○ Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. ○ Not indicated for pneumonia due to inactivation by pulmonary surfactant. ○ Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid ○ Gram-positive organisms including VRE. ○ Hematologic toxicity (typically with prolonged cases over two weeks) may occur. ○ Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. ○ Treatment option for VRE and MRSA. ○ Peripheral/optic neuropathy with long-term use. Antibacterial agents: anti-pseudomonal • Cefepime ○ Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever. ○ Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime ○ Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. ○ Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. ○ Use for suspected intra-abdominal source. ○ Meropenem is preferred over imipenem for suspected/proven CNS infection. ○ Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. ○ Empiric therapy for neutropenic fever. ○ Data are limited, but it is expected that doripenem, like meropenem, would be efficacious.

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	• Piperacillin-tazobactam
	  ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms.
	  ○ Use for suspected intra-abdominal source.
	  ○ Not recommended for meningitis.
	  ○ Empiric therapy for neutropenic fever.
	
	<u>Antibacterial agents: other</u>
	• Aminoglycosides
	  ○ Activity primarily against gram-negative organisms.
	  ○ Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients.
	• Ciprofloxacin in combination with amoxicillin-clavulanate
	  ○ Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms.
	  ○ Ciprofloxacin alone has no activity against anaerobes.
	  ○ Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes.
	  ○ Oral combination therapy in low-risk patients.
	  ○ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis.
	  ○ Increasing Gram-negative resistance in many centers.
	  ○ Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered.
	• Levofloxacin/ moxifloxacin
	  ○ Good activity against gram-negative and atypical organisms.
	  ○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas.
	  ○ Prophylaxis may increase bacterial resistance and superinfection.
	• Metronidazole
	  ○ Good activity against anaerobic organisms.
	• Sulfamethoxazole-trimethoprim
	  ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients.
	  ○ Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia.
	  ○ Interactions with methotrexate.

Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology: **Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease (2020)[38]**	• Prophylactic antibiotic therapy is only recommended for adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal risk or low risk. If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high-risk only if it meets the following three criteria: the tick bite was from (a) an identified *Ixodes* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours. • For high-risk *Ixodes* spp. bites in all age groups, administer a single dose of oral doxycycline within 72 hours of tick removal over observation. • Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children. • For patients with erythema migrans, use oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil. For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin. • Patients with erythema migrans should be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses. If azithromycin is used, the indicated duration is five to

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	10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States.
Infectious Diseases Society of America: **Guideline on Diagnosis and Management of Babesiosis (2020)**[39]	• Treat babesiosis with the combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine. Atovaquone plus azithromycin is the preferred antimicrobial combination for patients experiencing babesiosis, while clindamycin plus quinine is the alternative choice. The duration of treatment is seven to 10 days in immunocompetent patients but often is extended when the patient is immunocompromised.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[40]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen

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	of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. <u>Biliary tract procedures</u> • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. <u>Appendectomy procedures</u> • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Small intestine procedures</u> • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Hernia repair procedures</u> • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. <u>Colorectal procedures</u> • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The

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	oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation. • Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity. <u>Head and neck procedures</u> • Clean procedures: o Antimicrobial prophylaxis is not required. • Clean-contaminated procedures: o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures. o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam. o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. <u>Neurosurgery procedures</u> • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). <u>Cesarean delivery procedures</u> • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. <u>Hysterectomy procedures</u> • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. <u>Ophthalmic procedures</u> • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. <u>Orthopedic procedures</u> • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials.

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	• Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. <u>Urologic procedures</u> • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. <u>Vascular procedures</u> • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. <u>Heart, lung, heart-lung, liver, pancreas, and kidney transplantation</u> • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. <u>Plastic surgery and breast procedures</u> • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cephalosporins are noted in Tables 5 through 7. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Single Entity Cephalosporins[1-8]

Indication	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Central Nervous System Infections								
Central nervous system infections								✔
Dermatological Infections								
Skin and skin-structure infections	✔ †‡	✔	✔	✔	✔			✔
Genitourinary Infections								
Endometritis								✔
Genital infections			✔					
Gonorrhea							✔	✔
Pelvic cellulitis								✔
Pelvic inflammatory disease								✔
Urinary tract infections	✔ †§	✔	✔		✔	✔	✔	✔
Respiratory Infections								
Acute bronchitis	✔ ‡							
Acute exacerbations of chronic bronchitis	✔ ‡			✔			✔	
Otitis media	✔ †§			✔			✔	
Pharyngitis and/or tonsillitis	✔ †‡§	✔		✔			✔	
Pneumonia	✔ ‡				✔	✔		✔
Pneumonia (community-acquired)				✔				
Sinusitis				✔				
Respiratory tract infections (lower)	✔ †§		✔					✔
Respiratory tract infections (upper)			✔					
Miscellaneous Infections								
Bacteremia/Septicemia			✔					✔
Biliary tract infections			✔					
Bone and/or joint infections			✔					✔
Empiric therapy for febrile neutropenic patients					✔			
Endocarditis			✔					
Intra-abdominal infections					✔			✔
Perioperative prophylaxis			✔					✔

†Capsule formulation.
‡Extended-release tablet formulation.
§Suspension formulation.

Table 6. FDA-Approved Indications for the Single Entity Cephalosporins (cont.)[1-9]

Indication	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Central Nervous System Infections							
Central nervous system infections				✔			
Meningitis				✔	✔	✔ §	
Dermatological Infections							
Impetigo						✔ ‡	
Skin and skin-structure infections	✔	✔	✔	✔	✔	✔ †§	✔
Genitourinary Infections							
Genitourinary infections							✔
Gonorrhea	✔				✔	✔ †§	
Gynecologic infections				✔	✔		
Urinary tract infections	✔			✔	✔	✔ †§	
Respiratory Infections							
Acute bronchitis		✔					
Acute exacerbations of chronic bronchitis	✔	✔				✔ †	
Otitis media	✔	✔			✔	✔ †‡	✔
Pharyngitis and/or tonsillitis	✔	✔				✔ †‡	
Pneumonia				✔			
Pneumonia (community-acquired)	✔		✔				
Sinusitis	✔	✔				✔ †	
Respiratory tract infections (lower)				✔	✔	✔ §	✔
Respiratory tract infections (upper)							✔
Miscellaneous Infections							
Bone and/or joint infections				✔	✔	✔ §	✔
Intra-abdominal infections				✔	✔		
Lyme disease (early)						✔ †	
Perioperative prophylaxis					✔	✔ §	
Septicemia				✔	✔	✔ §	

§Injection formulation.
‡Suspension formulation.
†Tablet formulation.

Table 7. FDA-Approved Indications for the Combination Product Cephalosporins[1-9]

Indication	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Complicated intra-abdominal infections, used in combination with metronidazole	✔	✔
Complicated urinary tract infections, including pyelonephritis	✔	✔
Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cephalosporins are listed in Table 8.

Table 8. Pharmacokinetic Parameters of the Cephalosporins[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Cefaclor	Well absorbed	25	Not reported	Renal (50 to 80) Bile	0.5 to 1.0
Cefadroxil	Well absorbed	20	Not reported	Renal (85)	1.2 to 1.7
Cefazolin	Not reported	80 to 86	Not metabolized	Renal (70 to 80)	1.5 to 2.5
Cefdinir	16 to 25	60 to 73	Not reported	Renal	1.7
Cefepime	IM: Complete	16 to 20	Liver	Renal (70 to 99)	2
Cefiderocol	Not reported	40 to 60	Minimally metabolized	Renal (98.6) Feces (2.8)	2 to 3
Cefixime	40 to 50	50 to 65	Not metabolized	Renal (50) Bile (5)	3 to 4
Cefotaxime	Not reported	27 to 38	Liver	Renal (50 to 85)	0.8 to 1.4
Cefpodoxime	41 to 64	18 to 33	Not reported	Renal (29 to 33)	2 to 3
Cefprozil	89 to 95	35 to 45	Not reported	Renal (60 to 70)	1 to 2
Ceftaroline	Not reported	20	Plasma	Renal (88) Feces (6)	2.6
Ceftazidime	IM: 91	5 to 17	Not metabolized	Renal (90 to 96)	1.6 to 2.0
Ceftriaxone	IM: 100 SC: 92	83 to 96	Intestinal wall	Renal (33 to 67) Bile (35 to 45)	5.8 to 8.7
Cefuroxime	37 to 52	50	Intestinal wall	Renal (66 to 100)	1.2 to 1.9
Cephalexin	Well absorbed	10 to 15	Not reported	Renal (>90)	0.7 to 1.0
Combination Products					
Ceftazidime and Avibactam	Not reported	C: <10 A: 5.7 to 8.2	Not reported	C: Renal (80 to 90) A: Renal (97)	C: 2.8 to 3.3 A: 2.2 to 2.7
Ceftolozane and Tazobactam	Not reported	C: 16 to 21 T: 30	C: Not metabolized T: Hydrolysis	C: Renal (>95) T: Renal (80)	C: 3.12 T: 1.03

IM=intramuscular, SC=subcutaneous.

V. Drug Interactions

Major drug interactions with the cephalosporins are listed in Table 9.

Table 9. Major Drug Interactions with the Cephalosporins[2]

Generic Name(s)	Interaction	Mechanism
Cephalosporins (cefaclor, cefadroxil, cefazolin, cefdinir, cefepime, cefixime, cefotaxime, cefpodoxime, cefprozil, ceftaroline, ceftazidime, ceftriaxone, cefuroxime, cephalexin, ceftolozane)	Live vaccines	Concurrent use of live vaccines and systemic antibiotics may result in reduced immune response to the vaccine.
Cephalosporins (cefadroxil, cefdinir, cefepime, cefixime, cefotaxime, cefpodoxime, ceftaroline, ceftazidime, cephalexin)	Warfarin	Concurrent use of certain cephalosporins and warfarin may result in an increased risk of bleeding.

Generic Name(s)	Interaction	Mechanism
Ceftriaxone	Calcium salts	Isolated neonatal deaths have been reported due to potential pulmonary and renal precipitation. Simultaneous administration of calcium-containing intravenous solutions and ceftriaxone in the same intravenous line should be avoided. A potential risk exists for calcium-ceftriaxone precipitation leading to gall bladder sludging, as well as precipitation, in the lungs and kidneys.
Avibactam	Probenecid	Concurrent use of avibactam and probenecid may result in decreased avibactam elimination and increased exposure.
Cephalexin	Probenecid	Concurrent use of cephalexin and probenecid may result in increased cephalexin exposure.

VI. Adverse Drug Events

The most common adverse drug events reported with the cephalosporins are listed in Tables 10 through 12.

Table 10. Adverse Drug Events (%) Reported with the Cephalosporins[1-8]

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Cardiovascular									
Arrhythmia	-	-	-	-	-	-	-	-	<1
Atrial fibrillation	-	-	-	-	-	-	<2	-	-
Bradycardia	-	-	-	-	-	-	<2	-	-
Cardiac failure	-	-	-	<1	-	-	<2	-	-
Chest pain	-	-	-	<1	-	-	-	-	-
Hypertension	-	-	-	<1	-	-	-	-	-
Myocardial infarction	-	-	-	≤1	-	-	-	-	-
Peripheral edema	-	-	-	-	-	-	<2	-	-
Shock	-	-	-	<1	-	<1	-	-	-
Central Nervous System									
Agitation	<1	-	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<1	-	-	-
Confusion	<1	-	-	-	-	<1	-	-	-
Dizziness	<1	-	-	<1	-	-	-	<2	-
Encephalopathy	-	-	-	-	-	<1	-	-	-
Fever	-	<1	✔	<1	-	1	-	<2	<1
Hallucinations	<1	-	-	-	-	<1	-	-	-
Headache	-	-	-	2	2 to 3	1	2	<2	<1
Hyperactivity	<1	-	-	-	-	-	-	-	-
Insomnia	<1	-	-	<1	-	-	<2	-	-
Irritability	<1	-	-	-	-	-	-	-	-
Loss of consciousness	-	-	-	<1	-	-	-	-	-
Nervousness	<1	-	-	-	-	-	-	-	-
Paresthesias	<1	-	-	-	-	-	-	-	-
Restlessness	-	-	-	-	-	-	<2	-	-
Seizures	<1	-	✔	-	-	<1	<2	<2	-
Somnolence	<1	-	-	<1	-	-	-	-	-
Stupor	-	-	-	-	-	<1	-	-	-
Dermatological									
Angioedema	<1	<1	-	-	-	-	-	<2	-
Cutaneous moniliasis	-	-	-	<1	-	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Erythema at injection site	-	-	-	-	-	1	-	-	-
Erythema multiforme	-	<1	-	<1	<1	-	-	<2	<1
Erythema nodosum	-	-	-	<1	-	-	-	-	-
Exfoliative dermatitis	-	-	-	<1	-	-	-	-	-
Facial edema	-	-	-	<1	-	-	-	<2	-
Pruritus	<1	<1	✔	<1	-	1	<2	-	1 to 10
Rash	1 to 2	<1	✔	≤3	<1	1 to 4	3	<2	1 to 10
Stevens-Johnson syndrome	<1	<1	✔	<1	<1	-	-	<2	<1
Toxic epidermal necrolysis	<1	-	-	<1	<1	-	-	<2	<1
Urticaria	<1	<1	-	-	-	<1	-	<2	<1
Gastrointestinal									
Abdominal pain	-	<1	✔	≤1	2	-	<2	2 to 10	-
Appetite decreased	-	-	✔	<1	-	-	<2	-	-
Biliary colic	-	-	-	-	-	-	<2	-	-
Bloody diarrhea	-	-	-	<1	-	-	-	-	-
Cholecystitis	-	-	-	-	-	-	<2	-	-
Cholelithiasis	-	-	-	-	-	-	<2	-	-
Colitis	-	-	-	-	-	<1	-	-	1 to 10
Constipation	-	-	-	<1	-	-	3	-	-
Diarrhea	3	1 to 10	✔	8 to 15	11 to 15	≤3	4	16	1 to 10
Dysgeusia	-	-	-	-	-	-	<2	-	-
Dyspepsia	-	<1	-	<1	1 to 2	-	-	2 to 10	-
Enterocolitis	-	-	-	<1	-	-	-	-	-
Flatulence	-	-	-	<1	-	-	-	2 to 10	-
GI bleed	-	-	-	<1	-	-	-	-	-
Hemorrhagic colitis	-	-	-	<1	-	-	-	-	-
Ileus	-	-	-	<1	-	-	-	-	-
Loose stools	-	-	-	-	-	-	-	2 to 10	-
Melena	-	-	-	<1	-	-	-	-	-
Nausea	<1	<1	✔	≤3	4 to 6	≤2	2	2 to 10	1 to 10
Oral candidiasis	-	-	✔	-	-	-	-	-	-
Oral moniliasis	-	-	-	-	-	<1	-	-	-
Peptic ulcer	-	-	-	<1	-	-	-	-	-
Pseudomonas colitis	<1	<1	✔	<1	<1	<1	-	-	<1
Stomatitis	-	-	-	<1	-	-	<2	-	-
Stools abnormal	-	-	-	<1	-	-	-	-	-
Vomiting	<1	<1	✔	≤1	1	≤1	2	<2	1 to 10

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Xerostomia	-	-	-	<1	-	-	<2	-	-
Genitourinary									
Glycosuria	-	-	-	≤1	-	-	-	-	-
Hematuria	-	-	-	-	3	-	<2	-	-
Interstitial nephritis	<1	-	-	-	-	-	-	-	<1
Leukorrhea	-	-	-	<1	<1	-	-	-	-
Microhematuria	-	-	-	≤1	-	-	-	-	-
Nephropathy	-	-	-	<1	-	-	-	-	-
Proteinuria	-	-	-	≤1	-	-	-	-	-
Pyuria	-	-	-	-	2	-	-	-	-
Renal failure	-	-	✔	<1	<1	-	-	<2	-
Urine leukocytes increased	-	-	-	≤2	-	-	-	-	-
Urine pH increased	-	-	-	≤1	-	-	-	-	-
Urine specific gravity decreased	-	-	-	<1	-	-	-	-	-
Urine specific gravity increased	-	-	-	≤1	-	-	-	-	-
Vaginal moniliasis	-	-	-	<4	3 to 6	-	-	-	-
Vaginitis	2	<1	✔	≤1	-	<1	-	<2	<1
Hematologic									
Agranulocytosis	<1	<1	-	-	-	<1	-	-	-
Aplastic anemia	<1	-	-	-	-	-	-	-	-
Coagulation disorder	-	-	-	<1	-	-	-	-	-
Coagulation time increased	-	-	-	-	<1	-	-	-	-
Disseminated intravascular coagulation	-	-	-	<1	-	-	-	-	-
Eosinophilia	2	-	✔	1	-	2	-	<2	<1
Granulocytopenia	-	-	-	<1	-	-	-	-	-
Hematocrit decreased	-	-	-	-	2	<1	-	-	-
Hemoglobin decreased	-	-	-	<1	-	-	-	-	-
Hemolytic anemia	<1	-	-	<1	-	-	-	-	-
Leukocytosis	-	-	-	≤1	-	-	-	-	-
Leukopenia	-	-	✔	≤1	<1	<1	-	<2	-
Lymphocytes decreased	-	-	-	1	-	-	-	-	-
Lymphocytes increased	-	-	-	≤2	-	-	-	-	-
Monocytes increased	-	-	-	<1	-	-	-	-	-
Neutropenia	<1	<1	✔	-	-	<1	-	<2	<1
Pancytopenia	-	-	-	<1	-	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Prothrombin time abnormal	-	-	-	-	-	1	-	-	-
Prothrombin time prolonged	<1	-	-	-	-	-	<2	<2	-
Partial thromboplastin time abnormal	-	-	-	-	-	2	-	-	-
Thrombocythemia	-	-	-	-	<1	-	-	-	-
Thrombocytopenia	<1	<1	✔	<1	<1	<1	<2	<2	<1
Thrombocytopenia purpura	-	-	-	<1	-	-	-	-	-
Thrombocytosis	-	-	✔	≤1	-	-	-	-	-
White blood cells decreased	-	-	-	<1	<1	-	-	-	-
White blood cells increased	-	-	-	<1	<1	-	-	-	-
Hepatic									
Cholestasis	-	<1	-	<1	-	-	-	-	-
Hepatic failure	-	-	-	<1	-	-	-	-	-
Hepatitis	<1	-	✔	<1	-	-	-	<2	-
Jaundice	<1	-	-	<1	-	-	-	<2	-
Laboratory Test Abnormalities									
Albumin decreased	-	-	-	-	<1	-	-	-	-
Alkaline phosphatase increased	-	-	-	≤1	-	<1	-	-	-
Amylase increased	-	-	-	<1	-	-	-	-	-
Bicarbonate decreased	-	-	-	≤1	-	-	-	-	-
Blood urea nitrogen increased	-	-	✔	<1	<1	<1	-	<2	<1
Gamma-glutamyl transferase increased	-	-	-	≤1	-	-	-	-	-
Hyperbilirubinemia	-	-	-	-	-	<1	-	<2	-
Hyperglycemia	-	-	-	≤1	1 to 2	-	-	-	-
Hyperkalemia	-	-	-	<1	<1	<1	2	-	-
Hyperphosphatemia	-	-	-	≤1	-	<1	-	-	-
Hypocalcemia	-	-	-	<1	<1	<1	<2	-	-
Hyponatremia	-	-	-	-	<1	-	-	-	-
Hypophosphatemia	-	-	-	<1	-	3	-	-	-
Lactate dehydrogenase increased	-	-	-	≤1	-	-	-	-	-
Increased liver enzymes	-	-	-	-	-	-	2	-	-
Positive Coombs' test	-	-	-	-	<1	16	-	-	-
Serum creatinine increased	-	-	✔	-	-	<1	-	<2	<1

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefiderocol	Cefixime	Cefotaxime
Transaminases increased	3	<1	✔	<1	-	2 to 3	-	<2	<1
Musculoskeletal									
Arthralgia	<1	<1	-	-	<1	-	-	-	-
Hyperkinesia	-	-	-	<1	-	-	-	-	-
Involuntary movement	-	-	-	<1	-	-	-	-	-
Myoclonus	-	-	-	-	-	<1	-	-	-
Rhabdomyolysis	-	-	-	<1	-	-	-	-	-
Respiratory									
Asthma	-	-	-	<1	<1	-	-	-	-
Cough	-	-	-	-	-	-	2	-	-
Dyspnea	-	-	-	-	-	-	<2	-	-
Eosinophilic pneumonia	-	-	-	<1	<1	-	-	-	-
Interstitial pneumonia	-	-	-	<1	<1	-	-	-	-
Pleural effusion	-	-	-	-	-	-	<2	-	-
Pneumonia	-	-	-	<1	-	-	-	-	-
Respiratory failure	-	-	-	<1	-	-	-	-	-
Other									
Allergic reaction	-	-	-	-	<1	-	<2	-	-
Allergic vasculitis	-	-	-	<1	-	-	-	-	-
Anaphylaxis	<1	<1	✔	<1	-	<1	-	<2	<1
Bleeding tendency	-	-	-	<1	-	-	-	-	-
Candidiasis	-	-	-	-	-	-	2	<2	<1
Conjunctivitis	-	-	-	<1	-	-	-	-	-
Fungal infection	-	-	-	-	<1	-	-	-	-
Hypervolemia	-	-	-	-	-	-	<2	-	-
Laryngeal edema	-	-	-	<1	-	-	-	-	-
Moniliasis	2	-	-	<1	-	-	-	-	-
Pain at injection site	-	-	✔	-	-	1	4	-	1 to 10
Phlebitis	-	-	✔	-	-	1	-	-	<1
Serum sickness-like reaction	<1	<1	-	<1	-	-	-	<2	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Adverse Drug Events (%) Reported with the Cephalosporins (cont.)[1-8]

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Cardiovascular							
Bradycardia	-	-	<2	-	-	-	-
Chest pain	<1	-	-	-	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Edema	-	-	-	-	<1	-	-
Hypotension	<1	-	-	-	-	-	-
Palpitation	-	-	<2	-	<1	-	-
Tachycardia	-	-	-	-	-	<1	-
Central Nervous System							
Agitation	-	-	-	-	-	-	✔
Anxiety	<1	-	-	-	-	-	-
Confusion	-	<1	-	-	-	-	✔
Dizziness	<1	1	<2	<1	<1	-	✔
Encephalopathy	-	-	-	<1	-	-	-
Fatigue	<1	-	-	-	-	-	✔
Fever	<1	<1	<2	<1	<1	<1	-
Hallucinations	-	-	-	-	-	-	✔
Headache	1	<1	3 to 5	<1	<1	-	✔
Hyperactivity	-	<1	-	-	-	-	-
Insomnia	<1	<1	3 to 4	-	-	-	-
Nightmares	<1	-	-	-	-	-	-
Paresthesias	-	-	-	<1	-	-	-
Seizures	-	-	<2	-	<1	<1	-
Somnolence	-	<1	-	-	-	-	-
Dermatological							
Allergic dermatitis	-	-	-	-	<1	-	-
Angioedema	-	<1	-	<1	-	<1	✔
Diaper rash	12	2	-	-	-	3	-
Erythema multiforme	-	<1	-	<1	<1	<1	✔
Exanthema	-	-	-	-	<1	-	-
Flushing	<1	-	-	-	<1	-	-
Lyell's syndrome	-	-	-	-	<1	-	-
Pruritus	<1	-	3 to 4	<1	<1	-	-
Rash	1	<1	3	<1	2	<1	✔
Stevens-Johnson syndrome	-	<1	-	<1	<1	<1	✔
Toxic epidermal necrolysis	-	-	-	<1	<1	<1	✔
Urticaria	-	<1	<2	-	<1	<1	✔
Gastrointestinal							
Abdominal pain	2	1	<2	-	<1	<1	✔
Appetite decrease	<1	-	-	-	-	-	-
Clostridium difficile-associated diarrhea	-	-	<2	-	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Colitis	-	-	-	-	<1	<1	-
Constipation	-	-	2	-	-	-	-
Diarrhea	7 to 15	3	5	1	3	4 to 11	✔
Dysgeusia	-	-	-	-	<1	-	-
Dyspepsia	-	-	-	-	<1	-	✔
Flatulence	<1	-	-	-	<1	-	-
Gastritis	-	-	-	-	-	-	✔
Gastrointestinal bleed	-	-	-	-	-	<1	-
Glossitis	-	-	-	-	<1	-	-
Nausea	4	4	4	<1	<1	3 to 7	✔
Pseudomonas colitis	<1	<1	-	<1	<1	<1	✔
Salivation decreased	<1	-	-	-	-	-	-
Stomatitis	-	-	-	-	<1	-	-
Taste alteration	<1	-	-	-	-	-	-
Tongue swelling	-	-	-	-	-	<1	-
Vomiting	1 to 2	1	2	<1	<1	3 to 7	✔
Genitourinary							
Genital moniliasis	-	-	-	-	-	-	✔
Genital pruritus	-	2	-	-	-	-	✔
Glycosuria	-	-	-	-	<1	-	-
Hematuria	-	-	-	-	<1	-	-
Interstitial nephritis	-	-	-	-	-	<1	✔
Nephrolithiasis	-	-	-	-	<1	-	-
Oliguria	-	-	-	-	<1	-	-
Purpuric nephritis	<1	-	-	-	-	-	-
Renal dysfunction	-	-	-	-	-	<1	-
Renal failure	-	-	<2	-	-	-	-
Renal precipitations	-	-	-	-	<1	-	-
Urinary casts	-	-	-	-	<1	-	-
Vaginal candidiasis	<1	-	-	-	-	-	-
Vaginal discharge	-	-	-	-	-	-	✔
Vaginal infection	3	-	-	-	-	-	-
Vaginitis	-	1 to 10	-	<1	<1	≤5	✔
Hematologic							
Agranulocytosis	-	-	-	-	<1	-	-
Anemia	-	-	<2	-	<1	-	-
Basophilia	-	-	-	-	<1	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Eosinophilia	-	<1	<2	<1	6	7	✔
Hematocrit decreased	-	-	-	-	-	10	-
Hemoglobin decreased	-	-	-	-	-	10	-
Hemolytic anemia	-	-	-	<1	<1	<1	✔
Leukocytosis	-	-	-	-	<1	-	-
Leukopenia	-	<1	-	<1	2	<1	-
Lymphocytosis	-	-	-	-	<1	-	-
Lymphopenia	-	-	-	-	<1	-	-
Monocytosis	-	-	-	-	<1	-	-
Neutropenia	-	-	<2	-	<1	<1	✔
Pancytopenia	-	-	-	-	-	<1	-
Prothrombin time decreased	-	-	-	-	<1	-	-
Prothrombin time prolonged	-	-	-	-	<1	<1	-
Thrombocytopenia	-	<1	<2	-	<1	<1	✔
Thrombocytosis	-	-	-	<1	5	-	-
Hepatic							
Cholestasis	-	-	-	-	-	<1	-
Hepatitis	-	-	<2	-	-	<1	✔
Jaundice	-	<1	-	<1	<1	<1	✔
Laboratory Test Abnormalities							
Alkaline phosphatase increased	-	-	-	-	<1	2	-
Blood urea nitrogen increased	-	<1	-	<1	1	<1	-
Hyperbilirubinemia	-	-	-	<1	<1	<1	-
Hyperglycemia	-	-	<2	-	-	-	-
Hyperkalemia	-	-	<2	-	-	-	-
Hypokalemia	-	-	2	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	1	-
Positive Coombs' test	-	-	11	-	-	<1	-
Serum creatinine increased	-	<1	-	<1	<1	<1	-
Transaminases increased	-	2	2	<1	3	2 to 4	✔
Musculoskeletal							
Arthralgia	-	<1	-	-	-	-	✔
Arthritis	-	-	-	-	-	-	✔
Asterixis	-	-	-	<1	-	-	-
Joint disorder	-	-	-	-	-	-	✔
Malaise	<1	-	-	-	-	-	-
Myoclonus	-	-	-	<1	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftriaxone	Cefuroxime	Cephalexin
Neuromuscular excitability	-	-	-	<1	-	-	-
Weakness	<1	-	-	-	-	-	-
Respiratory							
Allergic pneumonitis	-	-	-	-	<1	-	-
Bronchospasm	-	-	-	-	<1	-	-
Cough	<1	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	<1	-
Pulmonary precipitations	-	-	-	-	<1	-	-
Other							
Allergic reactions	-	-	-	-	-	-	✔
Anaphylaxis	<1	<1	<2	<1	<1	<1	✔
Biliary lithiasis	-	-	-	-	<1	-	-
Candidiasis	-	-	-	<1	-	-	-
Chills	-	-	-	-	<1	-	-
Diaphoresis	-	-	-	-	<1	-	-
Epistaxis	<1	-	-	-	<1	-	-
Eye itching	<1	-	-	-	-	-	-
Fungal infection	<1	-	-	-	-	-	-
Gallbladder sludge	-	-	-	-	<1	-	-
Gallstones	-	-	-	-	<1	-	-
Hypersensitivity reactions	-	-	<2	2	-	<1	-
Moniliasis	-	-	-	-	<1	-	-
Pain at injection site	-	-	-	1	1	<1	-
Pancreatitis	-	-	-	-	<1	-	-
Phlebitis	-	-	2	<1	<1	-	-
Serum sickness-like reaction	-	<1	-	-	<1	-	-
Superinfection	-	1 to 10	-	-	-	-	-
Thrombophlebitis	-	-	-	-	-	2	-
Tinnitus	<1	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 12. Adverse Drug Events (%) Reported with the Combination Product Cephalosporins (cont.)[1-8]

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Cardiovascular		
Atrial fibrillation	-	0.2 to 1.2
Hypotension	-	0.4 to 1.7

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Central Nervous System		
Anxiety	✔	0.2 to 1.9
Dizziness	✔	0.8 to 1.1
Headache	✔	2.5 to 5.8
Insomnia	-	1.3 to 3.5
Dermatological		
Angioedema	✔	-
Erythema multiforme	✔	-
Pruritus	2	-
Rash	✔	0.9 to 1.7
Stevens-Johnson syndrome	✔	-
Toxic epidermal necrolysis	✔	-
Urticaria	✔	-
Gastrointestinal		
Abdominal pain	-	0.8 to 1.2
Constipation	2 to 10	1.9 to 3.9
Diarrhea	3 to 8	1.9 to 6.2
Nausea	3 to 7	2.8 to 7.9
Upper abdominal pain	1 to 7	-
Vomiting	≥5	1.1 to 3.3
Genitourinary		
Acute renal failure	✔	-
Nephritis	✔	-
Renal impairment	✔	-
Hematologic		
Agranulocytosis	✔	-
Anemia	-	0.4 to 1.5
Eosinophilia	✔	-
Hemolytic anemia	✔	-
Leukopenia	✔	-
Lymphocytosis	✔	-
Neutropenia	✔	-
Thrombocytopenia	✔	-
Thrombocytosis	✔	0.4 to 1.9
Hepatic		
Jaundice	✔	-
Laboratory Test Abnormalities		

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Hypokalemia	✔	0.8 to 3.3
Lactate dehydrogenase increased	✔	-
Positive Coombs' test	3 to 21	-
Serum creatinine increased	-	-
Transaminases increased	✔	1 to 1.7
Other		
Candidiasis	✔	-
Phlebitis	✔	-
Pyrexia	-	1.7 to 5.6
Taste alterations	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the cephalosporins are listed in Table 13.

Table 13. Usual Dosing Regimens for the Cephalosporins[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Cefaclor	Acute bronchitis: Extended release tablet: 500 mg every 12 hours for seven days Acute exacerbations of chronic bronchitis: Extended release tablet: 500 mg every 12 hours for seven days Otitis media: Capsule, suspension: 250 mg every eight hours Pharyngitis and/or tonsillitis: Capsule, suspension: 250 mg every eight hours Suspension, extended release tablet: 375 mg every 12 hours for 10 days Respiratory tract infections (lower): Capsule, suspension: 250 mg every eight hours Skin and skin-structure infections: Capsule: 250 mg every eight hours Extended release tablet: 375 mg every 12 hours for seven to ten days Urinary tract infections: Capsule, suspension: 250 mg every eight hours	Otitis media: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Pharyngitis and/or tonsillitis: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Respiratory tract infections (lower): Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Skin and skin-structure infections: Capsule: 20 mg/kg/day in divided doses every eight hours Urinary tract infections: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours	Capsule: 250 mg 500 mg Extended release tablet: 500 mg Suspension: 125 mg/5 mL 250 mg/5 mL 375 mg/5 mL
Cefadroxil	Pharyngitis and/or tonsillitis: Capsule, suspension, tablet: 1 g per day in single (once daily) or divided doses (twice daily) for 10 days Skin and skin-structure infections (uncomplicated): Capsule, suspension, tablet: 1 g per day in single (once daily) or divided doses (twice daily)	Pharyngitis and/or tonsillitis: Capsule, suspension, tablet: 30 mg/kg/day in a single dose or in equally divided doses every 12 hours for 10 days Skin and skin-structure infections (uncomplicated): Capsule, suspension, tablet: 30 mg/kg/day in equally divided doses every 12 hours	Capsule: 500 mg Suspension: 250 mg/5 mL 500 mg/5 mL Tablet: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Urinary tract infections (complicated): Capsule, suspension, tablet: complicated: 2 g per day in divided doses (twice daily) Urinary tract infections (uncomplicated): 1 or 2 g per day in single (once daily) or divided doses (twice daily)	Urinary tract infections: Capsule, suspension, tablet: 30 mg/kg/day in divided doses every 12 hours	
Cefazolin	Life-threatening infections: Injection: 1 to 1.5 g every six hours Mild infections: Injection: 250 to 500 mg every eight hours Moderate to severe infections: Injection: 500 mg to 1 g every six to eight hours Perioperative prophylaxis (preoperative): Injection: 1 g IV/IM administered 30 minutes to one hour prior to the start of surgery Perioperative prophylaxis (intraoperative): Injection: 500 mg to 1 g IV/IM during surgery Perioperative prophylaxis (postoperative): Injection: 500 mg to 1 g IV/IM every six to eight hours for 24 hours Pneumonia: Injection: 500 mg every 12 hours Urinary tract infections (uncomplicated): Injection: 1 g every 12 hours	Mild to moderately severe infections in patients >1 month of age: Injection: 25 to 50 mg/kg divided into three or four equal doses Severe infections >1 month of age: Injection: 25 to 100 mg/kg divided into three or four equal doses	Injection: 500 mg 1 g 2 g 10 g
Cefdinir	Acute exacerbations of chronic bronchitis: Capsule: 300 mg every 12 hours for five to 10 days or 600 mg every 24 hours for 10 days Pharyngitis and/or tonsillitis: Capsule: 300 mg every 12 hours for five to 10 days or 600 mg every 24 hours for 10 days	Otitis media in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours for five to 10 days or 14 mg/kg every 24 hours for 10 days Pharyngitis and/or tonsillitis in patients six months to 12 years of age: Suspension: 7 mg/kg every 12	Capsule: 300 mg Suspension: 125 mg/5 mL 250 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pneumonia (community-acquired): Capsule: 300 mg every 12 hours for 10 days Sinusitis: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days Skin and skin-structure infections: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days	hours for five to ten days or 14 mg/kg every 24 hours for 10 days Sinusitis in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours or 14 mg/kg every 24 hours for 10 days Skin and skin-structure infections (uncomplicated) in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours for 10 days	
Cefepime	Empiric therapy for febrile neutropenic patients: Injection: 2 g IV every eight hours for seven days or until resolution of neutropenia Intra-abdominal infections (complicated, used in combination with metronidazole): Injection: 2 g IV every 12 hours for seven to 10 days Pneumonia (moderate to severe): Injection: 1 to 2 g IV every 12 hours for 10 days Skin and skin-structure infections (moderate to severe): Injection: 2 g IV every 12 hours for 10 days Urinary tract infections (mild to moderate): Injection: 0.5 to 1 g IM/IV every 12 hours for seven to 10 days Urinary tract infections (severe): Injection: 2 g IV every 12 hours for 10 days	Empiric therapy for febrile neutropenic patients in patients two months to 16 years of age: Injection: 50 mg/kg IV every eight hours for seven days or until resolution of neutropenia Intra-abdominal infections (complicated, used in combination with metronidazole) in patients ≥16 years of age: Injection: 2 g IV every eight to 12 hours for seven to 10 days Pneumonia in patients two months to 16 years of age: Injection: 50 mg/kg IV every 12 hours for 10 days Skin and skin-structure infections (uncomplicated) in patients two months to 16 years of age: Injection: 50 mg/kg IV every 12 hours for 10 days Urinary tract infections (mild to moderate) in patients two months to 16 years of age: Injection: mild to moderate, 50 mg/kg IV every 12 hours for seven to 10 days Urinary tract infections (severe) in patients two months to 16 years of age: Injection: severe, 50 mg/kg IV every 12 hours for 10 days	Injection: 1 g 2 g
Cefiderocol	Complicated urinary tract infections, including pyelonephritis:	Safety and efficacy in pediatric patients have not been established.	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: 2 g every 8 hours IV over 3 hours Pneumonia (hospital-acquired and ventilator-associated): Injection: 2 g every 8 hours IV over 3 hours		
Cefixime	Gonorrhea (Uncomplicated): Capsule, chewable tablet, suspension: 400 mg as a single dose Unspecified Infections: Capsule, chewable tablet, suspension: 400 mg once daily or 200 mg every 12 hours	Unspecified Infections: Six months to 12 years of age: Chewable tablet, suspension: 8 mg/kg once daily or 4 mg/kg every 12 hours	Capsule: 400 mg Chewable tablet: 100 mg 200 mg Suspension: 100 mg/5 mL 200 mg/5 mL 500 mg/5 mL
Cefotaxime	Gonococcal infections (rectal): Injection: 0.5 g IM as a single dose in females and 1 g IM as a single dose in males Gonococcal infections (urethritis/cervicitis): Injection: 0.5 g IM as a single dose Life-threatening infections: Injection: 2 g IV every four hours Moderate to severe infections: Injection: 1 to 2 g IM/IV every eight hours Perioperative prophylaxis: Injection: 1 g IM/IV as a single dose administered 30 to 90 minutes prior to the start of surgery Uncomplicated infections: Injection: 1 g IM/IV every 12 hours	Unspecified infections in patients zero to one week of age: Injection: 50 mg/kg IV per dose every 12 hours Unspecified infections in patients one to four weeks of age: Injection: 50 mg/kg IV per dose every eight hours Unspecified infections in patients one month to 12 years of age: Injection: <50 kg, 50 to 180 mg/kg IM/IV divided into four to six equal doses; ≥50 kg, usual adult dosage	Injection: 1 g 2 g 10 g
Cefpodoxime	Acute exacerbations of chronic bronchitis: Tablet: 200 mg every 12 hours for 10 days Gonococcal infections (rectal): Suspension, tablet: 200 mg as a single dose in females Uncomplicated gonorrhea: Suspension, tablet: 200 mg as a	Acute exacerbations of chronic bronchitis in patients ≥12 years of age: Tablet: 200 mg every 12 hours for 10 days Gonococcal infections (rectal) in patients ≥12 years of age: Suspension, tablet: rectal, 200 mg as a single dose in females	Suspension: 50 mg/5 mL 100 mg/5 mL Tablet: 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	single dose Pharyngitis and/or tonsillitis: Suspension, tablet: 100 mg every 12 hours for five to 10 days Pneumonia (community-acquired): Suspension, tablet: 200 mg every 12 hours for 14 days Sinusitis: Suspension, tablet: 200 mg every 12 hours for 10 days Skin and skin-structure infections: Suspension, tablet: 400 mg every 12 hours for seven to 14 days Urinary tract infections (uncomplicated): Suspension, tablet: 100 mg every 12 hours for seven days	Uncomplicated gonorrhea in patients ≥12 years of age: Suspension, tablet: 200 mg as a single dose Otitis media in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for five days Pharyngitis and/or tonsillitis in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for five to 10 days Pharyngitis and/or tonsillitis in patients ≥12 years of age: Suspension, tablet: 100 mg every 12 hours for five to 10 days Pneumonia (community-acquired in patients ≥12 years of age: Suspension, tablet: 200 mg every 12 hours for 14 days Sinusitis in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for 10 days Sinusitis in patients ≥12 years of age: Suspension, tablet: 200 mg every 12 hours for 10 days Skin and skin-structure infections in patients ≥12 years of age: Suspension, tablet: 400 mg every 12 hours for seven to 14 days Urinary tract infections (uncomplicated) in patients ≥12 years of age: Suspension, tablet: 100 mg every 12 hours for seven days	
Cefprozil	Acute bronchitis: Suspension, tablet: 500 mg every 12 hours for 10 days Acute exacerbations of chronic bronchitis: Suspension, tablet: 500 mg every 12 hours for 10 days Pharyngitis and/or tonsillitis:	Acute bronchitis in patients ≥13 years of age: Suspension, tablet: 500 mg every 12 hours for 10 days Acute exacerbations of chronic bronchitis in patients ≥13 years of age: Suspension, tablet: 500 mg every 12 hours for 10 days	Suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension, tablet: 500 mg every 24 hours for 10 days Sinusitis: Suspension, tablet: 250 to 500 mg every 12 hours for 10 days Skin and skin-structure infections: Suspension, tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	Otitis media in patients six months to 12 years of age: Suspension, tablet: 15 mg/kg every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients two to 12 years of age: Suspension, tablet: 7.5 mg/kg every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients ≥13 years of age: Suspension, tablet: 500 mg every 24 hours for 10 days Sinusitis in patients six months to 12 years of age: Suspension, tablet: 7.5 mg/kg to 15 mg/kg every 12 hours for 10 days Sinusitis in patients ≥13 years of age: Suspension, tablet: 250 to 500 mg every 12 hours for 10 days Skin and skin-structure infections in patients two to 12 years of age: Suspension, tablet: 20 mg/kg every 24 hours for 10 days Skin and skin-structure infections in patients ≥13 years of age: Suspension, tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	
Ceftaroline	Pneumonia (community-acquired): Injection: 600 mg every 12 hours for five to seven days Skin and skin-structure infections: Injection: 600 mg every 12 hours for five to 14 days	Pneumonia (community-acquired): Injection: two to 18 years of age and >33 kg, 400 mg IV every eight hours or 600 mg IV every 12 hours; two to 18 years of age and ≤ 33 kg, 12 mg/kg/dose IV every eight hours; two months to <2 years of age, 8 mg/kg/dose IV every eight hours; all for five to 14 days Skin and skin-structure infections: Injection: two to 18 years of age and >33 kg, 400 mg IV every eight hours or 600 mg IV every 12 hours; two to 18 years of age and ≤ 33 kg, 12 mg/kg/dose IV	Injection: 400 mg 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		every eight hours; two months to <2 years of age, 8 mg/kg/dose IV every eight hours; all for five to 14 days	
Ceftazidime	Bone and joint infections: Injection: 2 g IV every 12 hours Gynecologic infections (serious): Injection: 2 g IV every eight hours Intra-abdominal infections (serious): Injection: 2 g IV every eight hours Life-threatening infections (very severe): Injection: 2 g IV every eight hours Lung infections (cystic fibrosis patients): Injection: 30 to 50 mg/kg IV every eight hours Meningitis: Injection: 2 g IV every eight hours Pneumonia (uncomplicated): Injection: 500 mg to 1 g IM/IV every eight hours Skin and skin-structure infections (mild): Injection: 500 mg to 1 g IM/IV every eight hours Urinary tract infections (uncomplicated): Injection: 250 mg IM/IV every 12 hours Urinary tract infections (complicated): Injection: 500 mg IM/IV every eight to 12 hours	Unspecified infections in patients zero to four weeks of age: Injection: 30 mg/kg IV every 12 hours Unspecified infections in patients one month to 12 years of age: Injection: 30 to 50 mg/kg IV every eight hours	Injection: 500 mg 1 g 2 g 6 g
Ceftriaxone	Gonococcal infections (uncomplicated): Injection: 250 mg IM as a single dose (in combination with oral azithromycin) Meningitis: Injection: 2 g IV every 12 hours;	Meningitis: Injection: 100 mg/kg once daily or divided every 12 hours Otitis media: Injection: 50 mg/kg IM as a single dose	Injection: 250 mg 500 mg 1 g 2 g 10 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for empiric therapy, use in combination with other appropriate agents Preoperative prophylaxis: Injection: 1 g IV as a single dose administered 30 minutes to two hours prior to surgery Unspecified infections: Injection: 1 to 2 g IM/IV once daily or in divided doses twice daily	Skin and skin-structure infections: Injection: 50 to 75 mg/kg once daily or in equally divided doses twice daily Unspecified infections: Injection: 50 to 75 mg/kg/day given in divided doses every 12 hours	
Cefuroxime	Acute bronchitis: Tablet: 250 to 500 mg twice daily for five to 10 days Acute exacerbations of chronic bronchitis: Tablet: 250 to 500 mg twice daily for 10 days Bone and joint infections: Injection: 1.5 g IM/IV every eight hours Gonococcal infections (disseminated): Injection: 750 mg IM/IV every eight hours Gonococcal infections (uncomplicated): Injection: 1.5 g IM as a single dose Tablet: 1,000 mg as a single dose Life-threatening infections: Injection: 1.5 g IM/IV every six hours Lyme disease (early): Tablet: 500 mg twice daily for 20 days Meningitis: Injection: 3 g IM/IV every eight hours Perioperative prophylaxis (clean-contaminated procedures: Injection: 1.5 g IV one hour prior to surgery, then 750 mg IM/IV every eight hours when the surgery is prolonged	Acute bronchitis in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for five to 10 days Acute exacerbations of chronic bronchitis in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Bone and joint infections in patients >3 months of age: Injection: 150 mg/kg/day IM/IV divided every eight hours Gonorrhea (uncomplicated) in patients ≥13 years of age: Tablet: 1,000 mg as a single dose Lyme disease (early) in patients ≥13 years of age: Tablet: 500 mg twice daily for 20 days Meningitis in patients >3 months of age: Injection: 200 to 240 mg/kg/day IV divided every six to eight hours Otitis media in patients three months to 12 years of age: Tablet: 250 mg twice daily for 10 days Pharyngitis and/or tonsillitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Sinusitis in patients three months to 12 years of age:	Injection: 750 mg 1.5 g 7.5 g Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Perioperative prophylaxis (open heart surgery): Injection: 1.5 g IV every 12 hours for a total of 6 g Pharyngitis and/or tonsillitis: Tablet: 250 mg twice daily for 10 days Pneumonia (uncomplicated): Injection: 750 mg IM/IV every eight hours Severe or complicated infections (unspecified): Injection: 1.5 g IM/IV every eight hours Sinusitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Skin and skin-structure infections (uncomplicated): Injection: 750 mg IM/IV every eight hours Tablet: 250 to 500 mg twice daily for 10 days Unspecified infections: Injection: 750 mg to 1.5 g IM/IV every eight hours for five to 10 days Urinary tract infections (uncomplicated): Injection: 750 mg IM/IV every eight hours Tablet: 250 mg twice daily for seven to 10 days	Tablet: 250 mg twice daily for 10 days Sinusitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Skin and skin-structure infections (uncomplicated) in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Unspecified infections in patients >3 months of age: Injection: 50 to 100 mg/kg/day IM/IV divided every six to eight hours Urinary tract infections (uncomplicated) in patients ≥13 years of age: Tablet: 250 mg twice daily for seven to 10 days	
Cephalexin	Cystitis (uncomplicated): Capsule, suspension, tablet: 500 mg every 12 hours for seven to 14 days Skin and skin-structure infections: Capsule, suspension, tablet: 500 mg every 12 hours Streptococcal pharyngitis: Capsule, suspension, tablet:	Otitis media: Capsule, suspension, tablet: 75 to 100 mg/kg/day in four divided doses Streptococcal pharyngitis in patients >1 year of age: Capsule, suspension, tablet: 25 to 50 mg/kg/day every 12 hours for at least 10 days Unspecified infections:	Capsule: 250 mg 500 mg 750 mg Suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	500 mg every 12 hours Unspecified infections: Capsule, suspension, tablet: 250 mg every six hours	Capsule, suspension, tablet: 25 to 50 mg/kg/day in divided doses	
Combination Products			
Ceftazidime and Avibactam	Complicated intra-abdominal infections: Injection: 2.5 grams every eight hours for five to 14 days in conjunction with metronidazole Complicated urinary tract infections: Injection: 2.5 grams every eight hours for seven to 14 days Pneumonia: Injection: 2.5 grams every eight hours for seven to 14 days	Complicated intra-abdominal infections: Injection: 2 years to <18 years, 62.5 mg/kg to a maximum of 2.5 grams; 6 months to <2 years, 62.5 mg/kg; 3 months to <6 months, 50 mg/kg; all every 8 hours for five to 14 days in conjunction with metronidazole Complicated urinary tract infections: Injection: 2 years to <18 years, 62.5 mg/kg to a maximum of 2.5 grams; 6 months to <2 years, 62.5 mg/kg; 3 months to <6 months, 50 mg/kg; all every 8 hours for seven to 14 days Pneumonia: Injection: 2 years to <18 years, 62.5 mg/kg to a maximum of 2.5 grams; 6 months to <2 years, 62.5 mg/kg; 3 months to <6 months, 50 mg/kg; all every 8 hours for seven to 14 days	Injection: 2.5 g
Ceftolozane and Tazobactam	Complicated intra-abdominal infections: Injection: 1.5 grams every eight hours for four to 14 days in conjunction with metronidazole Complicated urinary tract infections: Injection: 1.5 grams every eight hours for seven days Pneumonia: Injection: 3 g every eight hours for eight to 14 days	Complicated intra-abdominal infections (birth to <18 years of age): Injection: 30 mg/kg up to a maximum dose of 1.5 grams every eight hours for five to 14 days in conjunction with metronidazole Complicated urinary tract infections (birth to <18 years of age): Injection: 30 mg/kg up to a maximum dose of 1.5 grams every eight hours for seven to 14 days	Injection: 1.5 g

IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cephalosporins are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Cephalosporins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Ballantyne[41] (1985) Cefaclor 250 mg PO TID vs cefadroxil 1,000 mg PO QD	OL, RCT Patients six to 80 years of age with skin and soft-tissue infections	N=200 10 days	Primary: Clinical and bacteriological efficacy, medication adherence Secondary: Not reported	Primary: There was no statistically significant difference in terms of clinical efficacy for patients treated with cefadroxil and cefaclor (91 vs 95%, respectively; P=0.41). Medication adherence was greater in patients treated with cefadroxil compared to patients treated with cefaclor based on the percentage of patients returning unused capsules (2 vs 77%, respectively). Secondary: Not reported
Ballantyne[42] (1980) Cefadroxil 500 mg PO BID vs cefadroxil 1,000 mg PO QD vs cefadroxil 1,000 mg PO BID vs cephalexin 500 mg PO QID	DB, MC (2 trials) Patients with skin and soft-tissue infections	N=224 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: In study A, improvement in clinical and bacteriologic evaluations were reported in patients treated with cefadroxil and cephalexin (100 vs 91%, respectively). In study B, improvement in clinical and bacteriologic evaluations was reported in patients treated with both cefadroxil doses and cephalexin (98 vs 97 vs 98%, respectively). Based on the studies in this MA, overall clinical and bacteriologic response to cefadroxil and cephalexin were both reported as 96%. Secondary: No significant drug-related adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In study A, participants received either cefadroxil 1,000 mg BID or cephalexin; in study B, participants received either cefadroxil 500 mg BID or 1,000 mg QD or cephalexin.				
Bucko et al.[43] (2002) Cefadroxil 500 mg PO BID vs cefditoren 200 mg PO BID vs cefditoren 400 mg PO BID vs cefuroxime 250 mg PO BID In study A, participants received cefditoren	DB, MC, PG (2 trials) Patients with uncomplicated skin and skin structure infections	N=1,685 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: Clinical cure rates were reported as 85, 83, 88, and 85% for patients treated with cefditoren 200 mg, cefditoren 400 mg, cefuroxime, and cefadroxil, respectively. At seven to 14 days after treatment completion, eradication rates were higher in patients treated with cefuroxime compared to patients treated with cefditoren 200 mg in study 1 (P=0.043). At seven to 14 days after treatment completion, eradication rates were higher for cefditoren 400 mg compared to patients treated with cefadroxil in study 2 (P=0.018). Secondary: A higher rate of drug-related adverse events was reported for patients treated with cefditoren 400 mg compared to all other treatment groups (P<0.05 for each comparison). The most common adverse events were mild cases of diarrhea, nausea, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg or cefuroxime; in study B, participants received cefditoren 400 mg or cefadroxil.				
Gooch et al.[44] (1991) Cefadroxil 500 mg PO BID vs cefuroxime 250 mg PO BID vs cephalexin 500 mg PO BID	DB, MC, PG, RCT Patients with mild to moderate infections of the skin or skin structures	N=330 10 days	Primary: Clinical and bacteriological response Secondary: Adverse events	Primary: A positive clinical outcome was achieved in 97, 89, and 94% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.047, cefuroxime vs cephalexin). A positive bacteriological outcome was achieved in 96, 85, and 93% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.026, cefuroxime vs cephalexin). Secondary: There was no significant difference in reported drug-related gastrointestinal adverse events by patients treated with cefuroxime, cephalexin, or cefadroxil (9.3 vs 7.2 vs 9.8%, respectively).
Leder et al.[45] (1998) Cefazolin 2 g IV BID	OS, PRO Patients 18 to 90 years of age with moderate to severe cellulitis using home-based therapy	N=57 3 to 13 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical cure was reported in 93% of patients treated with cefazolin; failure occurred in three patients. Secondary: Cefazolin was well tolerated.
Tack et al.[46] (1997) Cefdinir 7 mg/kg PO BID vs	DB, MC, RCT Patients aged six months to 12 years diagnosed with uncomplicated mild to moderate skin or skin-structure infec-	N=231 10 days	Primary: Clinical cure rate, microbiologic eradication rate Secondary: Adverse events	Primary: Clinical cure rates were reported as 98.3 and 93.8% in patients treated with cefdinir and cephalexin, respectively (P=0.056). Microbiologic eradication rates were reported as 99.4 and 97.4% in patients treated with cefdinir and cephalexin, respectively (P=0.14). Secondary: Drug-related adverse events were reported in 16 and 11% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cephalexin 10 mg/kg PO QID	tion warranting systemic anti-microbial therapy and/or drainage			treated with cefdinir and cephalexin, respectively (P=0.11). The most common side effect was diarrhea.
Giordano et al.[47] (2006) Cefdinir 300 mg BID vs cephalexin 250 mg QID	MC, RCT, SB Patients ≥13 years of age with mild to moderate uncomplicated skin and skin structure infections	N=391 24 days	Primary: Clinical cure rates in clinically evaluable patients at the test-of-cure visit Secondary: Bacteriological cure, pathogen eradication rates, adverse events	Primary: There were no statistically significant differences between the treatment groups in clinical response. At the test-of-cure visit, the clinical cure rate was 89% for cefdinir and 89% for cephalexin in clinically evaluable patients (95% CI, -6.7 to 7.3) and 88% among clinically and bacteriologically evaluable patients (95% CI, –7.7 to 7.5). In the intent-to-treat analysis, cure rates were 83% for cefdinir and 82% for cephalexin. Clinical cure rates for infections caused by methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* were 93 and 92%, respectively for cefdinir compared to 91 and 90%, respectively for cephalexin (P>0.999 comparing treatment groups for methicillin-susceptible *Staphylococcus aureus*; P>0.999 comparing treatments for methicillin-resistant *Staphylococcus aureus*). Secondary: The treatment groups were similar based on patient bacteriological cure rates in the clinically and bacteriologically evaluable patients: 87% for cefdinir and 86% for cephalexin in patients with any isolate at baseline. The usefulness questionnaire demonstrated that cefdinir was more highly rated in the mean composite score (87.4 vs 83.6; P=0.04), with the difference primarily due to the respondents' preference for the convenience of taking the study medication (mean score 93.5 vs 74.1 for cephalexin, P<0.001). There were no statistically significant differences between treatment groups in the patient self-assessment questionnaire, the healthcare resource utilization questionnaire, and patient diary data. Both study drugs were well tolerated. The most common treatment-related adverse events were diarrhea, (10% cefdinir, 4% cephalexin; P=0.017), nausea (3 and 6%, respectively; P=0.203), and vaginal mycosis (3% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				6% of females, respectively; P=0.500).
Gentry et al.[48] (1989) Cefotaxime 2 g IV TID and one placebo tablet PO BID vs ciprofloxacin 750 mg PO BID and placebo IV over 30 minutes TID	DB, MC, PRO, RCT Patients with culture-confirmed skin or skin structure infections requiring hospitalization	N=461 4 to 34 days	Primary: Clinical response, bacteriologic response, overall response rate Secondary: Adverse events	Primary: For patients treated with cefotaxime, clinical response was reported as 74, 20, and 6% characterized as resolution, improvement, and failure, respectively. For patients treated with ciprofloxacin, clinical response was reported as 81, 16, and 3% characterized as resolution, improvement, and failure, respectively. For all comparisons; P=NS. Bacteriologic eradication was reported as 87 and 84% for patients treated with ciprofloxacin and cefotaxime, respectively (P=0.0123). Overall efficacy rate was reported as 76 and 75% for patients treated with ciprofloxacin and cefotaxime, respectively. Overall failure rate was higher in patients treated with cefotaxime compared to ciprofloxacin (8 vs 2%, respectively; P=0.0081). Secondary: There was no statistically significant difference in adverse events for treatment groups. However, there was a higher incidence of metabolic and nutritional systems-related events in patients treated with ciprofloxacin (0.01<P<0.05).
Stevens et al.[49] (1993) Cefpodoxime 400 mg PO BID vs cefaclor 500 mg PO TID	DB, MC, PC, RCT Patients ≥12 years of age with acute single-site skin or skin-structure infections	N=371 7 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Not reported	Primary: Both cefpodoxime and cefaclor were highly effective for the treatment of single-site skin or skin-structure infections (99% pathogen eradication and 86% cure rate). There were no significant differences in the failure rate with cefpodoxime and cefaclor. Both active drug regimens were well tolerated. Secondary: Not reported
Corey et al.[50] (2010) Aztreonam 1 g	AC, DB, MC, RCT Patients ≥18 years of age with	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy		days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	populations, respectively. Secondary: The clinical cure rate for methicillin-resistant *Staphylococcus aureus* complicated skin or skin structure infections were 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with methicillin-susceptible *Staphylococcus aureus* (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for methicillin-resistant *Staphylococcus aureus*. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[51] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary:	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary: In patients with methicillin-resistant *Staphylococcus aureus* isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with methicillin-susceptible *Staphylococcus aureus* (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Microbiological success rate, safety	was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[52] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with methicillin-resistant *Staphylococcus aureus* (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable). Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Dryden et al.[53] COVERS (2016) Ceftaroline 600 mg every eight hours vs aztreonam 1 g every eight hours plus vancomycin 15 mg/kg every 12 hours	DB, MC, NI, RCT Patients ≥ 18 years of age with complicated skin and soft-tissue infections and signs of systemic inflammatory response and/or underlying comorbidities associated with impair immune response	N=772 35 days after last dose of antibiotic therapy	Primary: Proportion of patients clinically cured at the test-of-cure visit (eight to 15 days after the last dose) in the co-primary clinically evaluable and modified intent-to-treat populations Secondary: Clinical response at test-of-cure in the microbiological modified intent-to-treat and microbiologically evaluable populations, clinical and per-pathogen microbiological response at test-of-cure in the microbiologically	Primary: The proportion of patient clinically cured at the test-of-cure visit for the modified intent-to-treat population was 78.3% in the ceftaroline group compared with 79.2% in the vancomycin plus aztreonam group. In the clinically evaluable group, the proportion of patients clinically cured was 86.6 and 85.3%. Non-inferiority was demonstrated for the modified intent-to-treat (difference, -0.95%; 95% CI, -6.90 to 5.41) and clinically evaluable (difference, 1.27%; 95% CI, -4.32 to 7.48) populations. Secondary: Clinical response at the test-of-cure visit in the microbiological modified intent-to-treat population was 80.2 and 79.4% for the ceftaroline and vancomycin plus aztreonam groups, respectively and 90.1 and 86.6% in the microbiologically evaluable population. Microbiological responses were predominately derived from clinical responses; therefore, clinical and microbiological response rates were similar at test-of-cure by baseline pathogen and for patients with monomicrobial and polymicrobial infections. Among patients who were clinically cured at the test-of-cure visits, relapse at the late follow-up visits occurred in 0.9% of patients in the ceftaroline group and 1.7% of patients in the vancomycin plus aztreonam group. There were no new infections, reinfections or recurrences reported. The study treatments were generally well tolerated and the incidence of adverse events was similar for the ceftaroline and vancomycin plus aztreonam groups (45.8 vs 45.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			evaluable population, clinical relapse and reinfection or recurrence at the late follow-up visit, safety	
Korczowski et al.[54] (2016) Ceftaroline fosamil IV vs IV comparator (vancomycin or cefazolin, plus optional aztreonam) optional switch to oral antibacterials from day four	MC, RCT, SB Hospitalized pediatric patients aged between two months and 17 years with acute bacterial skin and skin structure infections	N=159 21 to 35 days	Primary: Safety Secondary: Clinical efficacy (at study day three [early clinical response], end of IV treatment, end of therapy, and test-of-cure [8 to 15 days after last dose])	Primary: A similar proportion of patients in each study group experienced at least one treatment-emergent adverse event (48% of patients in the ceftaroline fosamil group and 43% of patients in the comparator group). Rates of study drug-related treatment-emergent adverse events were similar for ceftaroline fosamil (22%) and comparator (23%). One serious adverse event, considered to be related to IV study drug, occurred in the ceftaroline fosamil group (hypersensitivity). A total of six patients discontinued study drug (IV or oral) because of an adverse event. There were four patients (4%) who discontinued ceftaroline fosamil because of adverse events: hypersensitivity, osteomyelitis, a gastrointestinal viral infection, and a rash. In the comparator group, two patients (4%) discontinued treatment because of adverse events of vomiting and drug hypersensitivity. Secondary: At Study Day three, the clinical response of a ≥20% reduction in infection area from baseline was seen in 85% of patients in both the ceftaroline fosamil and the comparator group. Clinical cure rates were numerically higher in the ceftaroline fosamil group compared with the comparator group at both the end of treatment (96 and 88%, respectively) and the test-of-cure visits (94 and 87%, respectively). Clinical cure rates were numerically higher in the ceftaroline fosamil group in all age groups. Of the patients clinically cured at test-of-cure, 98% reached sustained cure in the ceftaroline fosamil group, compared with 100% in the comparator group.
Gentry et al.[55] (1989) Ceftazidime 2 g IV	PRO, RCT Patients with serious infections of	N=51 19 to 25 days	Primary: Cure rate Secondary:	Primary: Cure rate was reported as 75 and 58% in patients treated with ciprofloxacin and ceftazidime, respectively (P<0.05). Bacteriologic cure was reported as 78 and 72% in patients treated with ciprofloxacin and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every eight hours vs ciprofloxacin 200 mg IV every 12 hours, then ciprofloxacin 750 mg PO every 12 hours	the skin and skin structures caused by gram-negative organisms		Adverse events	ceftazidime, respectively. Superinfection was reported as 28 and 11% in patients treated with ciprofloxacin and ceftazidime, respectively ($0.01<P<0.05$). Secondary: Adverse events were reported in 6 and 5% of patients treated with ciprofloxacin and ceftazidime, respectively.
Eron et al.[56] (1983) Ceftriaxone 1 g IV BID vs ceftriaxone 2 g IV QD (children ≤15 years old: 50 mg/kg/day in divided doses)	PRO, XO Patients two to 86 years of age with bone or soft tissue infection	N=100 3 to 56 days	Primary: Clinical response Secondary: Adverse events	Primary: Positive clinical response was reported as 91% of patients for both the twice-daily and once-daily treatment groups; 89 vs 94%, respectively. Failed therapy was reported in nine patients caused by resistance, superinfection, or an underlying disease. IV therapy was continued in 41 patients in the outpatient setting. Secondary: Ten percent of patients treated with ceftriaxone reported diarrhea; of these, three patients required discontinuation of treatment.
Khawcharoenporn et al.[57] (2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety Secondary: Not reported	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91 vs 74%; $P<0.001$). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; $P=0.22$). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male ($P=0.001$), were Pacific Islanders ($P=0.001$), had diabetes mellitus ($P=0.001$), were obese ($P=0.002$), had positive cultures for methicillin-resistant *Staphylococcus aureus* ($P=0.01$), and were cigarette smokers ($P=0.04$). The treatment success rate with clindamycin was higher than with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clindamycin 300 mg QID				cephalexin in patients who had methicillin-resistant *Staphylococcus aureus* infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated methicillin-resistant *Staphylococcus aureus* (P<0.001) and severity of cellulitis (P<0.001). Secondary: Not reported
Moran et al.[58] (2017) Cephalexin 500 mg four times daily, plus trimethoprim-sulfamethoxazole, 320 mg-1,600 mg twice daily, for seven days vs cephalexin plus placebo for seven days	DB, MC, RCT Outpatients >12 years of age with cellulitis and no wound, purulent drainage, or abscess	N=500 9 weeks	Primary: Clinical cure [absence of these clinical failure criteria at follow-up visits: fever; increase in erythema (>25%), swelling, or tenderness (days 3-4); no decrease in erythema, swelling, or tenderness (days 8-10); and more than minimal erythema, swelling, or tenderness (days 14-21)] of cellulitis at the test-of-clinical-cure visit,	Primary: Among 500 randomized participants, 496 (99%) were included in the modified intention-to-treat analysis and 411 (82.2%) in the per-protocol analysis (median age, 40 years [range, 15 to 78 years]; 58.4% male; 10.9% had diabetes). Clinical cure occurred at 14 to 21 days after enrollment in 83.5% of participants in the cephalexin plus trimethoprim-sulfamethoxazole group and 85.5% of participants in the cephalexin group in the per-protocol population (difference, −2.0%; 95% CI, −9.7 to 5.7%; P=0.50). In the modified intention-to-treat population, clinical cure occurred in 76.2% of participants in the cephalexin plus trimethoprim-sulfamethoxazole group vs 69.0% of in the cephalexin group (difference, 7.3%; 95% CI, -1.0 to 15.5%; P=0.07). Secondary: Secondary outcomes were not significantly different between treatment groups, including drainage procedures, changes in erythema size and swelling/induration and tenderness, invasive infections, new skin infections at same or different site, overnight hospitalizations, similar infections in household contacts, days missed of normal activities and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			14 to 21 days after enrollment Secondary: Surgical drainage procedures, changes in erythema size, presence of swelling/induration and tenderness, invasive infections, skin infections at the same or different site, hospitalizations, similar infections in household contacts, days missed from normal activities and work/school, and days of analgesic use	work/school, and analgesic use.
Genitourinary Infections				
Leigh et al.[59] (2000) Cefaclor 250 PO TID vs cefdinir 100 mg PO BID	DB, MC, PG, RCT Patients ≥13 years of age with uncomplicated urinary tract infections	N=383 5 days	Primary: Clinical and microbiologic efficacy Secondary: Adverse events	Primary: A greater number of pathogens were resistant to treatment with cefaclor compared to cefdinir (6.7 vs 3.7%, respectively; P<0.003). Isolates of *Escherichia coli* were more resistant to treatment with cefaclor compared to cefdinir (5.1 vs 2.0%, respectively; P<0.007). At five to nine days post treatment, patients treated with cefdinir and cefaclor reported statistically equivalent clinical (91.3 vs 93.0%, respectively; P=0.539) and microbiologic (84.7 vs 79.7%, respectively; P=0.184) response rates. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Drug-related side effects were greater in patients treated with cefdinir compared to patients treated with cefaclor (20.2 vs 13.0%, respectively; P=0.025).
Christenson et al.[60] (1991) Cefaclor 250 mg PO TID vs cefprozil 500 mg PO QD	OL, RCT Patients ≥18 years of age with acute, uncomplicated urinary tract infection	N=98 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87 and 78% in patients treated with cefprozil and cefaclor, respectively (P=NS). Bacteriologic eradication was reported as 80 and 82% in patients treated with cefprozil and cefaclor, respectively (P=NS). Secondary: Leukopenia and nausea were more commonly reported by patients treated with cefprozil though the difference is not statistically significant (P=0.08 and P=0.07, respectively).
Bolding et al.[61] (1980) Cefadroxil 1,000 mg PO BID vs cephalexin 500 PO mg QID	DB, RCT Females 18 to 63 years of age with urinary tract infections	N=26 10 to 13 days	Primary: Clinical cure rate Secondary: Adverse event	Primary: Clinical cure rates were achieved in 100 and 92% of patients treated with cephalexin and cefadroxil, respectively, within five to nine days. One patient treated with cefadroxil was not cured due to an *Escherichia coli* urinary tract infection. Secondary: One patient taking cefadroxil reported side effects of nausea and vomiting which may be associated with concurrent therapy with propoxyphene-acetaminophen. Patients treated with cefadroxil reported less vaginal itching or irritation compared to patients treated with cephalexin.
Madsen et al.[62] (1981) Cefazolin 1,000 mg IM every eight hours vs cefotaxime 500 mg IM every eight hours	2 RCT Males aged 83 to 89 years with complicated urinary tract infections	N=91 7 to 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: One week after treatment completion, clinical cure rates were reported as 71 and 60% in patients treated with cefotaxime and cefazolin, respectively. One week after treatment completion, clinical cure rates were reported as 64 and 59% in patients treated with cefotaxime 500 and 1,000 mg, respectively. No significant difference was found between the two groups. Secondary: Both treatments were well-tolerated by study participants.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefotaxime 1,000 mg IM every eight hours In study A, participants received one or two doses of cefotaxime; in study B, participants received cefotaxime 500 mg or cefazolin.				
Sanchez-Ramos et al.[63] (1995) Cefazolin 2 g IV every eight hours vs ceftriaxone 1 g IV QD and normal saline IV every eight hours from the ceftriaxone dose for two doses	DB, MC, RCT Pregnant patients with acute pyelo-nephritis confirmed by chill symptoms, costovertebral angle tenderness, urinalysis showing bacteria and white cells	N=178 48 hours to 10 days	Primary: Febrile morbidity, length of hospital stay, treatment failures Secondary: Not reported	Primary: There was no statistically significant difference between patients treated with ceftriaxone and cefazolin in terms of mean length of hospital stay (3.7 vs 4.0 days, respectively), temperature (101 vs 101.4 degrees F, respectively), length of fever (1.0 vs 1.3 days, respectively), or required IV doses (8.1 vs 8.8. doses, respectively; P=NS). Treatment failures were reported in 5.7 and 3.3% of patients treated with cefazolin and ceftriaxone, respectively (P=0.71). Secondary: Not reported
Iversen et al.[64] (1981) Cefazolin 1 g IM every eight hours	PRO, RCT Males 38 to 91 years of age with urinary tract infections	N=58 5 to 10 days	Primary: Therapeutic efficacy Secondary: Adverse events	Primary: After one day of treatment, 97% of patients reported negative urine cultures for both treatment groups; one week after treatment completion, 62 and 63% of cultures were negative for patients treated with cefuroxime and cefazolin, respectively; P=NS.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefuroxime 0.75 g IM every eight hours	associated with benign hyperplasia of the prostate, carcinoma of the prostate or bladder, or urethral stricture			Secondary: Minor pain at the injection site was the most common adverse event reported. Both treatments were well tolerated.
Newton et al.[65] (1993) Cefepime 2 g IM (or by a 30-minute IV infusion) BID vs cefotaxime 2 g IM (or by a 30-minute IV infusion) TID	MC, OL, RCT Female patients ≥18 years of age with acute obstetric and gynecological infections	N=131 2 to 10 days	Primary: Clinical response, microbiological eradication, overall response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 85 and 83% of patients treated with cefepime and cefotaxime, respectively (P=0.802); microbiological eradication was reported as 81 and 86%, respectively (P=0.379). Overall response of effective, partially effective, and ineffective was reported as 77, 13 and 11%, respectively, in patients treated with cefepime; for patients treated with cefotaxime, percentages of 75, 19, and 6%, respectively, were reported for overall response. Secondary: Drug-related adverse events were reported in 6 and 1% of patients treated with cefepime and cefotaxime, respectively (P=0.342). Drug-related discontinuation of therapy was reported in five and one patient(s) treated with cefepime and cefotaxime, respectively (P=0.476).
Gentry et al.[66] (1991) Cefepime 2 g IV BID vs ceftazidime 2 g IV every eight hours	OL, PRO, RCT Patients with skin or wound infections and complicated nosocomial urinary tract infections	N=112 4 to 28 days	Primary: Clinical efficacy, microbiologic eradication Secondary: Adverse events	Primary: Relative to skin/skin structure and wound infections, clinical efficacy was reported as 90 and 96% of patients treated with cefepime and ceftazidime, respectively (P=0.68); microbiologic eradication rate was reported as 94 and 95%, respectively. Relative to nosocomial urinary tract infections, clinical efficacy was reported as 84 and 88% of patients treated with cefepime and ceftazidime, respectively (P=1.0); microbiologic eradication was reported as 100 and 95%, respectively. Secondary: Both treatments were well tolerated. Increased serum creatinine and diarrhea were the only mild adverse events reported.
Arrieta et al.[67] (2001) Cefepime 50 mg/kg IV every	MA Patients one month to 18 years of age with serious urinary	N=521 (5 trials) 2 to 14 days	Primary: Clinical efficacy, microbiologic efficacy	Primary: In study A, clinical efficacy was reported as 98 and 96% for patients treated with cefepime and ceftazidime, respectively; at treatment completion, bacteriologic eradication was reported as 96 and 94%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eight hours vs cefepime 50 mg/kg IV every 12 hours vs ceftazidime 50 mg/kg IV every eight hours vs cefotaxime 30 mg/kg IV every six hours In studies A and B, participants received either cefepime or ceftazidime every eight hours. In study C, D, and E, participants received either cefepime every eight hours or cefepime every 12 hours or cefotaxime.	tract infections, including pyelonephritis		Secondary: Adverse events	In study B, clinical efficacy was reported as 97 and 100% for patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95 and 92%, respectively. In studies C, D, and E, overall clinical efficacy was reported as 91 and 100% in patients treated with cefepime and cefotaxime, respectively; bacteriologic eradication was reported as 94 and 100%, respectively. Secondary: In study A, there was no statistically significant difference in drug-related adverse events between treatment groups (P=0.40). In studies D and E, both treatment regimens were well tolerated. The most commonly reported adverse events were gastrointestinal in nature.
Seo et al.[68] (2017)	MC, OL, PRO, RCT	N=66 28 to 30 days	Primary: Clinical response at three to five	Primary: After recruitment of six participants to the cefepime treatment group, allocation to this treatment group was stopped due to an unexpectedly high

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ertapenem 1 g every 24 hours vs cefepime 2 g every 12 hours vs piperacillin-tazobactam 4.5 g every six hours	Hospitalized patients ≥ 19 years of age with healthcare-associated UTI caused by extended-spectrum β-lactamase-producing *Escherichia coli*		days and microbiological response at 10 to 14 days Secondary: 28 day mortality rate	treatment failure rate. Clinical success rate was 93.9% with piperacillin-tazobactam and 97.0% with ertapenem (P=0.500). Clinical success rate with cefepime was 33.3% (P<0.001). Microbiological success rates were 97.0% with both piperacillin-tazobactam and ertapenem, and 33.3% with cefepime. Secondary: The 28-day mortality rate was 6.1% with both piperacillin-tazobactam and ertapenem and 33.3% (two of six patients) with cefepime (P=0.108)
Portsmouth et al.[69] (2018) Cefiderocol 2 g TID for seven to 14 days vs imipenem/ cilastatin 1 g/1 g TID for seven to 14 days	DB, MC, NI, PG, RCT Adults ≥18 years of age, admitted to hospital with a clinical diagnosis of complicated urinary tract infection with or without pyelonephritis, or patients with acute uncomplicated pyelonephritis	N=448 14 to 21 days (seven days after end of antibiotic treatment)	Primary: Composite of clinical response and microbiological response at the test of cure assessment, defined as seven days after the end of antibiotic treatment Secondary: Safety, clinical and microbiological response	Primary: At test of cure, the primary efficacy endpoint was achieved by 183 (73%) of 252 subjects in the cefiderocol group and 65 (55%) of 119 subjects in the imipenem/cilastatin group, with an adjusted treatment difference of 18.58% (95% CI, 8.23 to 28.92; P=0.0004), establishing the non-inferiority of cefiderocol. Secondary: Adverse events occurred in 122 (41%) of 300 subjects in the cefiderocol group and 76 (51%) of 148 subjects in the imipenem/cilastatin group, with gastrointestinal disorders (i.e. diarrhea, constipation, nausea, vomiting, and abdominal pain) the most common adverse events for both treatment groups (35 [12%] subjects in the cefiderocol group and 27 [18%] subjects in the imipenem-cilastatin group). At test of cure, the proportion of subjects who had a microbiological response was higher in the cefiderocol group than the imipenem/cilastatin group (184 [73%] of 252 subjects vs 67 [56%] of 119 subjects; difference, 17.25%; 95% CI, 6.92 to 27.58), whereas the proportion of patients who had a clinical response was similar between the two groups (226 [90%] of 252 subjects vs 104 [87%] of 119 subjects; difference, 2.39%; 95% CI, -4.66 to 9.44).
Ho et al.[70]	OL, PRO, RCT	N=45	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Cefixime 200 mg PO BID vs ceftibuten 200 mg PO BID	Patients ≥18 years of age with complicated urinary tract infections	10 to 14 days	Clinical efficacy rate, bacteriological eradication rate Secondary: Adverse events	There was no statistically significant difference in rates of clinical efficacy (78.3 vs, 77.3%; P=0.9) and bacteriological eradication (52.2 and 63.6%; P=0.08) for patients taking ceftibuten and cefixime, respectively. Secondary: Adverse events were minimal for both treatment groups. Patients treated with ceftibuten reported diarrhea and increased transaminase serum levels; patients treated with cefixime reported skin rash and increased transaminase serum levels.
Tripi et al.[71] (1985) Cefotaxime 0.5 to 1 g IV/IM BID vs ceftizoxime 0.5 to 1 g IV/IM BID	DB, PRO, RCT Patients with acute or chronic urinary tract infections	N=80 10 days	Primary: Therapeutic efficacy Secondary: Adverse events	Primary: For either the ceftizoxime and cefotaxime study groups, clinical responses classified as excellent, good, or fair were reported as 90, 7.5 and 2.5%, respectively. Secondary: Excellent tolerance rates to ceftizoxime and cefotaxime were reported as 100 and 97.5%, respectively.
Mårild et al.[72] (2009) SMX-TMP 3-15 mg/kg PO suspension BID for 10 days vs ceftibuten 9 mg/kg PO suspension QD for 10 days	MC, OL, RCT Patients 1 month to 12 years of age with a first-time febrile urinary tract infections	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes Secondary: Not reported	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients treated with ceftibuten and SMX-TMP were 93 and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93 and 90%, respectively (P=NS). Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the SMX-TMP group (P=NS). Gastrointestinal symptoms

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were reported most frequently. There were no serious adverse events reported. Secondary: Not reported
Bradley et al.[73] (2019) Ceftazidime–avibactam IV for ≥72 hour vs cefepime IV for ≥72 hours both with subsequent optional oral switch. Total treatment duration was 7 to 14 days.	AC, MC, RCT, SB Children ≥3 months to <18 years hospitalized with complicated urinary tract infection (cUTI), including acute pyelonephritis	N=95 20 to 36 days after the last dose of IV/oral therapy	Primary: Safety Secondary: Descriptive efficacy	Primary: Adverse events occurred in 53.7% and 53.6% patients in the ceftazidime–avibactam and cefepime groups, respectively. Serious adverse events occurred in 11.9% (ceftazidime–avibactam) and 7.1% (cefepime) patients. One serious adverse event (ceftazidime–avibactam group) was considered drug related. Secondary: In the microbiologic intent-to-treat analysis set, favorable clinical response rates >95% were observed for both groups at end-of-IV and remained 88.9% (ceftazidime–avibactam) and 82.6% (cefepime) at test-of-cure. Favorable per-patient microbiologic response at test-of-cure was 79.6% (ceftazidime–avibactam) and 60.9% (cefepime).
Wagenlehner et al.[74] RECAPTURE (2016) Ceftazidime-avibactam 2,000 mg/500 mg every eight hours vs doripenem 500 mg every eight hours	DB, DD, MC, PG, RCT Patients 18 to 90 years of age with complicated urinary tract infections or acute pyelonephritis who required hospitalization for IV antibiotics, positive urine cultures obtained within 48 hours of	N=1,033 Test-of-cure: 21 to 25 days post-randomization Late follow-up: 45 to 52 days post-randomization	Primary: Symptomatic resolution of UTI-specific symptoms, microbiological eradication and UTI symptomatic resolution at test-of-cure visit in the microbiological modified intent-to-treat population Secondary:	Primary: The proportion of patients with patient-assessed symptomatic resolution at day five in the microbiological modified intent-to-treat (N=810) was 70.2% for ceftazidime-avibactam and 66.2% for doripenem (difference, 4.0; 95% CI, -2.39 to 10.42). Favorable microbiological response at test-of-cure was 77.4% with ceftazidime-avibactam and 71.0% with doripenem (difference, 6.4%; 95% CI, 0.33 to 12.36). Combined patient-assessed symptomatic resolution and favorable per-patient microbiological response at test-of-cure occurred in 71.2% in the ceftazidime-avibactam group and 64.5% in the doripenem group (difference, 6.7; 95% CI, 0.30 to 13.12). Secondary: Per-patient favorable microbiological response at end of IV treatment was 95.2 and 94.7% (difference, 0.4%; 95% CI, -2.7 to 3.56) and at late

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients could be switched to PO ciprofloxacin 500 mg every 12 hours or sulfamethoxazole-trimethoprim 800 mg/160 mg every 12 hours if they demonstrated clinical improvement after five days of IV therapy	enrollment, and polyuria		Microbiological response at end of IV study treatment and late follow-up, microbiological response at test-of-cure and late follow-up in patients with ≥ one ceftazidime-nonsusceptible or only ceftazidime-susceptible pathogens at baseline, clinical cure at the end of IV treatment, test-of-cure, and late follow-up and sustained clinical cure at late follow-up visit	follow-up was 68.2 and 60.9% (difference, 7.3%; 95% CI, 0.68 to 13.81), for the ceftazidime-avibactam and doripenem arms, respectively. Per-patient favorable microbiological response in patients with a ceftazidime-nonsusceptible pathogen at test-of-cure was 62.7 and 60.7% (difference, 2.0; 95% CI, -13.18 to 16.89) and at late follow-up was 61.3 and 45.2% (difference, 16.1%; 95% CI, 0.50 to 30.89), respectively, and 81.0 and 73.0% (difference, 8.0%; 95% CI, 1.50 to 14.48) at test-of-cure and 69.9 and 64.1% (difference, 5.8%; 95% CI, -1.46 to 13.05) at late follow-up in patients with a ceftazidime-susceptible pathogen. Investigator-determined clinical cure was 96.2% for the ceftazidime-avibactam group and 97.6% for the doripenem group (difference, -1.4%; 95% CI, -4.07 to 1.02) at the end of IV treatment, 90.3 and 90.4% (difference, -0.1%; 95% CI, -4.23 to 4.03) at test-of-cure, and 85.2 and 83.9% (difference, 1.3%; 95% CI, -3.71 to 6.30) at the late follow-up visit. Sustained clinical cure at the late follow up visit in patients who were cured at the test-of-cure visit was 93.0 and 91.5% (difference, 1.4%; 95% CI, -2.5 to 5.4%) for the ceftazidime-avibactam and doripenem groups, respectively.
Vazquez et al.[75] (2012) Ceftazidime–avibactam (500-125 mg) every eight hours vs imipenem–cilastatin (500 mg) every six hours	DB, MC, PRO, RCT Patients 18 to 90 years of age with complicated urinary tract infection due to Gram-negative pathogens	N=137 Microbiologi-cally evaluable patients=62 12 to 23 days	Primary: Favorable microbiological response at the test-of-cure visit five to nine days post-therapy in microbiologically evaluable patients Secondary: Microbiological response at the end of IV therapy and	Primary: Favorable microbiological response in the microbiologically evaluable population at the test-of-cure visit was observed in 19/27 (70.4%) patients in the ceftazidime–avibactam arm and 25/35 (71.4%) in the imipenem–cilastatin arm (observed difference −1.1% [95% CI, −27.2 to 25.0%]). Secondary: Favorable microbiological response rates at the end of IV therapy were 25/26 (96.2%) and 34/34 (100%) in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, and 15/26 (57.7%) and 18/30 (60.0%) at the late follow-up visit. Over the course of the study, adverse events were reported in 46/68 (67.6%) patients in the ceftazidime–avibactam arm and 51/67 (76.1%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients meeting pre-specified improvement criteria after four days could be switched to oral ciprofloxacin. Patients were treated for a total of seven to 14 days.			at the late follow-up visit, four to six weeks post-therapy in the microbiologically evaluable population; safety and tolerability	patients in the imipenem–cilastatin arm. The most common adverse events in both treatment arms included constipation, diarrhea, abdominal pain, headache, anxiety, and injection/infusion site reactions. Treatment-emergent serious adverse events were reported in 6/68 (8.8%) and 2/67 (3.0%) of patients in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, during the course of the study. Three of the serious adverse events in the ceftazidime–avibactam arm were considered to be drug-related: renal failure, diarrhea, and accidental overdose of ceftazidime–avibactam. Although the accidental overdose of ceftazidime–avibactam was recorded as a serious adverse event, there were no adverse events associated with this event. One patient in the imipenem–cilastatin arm developed a drug-related serious adverse event associated with an increase in serum creatinine level.
Goldstein et al.[76] (1991) Ceftizoxime 250 mg IM for one dose vs ceftriaxone 250 mg IM for one dose	DB, PRO Adult heterosexual male inmates with documented uncomplicated urethral gonorrhea	N=204 1 day	Primary: Clinical cure Secondary: Adverse events	Primary: At seven to 10 days post-treatment, all patients in both treatment groups achieved cure (100%). Secondary: No adverse events were reported.
Wagenlehner et al.[77] (2015) ASPECT-cUTI ceftolozane-tazobactam 1.5 g IV every eight hours for seven days vs	DB, DD, NI, RCT Hospital inpatients ≥18 years of age who had pyuria and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis	N=800 12 to 16 days	Primary: Difference in composite cure rates at the test-of-cure visit in the microbiological modified intention to treat population Secondary: Difference in composite cure rates at the test-of-	Primary: Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure in the microbiological modified intention to treat population (ceftolozane-tazobactam, 306/398 [76.9%] vs levofloxacin, 275/402 [68.4%]; 95% CI, 8.5 [2.3 to 14.6]). Secondary: Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure in the per-protocol population (ceftolozane-tazobactam, 284/341 [83.3%] vs levofloxacin, 266/353 [75.4%]; 95% CI, 8.0 [2.0 to 14.0]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levofloxacin 750 mg IV QD for seven days			cure visit in the per-protocol population	
Cooper et al.[78] (1992) Cefuroxime 125 mg PO BID vs cephradine 500 mg PO BID	PRO, RCT Patients ≥17 years of age with dysuria or frequency and diagnosed urinary tract infection	N=113 7 days	Primary: Clinical cure, bacteriological cure Secondary: Adverse events	Primary: At seven days post-treatment, clinical cure rates were reported as 56 and 81% in patients treated with cephradine and cefuroxime, respectively (P<0.05). Bacteriological cure at one week post-treatment and five weeks post-treatment were reported as 97 and 96%, respectively, for both study groups (P>0.05). Secondary: Fourteen percent and 6% of patients treated with cephradine and cefuroxime, respectively, reported adverse events; patients receiving cefuroxime reported a higher incidence of increased frequency of bowel movements (35.0 vs 17.5%, respectively; P<0.05).
Ziogos et al.[79] (2010) Cefuroxime 1.5 g IV as a single dose vs ampicillin-sulbactam 3 g IV as a single dose	RCT Women scheduled for cesarean delivery	N=176 30 days	Primary: Development of an infection Secondary: Not reported	Primary: Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses six or more vaginal examinations prior to the operation (P=0.004), membrane rupture for more than six hours (P=0.08) and blood loss greater than 500 mL (P=0.018) were associated with developing a postoperative surgical site infection. In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative surgical site infection (OR, 6.8; 95% CI, 1.4 to 33.4; P=0.019). Regular prenatal follow-up was associated with a protective effect (OR, 0.04; 95% CI, 0.005 to 0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of five vs four days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Friman et al.[80] (1989) Aztreonam 1 g IV every eight hours vs cefuroxime 1.5 g IV every eight hours	RCT Patients 18 to 99 years of age with symptoms of an upper urinary tract infection	N=171 1 month	Primary: Clinical response rates, bacteriologic response rates Secondary: Not reported	Primary: Clinical response rates were 89% in the aztreonam group and 87% in the cefuroxime group. Bacteriologic response rates at one week post-therapy were 70% in the aztreonam group and 73% in the cefuroxime group, while rates at one month were 43 and 40% respectively. Secondary: Not reported
Respiratory Infections—Upper Respiratory Tract				
Randolph et al.[81] (1988) Cefaclor 20 mg/kg PO TID vs cefadroxil 30 mg/kg PO QD	PRO, RCT Patients between three and 21 years of age with clinical signs and symptoms of acute group A β-hemolytic streptococcal pharyngitis	N=250 10 days	Primary: Clinical evaluation, microbiologic evaluations Secondary: Adverse event	Primary: On day 14 (P=0.020) and days 21 to 28 (P=0.043), a greater number of patients treated with cefadroxil had good therapeutic response to therapy compared to patients treated with cefaclor. Patients treated with cefadroxil had a lower failure or clinical recurrence compared to patients treated with cefaclor (4.6 vs 22.1%, respectively). Secondary: No significant drug-related adverse event reported.
Piippo et al.[82] (1991) Cefaclor 40 mg/kg/day PO divided BID vs cefixime 8 mg/kg/day PO divided BID	DB, PG, RCT Pediatric patients six months to 12 years of age with acute otitis media	N=345 7 days	Primary: Clinical cure Secondary: Adverse events	Primary: At days 10 to 12, clinical cure was reported in 93.5 and 90.5% of patients treated with cefixime and cefaclor, respectively (P=0.081). At days 28 to 35, clinical cure was reported in 90.1 and 86.6% of patients treated with cefixime and cefaclor, respectively (P=0.12). Secondary: Adverse events were reported in 17.9 and 10.6% of patients treated with cefixime and cefaclor, respectively.
Gehanno et al.[83] (1990)	DB, MC, PC, PRO, RCT	N=236	Primary: Clinical cure,	Primary: At the end of the treatment, clinical cure was reported as 84 and 68% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefaclor 500 mg PO TID vs cefpodoxime 200 mg PO BID	Adult outpatients with acute sinusitis	Mean days 9.9	overall clinical efficacy (cure and improvement), bacteriological eradication Secondary: Adverse events	patients treated with cefpodoxime and cefaclor, respectively (P=0.01). Overall clinical efficacy was reported as 95 and 93% of patients treated with cefpodoxime and cefaclor, respectively (P=NS). Bacteriological eradication was reported as 95 and 91% in patients treated with cefpodoxime and cefaclor, respectively (P=NS). Secondary: Possible drug-related adverse events were reported in nine and 10 patients treated with cefpodoxime and cefaclor, respectively.
MacLoughlin et al.[84] (1996) Cefaclor suspension 40 mg/kg/day PO divided TID vs cefpodoxime suspension 10 mg/kg/day PO divided BID	MC, OL, RCT Pediatric patients one month to 11 years of age with acute otitis media	N=167 5 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical success was reported as 93.6 and 91.6% of patients treated with cefpodoxime and cefaclor, respectively (P >0.05); at study day 30, clinical recurrence was reported as 99 and 94%, respectively (P>0.05). Secondary: Patients were able to tolerate both cefpodoxime and cefaclor (99 vs 94%, respectively; P>0.05).
Blumer et al.[86] (1995) Cefaclor 40 mg/kg/day PO in three divided doses (maximum 1 g/day) vs ceftibuten 9 mg/kg/day PO for	MC, RCT, SB Pediatric patients aged three months to 17 years with acute otitis media	N=154 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At one to three days post-treatment, clinical cure was reported in 89 and 88% of patients treated with ceftibuten and cefaclor, respectively (P=NS). At two to four weeks post-treatment, clinical cure was reported in 88 and 82% of patients treated with ceftibuten and cefaclor, respectively (P=NS). Secondary: Mild to moderate drug-related adverse events were reported in 8 and 14% of patients treated with ceftibuten and cefaclor, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 dose (maximum 400 mg/day)				
Block et al.[86] (2000) Cefdinir 14 mg/kg/day PO divided BID (for five days) vs cefprozil 30 mg/kg/day PO divided BID (for 10 days)	DB, MC, PRO Pediatric patients six months to 12 years of age with acute otitis media	N=373 5 to 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At the end of therapy (study days nine to 11), clinical efficacy was reported as 80.0 and 82.5% in patients treated with cefdinir and cefprozil (P= NS). Secondary: Diarrhea and overall adverse events were reported in cefdinir-treated patients (7.8 and 13.0%, respectively) and cefprozil-treated patients (4.2 and 12.0%, respectively; P=0.116).
Asmar et al.[87] (1994) Cefixime oral suspension 8 mg/kg/day PO QD vs cefpodoxime oral suspension 10 mg/kg/day PO QD	DB, MC, PRO, RCT Patients two months to 17 years of age with acute suppurative otitis media	N=368 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: On days 12 through 15, clinical cure or improvement was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively (P=0.541). On days 12 to 15, end-of-therapy response rates were reported as 53 and 51% in patients treated with cefpodoxime and cefixime, respectively (P=0.404). Overall microbiologic susceptibility was reported as 89 and 86% in patients treated with cefpodoxime and cefixime, respectively (P=0.70). Secondary: Drug-related adverse effects (e.g., diarrhea, diaper rash, vomiting, and rash) occurred in 23.3 and 17.9% of patients taking cefpodoxime and cefixime, respectively.
Respiratory Infections—Lower Respiratory Tract				
ZeLuff et al.[88] (1986) Cefaclor 500 mg	PRO, RCT Black African gold miners 13 to 59	N=103 10 days	Primary: Clinical evaluations, microbiologic	Primary: Clinical cure was reported as 94% of patients treated with either cefadroxil or cefaclor.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PO every eight hours vs cefadroxil 1 g PO every 12 hours	years of age with pneumococcal pneumonia confirmed by culture/serology		evaluations Secondary: Adverse events	Microbiologic cure was reported in 98 and 96% of patients treated with cefadroxil and cefaclor, respectively. Secondary: One patient treated with cefaclor withdrew from the study due to severe diarrhea. Otherwise, minimal side effects were reported for both therapies.
Drehobl et al.[89] (1997) Cefaclor 500 mg PO TID vs cefdinir 300 mg PO BID	DB, MC, RCT Patients with community acquired-pneumonia	N=538 10 days	Primary: Clinical response, microbiological eradication Secondary: Adverse events	Primary: Satisfactory clinical response was reported as 89 and 86% of patients treated with cefdinir and cefaclor, respectively; microbiological eradication was reported as 92 and 93%, respectively. For all comparisons, P=NS. Secondary: Patients taking cefdinir reported a higher incidence of diarrhea compared to patients treated with cefaclor (13.7 vs 5.3%, respectively; P<0.001).
Phillips et al.[90] (1993) Cefaclor 250 mg PO TID vs cefpodoxime 200 mg PO BID	DB, MC, RCT Patients with signs and symptoms of acute bacterial exacerbation of chronic obstructive pulmonary disease	N=301 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: There were no statistically significant differences between cefpodoxime and cefaclor in the eradication of the original pathogen (91 vs 92%, respectively) or in clinical response at three to seven days post-treatment (99 vs 92%, respectively). More bacterial isolates were susceptible to cefpodoxime compared to cefaclor (91 vs 84%, respectively; P<0.001). Secondary: There were no significant differences between cefpodoxime and cefaclor in adverse events (11 vs 12%, respectively).
Chirurgi et al.[91] (1991) Cefaclor 250 mg PO every eight hours vs	PRO, RCT Patients with acute bronchitis, not pneumonia	N=45 7 to 14 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87.5 and 92.3% of patients treated with ceftibuten and cefaclor, respectively. Bacteriologic efficacy was reported as 87.5 and 80.0% of patients treated with ceftibuten and cefaclor, respectively. Secondary: The rates of adverse events were reported as 7.9 and 5.6% in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftibuten 400 mg PO QD				treated with ceftibuten and cefaclor, respectively.
Blaser et el.[92] (1983) Cefadroxil 500 mg PO BID vs cephalexin 250 mg PO QID	PRO, RCT Patients 19 to 92 years of age with community-acquired pneumonia of mild to moderate severity	N=34 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: All 34 cases achieved clinical cure; no additional information in regards to differences in clinical cure rates were reported between cefadroxil and cephalexin. Clearing of chest exam findings were reported in 79 and 73% of patients treated with cefadroxil and cephalexin, respectively. Secondary: Drug-related adverse effects were minimal.
Fogarty et al.[93] (2000) Cefdinir 300 mg PO BID (for five days) vs cefprozil 500 mg PO BID (for 10 days)	DB, MC, PRO, RCT Patients with acute exacerbations of chronic bronchitis	N=281 5 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: The observed clinical cure rate among cefdinir-treated patients was 80% compared to 72% of cefprozil-treated patients (95% CI, -1.6 to 18.3). The overall rates of microbiological eradication of pathogens were 81% for cefdinir-treated patients and 84% for cefprozil-treated patients (95% CI, –10.0 to 5). Secondary: Safety of the drugs was analyzed for all patients who received study medication. Of these patients, 95 (34%) patients receiving cefdinir and 89 (33%) patients receiving cefprozil experienced at least one adverse event during treatment (P=0.90). The most frequent adverse events on therapy for both cefdinir- and cefprozil-treated patients were diarrhea and headache. Seventeen percent of cefdinir-treated patients and 6% of cefprozil-treated patients experienced diarrhea during treatment (P<0.01).
Alvarez-Sala et al.[94] (2006) Cefditoren 200 mg PO BID (for five	DB, DD, PG, RCT Patients ≥18 years of age with acute exacerbations of chronic bronchitis	N=541 5 to 10 days	Primary: Clinical evaluation, bacteriologic evaluation	Primary: On day 11, clinical success rate was reported as 79.9 and 82.7% for patients treated with cefditoren and cefuroxime, respectively (P=NS). On day 30, clinical success rate was reported as 81.0 and 85.5% for patients treated with cefditoren and cefuroxime, respectively (P=NS). On day 11, bacteriological response was reported as 72.8 and 67.0% for patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days) vs cefuroxime 250 mg PO BID (for 10 days)			Secondary: Adverse events	treated with cefditoren and cefuroxime, respectively (P=NS). Secondary: Drug-related adverse events were reported in 7.7 and 11.4% of patients treated with cefditoren and cefuroxime, respectively.
Leophonte et al.[95] (1993) Cefepime 1 g IV/IM BID vs ceftazidime 1 g IV/IM TID	AC, MC, OL, RCT Adult patients with moderate to severe community-acquired lower respiratory tract infections	N=111 1 to 15 days	Primary: Clinical cure rate, pathogen eradication rate Secondary: Adverse events	Primary: Clinical cure was reported in 87 and 86% of patients treated with cefepime and ceftazidime, respectively (P=0.8); pathogen eradication rates were reported as 95% for both treatment groups (P=0.7). Secondary: Both treatments were well tolerated and a similar incidence of adverse events.
Grossman et al.[96] (1999) Cefepime 2 g every 12 hours vs ceftriaxone 1 g every 12 hours	DB, MC, PRO, RCT Patients ≥65 years of age who had been admitted to the hospital after being diagnosed with community-acquired pneumonia	N=151 3 to 14 days	Primary: Clinical response, bacteriologic eradication Secondary: Adverse events	Primary: Clinical response was reported as 79.1 and 75.4% in patients treated with cefepime and ceftriaxone, respectively (P=0.62). Relative to evaluable study participants, all but one patient treated with cefepime achieved bacteriologic eradication. Secondary: There was no statistically significant difference in the incidence of adverse events reported by patients treated with either cefepime or ceftriaxone (76.3 vs 84.0%, respectively; P=0.24). Diarrhea was the most common adverse event reported in patients treated with cefepime and ceftriaxone (five vs two patients, respectively).
Bradley et al.[97] (2001) Cefepime 50 mg/kg IV every eight hours (maximum 6 g/day)	4 trials MC, OL, RCT Pediatric patients two months to 18 years of age with serous lower respiratory tract	N=646 Up to 21 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: In study A, clinical efficacy was reported as 91% for patients treated with cefepime; bacteriologic eradication was 93%. In study B, clinical efficacy, at the end of treatment, was reported as 100% for patients treated with cefepime and cefuroxime; bacteriologic eradication was also reported as 100%. The study consisted of 10 evaluable study participants.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefepime 50 mg/kg IV every 12 hours (maximum 4 g/day) vs cefotaxime 120 mg/kg/day IV in four divided doses (maximum 4.5 g/day) vs ceftazidime 150 mg/kg/day IV in three divided doses (maximum 6 g/day) vs cefuroxime 100 mg/kg/day IV in three divided doses (maximum 4.5 g/day) vs placebo In study A,	infections			In study C, clinical efficacy was 100% for patients treated with either cefepime or cefotaxime; bacteriologic eradication was reported in 75% and 100% of patients treated with cefepime and cefotaxime, respectively. The study consisted of 13 evaluable study participants. In study D, clinical efficacy was reported, at the end of treatment, as 93% and 95% of patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95 and 100%, respectively. Secondary: Overall, adverse events reported by study participants were generally mild except for one case of rash and one case of vaginitis for patients treated with cefepime.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
participants received either cefepime every eight or 12 hours. In studies B, C, and D, participants received either cefepime or a comparator (cefuroxime, cefotaxime, ceftazidime, respectively).				
Paladino et al.[98] (2007) Cefepime 1 g IM every 24 hours vs ceftriaxone 1 g IM every 24 hours After three days, patients with objective evidence of improvement could be switched to oral antibiotics.	DB, RCT Patients 60 years of age and older with nursing home-acquired pneumonia who did not require hospitalization	N=69 10 to 14 days	Primary: Clinical success (cure or improvement) and safety Secondary: Not reported	Primary: Clinical success occurred in 78% of cefepime- and 66% of ceftriaxone-treated patients (P=0.39). Ninety-three percent of patients were switched to oral antibiotics after three days. Most patients experienced mild to no discomfort at the site of IM injection of ceftriaxone or cefepime; if present, it abated quickly. One patient with a history of diabetes mellitus had high blood glucose while receiving ceftriaxone. Other drug-related adverse events occurred rarely and only with the oral antibiotics. The overall mortality rate was 8%. Secondary: Not reported
Verghese et al.[99] (1990) Cefixime 400 mg PO for one dose	RCT Patients with purulent exacerbation of chronic bronchitis	N=86 1 to 14 days	Primary: Clinical cure, clinical improvement Secondary:	Primary: Clinical cure was reported as 70.8 and 50.0% in patients treated with cefixime and cephalexin, respectively (P<0.05). Combined percentages for clinical cure and improvement were reported as 95.8 and 84.2% in patients treated with cefixime and cephalexin, respectively (P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cephalexin 250 mg PO QID			Adverse events	Secondary: Both treatments were well tolerated. Diarrhea occurred more often in patients treated with cefixime compared to patients treated with cephalexin (P=0.013).
Sengupta et al.[100] (2004) Cefixime 4 mg/kg PO BID vs cefpodoxime 5 mg/kg PO BID	AC, MC, OL, PRO, RCT Pediatric patients six months to 12 years of age with community-acquired lower respiratory tract infections, including community-acquired pneumonia and acute exacer-bations of chronic bronchitis	N=776 10 to 14 days	Primary: Clinical cure, bacteriologic eradication Secondary: Adverse events	Primary: Clinical cure was reported as 97.0 and 86.8% for patients treated with cefpodoxime and cefixime, respectively; bacteriologic eradication was reported as 93.4 and 82.9%, respectively. Secondary: Both treatments were well tolerated.
Zuck et al.[101] (1999) Cefixime 200 mg PO BID vs cefuroxime 250 mg PO BID	DB, MC, PG, RCT Hospitalized patients 30 to 75 years of age experiencing acute exacerbations of chronic bronchitis	N=58 8 days	Primary: Clinical cure, microbiological eradication Secondary: Adverse events	Primary: At two to four days post-treatment, clinical cure was reported in 94 and 71% of patients treated with cefuroxime and cefixime, respectively (P=NS); microbiological eradication occurred more quickly in patients treated with cefuroxime compared to cefixime (P=0.002 at two to four weeks post-treatment). Secondary: Both treatments were well tolerated. One patient treated with cefuroxime reported fever; one patient treated with cefixime reported buccal mycosis.
File et al.[102] (2011) Ceftaroline 600 mg IV every 12 hours for five to seven days	AC, DB, MC, RCT Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class	N=613 Variable duration	Primary: Clinical cure rates at the test-of-cure visit (eight to 15 days post-therapy) in the clinically evaluable and modified intent-to-	Primary: Clinical cure rates were 86.6% for ceftaroline and 78.2% for ceftriaxone in the clinically evaluable population (95% CI, 1.4 to 15.4). Clinical cure rates in the modified intent-to-treat efficacy population were 83.8% for ceftaroline and 77.7% for ceftriaxone (95% CI, -0.2 to 12.6). Secondary: Clinical cure was observed in 89.9 and 76.1% of patients in the ceftaroline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftriaxone 1 g IV every 24 hours for five to seven days Patients also received two 500 mg doses of oral clarithromycin every 12 hours on day 1.	III or IV		treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations, overall success rate, clinical and microbiological response by pathogen, clinical relapse at the late follow-up visit, and safety	and ceftriaxone groups, respectively, in the microbiologically evaluable population (95% CI, 1.3 to 26.4). In the microbiological modified intent-to-treat efficacy population, clinical cure was observed in 88.0 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, 0.7 to 25.2). At the test-of-cure visit, overall (clinical and radiographic) success was observed in 86.6% of patients in the ceftaroline group and 78.2% of patients in the ceftriaxone group in the clinically evaluable population (95% CI, 1.4 to 15.4). In the modified intent-to-treat efficacy population, 83.5% of ceftaroline patients and 77.7% of ceftriaxone patients experienced overall success (95% CI, -0.6 to 12.2). At the late follow-up visit, clinical relapse was noted in 1.1% of patients in the ceftaroline group and 1.8% of patients in the ceftriaxone group (95% CI, -4.2 to 2.4) of the clinically evaluable population. In the modified intent-to-treat efficacy population, 1.2% of patients in the ceftaroline group and 1.3% of patients in the ceftriaxone group (95% CI, -2.6 to 2.4) were considered a clinical relapse. Per-patient favorable microbiological response rates in the microbiologically evaluable population were 89.9% in the ceftaroline group compared to 78.9% in the ceftriaxone group (95% CI, -1.2 to 23.3). Consistent results were observed in the microbiological modified intent-to-treat efficacy population; 88.0% in the ceftaroline group and 78.8% in the ceftriaxone group (95% CI, -2.7 to 21.1). The most common adverse events for ceftaroline-treated patients were diarrhea, headache, insomnia and nausea, compared to hypokalemia, hypertension, nausea and diarrhea for ceftriaxone-treated patients. The most common study drug-related treatment-emergent adverse events were diarrhea (4.4% for ceftaroline and 1.0% for ceftriaxone), sinus bradycardia (1.0% for ceftaroline and 1.0% for ceftriaxone), nausea (1.3% for ceftaroline and 0.6% for ceftriaxone) and phlebitis (1.3% for ceftaroline and 0.6% for ceftriaxone).
Low et al.[103] (2011)	AC, DB, MC, RCT	N=627	Primary: Clinical cure rates	Primary: Clinical cure rates were 82.1% for ceftaroline and 77.2% for ceftriaxone in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ceftaroline 600 mg IV every 12 hours for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	Variable duration	at the test-of-cure visit (eight to 15 days post-therapy) in the clinically evaluable and modified intent-to-treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations, overall success rate, clinical and microbiological response by pathogen, clinical relapse at the late follow-up visit, and safety	the clinically evaluable population (95% CI, -2.5 to 12.5). Clinical cure rates in the modified intent-to-treat efficacy population were 81.3% for ceftaroline and 75.5% for ceftriaxone (95% CI, -1.0 to 12.7). Secondary: Clinical cure was observed in 81.2 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively, in the microbiologically evaluable population (95% CI, -6.7 to 19.2). In the microbiological modified intent-to-treat efficacy population, clinical cure was observed in 80.0 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, -7.4 to 17.4). Clinical cure rates at the end of treatment were 86.0% for ceftaroline and 80.0% for ceftriaxone in the clinically evaluable population (95% CI, -1.0 to 13.0). Clinical cure rates were 86.2% for ceftaroline and 78.8% for ceftriaxone in the modified intent-to-treat efficacy population at the end of treatment (95% CI, 1.1 to 13.8). At the test-of-cure visit, the overall (clinical and radiographic) success rates were 81.7% for ceftaroline and 77.2% ceftriaxone in the clinically evaluable population (95% CI, -3.0 to 12.1). Overall success rates were 81.0% with ceftaroline and 75.5% with ceftriaxone in the modified intent-to-treat efficacy population (95% CI, -1.3 to 12.4). Clinical relapse at the late follow-up visit was reported for 2.8% of patients in the ceftaroline group and 0.6% of patients in the ceftriaxone group of the clinically evaluable population (95% CI, -1.0 to 5.8). In the modified intent-to-treat efficacy population, clinical relapse was determined in 2.1% of patients in the ceftaroline group and 1.0% of patients in the ceftriaxone group (95% CI, -1.6 to 4.0). Favorable per-patient microbiological response rates were observed for 84.7% of patients in the ceftaroline group and 82.9% of patients in the ceftriaxone group in the microbiologically evaluable population (95% CI, -9.7 to 13.7). In the microbiological modified intent-to-treat efficacy population, 82.2% of patients in the ceftaroline group and 81.8% of patients in the ceftriaxone group had a favorable microbiological response

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rate (95% CI, -11.1 to 11.9). There were no occurrences of microbiological reinfection or recurrence at the late follow-up visit. The most common adverse events for ceftaroline-treated patients were diarrhea, headache, hypokalemia, insomnia and phlebitis, compared to diarrhea, hypertension, insomnia and phlebitis for ceftriaxone-treated patients. Similar incidence rates of serious adverse events were demonstrated across both treatment groups (13.0% for ceftaroline vs 12.7% for ceftriaxone).
File et al.[104] (2010) Ceftaroline 600 mg IV every 12 hours for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	Pooled analysis (2 trials) Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	N=1,228 Variable duration	Primary: Clinical cure rates at the test-of-cure visit (eight to 15 days post-therapy) in the clinically evaluable and modified intent-to-treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations, clinical and microbiological clinical relapse at the late follow-up visit, and safety	Primary: Clinical cure rates were 6.7% (95% CI, 1.6 to 11.8) and 6.0% (95% CI, 1.4 to 10.7) higher for ceftaroline than for ceftriaxone in the clinically evaluable and modified intent-to-treat efficacy populations, respectively. Secondary: Clinical cure rates in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations were 85.1 and 83.6%, respectively, for ceftaroline, compared to 75.5 and 75.0%, respectively, for ceftriaxone. Clinical relapse rates at late follow-up were 1.9% for ceftaroline and 1.2% for ceftriaxone in the clinically evaluable population (95% CI, -1.4 to 2.9). Clinical relapse rates were 1.7% for ceftaroline and 1.1% for ceftriaxone in the modified intent-to-treat efficacy population (95% CI, -1.2 to 2.3). Favorable per-patient microbiological response rates in the microbiologically evaluable population were 87.0% for ceftaroline and 81.0% for ceftriaxone (95% CI, -2.3 to 14.6). In the modified intent-to-treat efficacy population, microbiological response rates were 84.8% for ceftaroline and 80.4% for ceftriaxone (95% CI, -3.7 to 12.8). The incidences of treatment-emergent adverse events were similar among the treatment groups. The most common adverse events were diarrhea, headache, and insomnia for patients receiving ceftaroline and diarrhea, hypertension, and hypokalemia for patients receiving ceftriaxone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lodise et al.[105] (2015) Ceftaroline 600 mg IV every 12 hours for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	DB, MC, RCT (Pooled analysis of FOCUS 1 and FOCUS 2) Clinically evaluable patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	N=908 Variable duration	Primary: Time to discharge readiness (clinical response), clinical stability, symptom improvement Secondary: Not reported	Primary: Time to a clinical response (i.e., discharge readiness) was shorter among patients treated with ceftaroline than among patients treated with ceftriaxone (P=0.0335). The time to clinical stability was also shorter among patients treated with ceftaroline (P=0.0190). Patients treated with ceftaroline had a nonsignificantly shorter time to the improvement of at least one clinical symptom without deterioration from the baseline. Secondary: Not reported
Friedland et al.[106] (2004) Ertapenem 1 g IV daily vs ceftriaxone 1 g IV daily Patients with clinical improvement meeting pre-specified criteria could be switched to PO amoxicillin-clavulanate or other PO antimicrobial based on pathogen susceptibility for a total of 10 to 14	DB, MC, RCT Patients 18 years of age and older with typical community-acquired pneumonia admitted to the hospital for parenteral antimicrobial therapy	N=857 7 to 14 days post-therapy	Primary: Clinical response at the test-of-cure visit, clinical response at the completion of parenteral therapy Secondary: Not reported	Primary: At the test-of-cure visit, the combined response rates were 90% in patients with chronic obstructive pulmonary disease and 93% in patients without chronic obstructive pulmonary disease. In the patients without chronic obstructive pulmonary disease, favorable results were seen in 93% of both ertapenem and ceftriaxone patients. There were no significant differences between treatment groups (P=0.94) or between patients with and without chronic obstructive pulmonary disease (P=0.17). Clinical response at the completion of parenteral therapy was seen in 95% of ertapenem patients and 94% of ceftriaxone patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days.				
Kollef et al.[107] (2019) ASPECT-NP Ceftolozane-tazobactam 3 g IV every 8 hours for 8 to 14 days vs meropenem 1 g IV every 8 hours for 8 to 14 days	DB, MC, NI, RCT Patients ≥18 years of age undergoing mechanical ventilation, and had nosocomial pneumonia (either ventilator-associated pneumonia or ventilated hospital-acquired pneumonia)	N=726 7 to 14 days post-therapy	Primary: 28-day all-cause mortality Secondary: Clinical response at the test-of-cure visit (7 to 14 days after the end of therapy)	Primary: At 28 days, 87 (24.0%) patients in the ceftolozane–tazobactam group and 92 (25.3%) in the meropenem group had died (weighted treatment difference 1.1%; 95% CI, −5.1 to 7.4). Ceftolozane–tazobactam was thus non-inferior to meropenem in terms of 28-day all-cause mortality. Secondary: At the test-of-cure visit 197 (54%) patients in the ceftolozane–tazobactam group and 194 (53%) in the meropenem group were clinically cured (weighted treatment difference, 1.1%; 95% CI, −6.2 to 8.3). Ceftolozane–tazobactam was thus non-inferior to meropenem in terms of clinical cure at test of cure.
Miscellaneous Infections				
Nungu et al.[108] (1995) Cefadroxil 1 g/100 mL water PO two hours before surgery and 12 hours later vs cefuroxime 0.75 g IV 30 minutes prior to surgery and every eight hours for two additional doses	PRO, RCT Patients undergoing intra- or subtrochanteric femoral hip fracture surgery	N=559 1 to 2 days	Primary: Absence or presence of surgical wound infection Secondary: Not reported	Primary: One study participant treated with cefadroxil reported a case of superficial wound infection with methicillin-sensitive *Staphylococcus aureus*. Six study participants treated with cefuroxime reported infections post-surgery; the infections included both superficial and deep infections. The difference in efficacy for preventing infections between the two treatment groups was not statistically significant (P=0.07). Secondary: Not reported
Jones et al.[109] (1987) Cefazolin 1 g IV	PRO, RCT, SB Patients ≥18 years of age undergoing	N=914 2 days	Primary: Absence or presence of surgical wound	Primary: The mean time to onset of infection was reported as 9.9, 15.8, and 11.8 days for patients treated with cefazolin, cefoxitin, and cefotaxime, respectively. There was no statistically significant difference in wound

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bolus prior to surgery and cefazolin 1 g every eight hours for 24 hours; cefazolin 1 g during surgery if surgery lasts longer than two hours vs cefotaxime 1 g IV bolus prior to surgery; cefotaxime 1 g during surgery if surgery lasts longer than two hours vs cefoxitin 2 g IV bolus prior to surgery and cefoxitin 2 g every six hours for 24 hours	elective surgery		infection Secondary: Adverse events	infection morbidity rate for all treatment groups (P>0.05). Secondary: Although not statistically significant, a greater number of adverse events were reported in patients treated with cefoxitin vs cefazolin and cefazolin vs cefotaxime. Allergic reactions were most commonly reported with cefoxitin.
Curtis et al.[110] (1993) Cefazolin 1 g IV 1 hour prior to surgery and every eight hours (for 48 hours) plus	PRO, RCT Patients undergoing open heart surgery	N=702 2 to 3 days	Primary: Absence or presence of surgical wound infection (draining wound with or without positive culture)	Primary: There was no statistically significant difference in overall wound infection rate between treatment groups (P=0.68). Differences in infection rates for both treatment groups were reported as being not statistically significant for chest wound infections, true mediastinitis, and leg infections (P=0.79, P=0.84, P=0.83, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefazolin 1 g IV after four hours of surgery vs cefuroxime 1.5 g IV 1 hour prior to surgery plus cefuroxime 1.5 g every 12 hours for three additional doses			Secondary: Not reported	Not reported
Jewesson et al.[111] (1996) Cefazolin 1 g in 100 mL 0.9% NaCl IV 30 minutes prior to surgery and cefazolin 1 g every 12 hours for 24 hours vs ceftizoxime 1 g in 100 mL 0.9% NaCl IV 30 minutes prior to surgery and ceftizoxime 1 g every 12 hours for 24 hours	DB, PRO, RCT Patients ≥19 years of age undergoing elective biliary tract surgery	N=150 2 days	Primary: Absence or presence of surgical wound infection Secondary: Not reported	Primary: There was no clinical evidence of infection in 93 and 92% of patients treated with cefazolin and ceftizoxime, respectively (P=1.0). Clinical success of the treatments were not influenced by procedure type (P=0.48 to 0.59) nor the number of patients receiving less than two doses of the antibiotic (P=1.0). Secondary: Not reported
Ozturk et al.[112] (2007)	PC, RCT	N=120	Primary: Clinical outcomes	Primary: The occurrence rates of fever were 10.3, 16.0, 13.7, and 23.3% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefazolin 1 g IV as a single dose vs cefuroxime 750 mg IV as a single dose vs ceftazidime 1 g IV as a single dose vs placebo	Patients who underwent transurethral resection of the prostate for symptomatic benign prostatic hyperplasia	10 days	Secondary: Not reported	cefazolin, cefuroxime, ceftazidime, and placebo groups, respectively (P>0.05). The urine culture on the second postoperative day was positive only in one patient in the cefazolin group (3.4%) and in two patients in the placebo group. The second day, postoperative bacteriuria rates were similar in all groups. On the 10th postoperative day, a positive urine culture was observed in 10 patients in the cefazolin group (34%), two patients in the cefuroxime group (6.6%), two patients in the ceftazidime group (6.8%), and in 12 patients in the placebo group (40.0%) On the 10th day, the incidence rates of bacteriuria in the placebo group and the cefazolin group were similar (P=0.661). In the cefuroxime group, the bacteriuria incidence rate was 6.6%, and when compared to the placebo group, the difference was considered significant (P=0.002). The difference between the cefuroxime and the ceftazidime groups was also significant (P=0.003). There were statistically significant differences between the cefazolin and cefuroxime group (P=0.008) as well as between the cefazolin and ceftazidime groups (P=0.01). All antibiotics were generally well tolerated in all patients, and there were no significant drug-related side effects. Secondary: Not reported
Huang et al.[113] (2002) Cefepime 2 g IV every 12 hours vs ceftazidime 2 g IV every eight hours	OL, PRO, RCT Patients ≥18 years of age with severe infections including septicemia, urinary tract infection, bacterial bronchitis, bacterial pneumonia, intra-abdominal infection	N=42 10 to 14 days	Primary: Clinical response rates, bacteriological eradication rates Secondary: Adverse events	Primary: Clinical response rates of 71 and 61% were reported for patients treated with cefepime and ceftazidime, respectively. Bacteriological eradication rates were reported as 87.5 and 89.0% of patients treated with cefepime and ceftazidime, respectively. Clinical response and bacteriological eradication rates were not statistically different between treatment groups. Secondary: Adverse events reported with both treatments were minimal. The most common adverse events were hyperkalemia (12%), impaired liver biochemistry (12%), diarrhea (10%), and hypoalbuminemia (10%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chandrasekar et al.[114] (2000) Cefepime 2 g IV every eight hours vs ceftazidime 2 g IV every eight hours	DB, MC, PRO, RCT Hospitalized patients ≥18 years of age with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=188 1 to 35 days	Primary: Presence or absence of febrile episodes, bacteremic clearance Secondary: Adverse events	Primary: Prevention of febrile episodes was reported in 57 and 60% of patients treated with cefepime and ceftazidime, respectively (P=0.77). Success rates in microbiologically documented infections were reported as 39 and 16% of patients treated with cefepime and ceftazidime, respectively (P=0.17). Bacteremic clearance was reported in 71 and 40% of patients treated with cefepime and ceftazidime, respectively (P=0.3). Treatment failure was reported in 43 and 40% of patients treated with cefepime and ceftazidime, respectively (P=NS). Of the treatment failures in microbiologically documented infections, 43 and 63% of patients treated with cefepime and ceftazidime, respectively, had resistant infections. Secondary: Overall non-drug-related mortality within 30 days of drug discontinuation of cefepime and ceftazidime was reported as 15 and 8%, respectively (P=0.06). The most common adverse effects of cefepime were rash, nausea and vomiting; for ceftazidime, rash and diarrhea.
Chuang et al.[115] (2002) Cefepime 50 mg/kg/dose IV BID to TID vs ceftazidime 50 mg/kg/dose IV BID to TID	OL, PRO, RCT Children aged two months to 15 years with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=96 3 to 20 days	Primary: Overall success rate of febrile prophylaxis, bacteremic clearances, new infection rate Secondary: Adverse events	Primary: After 72 hours of treatment, positive clinical response was reported as 82.8 and 87.9% in patients treated with cefepime and ceftazidime, respectively (P=0.94). Overall success rate of the empiric therapy was reported as 69 and 71% in patients treated with cefepime and ceftazidime, respectively (P=0.95). Bacteremic clearance was reported as 33 and 20% for patients treated with cefepime and ceftazidime, respectively (P=0.85). New infection rates were reported as 10.4 and 4.2% in patients treated with cefepime and ceftazidime, respectively (P=0.67). Secondary: Both treatments were well tolerated.
Gómez et al.[116] (2010) Cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a single dose (C-A)	OL, RCT Patients >18 years of age with an episode of febrile neutropenia	N=190 (317 episodes) Variable duration	Primary: Clinical efficacy and toxicity Secondary: Not reported	Primary: The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs piperacillin-tazobactam 4 g/500 mg IV every eight hours plus amikacin 15 mg/kg/day as a single dose (PT-A)				The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS). A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group. Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group. Secondary: Not reported
Uygun et al.[117] (2009) Cefepime 50 mg/kg IV every eight hours (CEF) vs piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every six hours (PIP/TAZO)	RCT, OL Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and had febrile neutropenia	N=70 (131 episodes) Variable duration	Primary: Success without modification Secondary: Not reported	Primary: Success without modification was similar between the two groups (60.0 vs 61.3% for PIP/TAZO and CEF, respectively; P>0.05). Success without modification was 84.8 and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin episodes. Success without modification was 29.2 and 12.5% in microbiologically documented infection episodes (P>0.05). Modifications were done with only glycopeptides in eight episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in two episodes. Duration of fever and neutropenia was similar in both groups. There was no significant difference in the duration of hospitalization between the treatment groups. No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Bassetti et al.[118] (2021) CREDIBLE-CR Cefiderocol 2 g every 8 h for 7 to 14 days vs best available therapy (pre-specified by the investigator before randomization and comprised of a maximum of three drugs) for 7 to 14 days	MC, OL, PG, RCT Patients ≥18 years of age admitted to hospital with nosocomial pneumonia, bloodstream infections or sepsis, or complicated urinary tract infections (UTI), and evidence of a carbapenem-resistant Gram-negative pathogen	N=152 28 days	Primary: For patients with nosocomial pneumonia or bloodstream infection or sepsis was clinical cure at test of cure (7 days [plus or minus 2] after the end of treatment). For patients with complicated UTI, the primary endpoint was microbiological eradication at test of cure Secondary: Safety	Primary: For patients with nosocomial pneumonia, clinical cure was achieved by 20 (50%; 95% CI, 33.8 to 66.2) of 40 patients in the cefiderocol group and ten (53%; 95% CI, 28.9 to 75.6) of 19 patients in the best available therapy group; for patients with bloodstream infection or sepsis, clinical cure was achieved by ten (43%; 95% CI, 23.2 to 65.5) of 23 patients in the cefiderocol group and six (43%; 95% CI, 17.7 to 71.1) of 14 patients in the best available therapy group. For patients with complicated UTIs, microbiological eradication was achieved by nine (53%; 95% CI, 27.8 to 77.0) of 17 patients in the cefiderocol group and one (20%; 95% CI, 0.5 to 71.6) of five patients in the best available therapy group. Secondary: In the safety population, treatment-emergent adverse events were noted for 91% (92 patients of 101) of the cefiderocol group and 96% (47 patients of 49) of the best available therapy group. Thirty-four (34%) of 101 patients receiving cefiderocol and nine (18%) of 49 patients receiving best available therapy died by the end of the study; one of these deaths (in the best available therapy group) was considered to be related to the study drug.
LeFrock et al.[119] (1982) Cefotaxime 2 to 6 g/day IV	PRO Patients 15 to 91 years of age with serious bone and joint infections including septic arthritis, bursitis, acute/chronic osteomyelitis	N=51 4 to 54 days	Primary: Clinical response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 39 of 51 patients; clinical failure was reported in six patients. Secondary: Cefotaxime therapy was well tolerated with transient adverse events.
Mauceri et al.[120] (1994)	MC, OL, PRO Patients ≥18 years	N=18 30.5±17.52	Primary: Clinical response, bacteriological	Primary: Satisfactory clinical response was reported in 83.8% of patients; satisfactory bacteriological response was reported in 78.6% of patients. All

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefotaxime 1 g (moderate infections) to 2 g (severe infections) IV TID using an ambulatory delivery system	of age with bone and joint infections using an ambulatory delivery system for medication	days	response Secondary: Adverse events	patients were eventually maintained on outpatient therapy. Secondary: Both the medication and delivery system were well tolerated. Two patients reported drug-related rash and one patient reported drug-related diarrhea.
Segev et al.[121] (1988) Cefotaxime 1 to 2 g IV TID vs ceftizoxime 1 to 2 g IV TID	MC, PRO, RCT Patients ≥17 years of age with moderate to severe infections	N=96 4 to 21 days	Primary: Clinical efficacy, bacteriological eradication Secondary: Adverse events	Primary: For both treatment groups, clinical efficacy and bacteriological eradication were reported as 90 and 95%, respectively. Secondary: Adverse events were more commonly reported by patients treated with cefotaxime compared to ceftizoxime (13.5 vs 6.8%, respectively); superinfection was more common with ceftizoxime therapy compared to cefotaxime therapy (25 vs 19%, respectively).
Hemsell et al.[122] (1995) Cefotetan 1 g IV as a single dose vs cefazolin 1 g IV as a single dose	DB, PRO, RCT Women undergoing elective abdominal hysterectomy	N=511 Single dose study	Primary: Prevention of major operative site infections Secondary: Not reported	Primary: A major operative site infection requiring parenteral antimicrobial therapy developed in 9.0% of evaluable women: 11.6% of women given cefazolin prophylaxis and 6.3% of women given cefotetan prophylaxis (RR, 1.84; 95% CI, 1.03 to 3.29; P<0.05). Risk factors for major operative site infection were younger age, lower postoperative hemoglobin concentration, and a proliferative endometrium. Of the women given cefazolin prophylaxis, 3.9%had a postoperative pelvic abscess compared to 0.8% of women given cefotetan prophylaxis (RR, 4.9; 95% CI, 1.09 to 22.16; P =0.04). A greater number of infections and more serious infections occurred following cefazolin prophylaxis; this treatment resulted in 234 additional hospital days for administration of IV antimicrobial therapy. Secondary: Not reported
Kobayashi et al.[123]	RCT	N=54	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into four doses Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.	Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	(177 episodes) 120 hours	Treatment success Secondary: Not reported	Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively (P≥0.05). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <0.5x10^9/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported
Lucasti et al.[124] (2013) Ceftazidime-avibactam (2000-500 mg) plus metronidazole (500 mg) IV every eight hours for five to 14 days	AC, DB, RCT Hospitalized patients 18 to 90 years of age with complicated intra-abdominal infection requiring surgical intervention and antibiotics	N=144 Test-of-cure: 2 weeks after last dose Late follow-up: 4 to 6 weeks post-therapy	Primary: Clinical response in microbiologically evaluable patients at the test-of-cure visit two weeks after the last dose of study therapy Secondary:	Primary: A favorable clinical response in the microbiologically evaluable population at the test-of-cure visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime-avibactam plus metronidazole and meropenem patients, respectively. The estimated difference in response rates was –2.2% (95% CI, –20.4 to 12.2%). Secondary: Adverse events were observed in 64.4% (65/101) and 57.8% (59/102) of patients in the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively. Overall, the types and frequencies of adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs meropenem 1000 mg plus placebo IV every 8 hours for 5 to 14 days			Safety	were similar in the two treatment groups, but there were more cases of nausea and vomiting and abdominal pain in the ceftazidime-avibactam plus metronidazole group and more cases of liver enzyme elevations in the meropenem group. In the majority of cases, adverse events were mild or moderate in intensity.
Mazuski et al.[125] (2016) Ceftazidime-avibactam (2,000-500 mg) IV plus metronidazole 500 mg IV every eight hours plus placebo vs meropenem 1,000 mg IV every eight hours plus placebo	DB, DD, MC, PRO, RCT Hospitalized patients 18 to 90 years of age with complicated intra-abdominal infection requiring surgical intervention or percutaneous drainage within 24 hours before or after randomization.	N=1,066 Test-of-cure: 28 to 35 days after randomization Late follow-up: 42 to 49 days after randomization	Primary: Clinical response at test-of-cure visit Secondary: Clinical response at end-of-treatment (up to 24 hours after the last infusion) and late follow-up visits, microbiological response at end-of-treatment, test-of-cure, and late follow-up visits, safety	Primary: The clinical cure rate at the test-of-cure visit for the ceftazidime-avibactam plus metronidazole group and the meropenem group was 82.5 and 84.9% (difference, -2.4%; 95% CI, -6.90 to 2.10); 81.6 and 85.1% (difference, -3.5%; 95% CI, -8.64 to 1.58); and 91.7 and 92.5% (difference, -0.8%; 95% CI, -4.61 to 2.89) in the modified intent-to-treat, microbiologically modified intent-to-treat, and clinically evaluable groups, respectively. Secondary: The difference in cure at the end-of-treatment between the ceftazidime-avibactam plus metronidazole group and the meropenem group was -3.9% (95% CI, -7.57 to -0.29) and -5.0% (95% CI, -9.24 to -0.93) in the and modified intent-to-treat and microbiologically modified intent-to-treat groups, respectively. At the late follow visit, the differences were -0.9% (95% CI, -5.45 to 3.72) and -2.3% (95% CI, -7.41 to 2.79) in the modified intent-to-treat and microbiologically modified intent-to-treat groups, respectively. Microbiological response was presumed based on clinical outcome. Intra-abdominal cultures require an invasive procedure and cultures were only obtained if clinically indicated. Microbiological outcomes in the microbiologically modified intent-to-treat population were similar to clinical responses. Adverse events were similar between treatment groups. Deaths due to an adverse reaction occurred in 2.5 and 1.5% of the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively.
Solomkin et al.[126] (2015) ASPECT-cIAI	DB, PC, RCT Patients ≥18 years of age with	N=806 24 to 32 days	Primary: Difference in clinical cure rates at the test-of-cure	Primary: Clinical cure rates were 83.0% (323/389) with ceftolozane-tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the modified intention to treat population at the test-of-cure visit. The weighted

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every eight hours IV for four to 14 days vs meropenem 1 g every eight hours IV for four to 14 days	complicated intra-abdominal infections		visit in the microbiological modified intention to treat population Secondary: Difference in clinical cure rates at the test-of-cure visit in the intention to treat and clinically evaluable populations	difference in clinical cure rates (ceftolozane-tazobactam plus metronidazole minus meropenem) was −4.2% with a 2-sided 95% CI of −8.91% to 0.54%, thus meeting the statistical criteria for noninferiority. Secondary: Clinical cure rates in the intention to treat population at test-of-cure were 83.6% for ceftolozane-tazobactam plus metronidazole and 86.2% for meropenem (difference, −2.6; 95% CI, −7.08 to 1.87), similar to those observed in the modified intention to treat population. In the clinically evaluable population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, −3.30 to 3.55). Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences recorded between treatments.
Bradley et al.[127] (2019) Ceftolozane-tazobactam plus metronidazole every eight hours IV for two to 13 days vs meropenem every eight hours IV for two to 13 days	MC, RCT, SB Hospitalized children (≥3 months to <18 years) with complicated intra-abdominal infection (cIAI)	N=83 8 to 15 days after the last dose of study drug	Primary: Safety and tolerability Secondary: Descriptive efficacy	Primary: In the safety analysis set, 52.5% of children in the ceftazidime-avibactam plus metronidazole group and 59.1% of children in the meropenem group experienced ≥1 treatment-emergent adverse event. The most common adverse events in the ceftazidime-avibactam plus metronidazole group were vomiting (14.8%), infusion site phlebitis (6.6%) and seroma (4.9%). Vomiting, cough and abdominal pain (each occurring in 9.1% of children) were the most common adverse events in the meropenem group. Secondary: In both treatment groups, per-patient favorable clinical and microbiologic response rates were ≥90% across all analysis sets early in the course of treatment and were sustained through to the test of cure visit.
Kaplinsky et al.[128] (1994) Ceftriaxone 50 mg/kg IV over 20 minutes	OL, non-RCT, PRO Pediatric outpatients with fever and neutropenia while being treated with various myelosuppressive	N=41 7 days	Primary: Clinical response, medication adherence Secondary: Not reported	Primary: Patients treated with ceftriaxone reported normalization of temperature within two to four days of treatment and resolution of neutropenia after about 10 days. Medication adherence to ceftriaxone regimens, by both patients and patients' parents, was rated excellent.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	agents for different malignancies			Secondary: Not reported
Metallidis et al.[129] (2008) Ceftriaxone 4 g IV every 24 hours plus ciprofloxacin 400 mg IV BID vs ceftazidime 2 g IV every eight hours plus amikacin 500 mg IV every eight hours or 20 mg/kg divided in three doses	RCT Patients with febrile neutropenia	N=95 ≥3 days	Primary: Microbiologically and clinically documented infections and adverse events Secondary: Not reported	Primary: The overall incidence of microbiologically and clinically documented infections was 81.3% (80.85% in the ceftriaxone/ciprofloxacin group and 82.14% in the ceftazidime/amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone/ciprofloxacin group and 37% in the ceftazidime/amikacin group; P=0.011). The ceftriaxone/ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime/amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive. There was a low incidence of adverse events in both groups. Secondary: Not reported
Bradley et al.[130] (1988) Ceftriaxone 50 mg/kg IV/IM QD (for non central nervous system infections) or ceftriaxone 100 mg/kg IV for day 1, then 80 mg/kg	PRO Pediatric outpatients one week to 15 years of age with serious bacterial soft tissue infections (egg cellulitis, arth-ritis, pyelonephritis) or meningitis using home therapy	N=101 1 to 6 days	Primary: Clinical failure, microbiologic failure Secondary: Adverse events	Primary: No clinical or microbiologic failures were reported in treatment groups. Pediatric patients with meningitis who were treated as outpatients did not report any neurologic dysfunction, cardiovascular instability, or relapse. Secondary: Diarrhea was reported in 13 and 6% of patients treated for meningitis and soft tissue infections, respectively. There were no discontinuations of therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV QD or BID (for meningitis)				
Dagan et al.[131] (1987) Ceftriaxone 75 mg/kg IM QD, then 50 mg/kg (maximum 1.5 g/day)	PRO Pediatric out-patients eight days to 17 years of age with serious community-acquired infection, including periorbital/buccal cellulitis, other cellulitis, urinary tract infection, pneumonia, osteomyelitis, mastoiditis, suppurative arthritis, orbital cellulitis	N=74 3 to 21 days	Primary: Clinical response Secondary: Adverse events	Primary: A 24-hour cure rate was reported for 72 patients (97%) treated with ceftriaxone in the outpatient setting. Three cases of new infection were reported within two months post ceftriaxone therapy. Secondary: No serious adverse events were reported. The most commonly reported side effect was mild diarrhea which occurred in 10% of patients.
Arguedas et al.[132] (2009) Ertapenem 1 g IV as a single daily dose (children aged 13 to 17 years) or 30 mg/kg/day divided BID (children aged 3 months to 12 years) vs ceftriaxone	AC, DB, RCT Patients ≥3 months and <18 years with complicated urinary tract infection, skin and skin structure infection and community-acquired pneumonia requiring initial parenteral antibiotic therapy	N=404 14 days	Primary: Incidence of clinical and laboratory drug-related serious adverse events Secondary: Incidence of any drug-related adverse events and any moderate-to-severe reactions at the parenteral infusion site	Primary: In each group, the mean duration of therapy (parenteral and oral antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was four days. Overall, 46.7% of the children had one or more clinical adverse events during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory adverse event (P=0.69). Secondary: The most common drug-related clinical adverse events during parenteral therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mg/kg/day as a single dose (children aged 13 to 17 years) or 50 mg/kg/day divided BID (children aged 3 months to 12 years)				(10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and one patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory adverse event in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group). In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Gupta et al.[133] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg QD as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-	OL, RCT, SC Pediatric patients two to 15 years of age with low-risk febrile neutropenia	N=88 (123 episodes) Variable duration	Primary: Treatment success Secondary: Not reported	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clavulanate 12.5 mg/kg orally every eight hours as outpatient therapy				
Solomkin et al.[134] (2009) Ceftriaxone 2 g IV QD plus metronidazole 500 mg IV BID for three to 14 days vs moxifloxacin 400 mg IV QD for three to 14 days	DB, MC, RCT Patients ≥18 years of age with community-origin complicated intra-abdominal infections with an expected duration of treatment with IV antimicrobials of 3 to 14 days	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure visit (10 to 14 days after the end of therapy) Secondary: Clinical and bacteriological success rates on days three and five during treatment and at the end-of-therapy; bacteriological success rate at the test-of-cure visit; and clinical success rate at the test-of-cure visit in patients with bacteriologically proven complicated intra-abdominal infections	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-to-treat populations. Secondary: During treatment, clinical improvement occurred in similar proportions of per protocol patients in the moxifloxacin group (31.0%) and the ceftriaxone plus metronidazole group (28.1%). In the intention-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole. In the per protocol population, clinical resolution at end-of-therapy occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at end-of-therapy occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Towfigh et al.[135] (2010) Ceftriaxone 2 g IV QD plus metronidazole 1 to	MC, OL, RCT, Patients ≥18 years of age with community-origin complicated intra-	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable population at the test-of-cure visit	Primary: In the clinically evaluable population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 g IV daily in divided doses for four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)	abdominal infections		Secondary: Bacteriological efficacy and safety	Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the microbiologically evaluable population, clinical cure rates for the different pathogens were similar between the two treatment groups. At test-of-cure in the microbiologically evaluable population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more serious adverse events among the treatment groups (P=1.000). The most frequently reported serious adverse events overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%), and ileus (1.3%).
Song et al.[136] (1998) Gentamicin plus metronidazole vs cefuroxime plus metronidazole vs	MA Patients scheduled to undergo elective surgery of the colon	147 trials 12 years	Primary: Rate of surgical wound infections Secondary: Not reported	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR, 1.17; 95% CI, 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy				cephalosporins are more effective than first generation cephalosporins (OR, 1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported
Chen et al.[137] (2011) Cephalexin 40 mg/kg/day orally in divided doses TID for seven days vs clindamycin 20 mg/kg/day orally in divided doses TID for seven days	RCT Patients six months to 18 years of age with uncomplicated skin and soft tissue infections not requiring hospitalization	N=200 3 months	Primary: Clinical improvement at 48 to 72 hours from the initiation of treatment Secondary: Resolution of disease at seven days	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary: A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by seven days (P=0.33). Only one patient developed a new skin and soft tissue infection while on therapy. Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the three-month follow-up, 18% of patients had a recurrent skin and soft tissue infection. The risk of new skin and soft tissue infection did not differ according to isolation of methicillin-resistant *Staphylococcus aureus* vs methicillin-susceptible *Staphylococcus aureus* from initial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				wound culture (21% methicillin-resistant *Staphylococcus aureus* vs 16% methicillin-susceptible *Staphylococcus aureus*; P=0.51) or by cephalexin or clindamycin assignment (20 vs 16%; P=0.46). There were no serious adverse events related to study treatment.
Phoolcharoen et al.[138] (2012) Ceftriaxone 1 g IV single dose before surgery vs cefazolin 1 g IV single dose before surgery	DB, RCT Patients undergoing elective total abdominal hysterectomy	N=320 4 weeks	Primary: Postoperative fever and infection Secondary: Not reported	Primary: Infectious events occurred in 23 (14.4%) patients who received ceftriaxone and in 21 (13.1%) patients who received cefazolin (P=0.74). Febrile morbidity occurred in 11.2% of patients in the ceftriaxone group and 9.4% of patients in the cefazolin group (P=0.55). Wound and vaginal cuff infection occurred in six (3.8%) and three (1.9%) patients in the ceftriaxone and cefazolin groups, respectively (P=0.32). Urinary tract infection occurred in three patients in each group (1.9%). Adverse clinical events were rare in both groups. Secondary: Not reported
Wu et al.[139] (2013) Cefazolin IV 1 g every eight hours for two to seven days vs ceftriaxone IV 1 g every 12 hours for two to seven days	RETRO Patients with acute variceal bleeding who had received endoscopic procedures from a university-affiliated tertiary care center and were enrolled in two groups based on severity of liver cirrhosis: group A (Child's A patients) and group B (Child's B and C patients)	N=102 34 months	Primary: Incidence of infections, time of rebleeding, death (during hospitalization) Secondary: Not reported	Primary: Infection prevention between patients who received prophylactic IV cefazolin and those who received IV ceftriaxone among all cirrhotic patients (85.7 vs 89.1%; P=0.319), for subgroup analysis for Child's A patients (93.1 vs 90.9%; P=0.641), and for subgroup analysis for Child's B and C patients (77.8 vs 87.5%; P=0.072) was similar. There was no significant difference in the actuarial probability of remaining free of overall rebleeding between patients prescribed cefazolin and those prescribed ceftriaxone (P=0.220). More rebleeding occurred in patients with Child's B and C who had received cefazolin compared to ceftriaxone (66.7 vs 25.0%; P=0.011); there was no difference between the two medications for patients with Child's A (P=0.376). The independent risk factors were thrombocytopenia (HR, 0.992; 95% CI, 0.985 to 0.999; P=0.029) and history of bleeding (HR, 2.674; 95% CI, 1.348 to 5.305; P=0.005). Death during hospitalization occurred in six patients (5.8%). Sepsis was the most frequent non-bleeding-related cause of death in three patients,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				followed by two patients with multiple organ failure. Secondary: Not reported
Winans et al.[140] (2012) Cefazolin IV (various dosing regimens) vs ceftriaxone IV (various dosing regimens)	RETRO Patients 18 years of age or older and discharged home on parenteral antibiotic therapy for a documented methicillin-susceptible *Staphylococcus aureus* infection	N=122 5 years	Primary: Clinical outcomes Secondary: Adverse events, complications, cost of therapy to the hospital	Primary: Sixty-eight percent of the patients in the cefazolin group and 79.5% patients in the ceftriaxone group had favorable clinical outcomes (P=0.17). Secondary: Adverse events were similar between the two groups (5.1% in the cefazolin group vs 2.3% in the ceftriaxone group; P=0.65). The most common adverse event reported in the cefazolin and ceftriaxone group was nausea/vomiting/diarrhea (2.6 vs 0%), followed by elevated blood urea nitrogen and serum creatinine (1.9 vs 0%), anemia (1.9 vs 0%), and rash (0 vs 2.3%). Complications occurred in 26.9% patients in the cefazolin group and 18.2% patients in the ceftriaxone group (P=0.38). Readmissions or emergency department visits due to the lack of improvement of the infectious process were similar in each group (P=0.68).
Nathan et al.[141] (2005) Chloramphenicol 100 mg/kg IM as a single dose vs ceftriaxone 100 mg/kg IM as a single dose	MC, OL, RCT Patients >2 months of age with meningitis	N=510 1 month	Primary: Treatment failure at 72 hours Secondary: Mortality within 72 hours, clinical sequelae at 72 hours, clinical failure between 24 and 48 hours requiring a second injection	Primary: Both treatment groups exhibited a treatment failure rate of 9% (90% CI, -3.8 to 4.5). Secondary: There was no significant difference in the mortality rate at 72 hours between the chloramphenicol and ceftriaxone groups (5 vs 6%, respectively; 90% CI, -2.3 to 3.8). Clinical failure took place in 4% of the chloramphenicol-group survivors and 3% of the ceftriaxone-treated patients (90% CI, -3.3 to 2.8). There was no significant difference in the re-injection rate between the chloramphenicol and ceftriaxone groups (8 vs 7%, respectively; 90% CI, -4.7 to 3.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Neurologic sequelae occurred in 5% of patients on chloramphenicol and 7% of patients on ceftriaxone therapy (90% CI, -2.1 to 5.1).
Peltola et al.[142] (1989) Chloramphenicol 100 mg/kg/day in four divided doses vs ampicillin 250 mg/kg/day in four divided doses plus chloramphenicol (administered until bacterial strain was shown to be susceptible to ampicillin alone) vs cefotaxime 150 mg/kg/day in four divided doses vs ceftriaxone 100 mg/kg QD	MC, RCT Children three months to 15 years of age with bacterial meningitis	N=220 7 days	Primary: Cerebrospinal fluid culture pathogens, time to sterile cerebrospinal fluid culture Secondary: Not reported	Primary: The cerebrospinal fluid became sterile significantly earlier in meningococcal meningitis compared to patients presenting with *H. influenzae* type b (P<0.01). At 24 hours, positive cultures were found only in patients receiving chloramphenicol. At 24 hours, the cerebrospinal fluid was sterile in a greater proportion of patients treated with cephalosporins compared to those treated with ampicillin-chloramphenicol or chloramphenicol (P<0.05). On day four, cerebrospinal fluid culture was positive in only one patient, who was treated with chloramphenicol. Secondary: Not reported
Girgis et al.[143] (1988) Chloramphenicol 100 mg/kg/day	RCT Patients with bacterial meningitis	N=100 6 days	Primary: Cerebrospinal fluid leukocyte count, glucose, protein content,	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus ampicillin 160 mg/kg/day every six hours (AMCL) vs ceftriaxone 100 mg/kg QD			disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate Secondary: Not reported	There was no significant difference between the two groups in the cerebrospinal fluid leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%. Secondary: Not reported
Girgis et al.[144] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every six hours (group 1) vs ceftriaxone 100 mg/kg IV QD (group 2)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary: Not reported	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *Streptococcus pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively. Secondary: Not reported
Jacobs et al.[145] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50 to 100 mg/kg/dose IV every six hours vs cefotaxime 50	PRO, RCT Patients one week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/dose IV every six hours				Secondary: Not reported
Rodriguez et al.[146] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 400 mg/kg/day IV in six divided doses vs ceftazidime 150 mg/kg/day IV divided into three doses, administered every eight hours	OL, RCT Patients one month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological sequelae, mean duration of therapy Secondary: Not reported	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime. Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported
Marks et al.[147] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 300 to 400 mg/kg/day IV every six hours vs cefuroxime 225 mg/kg/day IV divided into three	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, cerebrospinal fluid sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the cerebrospinal fluid sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses, administered every eight hours				
Johansson et al.[148] (1982) Chloramphenicol and ampicillin IV every six hours for at least five days (A+C) vs cefuroxime IV every eight hours for at least five days (CXM)	MC, RCT Patients with bacterial meningitis	N=67 ≥5 days	Primary: Efficacy and safety Secondary: Not reported	Primary: Complete resolution of symptoms was recorded in 18 of the 21 patients in the CXM group and in 14 of the 19 patients in the A+C group. Two patients died in each group. Adverse events were reported on eight occasions in seven patients in the CXM group and in four patients in the A+C group. Rashes developed in two CXM patients and three A+C patients. Fever was noted in two CXM patients. Moderately severe diarrhea which required symptomatic treatment developed in one patient in each group, and one CXM patient had repeated thrombophlebitis. Secondary: Not reported
Sexton et al.[149] (1998) Gentamicin 3 mg/kg QD plus ceftriaxone 2 g IV QD for two weeks vs ceftriaxone 2 g IV QD for four weeks	MC, OL, RCT Patients ≥18 years of age with endocarditis who had received <72 hours of parenteral antibiotic therapy	N=51 4 years	Primary: Clinical cure Secondary: Not reported	Primary: Clinical cure was observed for patients both at termination of therapy and at the three-month follow-up: 25 (96.2%) of the monotherapy patients and 24 (96%) of combination therapy patients were considered clinically cured. Ceftriaxone 2 g QD for four weeks and ceftriaxone 2 g QD plus gentamicin 3 mg/kg QD for two weeks were both judged effective for treatment of streptococcal endocarditis. Secondary: Not reported
Klugman et al.[150] (1995) Meropenem 40 mg/kg every eight hours for 7 to 14 days	PRO, RCT Children with a diagnosis of bacterial meningitis	N=190 6 weeks post-treatment	Primary: Clinical response (cure, cure with audiologic sequelae, cure with neurologic sequelae, cure with	Primary: In patients with pre-existing neurologic abnormalities, cure was achieved in 47% of meropenem patients compared to 60% of cefotaxime patients, cure with audiologic sequelae was reported in 6% of meropenem patients and 20% of cefotaxime patients, cure with neurologic sequelae was reported in 35% of meropenem patients and 0% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 12% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefotaxime 75 to 100 mg/kg every eight hours for 7 to 14 days			both audiologic and neurologic sequelae, death), bacteriologic response Secondary: Not reported	meropenem patients and 20% of cefotaxime patients, and death was not reported in any patients in either group. In patients without pre-existing neurological abnormalities, cure was achieved in 79% of meropenem patients compared to 83% of cefotaxime patients, cure with audiologic sequelae was reported in 16% of meropenem patients and 12% of cefotaxime patients, cure with neurologic sequelae was reported in 3% of meropenem patients and 2% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 2% of meropenem patients and 0% of cefotaxime patients, and death was reported in no patients in the meropenem group and 3% of cefotaxime patients. Bacteriologic eradication rates were 100% in both groups. Secondary: Not reported
Odio et al.[151] (1999) Meropenem 40 mg/kg every eight hours vs cefotaxime 45 mg/kg every six hours Treatment duration for both groups was 7 to 14 days depending on infection.	MC, PRO, RCT Patients 2 months to 12 years of age with a diagnosis of bacterial meningitis	N=266 5 to 7 months post-treatment	Primary: Clinical response (cure, survival with mild neurological sequelae, survival with severe neurological sequelae, death), microbiologic efficacy Secondary: Not reported	Primary: At the five to seven week follow-up, no significant differences between the meropenem group and the cefotaxime group were observed with respect to cure, survival with sequelae, or death (P=0.624). Severe sequelae were present in 30% of meropenem patients and in 17% of cefotaxime patients, and this difference was NS (P=0.056). At the five to seven week visit, severe sequelae in the form of audiology were present in 25% of children in the meropenem group and 15% in the cefotaxime group. By the five to seven month visit, the percentages had decreased to 18% in the meropenem group and 14% in the cefotaxime group. No significant differences were seen in any group at any time. At the end of treatment, bacterial eradication was observed in 95% of patients in the meropenem group and 96% in the cefotaxime group. Secondary: Not reported
Smyth et al. [152]	DB, RCT	N=244	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Tobramycin 10 mg/kg/day IV administered TID for 14 days plus ceftazidime vs tobramycin 10 mg/kg/day IV QD for 14 days plus ceftazidime IV	Patients older than five years of age with cystic fibrosis who had a pulmonary exacerbation	14 days	Change in forced expiratory volume in one second over 14 days of treatment, mean change in baseline forced expiratory volume in one second Secondary: Change in serum creatinine	The mean change in forced expiratory volume in one second (percent predicted) over 14 days was similar between the two regimens (10.4% [QD] vs 10.0% [TID] (adjusted mean difference, 0.4%; 95% CI, –3.3 to 4.1). Mean % change in forced expiratory volume in one second from baseline was also similar in both treatments (21.9 vs 22.1%; –0.1%; –8.0 to 7.9). Secondary: There was no significant difference in percent change in creatinine from baseline (–1.5% [QD] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean percent change in creatine, –4.5% [QD] vs 3.7% [TID] (adjusted mean difference, –8.0%; 95% CI, –15.7 to –0.4; P=0.04).

Drug regimen abbreviations: BID=twice daily, IM=intramuscularly, IV=intravenously, PO=by mouth, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel- group, PRO=prospective, RETRO=retrospective, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Other abbreviations: CI=confidence interval, HR=hazard ratio, IV=intravenous, NaCl=sodium chloride, NS=non-significant, OR=odds ratio, RR=relative risk, SMX-TMP=sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification:
Frequency of dosing is identified as a major factor in compliance for antibiotic treatment.[153] Average compliance is reduced as dosing frequency is increased. Acceptable compliance was observed most frequently with once or twice daily antibiotic regimens.[153] In a study of medication adherence, Ballantyne reported no significant difference in clinical efficacy for patients treated with once daily cefadroxil compared to cefaclor administered three times daily (91 vs 95%, respectively; P=0.41). However, medication adherence was greater in patients treated with cefadroxil once daily compared to patients treated with cefaclor three times daily (2 vs 77%, respectively).[41]

A study comparing intramuscular ceftriaxone (for up to two doses) and oral amoxicillin-clavulanate (three times daily for 10 days) in patients with acute otitis media demonstrated similar treatment failure rates in both groups (4.6 and 4.7%, respectively).[154] However, recurrence rates of acute otitis media between days 31 and 90 were observed significantly more frequently in children treated with amoxicillin-clavulanate than with ceftriaxone (29.4 vs 13.6%; P=0.012). Seventy-five percent of study participants took amoxicillin-clavulanate as prescribed or in excess; 25% of study participants took amoxicillin-clavulanate in a quantity less than that prescribed. More parents preferred the intramuscular route over oral therapy (68 vs 32%, respectively; P=0.0001).

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 15. Relative Cost of the Cephalosporins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Cefaclor	capsule, extended-release tablet, suspension	N/A	N/A	$$$$$
Cefadroxil	capsule, suspension, tablet	N/A	N/A	$
Cefazolin	injection	N/A	N/A	$$$
Cefdinir	capsule, suspension	N/A	N/A	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cefepime	injection	N/A	N/A	$$$$
Cefiderocol	injection	Fetroja®	$$$$$	N/A
Cefixime	capsule, chewable tablet, suspension	Suprax®*	$$$$$	$$$$$
Cefotaxime	injection	Claforan®*	$$-$$$$$	$$$
Cefpodoxime	suspension, tablet	N/A	N/A	$$$
Cefprozil	suspension, tablet	N/A	N/A	$
Ceftaroline	injection	Teflaro®	$$$$$	N/A
Ceftazidime	injection	Tazicef®*	$$$-$$$$$	$$$$$
Ceftriaxone	injection	N/A	N/A	$
Cefuroxime	injection, tablet	N/A	N/A	$
Cephalexin	capsule, suspension, tablet	N/A	N/A	$
Combination Products				
Ceftazidime and Avibactam	injection	Avycaz®	$$$$$	N/A
Ceftolozane and Tazobactam	injection	Zerbaxa®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] They are often grouped into generations according to their spectrum of activity. The majority of the cephalosporins are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the cephalosporins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the cephalosporin. The cephalosporins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, infectious diarrhea, sexually transmitted diseases, infectious exacerbations of chronic obstructive pulmonary disease, nosocomial pneumonia, febrile neutropenia, intra-abdominal infections, Lyme disease, and for surgical prophylaxis.[10,11-17,20,21,30,33,34,36,38,40] They are recommended as an alternative treatment option for urinary tract infections, otitis media, group A streptococcal pharyngitis, community-acquired pneumonia, and sinusitis, especially in situations where the patient is allergic to penicillin.[22-26,28,31,32]

Numerous studies have demonstrated comparable efficacy among the cephalosporins for the treatment of skin and soft-tissue infections, urinary tract infections, upper/lower respiratory tract infections, febrile neutropenia, and for surgical prophylaxis.[41,42,46,47,49,59-70,82,84-98,108-115] There are relatively few studies which demonstrate greater clinical cure or microbiological eradication rates with one cephalosporin over another.[43,44,78,81,83,99,101,129] Data from published studies supports similar safety profiles among the cephalosporins, particularly within each generation.

Both ceftazidime-avibactam and ceftolozane-tazobactam are indicated for the treatment of complicated intra-abdominal infections when used in combination with metronidazole, complicated urinary tract infections including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.[7,8] Clinical trials have suggested ceftolozane-tazobactam and ceftazidime-avibactam have similar efficacy to imipenem–cilastatin and levofloxacin, respectively in the treatment of complicated urinary-tract infections.[75,77] Both combination products, each in combination with metronidazole, have also demonstrated similar efficacy to meropenem in the treatment of complicated intra-abdominal infections.[124-126]

Cefiderocol is a siderophore cephalosporin indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections, including pyelonephritis and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible Gram-negative microorganisms. To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefiderocol and other antibacterial drugs,

cefiderocol should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.[4]

There is insufficient evidence to support that one brand cephalosporin is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand cephalosporins within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cephalosporin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous β-Lactam Antibiotics
AHFS Class 081207
May 3, 2023

I. Overview

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-9] With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4]

The β-lactam antibiotics exert their antibacterial activity by binding to penicillin-binding proteins, which inactivate the enzymes responsible for cell-wall synthesis in susceptible microorganisms. Aztreonam belongs to the monobactam class of antibiotics and has strong activity against susceptible gram-negative bacteria; however, it has no useful activity against gram-positive bacteria or anaerobes. Aztreonam is resistant to some β-lactamases but is inactivated by extended-spectrum β-lactamases. Cefotetan and cefoxitin are considered cephamycins and demonstrate a spectrum of activity similar to the second generation cephalosporins. The carbapenems include doripenem, ertapenem, imipenem-cilastatin, meropenem, and meropenem-vaborbactam. These agents have a broad spectrum of activity and their chemical structure renders them highly resistant to β-lactamases.[1-9] Recarbrio® (imipenem-cilastatin-relebactam) is a combination of imipenem/cilastatin and relebactam. Relebactam is a beta lactamase inhibitor and has no intrinsic antibacterial activity: it protects imipenem from degradation by certain serine beta lactamases.[8]

The miscellaneous β-lactam antibiotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the injectable products are available in a generic formulation, with the exception of meropenem-vaborbactam and imipenem-cilastatin-relebactam. This class was last reviewed in May 2021.

Table 1. Miscellaneous β-Lactam Antibiotics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Aztreonam	inhalation solution, injection	Azactam®*, Cayston®	aztreonam
Cefotetan	injection	Cefotan®*	cefotetan
Cefoxitin	injection	Mefoxin®*	cefoxitin
Ertapenem	injection	Invanz®*	ertapenem
Meropenem	injection	N/A	meropenem
Combination Products			
Imipenem and cilastatin	injection	Primaxin®*	imipenem and cilastatin
Imipenem, cilastatin, and relebactam	injection	Recarbrio®	none
Meropenem and vaborbactam	injection	Vabomere®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The miscellaneous β-lactam antibiotics have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the miscellaneous β-lactam antibiotics that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these

microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Miscellaneous β-Lactam Antibiotics[1-9]

Organism	Single Entity Agents					Combination Products		
	Aztreonam†	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Gram-Positive Aerobes								
Enterococcus faecalis					✔	✔ §‡		
Staphylococcus aureus		✔	✔	✔	✔	✔ §‡		
Staphylococcus epidermidis		✔	✔			✔ ‡		
Streptococcus species		✔	✔					
Streptococcus agalactiae		✔	✔	✔	✔	✔ ‡		
Streptococcus pneumoniae		✔	✔	✔	✔	✔ §‡		
Streptococcus pyogenes		✔	✔	✔	✔	✔ §‡		
Streptococcus viridans group					✔	✔ §		
Gram-Negative Aerobes								
Acinetobacter species						✔ §‡		
Acinetobacter calcoaceticus						✔ §	✔	
Citrobacter species	✔					✔ §‡		
Citrobacter freundii	✔						✔	✔
Citrobacter koseri								✔
Enterobacter species	✔					✔ §‡		
Enterobacter aerogenes								✔
Enterobacter cloacae	✔					✔ §	✔	✔
Escherichia coli	✔	✔	✔	✔	✔	✔ §‡	✔	✔
Gardnerella vaginalis						✔ ‡		
Haemophilus influenzae	✔	✔	✔	✔	✔	✔ §‡	✔	
Haemophilus parainfluenzae						✔ ‡		
Klebsiella species	✔	✔	✔	✔		✔ §‡		
Klebsiella aerogenes							✔	
Klebsiella oxytoca	✔						✔	✔
Klebsiella pneumoniae	✔	✔		✔	✔	✔ §	✔	✔
Moraxella catarrhalis				✔				
Morganella morganii		✔	✔			✔ ‡		✔
Neisseria gonorrhoeae		✔	✔					
Neisseria meningitidis					✔			
Proteus species		✔						
Proteus mirabilis	✔	✔	✔	✔	✔			✔
Proteus vulgaris		✔	✔			✔ ‡		
Providencia species			✔					✔
Providencia rettgeri		✔				✔ ‡		
Pseudomonas aeruginosa	✔				✔	✔ §‡	✔	✔

Organism	Single Entity Agents					Combination Products		
	Aztreonam†	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Serratia species	✔					✔ ‡		
Serratia marcescens	✔	✔				✔ ‡	✔	✔
Gram-Positive Anaerobes								
Bifidobacterium species						✔ ‡		
Clostridium species		✔	✔			✔ ‡		
Clostridium clostridioforme				✔				
Eubacterium species						✔ ‡		
Eubacterium lentum				✔				
Peptococcus species						✔ ‡		
Peptococcus niger		✔	✔					
Peptostreptococcus species		✔	✔	✔	✔	✔ §‡		
Porphyromonas asaccharolytica				✔				
Prevotella bivia		✔		✔				
Prevotella disiens		✔						
Prevotella melaninogenica		✔						
Propionibacterium species						✔ ‡		
Gram-Negative Anaerobes								
Bacteroides species			✔			✔ §‡		
Bacteroides caccae							✔	
Bacteroides distasonis			✔	✔		✔ §		
Bacteroides fragilis		✔	✔	✔	✔	✔ §‡	✔	
Bacteroides intermedius						✔ §		
Bacteroides ovatus			✔	✔			✔	
Bacteroides stercoris							✔	
Bacteroides thetaiotaomicron			✔	✔	✔	✔ §	✔	
Bacteroides uniformis				✔			✔	
Bacteroides vulgatus		✔					✔	
Fusobacterium species		✔				✔ §‡		
Fusobacterium nucleatum							✔	
Parabacteroides distasonis							✔	

† Injection formulation.
‡ Intravenous formulation.
§ Intramuscular formulation.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous β-lactam antibiotics are summarized in Table 3.

Table 3. Treatment Guidelines Using the Miscellaneous β-Lactam Antibiotics

Clinical Guideline	Recommendation(s)
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[10]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S*

Clinical Guideline	Recommendation(s)
	pneumoniae that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious disease specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable

Clinical Guideline	Recommendation(s)
	to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[11]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug

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	use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered. • Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[12]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  ○ Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  ○ Patients with previous IE.
	  ○ Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  ○ Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  ○ If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.

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	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. <u>Antimicrobial therapy: regimens</u> • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in β-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o β-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin.

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	○ *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. ○ *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): ○ Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). ○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[13]	<u>Empirical therapy</u> • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. <u>Pathogen specific therapy</u> • Penicillin-sensitive pneumococcal meningitis: ○ Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. ○ Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: ○ Ceftriaxone or cefotaxime plus vancomycin±rifampicin. ○ Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: ○ Benzyl penicillin, ceftriaxone, or cefotaxime. ○ Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: ○ Ceftriaxone or cefotaxime. ○ Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: ○ Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. ○ Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: ○ Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. ○ Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.

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	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem.
	• Pseudomonal meningitis:
	  o Meropenem±gentamicin.

Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[14]	<u>Empiric Therapy</u>
	• Empiric therapy should be used when infection is suspected but cultures are not yet available.
	• Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended.
	• Choice of anti-pseudomonal β-lactam should be based on local resistance patterns.
	• In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 µg/mL
	• For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin
	• Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens
	<u>Pathogen Specific Therapy</u>
	• Methicillin-susceptible *S. aureus*
	  o Recommended treatment includes nafcillin or oxacillin
	  o In patients who cannot receive β-lactams, vancomycin is recommended
	• Methicillin-resistant *S. aureus*
	  o Recommended treatment includes vancomycin
	• *P. acnes*
	  o Recommended treatment includes penicillin G
	• *Pseudomonas* species
	  o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone
	• Gram-negative bacilli
	  o Recommended treatment includes ceftriaxone or cefotaxime
	• Extended-spectrum β-lactamase–producing gram-negative bacilli
	  o Recommended treatment includes meropenem
	• *Acinetobacter* species
	  o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B
	• *Candida* species
	  o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine
	• *Aspergillus* or *Exserohilum*
	  o Recommended treatment includes voriconazole
	• In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain
	  o Use of rifampin as part of combination therapy is recommended
	<u>Duration of Therapy</u>
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms
	  o Duration is recommended to be 10 days
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features
	  o Duration is recommended to be 10 to 14 days

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	• Infections caused by *S. aureus* or gram-negative bacilli
	  o Duration is recommended to be 10 to 14 days
	• Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy
	  o It is recommended that therapy be continued for 10 to 14 days after the last positive culture

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[15]	<u>Impetigo and ecthyma</u>
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	<u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u>
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	<u>Recurrent skin abscesses</u>
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten-day course of an antibiotic active against the pathogen isolated.
	• Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection.
	• Adult patients should be evaluated for neutrophil disorders if recurrent

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	abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.

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	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. <u>Clostridial gas gangrene or myonecrosis</u> • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. <u>Animal bites</u> • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. <u>Bacillary angiomatosis and cat scratch disease</u> • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two

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	weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)**[16]	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended.
	• Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost.
	• A course of antibiotic therapy of one to two weeks is usually adequate for most mild and moderate infections.
	  o For more serious skin and soft tissue infections, three weeks is usually sufficient.
	  o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed.
	• Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding.
	• For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity.
	• For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection.
	• For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.

Centers for Disease	Genital herpes

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Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[17]	• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent

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	recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human

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	immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. <u>Pediculosis pubis (pubic lice infestation)</u> • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off. o Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or

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	pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. o Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days.

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	○ Tinidazole 1 g orally once daily for five days. ○ Clindamycin 300 mg orally twice daily for seven days. ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days. ○ Secnidazole 2 g oral granules in a single dose. • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: ○ Butoconazole 2% cream 5 g single intravaginal application. ○ Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. ○ Clotrimazole 2% cream 5 g intravaginally daily for three days. ○ Miconazole 2% cream 5 g intravaginally daily for seven days. ○ Miconazole 4% cream 5 g intravaginally daily for three days. ○ Miconazole 100 mg vaginal suppository one suppository daily for seven days. ○ Miconazole 200 mg vaginal suppository one suppository for three days. ○ Miconazole 1,200 mg vaginal suppository one suppository for one day. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida*

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	albicans respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and

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	risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal o Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal Intra-anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen. o Surgical removal. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)**[18] Reviewed and deemed current as of 07/2013	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis does not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven-day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects

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	compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute pyelonephritis • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24-hour dose of an aminoglycoside) may replace the initial one-time intravenous ciprofloxacin and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24-hour dose of an aminoglycoside) is recommended. • Oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24-hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24-hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.

American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[19]
 	
Reaffirmed 2016
	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows:
	  ○ Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days.
	  ○ Trimethoprim 100 mg twice daily for three days.
	  ○ Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days.
	  ○ Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days.
	  ○ Fosfomycin tromethamine, 3 g dose (powder) single dose.

American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in**	Evaluation • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index

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Women: Guideline (2022)[20]	patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. • Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)[21]**	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not

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	sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[22]	<u>Aerosolized antibiotics</u> • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. <u>Anti-inflammatory agents</u> • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with a forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. • For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations.

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	Antistaphylococcal antibiotics • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. Bronchodilators • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. Hypertonic saline • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. Ivacaftor • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. Macrolide antibiotics • For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. Recombinant human DNase • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in**	Outpatient treatment • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate

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Infants and Children Older Than 3 Months of Age (2011)[23] Reviewed and deemed current as of 04/2013	community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-acquired Pneumonia (2019)[24]**	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low

Clinical Guideline	Recommendation(s)
	quality of evidence for combination therapy) <u>Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting</u>: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. <u>Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting</u>: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid. • Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)[25]**	<u>Empiric Therapy</u> • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known o Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available <u>Pathogen-Specific Therapy</u>

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	• MRSA
	  o Vancomycin or linezolid are recommended treatments
	• *P. aeruginosa*
	  o It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy
	  o In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible
	• Extended-spectrum β-lactamase-producing gram-negative bacilli
	  o Therapy should be based on the results of susceptibility testing
	• *Acinetobacter* Species
	  o Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents
	• Carbapenem-Resistant Pathogens
	  o If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin
	<u>Duration of therapy</u>
	• Seven day course of treatment

Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children (2010)[26]**	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended.

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	• Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. Community-acquired infection in pediatric patients • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health care-associated infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression (2018)**[27]	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX),

Clinical Guideline	Recommendation(s)
	for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir). • Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)**[28]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate.

Clinical Guideline	Recommendation(s)
	○ Moxifloxacin. ○ Levofloxacin. ○ Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): ○ Intravenous antibiotic monotherapy is preferred. ○ Intravenous combination therapy could be considered especially in cases of resistance. <u>Antibacterial agents: empiric gram-positive activity</u> • Vancomycin ○ Gram-positive organisms with the exception of VRE and a number of rare organisms. ○ Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. ○ Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin ○ Has in vitro activity against VRE but is not FDA-approved for this indication. ○ Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. ○ Not indicated for pneumonia due to inactivation by pulmonary surfactant. ○ Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid ○ Gram-positive organisms including VRE. ○ Hematologic toxicity (typically with prolonged cases over two weeks) may occur. ○ Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. ○ Treatment option for VRE and MRSA. ○ Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime ○ Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever. ○ Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime ○ Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. ○ Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. ○ Use for suspected intra-abdominal source.

Clinical Guideline	Recommendation(s)
	○ Meropenem is preferred over imipenem for suspected/proven CNS infection. ○ Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. ○ Empiric therapy for neutropenic fever. ○ Data are limited, but it is expected that doripenem, like meropenem, would be efficacious. • Piperacillin-tazobactam ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Use for suspected intra-abdominal source. ○ Not recommended for meningitis. ○ Empiric therapy for neutropenic fever. <u>Antibacterial agents: other</u> • Aminoglycosides ○ Activity primarily against gram-negative organisms. ○ Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate ○ Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. ○ Ciprofloxacin alone has no activity against anaerobes. ○ Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes. ○ Oral combination therapy in low-risk patients. ○ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. ○ Increasing Gram-negative resistance in many centers. ○ Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered. • Levofloxacin/ moxifloxacin ○ Good activity against gram-negative and atypical organisms. ○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. ○ Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole ○ Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. ○ Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. ○ Interactions with methotrexate.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America:	<u>Common principles</u> • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is

Clinical Guideline	Recommendation(s)
Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)[29]	the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. <u>Cardiac procedures</u> • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. <u>Thoracic procedures</u> • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. <u>Gastroduodenal procedures</u> • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. <u>Biliary tract procedures</u> • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone.

Clinical Guideline	Recommendation(s)
	Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. Colorectal procedures • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation. • Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity. Head and neck procedures • Clean procedures: o Antimicrobial prophylaxis is not required. • Clean-contaminated procedures: o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures. o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam. o Clindamycin is a reasonable alternative in patients with a documented β-

Clinical Guideline	Recommendation(s)
	lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. Neurosurgery procedures • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). Cesarean delivery procedures • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. Hysterectomy procedures • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended.

Clinical Guideline	Recommendation(s)
	Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous β-lactam antibiotics are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Miscellaneous β-Lactam Antibiotics[1-9]

Indication	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Central Nervous System Infections								
Meningitis					✔			
Dermatological Infections								
Abscesses						✔ §		
Burns	✔ ‡							
Cellulitis						✔ §		
Cutaneous infections (adjunctive therapy to surgery)	✔ ‡							
Diabetic foot infections without osteomyelitis				✔				
Infected skin ulcers	✔ ‡					✔ §		
Postoperative wounds	✔ ‡							
Skin and skin-structure infections	✔ ‡	✔	✔	✔	✔	✔ § ‖		
Wounds infections						✔ §		
Genitourinary Infections								
Cystitis	✔ ‡							
Endometritis	✔ ‡		✔					
Gynecologic infections	✔ ‡	✔	✔			✔ § ‖		
Pelvic cellulitis	✔ ‡		✔					
Pelvic infections, acute				✔				
Pelvic inflammatory disease			✔					
Postpartum endomyometritis				✔		✔ §		
Postsurgical gynecologic infections				✔				
Pyelonephritis	✔ ‡			✔			✔	✔
Septic abortion				✔				
Urinary tract infections	✔ ‡	✔	✔	✔		✔ ‖	✔	✔
Respiratory Infections								

Indication	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Bronchitis	✔ ‡					✔ §		
Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*	✔ †							
Lung abscess			✔					
Pneumonia	✔ ‡		✔			✔ §	✔	
Pneumonia (community acquired)				✔				
Respiratory tract infections (lower)	✔ ‡	✔	✔			✔ § ‖		
Miscellaneous Infections								
Abscesses (adjunctive therapy to surgery)	✔ ‡							
Appendicitis					✔	✔ §		
Appendicitis with peritonitis						✔ §		
Bone and/or joint infections		✔	✔			✔ ‖		
Endocarditis						✔ ‖		
Infections complicating hollow viscus perforations (adjunctive therapy to surgery)	✔ ‡							
Infections of serous surfaces (adjunctive therapy to surgery)	✔ ‡							
Intra-abdominal infections	✔ ‡	✔	✔	✔	✔	✔ § ‖	✔	
Peritonitis	✔ ‡		✔		✔			
Perioperative prophylaxis		✔	✔	✔				
Septicemia	✔ ‡		✔			✔ ‖		

†Inhalation solution formulation.
‡Injection formulation.
§Intramuscular formulation.
‖Intravenous formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous β-lactam antibiotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous β-Lactam Antibiotics[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Aztreonam	INH: low IM: 100	INH: 56	Liver (7)	INH: Renal (10) IM/IV: Renal (60 to 70) Feces (12)	INH: 2.1 IM/IV: 1.6 to 2.9
Cefotetan	N/A	78 to 91	Not reported	Renal (51 to 81) Bile (12)	3.0 to 4.6
Cefoxitin	N/A	41 to 75	Liver (<2)	Renal (85) Bile (<1)	0.8 to 1.0
Ertapenem	IM: 90	85 to 95	Renal	Renal (>80) Feces (10)	4
Meropenem	N/A	2	Extrarenal (20 to 25)	Renal (70) Fecal (2)	1.0 to 1.5
Combination Products					
Imipenem and cilastatin	Imipenem: 75 Cilastatin: 95	Imipenem: 20 Cilastatin: 40	Renal	Imipenem: Renal (50 to 70) Cilastatin: Renal (70 to 75)	Cilastatin: 2 to 3 Imipenem: 1
Imipenem, cilastatin, and relebactam	Imipenem: 75 Cilastatin: 95 Relebactam: Not reported	Imipenem: 20 Cilastatin: 40 Relebactam:22	Renal	Imipenem: Renal (50 to 70) Cilastatin: Renal (70 to 75) Relebactam: Renal (90)	Cilastatin: 2 to 3 Imipenem: 1 Relebactam: 1.2
Meropenem and vaborbactam	N/A	Meropenem: 2 Vaborbactam: 33	Renal	Meropenem: Renal (40 to 60) Fecal (2) Vaborbactam: Renal (75 to 95)	Meropenem: 1.2 to 1.5 Vaborbactam: 1.7 to 2.0

IM=intramuscular, INH=inhalation, IV=intravenous

V. Drug Interactions

Major drug interactions with the miscellaneous β-lactam antibiotics are listed in Table 6.

Table 6. Major Drug Interactions with the Miscellaneous β-Lactam Antibiotics[1]

Generic Name(s)	Interaction	Mechanism
Ertapenem, imipenem-cilastatin, imipenem-cilastatin-relebactam, meropenem, meropenem-vaborbactam	Valproic acid	Plasma concentrations and pharmacologic effects of valproic acid may be decreased by carbapenems.
Imipenem-cilastatin, imipenem-cilastatin-relebactam	Valganciclovir	Concurrent use may result in increased central nervous system toxicity (e.g., seizures).
Imipenem-cilastatin, imipenem-cilastatin-relebactam	Theophylline	Concurrent use of imipenem and theophylline may result in theophylline toxicity (nausea, vomiting, palpitations, seizures).

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous β-lactam antibiotics are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous β-Lactam Antibiotics[1-9]

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Cardiovascular								
Arrhythmia	-	-	-	<1	-	-	-	-
Asystole	-	-	-	<1	-	-	-	-
Atrial fibrillation	-	-	-	<1	-	-	-	-
Bradycardia	-	-	-	<1	<1	-	-	-
Cardiac arrest	-	-	-	<1	<1	-	-	-
Chest pain/discomfort	<1†, 8‡	-	-	1 to 2	<1	<1	-	<1
Edema	-	-	-	3	-	-	-	-
Heart failure	-	-	-	<1	<1	-	-	-
Heart murmur	-	-	-	<1	-	-	-	-
Hypertension	-	-	-	1 to 2	<1	-	-	-
Hypotension	<1†	-	<1	1 to 2	<1	<1	-	<1
Myocardial infarction	-	-	-	-	<1	-	-	-
Palpitations	-	-	-	-	-	<1	-	-
Shock	-	-	-	-	1	-	-	-
Syncope	-	-	-	<1	<1	-	-	-
Tachycardia	-	-	-	1 to 2	<1	<2	-	-
Ventricular tachycardia	-	-	-	<1	-	-	-	-
Central Nervous System								
Agitation/delirium	-	-	-	-	<1	<1	-	-
Anxiety	-	-	-	1	<1	-	-	-
Confusion	<1†	-	-	-	<1	<1	-	-
Delirium	-	-	-	<1	-	-	-	-
Depression	-	-	-	<1	<1	-	-	-
Dizziness	<1†	-	-	2	<1	<1	-	<1
Encephalopathy	<1†	-	-	-	-	<1	-	-
Fatigue	-	-	-	<1	-	-	-	-
Fever	<1†, 13‡	<1	<1	2 to 5	<1	<1	4	1.5
Hallucinations	-	-	-	-	<1	<1	-	<1
Headache	<1†	-	-	6 to 7	2 to 8	<2	-	8.8
Insomnia	<1†	-	-	3	<1	-	-	<1
Mental status changes	-	-	-	3 to 5	-	-	-	-
Myasthenia gravis exacerbation	-	-	<1	-	-	-	-	-

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Myoclonus	-	-	-	<1	-	<1	-	-
Nervousness	-	-	-	<1	<1	-	-	-
Paresthesia	<1†	-	-	<1	<1	<1	-	<1
Psychic disturbances	-	-	-	-	-	<1	-	-
Seizures	<1†	✔	✔	<1	<1	<1	-	✔
Somnolence	-	-	-	<1	<1	<1	-	-
Tremor	-	-	-	<1	-	<1	-	<1
Vertigo	<1†	-	-	<1	-	<1	-	-
Dermatological								
Angioedema	<1†	✔	<1	-	<1	-	-	-
Angioneurotic edema	-	-	-	-	-	<1	-	-
Dermatitis	-	-	-	<1	-	-	-	-
Diaphoresis	<1†	-	-	<1	<1	-	-	-
Erythema	-	-	-	1 to 2	-	-	-	-
Erythema multiforme	<1†	-	✔	-	<1	<1	-	-
Exfoliative dermatitis	<1†	-	<1	-	-	-	-	-
Flushing	<1†	-	-	<1	-	<1	-	-
Hyperhidrosis	-	-	-	-	-	<1	-	-
Petechiae	<1†	-	-	-	-	-	-	-
Pruritus	<1†	<1	<1	1 to 2	1	<1	-	-
Rash	1 to 10†, 2‡	<1	<1	2 to 3	2 to 3	≤2	4	-
Skin ulcer	-	-	-	-	<1	-	-	-
Stevens-Johnson syndrome	-	✔	✔	-	<1	<1	-	-
Toxic epidermal necrolysis	<1†	✔	<1	-	<1	<1	-	✔
Urticaria	<1†	<1	<1	<1	<1	<1	-	✔
Gastrointestinal								
Abdominal cramps	<1†	-	-	-	-	-	-	-
Abdominal enlargement	-	-	-	<1	<1	-	-	-
Abdominal pain	7‡	-	-	4 to 5	<1	<1	-	-
Abnormal taste	<1†	-	-	<1	-	<1	-	-
Acid regurgitation	-	-	-	1 to 2	-	-	-	-
Anorexia	-	-	-	<1	<1	-	-	<1
Aphthous ulcer	<1†	-	-	<1	-	-	-	-
Clostridium difficile -associated colitis	✔	-	-	-	-	<1	-	-
Clostridium difficile-associated diarrhea	<1†	-	-	<1	✔	<1	✔	✔
Cholelithiasis	-	-	-	<1	-	-	-	-
Constipation	-	-	-	2 to 4	1 to 7	-	4	-
Diarrhea	1 to 10†	<1	1 to 10	9 to 12	4 to 7	1 to 2	8	3.3
Dyspepsia	-	-	-	1	<1	-	-	-

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Dysphagia	-	-	-	<1	-	-	-	-
Flatulence	-	-	-	<1	<1	-	-	-
Gastritis	-	-	-	<1	-	-	-	-
Gastroenteritis	-	-	-	-	-	<1	-	-
Gastrointestinal hemorrhage	✔	-	-	<1	<1	-	-	-
Glossitis	-	-	-	-	1	<1	-	-
Halitosis	<1†	-	-	-	-	-	-	-
Hemoperitoneum, nontraumatic	-	-	-	-	<1	-	-	-
Hemorrhagic colitis	-	-	-	-	-	<1	-	-
Ileus	-	-	-	<1	<1	-	-	-
Intestinal obstruction	-	-	-	-	<1	-	-	-
Melena	-	-	-	-	<1	-	-	-
Nausea	1 to 10†	<1	<1	2 to 9	1 to 8	2	-	1.8
Numb tongue	<1†	-	-	-	-	-	-	-
Oral candidiasis	-	-	-	≤1	≤2	<1	-	<1
Pancreatitis	-	-	-	<1	-	-	-	-
Pseudomembranous colitis	<1†	<1	<1	-	-	<1	-	-
Tongue papillar hypertrophy	-	-	-	-	-	<1	-	-
Vomiting	1 to 10†, 6‡	<1	<1	4 to 10	1 to 8	<2	-	-
Genitourinary								
Abnormal urinalysis	-	-	-	-	-	<1	-	-
Dysuria	-	-	-	-	<1	-	-	-
Hematuria	-	-	-	1 to 3	<1	<1	-	-
Interstitial nephritis	-	-	<1	-	-	-	-	-
Nephrotoxicity	✔	<1	<1	-	-	-	-	-
Oliguria/anuria	-	-	-	<1	-	<1	-	-
Pelvic pain	-	-	-	-	<1	-	-	-
Polyuria	-	-	-	-	-	<1	-	-
Pyuria	-	-	-	2 to 3	-	-	-	-
Renal impairment/failure	-	-	-	<1	<1	<1	-	<1
Urinary incontinence	-	-	-	-	<1	-	-	-
Vaginal candidiasis	<1†	-	-	-	<1	-	-	<1
Vaginitis	<1†	-	-	1 to 3	-	-	-	-
Hematologic								
Agranulocytosis	-	<1	-	-	<1	<1	-	-
Anemia	<1†	-	<1	-	≤6	<1	11	-
Bleeding	-	-	-	-	1	-	-	-
Bone marrow depression	-	-	<1	-	-	<1	-	-
Eosinophilia	<1†	<1	<1	1 to 2	<1	<1	-	-

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Hematocrit decreased	-	-	-	3 to 5	<1	<1	-	-
Hemoglobin decreased	-	-	-	3 to 5	<1	<1	-	-
Hemolytic anemia	-	<1	<1	-	<1	<1	-	-
Leukocytosis	<1†	-	-	-	<1	<1	-	-
Leukopenia	-	<1	<1	1 to 2	<1	<1	-	<1
Neutropenia	<1†	-	<1	1 to 2	<1	<1	-	-
Pancytopenia	<1†	-	-	-	-	<1	-	-
Partial thromboplastin time decreased	-	-	-	-	<1	-	-	-
Thrombocythemia	-	-	-	-	-	<1	-	-
Thrombocytopenia	<1†	<1	<1	1	<1	<1	<4	✔
Thrombocytosis	<1†	<1	-	4 to 7	<1	-	-	-
Hepatic								
Hepatic failure	-	-	-	-	<1	<1	-	-
Hepatitis	<1†	-	-	-	-	<1	-	-
Jaundice	<1†	-	<1	<1	<1	<1	-	-
Laboratory Test Abnormalities								
Albumin decreased	-	-	-	1 to 2	-	-	-	-
Alkaline phosphatase increased	<1†	<1	<1	4 to 7	<1	<1	-	-
Alanine aminotransferase increased	<1†	<1	<1	7 to 9	<1	<1	10	1.8
Aspartate aminotransferase increased	<1†	<1	<1	7 to 9	<1	<1	12	1.5
Blood urea nitrogen increased	-	<1	<1	-	<1	<1	-	-
Hyperbilirubinemia	-	-	-	<1	<1	-	-	-
Hyperchloremia	-	-	-	-	-	<1	-	-
Hyperglycemia	-	-	-	1 to 2	-	-	-	<1
Hyperkalemia	-	-	-	≤1	-	<1	-	<1
Hypoglycemia	-	-	-	-	✔	-	-	<1
Hypokalemia	-	-	-	2	<1	-	8	1.1
Hyponatremia	-	-	-	-	-	<1	6	-
Lactic acid dehydrogenase increased	-	-	-	-	<1	<1	-	-
Positive Coombs' test	✔	<1	<1	-	<1	<1	-	-
Prothrombin time decreased	-	-	-	-	<1	-	-	-
Prothrombin time prolonged	✔	<1	<1	<1	-	<1	-	-
Serum creatinine increased	✔	<1	<1	1	<1	<1	-	-
Musculoskeletal								
Asthenia	-	-	-	-	<1	<1	-	-
Back pain	-	-	-	-	<1	-	-	-
Dyskinesia	-	-	-	<1	-	-	-	-
Leg pain	-	-	-	≤1	-	-	-	-
Myalgia	<1†	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Polyarthralgia	<1†	-	-	-	-	<1	-	-
Weakness	<1†	-	-	1	<1	-	-	-
Respiratory								
Apnea	-	-	-	-	1	-	-	-
Asthma	-	-	-	<1	<1	-	-	-
Bronchoconstriction	-	-	-	<1	-	-	-	-
Bronchospasm	<1†, 3‡	-	-	-	-	-	-	-
Cough	54‡	-	-	1 to 2	<1	-	-	-
Cyanosis	-	-	-	-	-	<1	-	-
Dyspnea	<1†	-	<1	1 to 3	<1	<1	-	-
Hemoptysis	-	-	-	<1	-	-	-	-
Hypoxemia	-	-	-	<1	-	-	-	-
Hypoxia	-	-	-	-	<1	-	-	-
Hyperventilation	-	-	-	-	-	<1	-	-
Nasal congestion	<1†, 16‡	-	-	-	-	-	-	-
Pharyngeal pain	12‡	-	-	<1	-	<1	-	-
Pharyngitis	-	-	-	1	✔	-	-	<1
Pleural effusion	-	-	-	<1	<1	-	-	-
Pneumonia	-	-	-	-	✔	-	-	-
Pulmonary edema	-	-	-	-	<1	-	-	-
Pulmonary embolus	-	-	-	-	<1	-	-	-
Rales/rhonchi	-	-	-	1	-	-	-	-
Respiratory disorder	-	-	-	-	<1	-	-	-
Respiratory distress	-	-	-	≤1	-	-	-	-
Sneezing	<1†	-	-	-	-	-	-	-
Wheezing	<1†, 16‡	-	-	<1	-	-	-	-
Other								
Anaphylactoid reactions	-	-	-	<1	-	-	-	-
Anaphylaxis	<1†	<1	<1	<1	✔	<1	-	-
Bleeding	-	<1	-	-	-	-	-	-
Breast tenderness	<1†	-	-	-	-	-	-	-
Chills	-	-	-	<1	<1	-	-	-
Diplopia	<1†	-	-	-	-	-	-	-
Drug fever	-	-	-	-	-	<1	-	-
Epistaxis	-	-	-	<1	<1	-	-	-
Extravasation	-	-	-	1 to 2	-	-	-	-
Facial edema	<1‡	-	-	<1	-	-	-	-
Gout	-	-	-	<1	-	-	-	-
Hearing loss	-	-	-	-	-	<1	-	-

Adverse Events	Single Entity Agents					Combination Products		
	Aztreonam	Cefotetan	Cefoxitin	Ertapenem	Meropenem	Imipenem and Cilastatin	Imipenem, Cilastatin, and Relebactam	Meropenem and Vaborbactam
Hemoperitoneum	-	-	-	-	<1	-	-	-
Hypersensitivity	<1‡	1	-	-	-	<1	-	1.8
Hypervolemia	-	-	-	-	<1	-	-	-
Inflammation at injection site	-	-	-	-	2	-	-	-
Infused vein complication	-	-	-	5 to 7	-	-	-	-
Injection site edema	-	-	-	-	<1	-	-	-
Injection site pain	1 to 10†	-	-	<1	<1	<1	-	-
Injection site reaction	-	-	✔	✔	1	<1	-	✔
Opportunistic infection	-	-	-	-	-	-	-	✔
Ototoxicity	✔	-	-	-	-	-	-	-
Pain	-	-	-	<1	≤5	-	-	-
Peripheral edema	-	-	-	-	<1	-	-	-
Purpura	<1†	-	-	-	-	-	-	-
Septicemia	-	-	-	<1	2	-	-	-
Subdural hemorrhage	-	-	-	<1	-	-	-	-
Thoracic spine pain	-	-	-	-	-	<1	-	-
Throat tightness	<1‡	-	-	-	-	-	-	-
Thrombophlebitis/phlebitis	1 to 10†	<1	<1	<2	<1	3	-	4.4
Tinnitus	<1†	-	-	-	-	<1	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
‡ Inhalation formulation.
† Injection formulation.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous β-lactam antibiotics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Miscellaneous β-Lactam Antibiotics[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aztreonam	Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*: Inhalation solution: 75 mg inhaled three times daily for 28 days followed by 28 days off of therapy Moderately severe systemic infections: Injection: 1 to 2 g IM/IV every eight to 12 hours Severe systemic or life-threatening infections: Injection: 2 g IM/IV every six or eight hours Urinary tract infections: Injection: 500 mg to 1 g IM/IV every eight to 12 hours	Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa* in patients ≥7 years of age: Inhalation: 75 mg inhaled three times daily for 28 days followed by 28 days off of therapy Mild to moderate infections in patients ≥9 months of age: Injection: 30 mg/kg IV every eight hours Moderate to severe infections in patients >9 months of age: Injection: 30 mg/kg IV every six to eight hours	Inhalation solution: 75 mg/mL Injection: 1 g 2 g
Cefotetan	Life-threatening infections: Injection: 3 g IV every 12 hours Prophylaxis of postoperative infections: Injection: 1 to 2 g IV administered 30 to 60 minutes prior to surgery; in patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped Severe infections: Injection: 2 g IV every 12 hours Skin and skin-structure infections (mild to moderate): Injection: 2 g IV every 24 hours or 1 g IM/IV every 12 hours Unspecified infections: Injection: 1 to 2 g IM/IV every 12 hours Urinary tract infections: Injection: 500 mg IM/IV every 12 hours, 1 or 2 g IM/IV every	Safety and efficacy in children have not been established.	Injection: 1 g 2 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	24 hours, or 1 or 2 g IM/IV every 12 hours		
Cefoxitin	Infections needing antibiotics in higher doses: Injection: 2 g IV every four hours or 3 g IV every six hours Moderately severe or severe infections: Injection: 1 g IV every four hours or 2 g IV every six to eight hours Prophylaxis of infections (uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section): Injection: 2 g IV administered 30 to 60 minutes prior to surgery, followed by 2 g IV every six hours after the first dose for no more than 24 hours; for patients undergoing cesarean section, either a single 2 g dose administered IV as soon as the umbilical cord is clamped or a three-dose regimen consisting of 2 g given IV as soon as the umbilical cord is clamped, followed by 2 g IV four and eight hours after the initial dose Uncomplicated infections (pneumonia, urinary tract infection, cutaneous infection): Injection: 1 g IV every six to eight hours	Prophylaxis of infections (uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy in patients ≥3 months of age: Injection: 30 to 40 mg/kg administered 30 to 60 minutes prior to surgery, followed by 30 to 40 mg/kg every six hours after the first dose for no more than 24 hours Unspecified infections in patients ≥3 months of age: Injection: 80 to 160 mg/kg of body weight per day divided into four to six equal doses	Injection: 1 g 2 g 10 g
Ertapenem	Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections): Injection: 1 g IM/IV once daily Community-acquired pneumonia: Injection: 1 g IM/IV once daily Intra-abdominal infections (complicated): Injection: 1 g IM/IV once daily Prophylaxis of surgical site infections (colorectal surgery): Injection: single 1 g dose IV administered one hour prior to	Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Community-acquired pneumonia in patients three	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	surgical incision Skin and skin-structure infections (complicated): Injection: 1 g IM/IV once daily Urinary tract infections (complicated): Injection: 1 g IM/IV once daily	months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Community-acquired pneumonia in patients ≥13 years of age: Injection: 1 g IM/IV once daily Intra-abdominal infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Intra-abdominal infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Skin and skin-structure infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Skin and skin-structure infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Urinary tract infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Urinary tract infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily	
Meropenem	Intra-abdominal infections: Injection: 1 g IV every eight hours Skin and skin-structure infections (caused by *P. aeruginosa*): Injection: 1 g IV every eight hours Skin and skin-structure infections (not caused by *P. aeruginosa*): Injection: 500 mg IV every eight	Intra-abdominal infections in patients ≥3 months of age: Injection: ≤50 kg, 20 mg/kg IV every eight hours; >50 kg, 1 g IV every eight hours Meningitis in patients ≥3 months of age: Injection: ≤50 kg, 40 mg/kg IV every eight hours; >50 kg, 2 g IV every eight hours Skin and skin-structure infections (complicated) in	Injection: 500 mg 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	hours	patients ≥3 months of age: Injection: ≤50 kg, 10 mg/kg IV every eight hours; >50 kg, 500 mg IV every eight hours	
Combination Products			
Imipenem and cilastatin	Gynecologic infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Intra-abdominal infections (mild to moderate): Injection: 250 to 500 mg IV every six hours Intra-abdominal infections (severe): Injection: 500 mg IV every six hours or 1 g IV every eight hours Lower respiratory tract infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Mild infections (fully susceptible organisms): Injection: 250 mg IV every six hours Mild infection (moderately susceptible organisms): Injection: 500 mg IV every six hours Moderate infections (fully susceptible organisms): Injection: 500 mg IV every six to eight hours Moderate infections (moderately susceptible organisms): Injection: 500 mg IV every six hours or 1 g IV every eight hours Severe or life-threatening infections (fully susceptible organisms): Injection: 500 mg IV every six hours Severe or life-threatening infections (moderately susceptible organisms): Injection: 1 g IV every six to eight hours	Gynecologic infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours Intra-abdominal infections (mild to moderate) in patients ≥12 years of age: Injection: 750 mg IM every 12 hours Lower respiratory tract infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours Non-central nervous system infections in patients <1 week of age: Injection: 25 mg/kg IV every 12 hours Non-central nervous system infections in patients one to four weeks of age: Injection: 25 mg/kg IV every eight hours Non-central nervous system infections in patients four weeks to three months of age: Injection: 25 mg/kg IV every six hours Non-central nervous system infections in patients ≥3 months of age: Injection: 15 to 25 mg/kg/dose IV every six hours Skin and skin-structure infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours	Injection: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Skin and skin-structure infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Urinary tract infections (complicated): Injection: 500 mg IV every six hours Urinary tract infections (uncomplicated): Injection: 250 mg IV every six hours		
Imipenem, cilastatin, and relebactam	Complicated urinary tract infections, including pyelonephritis: Injection: 1.25 grams IV over 30 minutes every six hours Complicated intra-abdominal infections: Injection: 1.25 grams IV over 30 minutes every six hours Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia: Injection: 1.25 grams IV over 30 minutes every six hours	Safety and efficacy in children have not been established.	Injection: 1.25 g
Meropenem and vaborbactam	Urinary tract infection (complicated): Injection: 4 g IV every eight hours	Safety and efficacy in children have not been established.	Injection: 2 g

IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous β-lactam antibiotics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Miscellaneous β-Lactam Antibiotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Corey et al.[30] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin and cSSSIs who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA cSSSIs was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[31] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours	AC, DB, MC, RCT Patients ≥18 years of age with cSSSIs who required ≥5 days of parenteral	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat population, clinical cure rates for ceftaroline and vancomycin plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	antibacterial therapy		the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[32] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for	Pooled analysis (2 trials) Patients ≥18 years of age with cSSSIs who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 to 14 days			Secondary: Microbiological success rate, safety	Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable). Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Dryden et al.[33] COVERS (2016) Aztreonam 1 g every eight hours plus vancomycin 15 mg/kg every 12 hours vs ceftaroline 600 mg every eight hours	DB, MC, NI, RCT Patients ≥ 18 years of age with cSSTI and signs of systemic inflammatory response and/or underlying comorbidities associated with impair immune response	N=772 35 days after last dose of antibiotic therapy	Primary: Proportion of patients clinically cured at the test-of-cure visit (eight to 15 days after the last dose) in the co-primary clinically evaluable and modified intent-to-treat populations Secondary: Clinical response at test-of-cure in the microbiological modified intent-to-treat and microbiologically evaluable populations, clinical and per-	Primary: The proportion of patient clinically cured at the test-of-cure visit for the modified intent-to-treat population was 78.3% in the ceftaroline group compared with 79.2% in the vancomycin plus aztreonam group. In the clinically evaluable group, the proportion of patients clinically cured was 86.6 and 85.3%. Non-inferiority was demonstrated for the modified intent-to-treat (difference, -0.95%; 95% CI, -6.90 to 5.41) and clinically evaluable (difference, 1.27%; 95% CI, -4.32 to 7.48) populations. Secondary: Clinical response at the test-of-cure visit in the microbiological modified intent-to-treat population was 80.2 and 79.4% for the ceftaroline and vancomycin plus aztreonam groups, respectively and 90.1 and 86.6% in the microbiologically evaluable population. Microbiological responses were predominately derived from clinical responses; therefore, clinical and microbiological response rates were similar at test-of-cure by baseline pathogen and for patients with monomicrobial and polymicrobial infections. Among patients who were clinically cured at the test-of-cure visits, relapse at the late follow-up visits occurred in 0.9% of patients in the ceftaroline group and 1.7% of patients in the vancomycin plus aztreonam group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			pathogen microbiological response at test-of-cure in the microbiologically evaluable population, clinical relapse and reinfection or recurrence at the late follow-up visit, safety	There were no new infections, reinfections or recurrences reported. The study treatments were generally well tolerated and the incidence of adverse events was similar for the ceftaroline and vancomycin plus aztreonam groups (45.8 vs 45.5%).
O'Riordan et al.[34] (2018) Aztreonam 2 g IV every 12 hours plus vancomycin 15 mg/kg IV vs delafloxacin 300 mg IV every 12 hours for three days and then 450 mg PO every 12 hours	DB, MC, RCT Patients ≥18 years of age with ABSSSI	N=850 Variable duration	Primary: Objective response at 48 to 72 hours (±2 hours) following treatment initiation Secondary: Investigator-assessed response of signs and symptoms of infection at follow-up in the intent-to-treat population, microbiological response in the microbiological intent-to-treat population, safety	Primary: The percentage of responders at the 48 to 72 hours objective response assessment in the intent-to-treat analysis population (N=552) was 83.7% for delafloxacin and 80.6% for vancomycin plus aztreonam (difference, 3.1%; 95% CI, -2.0 to 8.3%), which met non-inferiority criteria. Secondary: The cure rate at follow-up in the intent-to-treat population was 57.7 and 59.7% for the delafloxacin and vancomycin plus aztreonam groups, respectively (difference, -2.0%; 95% CI, -8.6 to 4.6%). In the modified intent-to-treat population at follow-up, overall pathogen eradication rates were documented in 97.8% of patients treated in the delafloxacin group and 97.6% of patients treated with vancomycin pus aztreonam (difference, 0.2%; 95% CI, -2.9 to 3.5%). Treatment-emergent adverse events were observed in 43.6% in the delafloxacin group and 39.3% in the vancomycin plus aztreonam group. Treatment-emergent adverse events leading to drug discontinuation were higher in the vancomycin plus aztreonam group compared with the delafloxacin group, 2.8 and 2.4%, respectively.
Pullman et al.[35] (2017)	AC, DB, MC, RCT	N=660	Primary: Objective response	Primary: The percentage of responders at the 48 to 72 hours objective response

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aztreonam 2 g IV every 12 hours plus vancomycin 15 mg/kg IV vs delafloxacin 300 mg IV every 12 hours	Patients ≥18 years of age with ABSSSI	28 days	at 48 to 72 hours (± 2 hours) following treatment initiation Secondary: Microbiological response in the microbiological intent-to-treat and microbiologically evaluable populations, safety	assessment in the intent-to-treat population was 78.2% for delafloxacin and 80.9% for vancomycin plus aztreonam (difference, -2.6%; 95% CI, -8.78 to 3.57), which met non-inferiority criteria. Secondary: In the microbiologically evaluable population at follow-up, microbiological responses were documented in 97.8 and 98.4% of patients treated with delafloxacin and vancomycin plus aztreonam, respectively. Treatment-emergent adverse events were observed in 47.5% in the delafloxacin group and 59.2% in the vancomycin plus aztreonam group. Treatment-emergent adverse events leading to drug discontinuation were higher in the vancomycin plus aztreonam group compared with the delafloxacin group, 4.3 and 0.9%, respectively.
Chuang et al.[36] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with cSSSIs	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs. No MRSA isolates were noted among Indian patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Gesser et al.[37] (2004) Ertapenem 1 g IV daily vs piperacillin-tazobactam 13.5 grams IV divided every six hours Study medications were given as outpatient parenteral antimicrobial therapy or as inpatient therapy.	DB, MC, PRO, RCT Patients 18 years of age and older with SSSI requiring parenteral therapy	N=146 10 to 21 days post-therapy	Primary: Clinical response, adverse events Secondary: Not reported	Primary: For patients receiving outpatient parenteral antimicrobial therapy, 83.3% in the ertapenem group and 82.0% in the piperacillin-tazobactam group had a clinical response to therapy and were considered cured (P=0.78). The only significant difference in adverse event between the two treatment groups was that 10.5% of patients in the piperacillin-tazobactam group experienced moderate-severe tenderness compared to 0% in the ertapenem group; P=0.006). Secondary: Not reported
Lipsky et al.[38] (2005) Ertapenem 1 g IV daily vs piperacillin-tazobactam 3.375 g every six hours Investigators switched patients	DB, MC, RCT Adult patients with type 2 diabetes mellitus with a foot infection not extending above the knees	N=445 10 days after completion of antibiotic therapy	Primary: Proportion of patients with a favorable clinical response at the discontinuation of IV therapy Secondary: Proportion of patients with a favorable clinical response at follow-up assessment	Primary: At the discontinuation of IV therapy visit, 94% of patients in the ertapenem group and 92% in the piperacillin-tazobactam group had a favorable clinical response. Secondary: At the follow-up assessment visit, 87% of patients in the ertapenem group and 83% in the piperacillin-tazobactam group had a favorable clinical response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to PO therapy if appropriate after five days of IV therapy.				
Lauf et al.[39] (2014) Ertapenem 1 g IV every 24 hours, with or without adjunctive IV vancomycin for up to 28 days vs tigecycline 150 mg IV every 24 hours, with or without placebo for up to 28 days Patients with osteomyelitis were treated for up to 42 days.	DB, RCT Hospitalized men and women ≥18 years of age with diabetes mellitus who had a foot infection that did not extend above the knee, with or without osteomyelitis. The infection had to be of acute onset or a worsening within 14 days prior to the screening visit.	N=955 (without osteomyelitis) N=118 (with osteomyelitis) 12 to 92 days after the last dose for patients without osteomyelitis and 25 to 27 weeks for patients with osteomyelitis	Primary: Clinical response within the clinically evaluable and the clinically modified intent-to-treat populations at the test-of-cure visit Secondary: Microbiologic efficacy of tigecycline, in vitro susceptibility data on tigecycline	Primary: At the test-of-cure assessment in the patients without osteomyelitis, 77.5% of tigecycline-treated subjects and 82.5% of ertapenem ± vancomycin-treated subjects in the clinically evaluable population were considered cured, and 71.4% of those treated with tigecycline subjects and 77.9% of those who received ertapenem ± vancomycin in the clinically modified intent-to-treat population were considered cured. The tigecycline regimen did not meet the primary study endpoint of noninferiority to the ertapenem ± vancomycin regimen for the clinically evaluable population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, -5.5%; 95% CI, -11.0 to 0.1) or clinically modified intent-to-treat population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, -6.7; 95% CI, -12.3 to -1.1). Secondary: In the population without osteomyelitis, the cure rates for most baseline isolates were either slightly higher or similar for ertapenem ± vancomycin as compared with tigecycline-treated subjects. However, participants in the tigecycline regimen with *Escherichia coli* (21/28; 75.0%), MRSA (29/44; 65.9%), and *S. agalactiae* infections (35/40; 87.5%) had higher cure rates compared to subjects receiving ertapenem ± vancomycin (28/38, 73.7%; 17/26, 65.4%; and 40/48, 83.3%; respectively). The cure rates for tigecycline-treated participants with methicillin-susceptible *S. aureus* (MSSA) or *Klebsiella pneumoniae* infections were lower than expected compared with those treated with ertapenem ± vancomycin. For subjects with baseline bacteremia, excluding contaminants, in the primary study, the clinical cure rate at the test-of-cure visit was 6/7 (86%) for tigecycline-treated subjects and 14/14 (100%) for ertapenem-treated subjects.
Saltoglu et al.[40] (2010)	OL, RCT, SC	N=64	Primary: Clinical response	Primary: A successful clinical response was seen in 46.7% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 0.5 g IV every six hours for 14 to 28 days vs piperacillin-tazobactam 4.5 g IV every eight hours for 14 to 28 days	Patients ≥18 years of age with a diagnosis of moderate to severe diabetic lower extremity foot infection	2 months post-treatment	Secondary: Relapse rate after two months	piperacillin-tazobactam group and in 28.1% of patients in the imipenem group (RR, 1.6; 95% CI, 0.84 to 3.25; P=0.130). Secondary: During two months follow-up, two patients in the imipenem group and none in the piperacillin-tazobactam group relapsed (RR, 2; 95% CI, 0.94 to 4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the piperacillin-tazobactam and imipenem groups (60 vs 68.8%; P=0.739).
Nichols et al.[41] (1995) Meropenem 500 mg IV every eight hours vs imipenem-cilastatin 500 mg IV every six hours	MC, OL, PRO, RCT Hospitalized patients, 18 years of age or older, who required parenteral antibiotics for the treatment of SSSI	N=377 6 to 7 days	Primary: Clinical response (a response of cured or improved were considered satisfactory) Secondary: Bacteriologic Response	Primary: Satisfactory clinical responses were achieved in 98% of meropenem treated patients and in 95% of imipenem-cilastatin treated patients, a difference that was NS (95% CI, -2.29 to 6.93). Secondary: Satisfactory bacteriologic response rates were 94% with meropenem and 91% with imipenem-cilastatin, a difference that was NS (95% CI, -2.73 to 10.39).
Fabian et al.[42] (2005) Meropenem 500 mg IV every eight hours vs imipenem-cilastatin 500 mg	DB, MC, RCT Hospitalized patients with cSSSI	N=1,076 14 days	Primary: Clinical response at the post-treatment followup visit in the clinically evaluable and modified intent-to-treat populations	Primary: The proportion of patients assessed as cured in the clinically evaluable population at the post-treatment follow-up evaluation was 86.2% for the meropenem and 82.9% for the imipenem-cilastatin treatment groups (95% CI, -2.8 to 9.3). In the modified intent-to-treat population, the clinical cure rates at the follow-up assessment were 73.1% (meropenem) and 74.9% (imipenem-cilastatin; 95% CI, -8.4 to 4.7). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV every eight hours			Secondary: Clinical response at the post-treatment follow-up visit in the intent-to-treat population and at the end-of-treatment visit in the clinically evaluable, modified intent-to-treat, and intent-to-treat populations	The clinical response rates at the end of treatment were 93.5 vs 92.3% (clinically evaluable), 91.0 vs 91.1% (modified intent-to-treat), and 81.0 vs 83.5% (intent-to-treat) for meropenem and imipenem-cilastatin, respectively. The 95% CI for the difference between treatment groups in all three analyses demonstrated non-inferiority of meropenem to imipenem-cilastatin.
Genitourinary Infections				
Friman et al.[43] (1989) Aztreonam 1 g IV every eight hours vs cefuroxime 1.5 g IV every eight hours	RCT Patients 18 to 99 years of age with symptoms of an upper urinary tract infection	N=171 1 month	Primary: Clinical response rates, bacteriologic response rates Secondary: Not reported	Primary: Clinical response rates were 89% in the aztreonam group and 87% in the cefuroxime group. Bacteriologic response rates at one-week post-therapy were 70% in the aztreonam group and 73% in the cefuroxime group, while rates at one month were 43 and 40%, respectively. Secondary: Not reported
MacGregor et al.[44] (1992) Cefoxitin 2 g IV every six hours vs cefotetan 2 g IV every 12 hours	DB, RCT Patients with post-cesarean section endometritis	N=140 Duration varied	Primary: Clinical response, duration of therapy, length of hospital stay Secondary: Not reported	Primary: Cure rates were 83% in the cefotetan group compared to 79% in the cefoxitin group (P=0.56). The duration of therapy and length of hospital stay were similar in both groups. Secondary: Not reported
Wagenlehner et	DB, DD, MC, PG,	N=1,033	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[45] RECAPTURE (2016) Doripenem 500 mg every eight hours vs ceftazidime-avibactam 2,000 mg/500 mg every eight hours Patients could be switched to PO ciprofloxacin 500 mg every 12 hours or sulfamethoxazole-trimethoprim 800 mg/160 mg every 12 hours if they demonstrated clinical improvement after five days of IV therapy	RCT Patients 18 to 90 years of age with cUTI or acute pyelonephritis who required hospitalization for IV antibiotics, positive urine cultures obtained within 48 hours of enrollment, and polyuria	Test-of-cure: 21 to 25 days post-randomization Late follow-up: 45 to 52 days post-randomization	Symptomatic resolution of UTI-specific symptoms, microbiological eradication and UTI symptomatic resolution at test-of-cure visit in the microbiological modified intent-to-treat population Secondary: Microbiological response at end of IV study treatment and late follow-up, microbiological response at test-of-cure and late follow-up in patients with ≥ one ceftazidime-nonsusceptible or only ceftazidime-susceptible pathogens at baseline, clinical cure at the end of IV treatment, test-of-cure, and late follow-up and sustained clinical cure at late follow-up visit	The proportion of patients with patient-assessed symptomatic resolution at day five in the microbiological modified intent-to-treat (N=810) was 70.2% for ceftazidime-avibactam and 66.2% for doripenem (difference, 4.0; 95% CI, -2.39 to 10.42). Favorable microbiological response at test-of-cure was 77.4% with ceftazidime-avibactam and 71.0% with doripenem (difference, 6.4%; 95% CI, 0.33 to 12.36). Combined patient-assessed symptomatic resolution and favorable per-patient microbiological response at test-of-cure occurred in 71.2% in the ceftazidime-avibactam group and 64.5% in the doripenem group (difference, 6.7; 95% CI, 0.30 to 13.12). Secondary: Per-patient favorable microbiological response at end of IV treatment was 95.2 and 94.7% (difference, 0.4%; 95% CI, -2.7 to 3.56) and at late follow-up was 68.2 and 60.9% (difference, 7.3%; 95% CI, 0.68 to 13.81), for the ceftazidime-avibactam and doripenem arms, respectively. Per-patient favorable microbiological response in patients with a ceftazidime-nonsusceptible pathogen at test-of-cure was 62.7 and 60.7% (difference, 2.0; 95% CI, -13.18 to 16.89) and at late follow-up was 61.3 and 45.2% (difference, 16.1%; 95% CI, 0.50 to 30.89), respectively, and 81.0 and 73.0% (difference, 8.0%; 95% CI, 1.50 to 14.48) at test-of-cure and 69.9 and 64.1% (difference, 5.8%; 95% CI, -1.46 to 13.05) at late follow-up in patients with a ceftazidime-susceptible pathogen. Investigator-determined clinical cure was 96.2% for the ceftazidime-avibactam group and 97.6% for the doripenem group (difference, -1.4%; 95% CI, -4.07 to 1.02) at the end of IV treatment, 90.3 and 90.4% (difference, -0.1%; 95% CI, -4.23 to 4.03) at test-of-cure, and 85.2 and 83.9% (difference, 1.3%; 95% CI, -3.71 to 6.30) at the late follow-up visit. Sustained clinical cure at the late follow up visit in patients who were cured at the test-of-cure visit was 93.0 and 91.5% (difference, 1.4%; 95% CI, -2.5 to 5.4%) for the ceftazidime-avibactam and doripenem groups, respectively.
Naber et al.[46]	DB, MC, RCT	N=753	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Doripenem 500 mg IV every eight hours vs levofloxacin 250 mg IV QD Patients in both treatment arms were eligible to switch to PO levofloxacin after three days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological improvements.	Patients ≥18 years of age with cUTI or pyelonephritis who required initial treatment with a parenterally administered antibacterial agent	Up to 14 days	Microbiological cure rate in the microbiologically evaluable and microbiologically evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the test-of-cure visit for the clinically evaluable population and the microbiological cure rate for the microbiologically evaluable patients infected with *Escherichia coli*	The microbiologically evaluable population achieved microbiological cure rates of 82.1 and 83.4% with doripenem and levofloxacin, respectively. Patients in the microbiologically evaluable-modified intent-to-treat population achieved microbiological cure rates of 79.2 and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin for the treatment of cUTI or pyelonephritis. In the microbiologically evaluable population, the microbiological cure rates at the end-of-treatment were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the test-of-cure visit could be attributed to the IV portion of the therapeutic regimen, independently of a switch to PO levofloxacin. Secondary: In the clinically evaluable population, the clinical cure rates at end-of-treatment were 98.3 and 93.2% in the doripenem and levofloxacin arms, respectively. At the test-of-cure visit, the clinical cure rates were 95.1 and 90.2%, respectively (95% CI, 0.2 to 9.6). Clinical cure rates at the late follow-up visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were clinically evaluable were sustained. For the patients who received the IV study drug only, the clinical cure rates at the test-of-cure visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for *Escherichia coli* infections of microbiologically evaluable patients at the test-of-cure visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Redman et al.[47] (2010) <u>Study 1</u> Doripenem 500 mg IV every eight	DB, RCT Patients ≥18 years of age with cUTI and pyelonephritis	N=1,179 42 days after the last dose	Primary: Microbiological response at the test-of-cure visit (five to 11 days after the last dose);	Primary: Microbiological eradication rates in the microbiologically evaluable patient population at the test-of-cure visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours vs levofloxacin 250 mg IV QD <u>Study 2</u> Doripenem 500 mg IV every eight hours After a minimum of three days of IV therapy, investigators could switch patients from IV therapy to PO levofloxacin 250 mg daily.			clinical cure rates Secondary: Not reported	Microbiological eradication rates in the microbiologically evaluable-modified intent-to-treat population at the test-of-cure visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the evaluable-modified intent-to-treat population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the test-of-cure and end-of-treatment visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2 to 15.6). These results suggest that the eradication preceded a switch from IV to PO levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the test-of-cure visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the test-of-cure and end-of-treatment visits showed that clinical improvement preceded a switch to PO levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2. Secondary: Not reported
Seo et al.[48] (2017) Ertapenem 1 g every 24 hours vs cefepime 2 g every 12 hours vs	MC, OL, PRO, RCT Hospitalized patients ≥ 19 years of age with healthcare-associated UTI caused by extended-spectrum β-lactamase-producing	N=66 28 to 30 days	Primary: Clinical response at three to five days and microbiological response at 10 to 14 days Secondary: 28 day mortality rate	Primary: After recruitment of six participants to the cefepime treatment group, allocation to this treatment group was stopped due to an unexpectedly high treatment failure rate. Clinical success rate was 93.9% with piperacillin-tazobactam and 97.0% with ertapenem (P=0.500). Clinical success rate with cefepime was 33.3% (P<0.001) Microbiological success rates were 97.0% with both piperacillin-tazobactam and ertapenem, and 33.3% with cefepime. Secondary: The 28-day mortality rate was 6.1% with both piperacillin-tazobactam and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
piperacillin-tazobactam 4.5 g every six hours	*Escherichia coli*			ertapenem and 33.3% (two of six patients) with cefepime (P=0.108)
Bradley et al.[49] (2019) Meropenem every eight hours IV for two to 13 days vs ceftolozane-tazobactam plus metronidazole every eight hours IV for two to 13 days	MC, RCT, SB Hospitalized children (≥3 months to <18 years) with complicated intra-abdominal infection (cIAI)	N=83 8 to 15 days after the last dose of study drug	Primary: Safety and tolerability Secondary: Descriptive efficacy	Primary: In the safety analysis set, 52.5% of children in the ceftazidime-avibactam plus metronidazole group and 59.1% of children in the meropenem group experienced ≥1 treatment-emergent adverse event. The most common adverse events in the ceftazidime-avibactam plus metronidazole group were vomiting (14.8%), infusion site phlebitis (6.6%) and seroma (4.9%). Vomiting, cough and abdominal pain (each occurring in 9.1% of children) were the most common adverse events in the meropenem group. Secondary: In both treatment groups, per-patient favorable clinical and microbiologic response rates were ≥90% across all analysis sets early in the course of treatment and were sustained through to the test of cure visit.
Wagenlehner et al.[50] (2019) EPIC Meropenem (1 g every 8 hours IV) vs plazomicin (15 mg/kg of body weight once daily IV) option for oral step-down therapy	DB, MC, RCT Patients ≥18 years of age with complicated urinary tract infections (UTIs), including acute pyelonephritis	N=609 32 days	Primary: Noninferiority of plazomicin to meropenem (Composite cure at day 5 and test of cure defined as resolution or improvement of clinical cUTI symptoms and a microbiological outcome of eradication) Secondary: Composite cure (clinical cure and	Primary: Plazomicin was noninferior to meropenem with respect to the primary efficacy end points. Secondary: At day five, composite cure was observed in 88.0% of the patients in the plazomicin group and in 91.4% in the meropenem group (difference, –3.4 percentage points; 95% CI, –10.0 to 3.1). At the test-of-cure visit, composite cure was observed in 81.7% and 70.1%, respectively (difference, 11.6 percentage points; 95% CI, 2.7 to 20.3).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after a minimum of 4 days of IV therapy, for a total of 7 to 10 days of therapy (levofloxacin was the preferred oral agent)			microbiologic eradication) at day 5 and at the test-of-cure visit (15 to 19 days after initiation of therapy) in the microbiologic modified intention-to-treat population	
Vazquez et al.[51] (2012) Imipenem-cilastatin 500 mg every six hours vs ceftazidime-avibactam 500-125 mg every eight hours Patients meeting pre-specified improvement criteria after four days could be switched to oral ciprofloxacin. Patients were treated for a total of seven to 14 days.	DB, MC, PRO, RCT Patients 18 to 90 years of age with complicated urinary tract infection due to Gram-negative pathogens	N=137 12 to 23 days	Primary: Favorable microbiological response at the test-of-cure visit five to nine days post-therapy in microbiologically evaluable patients Secondary: Microbiological response at the end of IV therapy and at the late follow-up visit, four to six weeks post-therapy in the microbiologically evaluable population; safety and tolerability	Primary: Favorable microbiological response in the microbiologically evaluable population (N=62) at the test-of-cure visit was observed in 19/27 (70.4%) patients in the ceftazidime–avibactam arm and 25/35 (71.4%) in the imipenem–cilastatin arm (observed difference -1.1% [95% CI, -27.2 to 25.0%]). Secondary: Favorable microbiological response rates at the end of IV therapy were 25/26 (96.2%) and 34/34 (100%) in the ceftazidime–avibactam and imipenem-cilastatin arms, respectively, and 15/26 (57.7%) and 18/30 (60.0%) at the late follow-up visit. Over the course of the study, adverse events were reported in 46/68 (67.6%) patients in the ceftazidime–avibactam arm and 51/67 (76.1%) patients in the imipenem–cilastatin arm. The most common adverse events in both treatment arms included constipation, diarrhea, abdominal pain, headache, anxiety, and injection/infusion site reactions. Treatment-emergent serious adverse events were reported in 6/68 (8.8%) and 2/67 (3.0%) of patients in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, during the course of the study. Three of the serious adverse events in the ceftazidime–avibactam arm were considered to be drug-related: renal failure, diarrhea, and accidental overdose of ceftazidime–avibactam. Although the accidental overdose of ceftazidime–avibactam was recorded as a serious adverse event, there were no adverse events associated with this event. One patient in the imipenem–cilastatin arm developed a drug-related serious adverse event associated with an increase in serum creatinine level.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Portsmouth et al.[52] (2018) Imipenem/ cilastatin 1 g/1 g TID for seven to 14 days vs cefiderocol 2 g TID for seven to 14 days	DB, MC, NI, PG, RCT Adults ≥18 years of age, admitted to hospital with a clinical diagnosis of complicated urinary tract infection with or without pyelonephritis, or patients with acute uncomplicated pyelonephritis	N=448 14 to 21 days (seven days after end of antibiotic treatment)	Primary: Composite of clinical response and microbiological response at the test of cure assessment, defined as seven days after the end of antibiotic treatment Secondary: Safety, clinical and microbiological response	Primary: At test of cure, the primary efficacy endpoint was achieved by 183 (73%) of 252 subjects in the cefiderocol group and 65 (55%) of 119 subjects in the imipenem/cilastatin group, with an adjusted treatment difference of 18.58% (95% CI, 8.23 to 28.92; P=0.0004), establishing the non-inferiority of cefiderocol. Secondary: Adverse events occurred in 122 (41%) of 300 subjects in the cefiderocol group and 76 (51%) of 148 subjects in the imipenem/cilastatin group, with gastrointestinal disorders (i.e. diarrhea, constipation, nausea, vomiting, and abdominal pain) the most common adverse events for both treatment groups (35 [12%] subjects in the cefiderocol group and 27 [18%] subjects in the imipenem-cilastatin group). At test of cure, the proportion of subjects who had a microbiological response was higher in the cefiderocol group than the imipenem/cilastatin group (184 [73%] of 252 subjects vs 67 [56%] of 119 subjects; difference, 17.25%; 95% CI, 6.92 to 27.58), whereas the proportion of patients who had a clinical response was similar between the two groups (226 [90%] of 252 subjects vs 104 [87%] of 119 subjects; difference, 2.39%; 95% CI, -4.66 to 9.44).
Cox et al.[53] (1995) Imipenem-cilastatin 500 mg IV QID vs meropenem 500 mg IV TID	MC, OL, PG, PRO, RCT Hospitalized patients ≥18 years of age, with cUTI requiring IV antibiotic treatment	N=235 21 days after final dose	Primary: Clinical response (complete resolution or improvement in signs and symptoms of infection), bacteriological response rate (negative urine culture), superinfection, relapse, reinfection	Primary: There was no significant difference in clinical response between the groups (99% for each group) at the end of treatment. At follow-up 83% of the imipenem-cilastatin group and 87% of the meropenem group, reported a satisfactory clinical response. A satisfactory bacterial response was reported in 81% of the patients receiving imipenem-cilastatin and 90% of patients receiving meropenem (95% CI, -1.58 to 19.55; P=0.075). Response at follow-up was observed in 70% in those treated with imipenem-cilastatin and 79% in meropenem recipients. There were few incidences of superinfection or relapse. The same number of patients in each group experienced reinfection. Adverse events were reported in 52% of imipenem-cilastatin recipients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	and 32% of meropenem patients. There were three patients from the imipenem-cilastatin group and no patients from the meropenem group who withdrew from the study secondary to adverse events. Secondary: Not reported
Ryo et al.[54] (2005) Imipenem-cilastatin 500 mg IV BID for three days plus betamethasone 12 mg SC vs penicillin or a cephalosporin or no antibiotic treatment	RETRO Pregnant women admitted to hospital with preterm premature rupture of membranes at 24 weeks and 0 days to 31 weeks and 6 days gestation	N=140 1 year	Primary: Time from preterm premature rupture of membranes to delivery, prognosis of infants (death within one year, alive with or without handicap) Secondary: Sensitivity of imipenem-cilastatin to cultured bacteria obtained at admission compared to ampicillin	Primary: The mean time from preterm premature rupture of membranes to delivery was 11 days in the imipenem-cilastatin group and 6 days in the control group (P=0.016). Also 53% of women treated with imipenem-cilastatin were able to continue pregnancy for greater than one week after preterm premature rupture of membranes as opposed to 25% in the control group (P=0.005). There were no infant deaths in the imipenem-cilastatin group but 12.5% of the infants died in the control group (P=0.002). There was no difference in the incidence of infants with handicaps between each group (P=0.328). Secondary: All cultured bacteria specimens in 94% of the women in the study group were sensitive to imipenem-cilastatin while all specimens found in 25% of those in the control group were sensitive to ampicillin (P<0.0001).
Sims et al.[55] (2017) Imipenem/cilastatin 500 mg/500 mg plus relebactam 250 mg IV every six hours vs Imipenem/cilastati	DB, MC, NI, Pro, RCT Adults ≥18 years of age with clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis requiring hospitalization and	N=298 Up to 14 days	Primary: Proportion of patients with a favorable microbiological response at discontinuation of intravenous therapy (DCIV) in the microbiologically evaluable	Primary: At DCIV, the percentage of patients with favorable microbiological response was 98.7% with imipenem/cilastatin plus placebo, 95.5% with imipenem/cilastatin plus relebactam 250 mg (difference, -3.1; 95% CI, -11.2 to 3.2), and 98.6% with imipenem/cilastatin plus relebactam 125 mg (difference, -0.1; 95% CI, -6.4 to 5.9). Both the 250 mg and the 125 mg dose of relebactam combined with imipenem/cilastatin were non inferior to imipenem/cilastatin plus placebo (P value not reported). Secondary: The percentage of patients with favorable microbiological response at EFU was 70.4% in the imipenem/cilastatin plus placebo arm, compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
n 500 mg/500 mg plus relebactam 125 mg IV every six hours vs imipenem/cilastatin 500 mg/500 mg plus placebo IV every six hours Patients with adequate therapeutic response could be switched to open-label oral ciprofloxacin after 96 hours of IV study therapy. Total duration of study therapy (either IV alone or IV plus subsequent oral ciprofloxacin) could not exceed 14 days.	IV antibacterial therapy		population Secondary: Microbiological responses at EFU and LFU in the microbiologically evaluable population, microbiological response at DCIV in patients with imipenem resistant pathogens, clinical response at DCIV, early follow-up (EFU) and late follow-up (LFU)	61.5% in the imipenem/cilastatin plus relebactam 250 mg arm (difference, -2.4; 95% CI, -17.4 to 12.8), and 68.1% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, -0.1; 95% CI, -6.4 to 5.9). At LFU the microbiological response rates were 62.5%, 68.3% (difference, 5.8; 95% CI, -10.4 to 21.5), and 65.2% (difference, 2.7; 95% CI, -13.1 to 18.4) in the imipenem/cilastatin plus placebo, plus relebactam 250 mg and relebactam 125 mg groups respectively (P values not reported). At DCIV the clinical response rates were 98.8%, 97.1% (difference, -1.6; 95% CI, -8.9 to 4.2), and 98.7% (difference, 0.0; 95% CI, -5.8 to 5.6) in the imipenem/cilastatin plus placebo, plus relebactam 250 mg and relebactam 125 mg groups respectively. At EFU the clinical response rates were 93.4%, 89.1% (difference, -4.4; 95% CI, -15.2 to 5.3), and 91.8% (difference, -1.6; 95% CI, -11.2 to 7.5) in the imipenem/cilastatin plus placebo, plus relebactam 250 mg and relebactam 125 mg groups respectively. At LFU the clinical response rates were 88.2%, 88.7% (difference, -0.6; 95% CI, -11.2 to 11.6), and 87.3% (difference, -0.8; 95% CI, -12.1 to 10.2) in the imipenem/cilastatin plus placebo, plus relebactam 250 mg and relebactam 125 mg groups respectively (P values not reported).
Kaye et al.[56] (2018) TANGO I Meropenem-vaborbactam 4 g IV infusion every eight hours	AC, DB, DD, MC, RCT Patients ≥18 years of age with cUTI or acute pyelonephritis	N=550 Mean study duration of 25 days	Primary: Overall success defined as a composite of clinical cure (complete resolution or significant improvement of	Primary: Overall success at the end of the IV treatment in the microbiologic modified intent-to-treat population (n=545) was observed in 98.4% of patients in the meropenem-vaborbactam arm and 94.0% in the piperacillin-tazobactam arm (observed difference, -4.5%; 95% CI, 0.7 to 9.1%; P<0.001 for noninferiority). Secondary: Overall success at test-of-cure (TOC) in the meropenem-vaborbactam

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs piperacillin-tazobactam 4.5 g IV every eight hours Patients were treated for at least five days. After five days, patients could be switched to an oral antibiotic to complete a total of ten days of treatment.			baseline signs and symptoms of cUTI or acute pyelonephritis), and microbial eradication (baseline pathogens reduced to $<10^4$ CFU/mL urine) at the end of IV treatment visit for the microbiologic modified intent-to-treat population Secondary: Proportion of patients with overall success at end of IV treatment and at test-of-cure visits, clinical cure at end of IV treatment and at test-of-cure visits, microbial eradication	group was 74.5% compared to the piperacillin-tazobactam group of 70.3% (difference, 4.1%; 95% CI, -4.9 to 9.1%). In the microbiologic modified intent-to-treat population, clinical cure at the end of IV treatment was 98.4 and 95.6% in the meropenem-vaborbactam and piperacillin-tazobactam groups respectively (difference, 2.8%; 95% CI, -0.7 to 7.1%) and at TOC was 90.6 and 86.3% (difference, 4.4%; 95% CI, -2.2 to 11.1%). Microbial eradication at TOC in the microbiologic modified intent-to-treat was 74.2% in the meropenem-vaborbactam group and 63.4% in the piperacillin-tazobactam group (difference, 10.8%; 95% CI, -1.4 to 23.0%) in patients with acute pyelonephritis, 60.0 and 53.6% (difference, 7.4%; 95% CI, -15.4 to 29.3%) in patients with cUTI and a removable source of infection; and 48.6 and 48.8% (difference, -0.2%; 95% CI, -21.7 to 21.4%) in patients with cUTI and a nonremovable source of infection.
Respiratory Tract Infections				
McCoy et al.[57] (2008) AIR-CF2 Aztreonam inhalation solution 75 mg BID or TID for 28 days	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with FEV_1 >25 and <75% who were on maintenance	N=211 84 days	Primary: Time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of	Primary: The median time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation was 21 days longer for the aztreonam inhalation solution-pooled group than for the placebo group (92 vs 71 days; P=0.007). The median time to antibiotic need was also longer in the aztreonam inhalation solution-BID (>92 days; P=0.002) and aztreonam inhalation

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	therapy for *Pseudomonas aeruginosa* and who had completed a 28-day course of tobramycin inhalation solution		pulmonary exacerbation Secondary: Changes in clinical symptoms, pulmonary function, *Pseudomonas aeruginosa* density, time to hospitalization, hospitalizations, and weight	solution-TID (87 days; P=0.182) groups, compared to placebo (71 days). Secondary: Adjusted mean CFQ-R respiratory scores increased 5.01 points in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 0.81 to 9.21; P=0.020). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo and the responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. Adjusted mean FEV_1 improved 6.3% in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 2.5 to 10.1; P=0.001). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo. Responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. FEV_1 decreased during the follow-up period for all groups. Adjusted mean relative FEV_1 percent predicted improved in the aztreonam inhalation solution-pooled group compared to placebo (day 28; adjusted means; aztreonam inhalation solution-pooled, 4.1%; placebo, 22.5%; 95% CI, 2.8 to 10.4; P<0.001). Adjusted mean *Pseudomonas aeruginosa* sputum density decreased 0.66 $\log_{10}$ *Pseudomonas aeruginosa* cfu/g sputum in the aztreonam inhalation solution-pooled group compared to the placebo group (day 28: 95% CI, 21.13 to 20.19; P=0.006). Significant decreases were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID compared to placebo groups. Time to first hospitalization and median days per number of patients hospitalized did not differ significantly between the treatment groups (days 0 to 84). Weight increased 0.77% for the aztreonam inhalation solution-pooled group compared to placebo (day 28: 95% CI, 0.00 to 1.55; P=0.051).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Retsch-Bogart et al.[58] (2009) AIR-CF1 Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis, FEV_1 >25 and <75%, *Pseudomonas aeruginosa* airway infection, and no recent use of antipseudomonal antibiotics or azithromycin	N=164 42 days	Primary: Change in symptoms Secondary: Changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum *Pseudomonas aeruginosa* density	Primary: The adjusted mean CFQ-R-Respiratory scores increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% CI, 4.3 to 15.1; P<0.001). Two weeks after treatment, CFQ-R-Respiratory scores had declined but remained above baseline values for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; P<0.015). Secondary: The adjusted mean FEV_1 increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; P<0.001). Two weeks after treatment, the mean FEV_1 had declined but remained above baseline for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; P<0.002). The adjusted mean relative change in FEV% predicted values also increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; P<0.001) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; P=0.003). The adjusted mean sputum *Pseudomonas aeruginosa* density decreased for aztreonam inhalation solution-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 $\log_{10}$ cfu/g; 95% CI, -2.1 to -0.8; P<0.001). Two weeks after treatment (day 42), values were near baseline values for both treatment groups (P=0.822). There was a trend toward fewer hospitalized patients in the aztreonam inhalation solution group (5%) than in the placebo group (14%; days 0 to 42; P=0.064) and toward fewer mean hospitalization days (aztreonam inhalation solution group, 0.5 days; placebo group, 1.5 days; P=0.049).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Weight increased 1.1% for the aztreonam inhalation solution-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; P=0.004). The responses of aztreonam inhalation solution-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality.
Oermann et al.[59] (2010) AIR-CF3 Aztreonam inhalation solution 75 mg BID to TID for 28 days Patients received up to nine courses (28 days on/28 days off) of 75mg aztreonam inhalation solution BID or TID based on randomization in the previous trials.	OL Patients ≥6 years of age with cystic fibrosis and *Pseudomonas aeruginosa* airway infection, who previously participated in one of two Phase 3 studies (AIR-CF1 or AIR-CF2)	N=274 18 months	Primary: Disease-related endpoints (change from baseline FEV_1 percent predicted, FEV_1 absolute volume, CFQ-R-Respiratory scores, and density of *Pseudomonas aeruginosa* in sputum Secondary: Not reported	Primary: For treatment courses one through nine, percent change in FEV_1 (L) was positive at the end of each on-drug course. A greater response was observed for the TID regimen in general. The mean change in FVC from baseline ranged from -1.40 to 5.39% (BID) and from 0.97 to 6.18% (TID). The mean change in $FEF_{25–75}$ from baseline ranged from -4.20 to 16.05% (BID) and from -5.02 to 14.14% (TID). For the on-treatment months, the mean increase in CFQ-R-Respiratory score was >4. Changes on other symptom scales of the CFQ-R were consistent with treatment benefit. There was a greater improvement in the TID group than in the BID group. In the TID group, mean improvements from baseline for the Physical Functioning, Vitality and Health Perceptions domains tended to be greater during each of the intervals when the patient was on treatment and less during each of the intervals when the patient was off treatment. For the TID group, mean scores for the Weight domain tended to be above baseline throughout the nine treatment courses. Absolute changes from baseline for the remaining domains (emotional functioning, social functioning, body image, eating disturbances, role limitations/school performance and digestion) were variable and showed no apparent dose response. A total of 47.8% of patients were hospitalized at least once during the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study. The median time to the first hospitalization for a respiratory event was 449 days, with median times of 431 and 449 days for the BID- and TID-treated groups, respectively. Median time to IV antipseudomonal antibiotics was 247 days (95% CI, 210 to 287), with similar times between the two regimen groups: 276 days for the BID-treated group (95% CI, 217 to 316) and 232 days for the TID group (95% CI, 179 to 288). Repeated courses of aztreonam inhalation solution resulted in consistent weight gain, which were sustained over the 18-month period. Improvement was greater among patients receiving TID compared to BID treatment. Mean adherence was 92.0% in the BID group and 88.0% in the TID group. Secondary: Not reported
Wainwright et al.[60] (2011) Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with an FEV_1 >75%, *Pseudomonas aeruginosa* airway infection, and who did not require immediate antipseudomonal antibiotic treatment of an impending exacerbation	N=157 42 days	Primary: Change from baseline at Day 28 on the CFQ-R RSS Secondary: Change from baseline at Days 14 and 42 on the CFQ-R RSS, change from baseline at Day 28 on the CFQ-R Physical Functioning Scale, use of additional antipseudomonal antibiotics, proportion of	Primary: Adjusted mean change at Day 28 from baseline CFQ-R RSS scores was 3.22 for aztreonam inhalation solution-treated and 1.41 for placebo-treated patients (treatment effect 1.80; 95% CI, −2.83to 6.44; P=0.443). Secondary: Significant treatment effects favoring aztreonam inhalation solution were observed for several secondary efficacy endpoints: change from baseline at day 28 for adjusted mean log_{10} *Pseudomonas aeruginosa* CFUs in sputum (aztreonam inhalation solution, −1.4; placebo, −0.14; P=0.016) and adjusted mean relative change in FEV_1 percent predicted (aztreonam inhalation solution, 0.29%; placebo, −2.5%; P=0.021). Amongst other efficacy endpoints, significant treatment effects favoring aztreonam inhalation solution were observed for relative mean change from baseline FEV_1 (L) at day 28 and CFQ-R Social Functioning scores. Use of PO, IV, or additional inhaled antibiotics was similar for the aztreonam inhalation solution and placebo groups during the entire study,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients hospitalized, and change from baseline at Day 28 for log_{10} *Pseudomonas aeruginosa* CFUs in sputum and FEV_1 percent predicted	with most use occurring during the follow-up period for both treatment groups.
Tiddens et al.[61] (2015) ALPINE Aztreonam for inhalation solution 75 mg three times daily for 28 days	MC, OL Newly acquired *Pseudomonas aeruginosa* infection in cystic fibrosis patients three months to <18 years of age	N=105 24 weeks	Primary: Proportion of patients with cultures negative for *Pseudomonas aeruginosa* at all visits throughout the 24-week follow-up period Secondary: Proportion of patients with cultures negative for *Pseudomonas aeruginosa* at each follow-up visit, additional anti-pseudomonal antibiotic use, and for patients ≥6 years, changes from baseline in FEV1 % predicted and Cystic Fibrosis Questionnaire-Revised	Primary: Of 79 patients in the primary efficacy evaluable set, 46 patients (58.2%; 95% CI, 47.4 to 69.1%) remained culture-negative for *Pseudomonas aeruginosa* throughout the 24-week follow-up period. Secondary: Of the 101 patients who completed four weeks of aztreonam treatment, 89.1% had cultures negative for *Pseudomonas aeruginosa* at week 4, and 75.2, 63.4, and 47.5% were culture-negative at weeks eight, 16, and 28, respectively. Patients ≥ 6 years of age in the sensitivity analysis set who met the primary endpoint (n=25), had FEV1% predicted remain near baseline until week 16, with a 2.5% mean actual decrease from baseline at week 28. For patients not meeting the primary endpoint (n=27), corresponding decreases in observed values were 4.2, 5.1, and 8.9%, at weeks eight, 16, and 28, respectively. Mean changes in CFQ-R RSS for the patients in the sensitivity analysis set who met the primary eradication endpoint (n=25) were numerically higher or similar to patients who did not meet the endpoint (n=31), with mean changes above the minimum important difference score for stable patients (4.0 points [28]) at all but one time point (week 16 for patients who did not meet the primary endpoint).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Respiratory Symptoms Scale (CFQ-R-RSS) scores	
Flume et al.[62] (2016) Aztreonam inhalation solution 75 mg TID vs placebo All patients received tobramycin inhalation solution 300 mg BID for a 28-day run-in phase followed by three cycles of 28-days of study drug alternating with 28-days of open label tobramycin inhalation solution	DB, MC, PC, RCT Patients ≥ 6 years of age with cystic fibrosis, a documented *Pseudomonas aeruginosa* lung infection, FEV_1 >25 to <75% predicted, and had received at least one course of IV antibiotic treatment for a pulmonary exacerbation within the previous 12 months	N=90 196 days	Primary: Rate of protocol-defined pulmonary exacerbations (change or worsening from baseline of one or more documented signs or symptoms associated with use of IV or non-study inhaled antibiotics) Secondary: Average absolute change from baseline FEV_1% predicted, percent of subjects treated for a protocol-defined pulmonary exacerbation, time to first protocol-defined pulmonary exacerbation, rate of hospitalization for a respiratory event, and average change from baseline scores of the CFQ-R Respiratory Symptom Scale.	Primary: There was a 25.7% reduction in exacerbation rate for the aztreonam for inhalation solution group, however the difference between groups was not statistically significant (RR, 0.74; 95% CI, -0.45 to 1.24, P=0.25). Secondary: Adjusted mean FEV_1 improved 1.37% in the aztreonam for inhalation solution group compared to 0.04% in the placebo group (P=0.16). From Day one to Week 24, 55.3% of patients in the placebo group and 48.8% of patients treated with aztreonam for inhalation solution were treated for a protocol-defined pulmonary exacerbation. Median time to first protocol-defined pulmonary exacerbation was 175.0 days in the aztreonam for inhalation solution group and 140.0 days in the placebo group (P=0.71). The rate of hospitalization for a respiratory event was 1.04 per subject-year in the aztreonam for inhalation solution and 1.62 in the placebo group (P=0.14). Adjusted mean CFQ-R Respiratory Symptom Scale scores, averaged from weeks four, 12, and 20, increased 1.00 points from baseline in the inhaled aztreonam treated patients and worsened 2.06 for the placebo treated patients (P=0.21).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Réa-Neto et al.[63] (2008) Doripenem 500 mg IV every eight hours vs piperacillin-tazobactam 4.5 grams IV every six hours	MC, OL, PRO, RCT Patients aged 18 years or older with signs and symptoms of nosocomial pneumonia, including non-ventilated patients and those with early-onset ventilator-associated pneumonia	N=448 7 to 14 days	Primary: Clinical cure rate in the clinically evaluable population and in the clinically evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the end of IV therapy and at the late follow-up visit, clinical and microbiological cure rates in the microbiologically evaluable patients at the test-of-cure visit and in the microbiologically evaluable-modified intent-to-treat population, clinical and microbiological cure rates at the test-of-cure visit in microbiologically evaluable patients with early-onset ventilator-associated pneumonia, and all-cause mortality	Primary: The clinical cure rates in clinically evaluable patients at the test-of-cure visit were 81.3% in the doripenem arm and 79.8% in the piperacillin-tazobactam arm (95% CI, -9.1 to 12.1). In the clinically evaluable-modified intent-to-treat population, the clinical cure rates in the doripenem and piperacillin-tazobactam arms were 69.5 and 64.1%, respectively (95% CI, -4.1 to 14.8). Secondary: Clinical response rates at the end of IV study drug therapy in clinically evaluable patients were 87% in both treatment arms (95% CI, -9.2 to 9.2%). Clinical relapse rates at the late follow-up visits were low for both the doripenem (3%) and piperacillin-tazobactam (4%) treatment arms. The clinical cure rates in microbiologically evaluable patients at the test-of-cure visit were 82.1 and 78.3% (95% CI, -9.4 to 17.1) in the doripenem and piperacillin-tazobactam arms, respectively. In the microbiologically evaluable-modified intent-to-treat population, clinical cure rates were 67.6 and 67.4%, respectively (95% CI, -11.4 to 11.9). Microbiological responses in the microbiologically evaluable patients at the test-of-cure visit were achieved in 84.5% of patients in the doripenem arm and 80.7% of patients in the piperacillin-tazobactam arm (95% CI, -8.9 to 16.5). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 13.8% with doripenem and 14.6% with piperacillin-tazobactam (95% CI, -7.9 to 6.3). A Kaplan-Meier analysis found no difference in cumulative mortality rate between the two treatment arms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			at day 28 in the clinically evaluable-modified intent-to-treat population.	
Chastre et al.[64] (2008) Doripenem 500 mg IV every eight hours vs imipenem 500 mg IV every six hours or 1,000 mg every eight hours	AC, MC, OL, RCT Adults meeting clinical and radiologic criteria for ventilator-associated pneumonia	N=531 7 to 14 days	Primary: Clinical cure rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations Secondary: Clinical cure rates in the microbiologically evaluable-modified intent-to-treat, microbiological cure rates in the microbiologically evaluable population; clinical relapse rates at the late follow-up visit; per-pathogen clinical/ microbiological cure rates; emergence of *Pseudomonas aeruginosa* strains acquiring decreased susceptibility to	Primary: Clinical cure rates were 68.3% (doripenem) and 64.2% (imipenem) in the clinically evaluable (95% CI, -7.9% to 10.3%) and 59.0% (doripenem) and 57.8% (imipenem) in the clinically evaluable-modified intent-to-treat populations (95% CI, -9.1 to 16.1). Secondary: In the microbiologically evaluable patients, favorable microbiological response rates were 73.3% with doripenem and 67.3% with imipenem (95% CI, -6.8 to 18.8). In patients with *Pseudomonas aeruginosa*, clinical cure was 80.0% (doripenem) and 42.9% (imipenem) (P=NS); microbiological cure was 65.0% (doripenem) and 37.5% (imipenem). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 10.8% with doripenem and 9.5% with imipenem (95% CI, -4.4 to 7.0). The incidence and types of all adverse events and those considered drug-related by the investigators were similar in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			study drug; emergent infection rate; all-cause mortality	
Friedland et al.[65] (2004) Ertapenem 1 g IV daily vs ceftriaxone 1 g IV daily Patients with clinical improvement meeting pre-specified criteria could be switched to PO amoxicillin-clavulanate or other PO antimicrobial based on pathogen susceptibility for a total of 10 to 14 days.	DB, MC, RCT Patients 18 years of age and older with typical community-acquired pneumonia admitted to the hospital for parenteral antimicrobial therapy	N=857 7 to 14 days post-therapy	Primary: Clinical response at the test-of-cure visit, clinical response at the completion of parenteral therapy Secondary: Not reported	Primary: At the test-of-cure visit, the combined response rates were 90% in patients with COPD and 93% in patients without COPD. In the patients without COPD, favorable results were seen in 93% of both ertapenem and ceftriaxone patients. There were no significant differences between treatment groups (P=0.94) or between patients with and without COPD (P=0.17). Clinical response at the completion of parenteral therapy was seen in 95% of ertapenem patients and 94% of ceftriaxone patients. Secondary: Not reported
Kollef et al.[66] (2019) ASPECT-NP Meropenem 1 g IV every 8 hours for 8 to 14 days	DB, MC, NI, RCT Patients ≥18 years of age undergoing mechanical ventilation, and had nosocomial pneumonia (either	N=726 7 to 14 days post-therapy	Primary: 28-day all-cause mortality Secondary: Clinical response at the test-of-cure visit (7 to 14 days	Primary: At 28 days, 87 (24.0%) patients in the ceftolozane–tazobactam group and 92 (25.3%) in the meropenem group had died (weighted treatment difference 1.1%; 95% CI, −5.1 to 7.4). Ceftolozane–tazobactam was thus non-inferior to meropenem in terms of 28-day all-cause mortality. Secondary: At the test-of-cure visit 197 (54%) patients in the ceftolozane–tazobactam

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftolozane-tazobactam 3 g IV every 8 hours for 8 to 14 days	ventilator-associated pneumonia or ventilated hospital-acquired pneumonia)		after the end of therapy)	group and 194 (53%) in the meropenem group were clinically cured (weighted treatment difference, 1.1%; 95% CI, −6.2 to 8.3). Ceftolozane–tazobactam was thus non-inferior to meropenem in terms of clinical cure at test of cure.
Yanagihara et al.[67] (2006) Imipenem-cilastatin 0.5 g BID vs ampicillin-sulbactam 3 g BID	PRO, RCT Elderly patients >65 years of age with moderate-to-severe community-acquired pneumonia	N=67 7 to 14 days	Primary: Clinical efficacy Secondary: Bacteriological efficacy, adverse events	Primary: Overall clinical efficacy of ampicillin-sulbactam therapy was 91.4% compared to 87.5% for imipenem-cilastatin therapy (P=NS). Secondary: The eradication rate was 100% in both treatment arms (P=NS). The overall eradication rate for the pathogenic microorganism was 84% in the ampicillin-sulbactam group and 80%in the imipenem-cilastatin group (P=NS). All adverse reactions were mild or moderate and transient in both treatment groups.
Bartoloni et al.[68] (1999) Imipenem-cilastatin 2 g IV QD vs meropenem 1.5 g IV QD	MC, RCT Individuals aged 18 to 94 years of age with community-acquired pneumonia	N=144 9 to 10 days	Primary: Clinical efficacy (cure or improvement in signs and symptoms) Secondary: Bacteriological response (either presumed or confirmed eradication of all pathogens) and safety assessment	Primary: At the end of therapy, clinical response was observed in 90.9% of the patients receiving imipenem-cilastatin and 89.1% of meropenem-treated patients. In patients who were followed up for two to four weeks, the response was satisfactory (100%) for both treatments. Secondary Response was considered satisfactory in 100% of the meropenem group and 92.9% in the imipenem-cilastatin group and at follow-up; it was 100% for both treatments. Drug-related adverse events were reported in 4.2% of the meropenem-treated patients and in 11.0% of the imipenem-cilastatin-treated patients.
Schmitt et al.[69] (2006)	DB, MC, RCT Hospitalized	N=221 5 to 21 days	Primary: Clinical response at the end of the	Primary: Therapeutic response was seen in 66% [95% CI, 56.5 to 75] of patients receiving piperacillin-tazobactam and in 70% [95% CI, 60.4 to 78.2] of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 4 g-500 mg every eight hours vs piperacillin-tazobactam 1 g-1 g every eight hours Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present.	patients with nosocomial pneumonia		treatment period Secondary: Clinical responses on the last day of treatment or on day 21 and on day 14±7 days after treatment, bacteriological responses, safety	patients receiving imipenem-cilastatin. Failure rates were similar at 18.7 and 18.2%, respectively. On the last day of treatment or on day 21, therapeutic responses were higher and seen in 71% [95% CI, 61.3 to 79.2] and 77.3% [95% CI, 68.1 to 84.5] of patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. Failure rates were 17.8 and 16.4% respectively. Secondary: At the second follow-up (14±4 days after the end of treatment) clinical responses were 59.8% [95% CI, 49.9 to 69] and 66.4% [95% CI, 56.6 to 74.9] and failure rates were 19.6 and 15%, in patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. The majority of patients in both groups responded to treatment and the overall response rate was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods. Eradication immediately after treatment with piperacillin-tazobactam or imipenem-cilastatin was 45.7 and 52.7%, respectively compared to 40.3 and 50% at the first follow-up and 34.6 and 42.2% at the second follow-up, respectively. Overall, 74.5 and 64.9% of patients receiving piperacillin-tazobactam and imipenem-cilastatin, respectively reported adverse events, the majority of which were of mild intensity. The most common related adverse events were diarrhea and fever in the piperacillin-tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem-cilastatin group.
Joshi et al.[70] (2006) Imipenem-cilastatin 500 mg IV every six hours vs piperacillin-	DB, MC, RCT Hospitalized patients with acute nosocomial pneumonia	N=437 21 days	Primary: Clinical cure and microbiological response rates; pathogen eradication rates; length of hospital stay; hospital readmissions; adverse events	Primary: The overall clinical cure rate was 68% in piperacillin-tazobactam patients and 61% in imipenem patients in the efficacy evaluable population (P=0.256). Microbiological response rates were comparable among efficacy evaluable patients treated with piperacillin-tazobactam and those treated with imipenem. Microbiological responses for piperacillin-tazobactam and imipenem patients were: eradication, 64 vs 59%; persistence, 29 vs 21%; relapse, 0 vs 5%; and superinfection, 7 vs 15%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tazobactam 4.5 grams IV every six hours Patients also received aminoglycoside therapy.			Secondary: Not reported	Gram-positive isolates were eradicated in 83% of piperacillin-tazobactam patients and 75% of imipenem patients; Gram-negative pathogens were eradicated in 72% of piperacillin-tazobactam patients and 77% of imipenem patients. Piperacillin-tazobactam and imipenem patients had similar hospital and intensive care unit length of stay. Hospital readmission rates in both groups were small and were not significantly different. There were no significant differences in adverse events between the two treatment groups. Secondary: Not reported
Ito et al.[71] (2010) Imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days vs piperacillin-tazobactam 5 g IV every 12 hours for 7 to 14 days	OL, RCT, SC Patients aged ≥15 years of age with a risk for aspiration who had been hospitalized after developing moderate-to-severe pneumonia in the community or nursing home	N=469 30 days	Primary: Clinical response rate at the end of treatment in validated per protocol population Secondary: Clinical response during treatment (days four and seven) and at the end of study in validated per protocol population, and survival at day 30 in modified intention-to-treat Population	Primary: At the end-of-treatment visit, the clinical effective rate for the validated per protocol population was 83% for piperacillin-tazobactam and 82% for imipenem-cilastatin (P=0.92). Secondary: There were no significant differences between the groups in any of the secondary outcome measures. Mortality rate within 30 days of admission in modified intention-to-treat population was 15% in the piperacillin-tazobactam group and 24% in the imipenem-cilastatin group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving piperacillin-tazobactam and 31% of patients receiving imipenem-cilastatin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Titov et al.[72] (2020) RESTORE-IMI 2 Imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg IV every 6 hours for 7 to 14 days vs piperacillin/tazobactam 4 g/500 mg IV every 6 hours for 7 to 14 days	DB, MC, RCT Patients were ≥18 years old and required intravenous antibacterial therapy for nonventilated HABP, ventilated HABP, or VABP	N=537 MITT n=531 28 days	Primary: 28 all-cause mortality in the modified intent-to-treat (MITT) population (patients who received study therapy, excluding those with only gram-positive cocci at baseline) Secondary: Clinical response 7 to 14 days after completing therapy in the MITT population	Primary: Imipenem/cilastatin/relebactam was noninferior (P<0.001) to piperacillin/tazobactam: day 28 all-cause mortality was 15.9% with imipenem/cilastatin/relebactam and 21.3% with piperacillin/tazobactam (difference, -5.3%; 95% CI, -11.9 to 1.2%). Secondary: Imipenem/cilastatin/relebactam was noninferior (P<0.001) to piperacillin/tazobactam: favorable clinical response at early follow-up was 61.0% and 55.8%, respectively (difference, 5.0%; 95% CI, -3.2 to 13.2%). Serious adverse events occurred in 26.7% of imipenem/cilastatin/relebactam and 32.0% of piperacillin/tazobactam patients; adverse events leading to treatment discontinuation in 5.6% and 8.2%, respectively; and drug-related adverse events (none fatal) in 11.7% and 9.7%, respectively.
Miscellaneous Infections				
Kobayashi et al.[73] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success Secondary: Not reported	Primary: Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively (P≥0.05). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <$0.5x10^9$/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
into four doses Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.				Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported
Liberman et al.[74] (1995) Cefotetan 2 g IV as a single dose preoperatively (group one) vs cefoxitin 2 g IV as a single dose preoperatively (group two) vs cefoxitin 2 g IV as a single dose preoperatively followed by three doses postoperatively (group three)	DB, RCT Patients with nonperforated acute appendicitis undergoing appendectomy	N=136 Single dose study	Primary: Wound infection rates Secondary: Not reported	Primary: The overall wound infection rate was 4.4%. No post-operative infections were found in group one, 11.1% occurred in group two, and 1.9% occurred in group three. There was no significant difference between groups one and three; however, there were significant differences in infections rates between groups one and two (P=0.04) and groups two and three (P=0.05). Secondary: Not reported
Hemsell et al.[75] (1995)	DB, PRO, RCT Women undergoing	N=511 Single dose	Primary: Prevention of major operative	Primary: A major operative site infection requiring parenteral antimicrobial therapy developed in 9.0% of evaluable women: 11.6% of women given cefazolin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefotetan 1 g IV as a single dose vs cefazolin 1 g IV as a single dose	elective abdominal hysterectomy	study	site infections Secondary: Not reported	prophylaxis and 6.3% of women given cefotetan prophylaxis (RR, 1.84; 95% CI, 1.03 to 3.29; P<0.05). Risk factors for major operative site infection were younger age, lower postoperative hemoglobin concentration, and a proliferative endometrium. Of the women given cefazolin prophylaxis, 3.9%had a postoperative pelvic abscess compared to 0.8% of women given cefotetan prophylaxis (RR, 4.9; 95% CI, 1.09 to 22.16; P =0.04). A greater number of infections and more serious infections occurred following cefazolin prophylaxis; this treatment resulted in 234 additional hospital days for administration of IV antimicrobial therapy. Secondary: Not reported
Lucasti et al.[76] (2008) Doripenem 500 mg IV every eight hours vs meropenem 1 gram IV every eight hours Patients could be switched to PO amoxicillin-clavulanate after a minimum of nine doses and adequate clinical improvement.	DB, MC, RCT Hospitalized adult patients with cIAIs	N=476 21 to 60 days	Primary: Clinical cure rate at the test-of-cure visit (21 to 60 days after the last dose of study drug) and the clinical cure rate in the microbiological modified intent-to-treat population Secondary: Clinical cure rates at the end of IV treatment, early follow-up, and test-of-cure visits	Primary: Doripenem and meropenem were associated with clinical cure rates at the test-of-cure visit of 85.9 and 85.3%, respectively (95% CI, -7.7 to 9.0). In the microbiological modified intent-to-treat population, the clinical cure rates were 77.9 and 78.9%, respectively (95% CI, -9.7 to 7.7). Secondary: Clinical cures assessed in the clinically evaluable and microbiologically evaluable population at the end of IV treatment, early follow-up, and test-of-cure visits were not significantly different within or between populations of doripenem and meropenem. The proportions of patients experiencing adverse events were not significantly different between the two treatment arms (83.0 vs 78.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tazuma et al.[77] (2015) Doripenem 0.5 g IV three times daily vs imipenem-cilastatin 0.5 mg IV three times daily	OL, RCT Patients ≥20 years of age with moderate or severe biliary tract infection (acute cholangitis or cholecystitis) who were hospitalized	N=127 Mean duration of treatment was 7 days	Primary: Clinical response rate Secondary: Bacteriological efficacy, safety	Primary: The clinical response rate was not significantly different between the doripenem group (93.1%, 54/58 patients) and the imipenem-cilastatin group (93.8%, 60/64). There was no significant between-group difference (P=1.000). Non-inferiority assessment using confidence intervals demonstrated the non-inferiority in the clinical response rate between the two groups. The response rates in the doripenem and imipenem-cilastatin groups were, respectively, 100.0 and 94.6% for patients with cholangitis, 90.9 and 90.9% for those with cholecystitis, and 66.7 and 100.0% for those with both cholangitis and cholecystitis. For any of the diseases, the between-group difference was not significant (P=0.498, 1.000, and 0.455, respectively). Secondary: The bacteriological response rate was 69.0% (29/42 patients) in the doripenem group and 78.3% (36/46 patients) in the imipenem-cilastatin group (P=0.344). Two patients each in the two groups (3.3 and 3.1%, respectively) presented with adverse drug reactions, including one patient with watery diarrhea and one patient with drug eruption in the doripenem group, and one patient with vomiting and one patient with pseudomembranous colitis in the imipenem-cilastatin group.
Namias et al.[78] (2007) Ertapenem 1 gram IV QD vs piperacillin-tazobactam 3.375 grams IV every six hours	DB, MC, RCT Patients 18 to 90 years of age with presumptive (pre-operative) or confirmed cIAI	N=500 4 to 14 days	Primary: Clinical response rates Secondary: Microbiological efficacy, clinical failure, mortality	Primary: Favorable clinical responses were demonstrated for 82.1% of the patients in the ertapenem group and 81.7% of the patients in the piperacillin-tazobactam group (95% CI, -9.6 to 10.5). At the end of therapy, 89.6 and 86.2%, and at late follow-up assessment, 78.9 and 79.3%, of the microbiologically evaluable patients had favorable clinical responses in the ertapenem and piperacillin-tazobactam treatment groups, respectively. Clinical response rates of 63.2% for ertapenem and 60.9% were similar for piperacillin-tazobactam-treated patients in the modified intent-to-treat

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				population at early follow-up assessment (95% CI, -7.5 to 12.0). Secondary: There were no clinically important differences in the response rates of gram-positive, gram-negative, or anaerobic pathogens in the ertapenem and piperacillin-tazobactam treatment groups. Favorable overall microbiological responses were demonstrated in 82.2% in the ertapenem group and 82.5% in the piperacillin-tazobactam group (95% CI, -10.1 to 9.8) at early follow-up assessment. The pathogens isolated most frequently were *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*. At the early follow-up assessment, there were 22 clinical failures (17.9%) in the ertapenem group and 20 (18.5%) in the piperacillin-tazobactam group. The incidence of adverse events and study discontinuations because of adverse events was similar in the two groups. During the study and post-treatment follow-up period, clinical adverse events resulted in 21 deaths, nine of which occurred in the ertapenem group (3.6%) and 12 in the piperacillin-tazobactam group (4.9%; RR, 0.75; 95% CI, 0.30 to 1.77; risk difference, -1.21; 95% CI, -5.08 to 2.53).
Yellin et al.[79] (2007) Ertapenem 1 g IV QD (13 to 17 years of age) or 15 mg/kg (2 to 12 years of age) vs ticarcillin-clavulanate 50	MC, OL, RCT Children aged 3 months to 17 years of age with cIAI or acute pelvic infections	N=105 3 to 9 days	Primary: Incidence of any serious drug-related clinical and/or laboratory adverse experiences Secondary: Overall response rates, drug-related clinical and/or laboratory adverse	Primary: Forty-six percent of patients had one or more clinical adverse event as assessed by the investigator: 39% in the ertapenem group and 67% in the comparator group. Eleven patients (14%; 95% CI, 7.0 to 23.0) in the ertapenem group and eight patients (33%; 95% CI, 15.6 to 55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion site pain was the most common drug-related adverse event in both groups. Secondary:

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mg/kg four to six times daily (<60 kg) or 3.1 grams four to six times daily (≥60 kg)			experiences, incidence of moderate-to-severe administration site reactions	Overall response rates were 89% for ertapenem and 73% for the comparator. Comparable rates were seen across each of the age groups studied. In the modified intent-to-treat analysis, the age-adjusted posttreatment clinical response rates were 87 and 100% in the cIAI and acute pelvic infection patients, respectively, for ertapenem and 73and 100%, respectively, for ticarcillin-clavulanate. Overall age-adjusted response rates were 91% for ertapenem and 83% for the comparator. Eleven percent (95% CI, 5.2 to 20.0) in the ertapenem group and 25% (95% CI, 9.8 to 46.7) in the comparator group experienced ≥1 local reactions of any intensity at the infusion/injection site.
Solomkin et al.[80] (2017) IGNITE 1 Ertapenem 1 g every 24 hours vs eravacycline 1 mg/kg every 12 hours	DB, DD, MC, RCT Patients ≥18 years of age with clinical evidence of cIAI requiring urgent surgical or percutaneous intervention within 48 hours of diagnosis	N=541 Variable duration	Primary: Clinical response at the test of cure visit (25 to 31 days after the first dose) in the microbiological intent-to-treat, modified intent-to-treat, and clinically evaluable populations Secondary: Not Reported	Primary: In the modified intent-to-treat population (N=538) 87.0% of eravacycline and 88.8% of ertapenem achieved clinical cure with a difference of -1.8% (95% CI, -7.4 to 3.8%). In the microbiological intent-to-treat population (N=446) 86.8% of eravacycline and 87.6% of ertapenem achieved clinical cure with a difference of -0.8% (95% CI, -7.1 to 5.5%). In the clinically evaluable population 92.9% of eravacycline and 94.5% of ertapenem achieved clinical cure with a difference of -1.7% (95% CI, -6.3 to 2.8%). Secondary: Not reported
Falagas et al.[81] (2008) Ertapenem vs	MA Patients with cIAI infections or acute pelvic infections	7 trials 4 to 14 days	Primary: Clinical success Secondary: Mortality, laboratory adverse events, patient	Primary: No difference was found regarding clinical success in patients treated with ertapenem, compared to those treated with other antibiotics (OR, 1.11; 95% CI, 0.89 to 1.39). There was no difference in microbiological success of adult patients with cIAIs treated with ertapenem compared to those treated with comparator

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
piperacillin-tazobactam, ceftriaxone plus metronidazole, or ticarcillin-clavulanic acid			withdrawals because of adverse events	antibiotics (OR, 1.19, 95% CI, 0.83 to 1.71). Microbiological or clinical success did not differ between compared treatments for the subsets of patients infected with either *Pseudomonas aeruginosa* (OR, 1.00; 95% CI, 0.41 to 2.45) or *Enterococcus* spp. (OR, 1.19; 95% CI, 0.60 to 2.39). Secondary: There was no difference in mortality between adult patients with cIAIs treated with ertapenem or comparator antibiotics (OR, 1.14; 95% CI, 0.72 to 1.83). No difference was found regarding clinical adverse events between adult patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR, 0.86; 95% CI, 0.61 to 1.20). Significantly more laboratory adverse events were noted in patients with cIAIs, treated with ertapenem compared to patients treated with other antibiotics (OR, 1.73; 95% CI, 1.14 to 2.61). No difference was found regarding withdrawals from the included studies because of adverse events, between patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR, 0.94; 95% CI, 0.47 to 1.87).
Itani et al.[82] (2006) Ertapenem vs cefotetan	DB, RCT Patients undergoing elective colorectal surgery	N=1,002 4 weeks	Primary: Absence of surgical-site infection, anastomotic leakage, or antibiotic use four weeks postoperatively Secondary: Not reported	Primary: The rate of overall prophylactic failure was 40.2% in the ertapenem group and 50.9% in the cefotetan group in the intent-to-treat analysis (95% CI, -17.1 to -4.2). The rate of overall prophylactic failure was 28.0% in the ertapenem group and 42.8% in the cefotetan group in the per-protocol analysis (95% CI, -21.9 to -7.5). The most common reason for failure of prophylaxis in both groups was surgical-site infection: 17.1% in the ertapenem group and 26.2% in the cefotetan group (95% CI, -14.4 to -3.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the treated population, the overall incidence of *Clostridium difficile* infection was 1.7% in the ertapenem group and 0.6% in the cefotetan group (P=0.22). Secondary: Not reported
Arguedas et al.[83] (2009) Ertapenem 1 g IV as a single daily dose (children aged 13 to 17 years) or 30 mg/kg/day divided BID (children aged 3 months to 12 years) vs ceftriaxone 50 mg/kg/day as a single dose (children aged 13 to 17 years) or 50 mg/kg/day divided BID (children aged 3 months to 12 years)	AC, DB, RCT Patients ≥3 months and <18 years with cUTI, SSI and community-acquired pneumonia requiring initial parenteral antibiotic therapy	N=404 14 days	Primary: Incidence of clinical and laboratory drug-related serious adverse events Secondary: Incidence of any drug-related adverse events and any moderate-to-severe reactions at the parenteral infusion site	Primary: In each group, the mean duration of therapy (parenteral and PO antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was four days. Overall, 46.7% of the children had one or more clinical adverse events during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory adverse event (P=0.69). Secondary: The most common drug-related clinical adverse events during parenteral therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients (10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and one patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory adverse event in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group). In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Gutiérrez-Gutiérrez et al.[84] (2016) Ertapenem vs all other carbapenems	Cohort, RETRO Patients with clinically significant bloodstream infections due to extended-spectrum β-lactamase-producing *Enterobacteriaceae* or carbapenemase-producing *Enterobacteriaceae* treated with carbapenem monotherapy in one of the participating centers	N=195 (empirical therapy cohort) N=509 (targeted therapy cohort) Variable duration	Primary: Clinical response rate at day 14 and all-cause 30-day mortality Secondary: Not reported	Primary: The odds ratio for cure with ertapenem as compared to other carbapenems in the empirical therapy cohort was 1.87 (95% CI, 0.24 to 20.08; P=0.58) adjusted using logistic regression. The odds ratio for cure in the targeted therapy cohort was 1.04 (95% CI, 0.44 to 2.50; P=0.92) adjusted using logistical regression. The odds ratio for mortality with ertapenem as compared to all other carbapenems in the empirical therapy cohort was 0.12 (95% CI, 0.02 to 0.88; P=0.04) this is the crude value, an adjusted odds ratio was not provided. In the targeted therapy cohort, the odds ratio was 1.18 (95% CI, 0.43 to 3.29; P=0.74) this was adjusted using logistic regression. Secondary: Not reported
Hou et al.[85] (2001) Imipenem-cilastatin 500 mg IV BID (or 1 g IV BID) vs meropenem 500 mg IV BID (or 1 g	OL, RCT Hospitalized patients ≥16 years of age with lower respiratory infections, urinary tract infections and other acute infections	N=140 7 to 14 days	Primary: Cure rate, overall efficacy rate (the proportion of patients cured and markedly improved), clinical efficacy, and adverse events Secondary: Not reported	Primary: The cure rate was 57% in the imipenem-cilastatin group and 66% in the meropenem group (P=0.298). The overall efficacy rate was 87% for the imipenem-cilastatin group and 90% for the meropenem group (P=0.595). The bacterial eradication rates were 86% in both groups. There were 72 cases of adverse drug reactions in the meropenem group and 70 cases in the imipenem-cilastatin group that were evaluated resulting in an adverse drug reaction rate of 9.7 and 8.6%, respectively (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV BID)				Secondary: Not reported
Nelson et al.[86] (2002) Imipenem-cilastatin 20 mg/kg IV QID in addition to cytotoxic chemotherapy and total body irradiation vs meropenem 20 mg/kg IV TID in addition to cytotoxic chemotherapy and total body irradiation	RCT Pre-engrafted pediatric bone marrow transplant patients	N=32 3 to 31 days	Primary: Evidence of bacterial infection, need for concurrent antibiotics, incidence of vomiting and duration of concurrent total parenteral nutrition Secondary: Not reported	Primary: There was no detectable difference in the evidence of bacterial infection between the two treatment groups. Concurrent antibiotics were required for 7.1±2.0 days in the imipenem-cilastatin group compared to 7.2±1.7 days in the meropenem treatment group (P=0.944). There were 30.38±5.08 episodes of vomiting per course of imipenem-cilastatin, vs 9.75±3.53 episodes per course of meropenem, a difference that was statistically significant (P=0.0021). There was no significant difference in the duration of total parenteral nutrition support required between the imipenem-cilastatin group (19.2±2.9 days) and the meropenem group (13.9±2.4 days; P=0.1662). Secondary: Not reported
Vural et al.[87] (2010) Imipenem-cilastatin 60 mg/kg/day IV in four divided doses vs piperacillin-tazobactam 360 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate Secondary: Not reported	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71 and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62 and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Chen et al.[88] (2010) Imipenem-cilastatin 500-500 mg every six hours vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	OL, MC, RCT Patients ≥18 years of age with cIAI	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure visit (12 to 37 days after therapy) for the microbiologically evaluable and microbiologic modified intent-to-treat populations Secondary: Not reported	Primary: In the microbiologically evaluable population, 86.5% of patients receiving tigecycline and 97.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.05 to 0.7). In the microbiologic modified intent-to-treat population, 81.7% of patients receiving tigecycline and 90.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.4 to 4.9). In the clinically evaluable population, 87.0% of patients receiving tigecycline and 95.4% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -18.3 to 1.5). In the clinical microbiologic modified intent-to-treat population (those with complicated appendicitis), 80.4% of patients receiving tigecycline and 89.8% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for tigecycline compared to 53.9% for imipenem-cilastatin (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6 vs 3.9%; P<0.001) and vomiting (12.4 vs 2.0%; P=0.005). Secondary: Not reported
Lucasti et al.[89] (2016) Imipenem-cilastatin 500 mg IV plus relebactam 250 mg IV every six hours vs	DB, MC, PRO, RCT Patients ≥18 years of age with clinically suspected and/or bacteriologically documented cIAI requiring hospitalization and	N=351 Late follow-up was 28 to 42 days after IV therapy	Primary: Favorable clinical response (cure or sustained cure) in microbiologically evaluable subjects at discontinuation of IV therapy Secondary: Clinical response	Primary: Clinical response rate at discontinuation of IV therapy in the microbiologically evaluable population was 96.3% in subjects treated with imipenem-cilastatin plus relebactam 250 mg, 98.8% in subjects treated with imipenem-cilastatin plus relebactam 125 mg, and 95.2% in subjects treated with imipenem-cilastatin plus placebo. The clinical response rates in both relebactam groups were noninferior to imipenem-cilastatin alone (P<0.001). Secondary: Clinical response rates at early and late follow-up visits were generally

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imipenem-cilastatin 500 mg IV plus relebactam 125 mg IV every six hours vs imipenem-cilastatin 500 mg IV plus placebo every six hours	treatment with IV antibiotic therapy		at early and late follow-up, microbiological response, global response	similar across the treatment groups. Clinical response at early follow-up was 96.3% in the imipenem-cilastatin plus placebo group compared with 94.9% in the imipenem-cilastatin plus relebactam 250 mg (difference, -1.4%; 95% CI, -9.1 to 6.0) and 94.2% in the imipenem-cilastatin plus relebactam 125 mg group (difference, -2.1%; 95% CI, -9.7 to 5.3). At the late follow-up visit, the clinical response rate in subjects treated with imipenem-cilastatin plus placebo was 94.9% compared with 93.7% in the imipenem-cilastatin plus relebactam 250 mg group (difference, 1.3%; 95% CI, -9.6 to 6.9) and 95.3% in the imipenem-cilastatin plus relebactam 125 mg group (difference, 0.4%; 95% CI, -7.2 to 8.2). Microbiological response rates in the microbiologically evaluable population at the end of IV therapy was 97.6, 100.0, and 97.6% in the imipenem-cilastatin plus relebactam 250 mg, the imipenem-cilastatin plus 125 mg relebactam, and the imipenem-cilastatin plus placebo arms, respectively. The proportions of subjects with a favorable global response were generally similar among the three treatment groups: imipenem-cilastatin plus relebactam 250 mg, 86.5%, imipenem-cilastatin plus relebactam 125 mg, 89.6%, and imipenem-cilastatin plus placebo, 84.8%.
Lucasti et al.[90] (2016) Imipenem/cilastatin 500 mg/500 mg plus relebactam 250 mg IV every six hours vs Imipenem/cilastatin 500 mg/500 mg plus relebactam 125 mg IV every six hours	DB, MC, PRO, RCT Adults ≥18 years of age with clinically suspected and/or bacteriologically documented cIAI requiring hospitalization and treatment with IV antibiotic therapy	N= 277 Four to 14 days	Primary: Proportion of subjects in the microbiologically evaluable (ME) population who achieved a favorable clinical response at discontinuation of IV therapy (DCIV) Secondary: Clinical response at early follow-up (EFU) and late	Primary: At the DCIV visit, the proportions of subjects in the ME population with a favorable clinical response were generally similar among the three treatment groups. In the imipenem/cilastatin plus placebo group 95.2% had favorable response compared to 96.3% in the imipenem/cilastatin plus relebactam 250 mg group (difference, 1.1; 95% CI, -6.2 to 8.6) and 98.8% in the imipenem/cilastatin plus relebactam 125 mg (difference, 3.7; 95% CI, -2.0 to 10.8; P values not reported.). Secondary: At EFU the clinical response rate was 96.3% in the imipenem/cilastatin plus placebo compared to 94.9% in the imipenem/cilastatin plus relebactam 250 mg arm (difference, -1.4; 95% CI, -9.1 to 6.0) and 94.2% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, -2.1; 95% CI, -9.7 to 5.3). At LFU the clinical response rate was 94.9% in the imipenem/cilastatin plus placebo compared to 93.7% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs imipenem/cilastatin 500 mg/500 mg plus placebo IV every six hours			follow-up (LFU), microbiologic response, and global response	imipenem/cilastatin plus relebactam 250 mg arm (difference, -1.3; 95% CI, -9.6 to 6.9) and 95.3% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, 0.4; 95% CI, -7.2 to 8.2; P values not reported). The microbiological response rate at DCIV was 97.6% in the placebo arm compared to 97.6% in the in the imipenem/cilastatin plus relebactam 250 mg arm (difference, 0.0; 95% CI, -6.3 to 6.2) and 100.0% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, 2.4; 95% CI, -2.0 to 8.3). At EFU the microbial response rate was 97.5% in the placebo arm compared to 97.4% in the in the imipenem/cilastatin plus relebactam 250 mg arm (difference, -0.1; 95% CI, -6.7 to 6.4) and 97.6% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, 0.1; 95% CI, -6.3 to 6.5). At LFU the microbial response rate was 96.2% in the placebo arm compared to 96.2% in the in the imipenem/cilastatin plus relebactam 250 mg arm (difference, 0.0; 95% CI, -7.4 to 7.4) and 97.6% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, 1.4; 95% CI, -5.1 to 8.6; P values not reported). The percentage of patients with favorable microbial response at global follow-up was 96.2% in the imipenem/cilastatin plus placebo compared to 96.2% in the imipenem/cilastatin plus relebactam 250 mg arm (difference, 0.0; 95% CI, -7.4 to 7.4) and 97.5% in the imipenem/cilastatin plus relebactam 125 mg arm (difference, 1.4; 95% CI, -5.2 to 8.6; P values not reported).
Klugman et al.[91] (1995) Meropenem 40 mg/kg every eight hours for 7 to 14 days vs cefotaxime 75 to 100 mg/kg every eight hours for 7 to	PRO, RCT Children with a diagnosis of bacterial meningitis	N=190 6 weeks posttreatment	Primary: Clinical response (cure, cure with audiologic sequelae, cure with neurologic sequelae, cure with both audiologic and neurologic sequelae, death), bacteriologic response	Primary: In patients with pre-existing neurologic abnormalities, cure was achieved in 47% of meropenem patients compared to 60% of cefotaxime patients, cure with audiologic sequelae was reported in 6% of meropenem patients and 20% of cefotaxime patients, cure with neurologic sequelae was reported in 35% of meropenem patients and 0% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 12% of meropenem patients and 20% of cefotaxime patients, and death was not reported in any patients in either group. In patients without pre-existing neurological abnormalities, cure was achieved in 79% of meropenem patients compared to 83% of cefotaxime patients, cure with audiologic sequelae was reported in 16% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
14 days			Secondary: Not reported	meropenem patients and 12% of cefotaxime patients, cure with neurologic sequelae was reported in 3% of meropenem patients and 2% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 2% of meropenem patients and 0% of cefotaxime patients, and death was reported in no patients in the meropenem group and 3% of cefotaxime patients. Bacteriologic eradication rates were 100% in both groups. Secondary: Not reported
Odio et al.[92] (1999) Meropenem 40 mg/kg every eight hours vs cefotaxime 45 mg/kg every six hours Treatment duration for both groups was 7 to 14 days depending on infection.	MC, PRO, RCT Patients 2 months to 12 years of age with a diagnosis of bacterial meningitis	N=266 5 to 7 months posttreatment	Primary: Clinical response (cure, survival with mild neurological sequelae, survival with severe neurological sequelae, death), microbiologic efficacy Secondary: Not reported	Primary: At the five to seven-week follow-up, no significant differences between the meropenem group and the cefotaxime group were observed with respect to cure, survival with sequelae, or death (P=0.624). Severe sequelae were present in 30% of meropenem patients and in 17% of cefotaxime patients, and this difference was NS (P=0.056). At the five- to seven-week visit, severe sequelae in the form of audiology were present in 25% of children in the meropenem group and 15% in the cefotaxime group. By the five to seven-month visit, the percentages had decreased to 18% in the meropenem group and 14% in the cefotaxime group. No significant differences were seen in any group at any time. At the end of treatment, bacterial eradication was observed in 95% of patients in the meropenem group and 96% in the cefotaxime group. Secondary: Not reported
Mazuski et al.[93] (2016) Meropenem 1,000 mg IV every eight hours plus placebo	DB, DD, MC, PRO, RCT Hospitalized patients 18 to 90 years of age with cIAI requiring	N=1,066 Test-of-cure: 28 to 35 days after randomization	Primary: Clinical response at test-of-cure visit Secondary: Clinical response at end-of-treatment	Primary: The clinical cure rate at the test-of-cure visit for the ceftazidime-avibactam plus metronidazole group and the meropenem group was 82.5 and 84.9% (difference, -2.4%; 95% CI, -6.90 to 2.10); 81.6 and 85.1% (difference, -3.5%; 95% CI, -8.64 to 1.58); and 91.7 and 92.5% (difference, -0.8%; 95% CI, -4.61 to 2.89) in the modified intent-to-treat, microbiologically modified intent-to-treat, and clinically evaluable groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftazidime-avibactam (2,000-500 mg) IV plus metronidazole 500 mg IV every eight hours plus placebo	surgical intervention or percutaneous drainage within 24 hours before or after randomization.	Late follow-up: 42 to 49 days after randomization	(up to 24 hours after the last infusion) and late follow-up visits, microbiological response at end-of-treatment, test-of-cure, and late follow-up visits, safety	Secondary: The difference in cure at the end-of-treatment between the ceftazidime-avibactam plus metronidazole group and the meropenem group was -3.9% (95% CI, -7.57 to -0.29) and -5.0% (95% CI, -9.24 to -0.93) in the and modified intent-to-treat and microbiologically modified intent-to-treat groups, respectively. At the late follow visit, the differences were -0.9% (95% CI, -5.45 to 3.72) and -2.3% (95% CI, -7.41 to 2.79) in the modified intent-to-treat and microbiologically modified intent-to-treat groups, respectively. Microbiological response was presumed based on clinical outcome. Intra-abdominal cultures require an invasive procedure and cultures were only obtained if clinically indicated. Microbiological outcomes in the microbiologically modified intent-to-treat population were similar to clinical responses. Adverse events were similar between treatment groups. Deaths due to an adverse reaction occurred in 2.5 and 1.5% of the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively.
Lucasti et al.[94] (2013) Meropenem 1000 mg plus placebo IV every eight hours for 5 to 14 days vs ceftazidime-avibactam (2000-500 mg) plus metronidazole (500 mg) IV every eight hours for five	AC, DB, RCT Hospitalized patients 18 to 90 years of age with cIAI requiring surgical intervention and antibiotics	N=144 Test-of-cure: 2 weeks after last dose Late follow-up: 4 to 6 weeks post-therapy	Primary: Clinical response in microbiologically evaluable patients at the test-of-cure visit two weeks after the last dose of study therapy Secondary: Safety	Primary: A favorable clinical response in the microbiologically evaluable population at the test-of-cure visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime-avibactam plus metronidazole and meropenem patients, respectively. The estimated difference in response rates was –2.2% (95% CI, –20.4 to 12.2%). Secondary: Adverse events were observed in 64.4% (65/101) and 57.8% (59/102) of patients in the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively. Overall, the types and frequencies of adverse events were similar in the two treatment groups, but there were more cases of nausea and vomiting and abdominal pain in the ceftazidime-avibactam plus metronidazole group and more cases of liver enzyme elevations in the meropenem group. In the majority of cases, adverse events were mild or moderate in intensity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 14 days				
Solomkin et al.[95] (2015) ASPECT-cIAI Meropenem 1 g every eight hours IV for four to 14 days vs ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every eight hours IV for four to 14 days	DB, PC, RCT Patients ≥18 years of age with cIAI	N=806 24 to 32 days	Primary: Difference in clinical cure rates at the test-of-cure visit in the microbiological modified intention to treat population Secondary: Difference in clinical cure rates at the test-of-cure visit in the intention to treat and clinically evaluable populations	Primary: Clinical cure rates were 83.0% (323/389) with ceftolozane-tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the modified intention to treat population at the test-of-cure visit. The weighted difference in clinical cure rates (ceftolozane-tazobactam plus metronidazole minus meropenem) was -4.2% with a 2-sided 95% CI of -8.91% to 0.54%, thus meeting the statistical criteria for noninferiority. Secondary: Clinical cure rates in the intention to treat population at test-of-cure were 83.6% for ceftolozane-tazobactam plus metronidazole and 86.2% for meropenem (difference, -2.6; 95% CI, -7.08 to 1.87), similar to those observed in the modified intention to treat population. In the clinically evaluable population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, -3.30 to 3.55). Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences recorded between treatments.

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, PO=oral, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single center
Other abbreviations: ABSSSI=acute bacterial skin and skin structure infection, CFQ-R=cystic fibrosis questionnaire-revised, CFU=colony formulating unit, COPD=chronic obstructive pulmonary disease, cIAI=complicated intra-abdominal infection, cSSSI=complicated skin and skin structure infection, cUTI=complicated urinary tract infection, FEF_{25-75}=forced expiratory flow at 25 to 75%, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, MRSA=Methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*, RSS=respiratory symptom scale, SSSI=skin and skin structure infection

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Miscellaneous β-Lactam Antibiotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Aztreonam	inhalation solution, injection	Azactam®*, Cayston®	$$$$$	$$$$$
Cefotetan	injection	Cefotan®*	$$$$-$$$$$	$$$$-$$$$$
Cefoxitin	injection	Mefoxin®*	$$$$$	$$$
Ertapenem	injection	Invanz®*	$$$$$	$$$$$
Meropenem	injection	N/A	N/A	$$$$$
Combination Products				
Imipenem and cilastatin	injection	Primaxin®*	$$$$$	$$$$$
Imipenem, cilastatin, and relebactam	injection	Recarbrio®	$$$$$	N/A
Meropenem and vaborbactam	injection	Vabomere®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-9] All of the injectable products are available in a generic formulation, with the exception of meropenem-vaborbactam and imipenem-cilastatin-relebactam.

There are many guidelines that define the appropriate place in therapy for the miscellaneous β-lactam antibiotics. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the β-lactam. The miscellaneous β-lactam antibiotics are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, meningitis, skin and soft-tissue infections, pelvic inflammatory disease, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, febrile neutropenia, and for surgical prophylaxis.[12013-15,17,21,24-27,39]

Studies have demonstrated comparable efficacy among the miscellaneous β-lactam antibiotics for the treatment of skin and soft-tissue infections, urinary tract infections, endometritis, pneumonia, intra-abdominal infections, and for surgical prophylaxis.[41,42,44,53,64,68,76,77,84-86] Few studies have demonstrated greater efficacy with one agent over another.[83] The miscellaneous β-lactam antibiotics have also been shown to be comparable in efficacy to antibacterial agents in other classes.[30-35,37,38,40,43,45-48,56,62,63,65,67,69-73,78-81,87,88,91-95] Clinical data from published studies supports similar safety profiles among the miscellaneous β-lactam antibiotics.

Imipenem-cilastatin-relebactam (Recarbrio®) is approved for the treatment of adults with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, complicated urinary tract infections, including pyelonephritis, in patients who have limited or no alternative treatment options, and complicated intra-abdominal infections in patients who have limited or no alternative treatment options. To reduce the development of drug-resistant bacteria and maintain the effectiveness of imipenem-cilastatin-relebactam and other antibacterial drugs, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. Imipenem-cilastatin-relebactam offers an additional treatment option for patients with resistant or difficult to treat infections caused by gram negative bacteria.[8]

Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*. Treatment with aztreonam has been associated with improvements in pulmonary function, improved quality of life, and decreased requirement for inhaled or intravenous anti-pseudomonal antibiotics compared to placebo.[57,58,60] An open-label study following patients for 18 months demonstrated continued benefit over time.[59]

There is insufficient evidence to support that one brand miscellaneous β-lactam is safer or more efficacious than another within its given indication. With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. Since these agents are not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use and due to concerns for the development of resistance, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous β-lactam antibiotics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Aztreonam inhalation solution has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[26] Therefore, these patients should be allowed approval for aztreonam inhalation solution through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand miscellaneous β-lactam antibiotics product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Chloramphenicol
AHFS Class 081208
May 3, 2023

I. Overview

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] However, it should only be used when less potentially dangerous drugs are ineffective or contraindicated. Chloramphenicol exhibits its antibacterial effect by interfering with the ribosomal transfer of activated amino acids from ribonucleic acid and thus inhibiting bacterial protein synthesis.[3]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred following treatment with chloramphenicol.[1-3] There have also been reports of aplastic anemia progressing to leukemia that were attributed to chloramphenicol. Blood dyscrasias have occurred after both short- and long-term therapy.

The chloramphenicol products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Chloramphenicol is available in a generic formulation. This class was last reviewed in May 2021.

Table 1. Chloramphenicol Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chloramphenicol	injection	N/A	chloramphenicol

PDL=Preferred Drug List
N/A=Not available

Chloramphenicol has been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for chloramphenicol that are noted in Table 4. This agent may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since its safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to Chloramphenicol[1-3]

Organism	Chloramphenicol
Gram-Negative Aerobes	
Haemophilus influenzae	✔
Salmonella species, including *Salmonella typhi*	✔
Miscellaneous Organisms	
Lymphogranuloma-psittacosis group	✔
Rickettsia	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of chloramphenicol are summarized in Table 3.

Table 3. Treatment Guidelines Using Chloramphenicol

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America: **Clinical Practice**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending

Clinical Guideline	Recommendation(s)
Guidelines: Management of Encephalitis (2008)[4] **(Was reviewed and deemed current as of July 2011)**	results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. <u>Spirochetes</u> • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. <u>Protozoa</u> • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an

Clinical Guideline	Recommendation(s)
	alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[5]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[6]	Empiric Therapy • Empiric therapy should be used when infection is suspected but cultures are not yet available. • Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended. • Choice of anti-pseudomonal β-lactam should be based on local resistance patterns. • In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 µg/mL • For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative

Clinical Guideline	Recommendation(s)
	coverage is aztreonam or ciprofloxacin • Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens <u>Pathogen Specific Therapy</u> • Methicillin-susceptible *S. aureus* o Recommended treatment includes nafcillin or oxacillin o In patients who cannot receive β-lactams, vancomycin is recommended • Methicillin-resistant *S. aureus* o Recommended treatment includes vancomycin • *P. acnes* o Recommended treatment includes penicillin G • *Pseudomonas* species o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone • Gram-negative bacilli o Recommended treatment includes ceftriaxone or cefotaxime • Extended-spectrum β-lactamase–producing gram-negative bacilli o Recommended treatment includes meropenem • *Acinetobacter* species o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B • *Candida* species o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine • *Aspergillus* or *Exserohilum* o Recommended treatment includes voriconazole • In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain o Use of rifampin as part of combination therapy is recommended <u>Duration of Therapy</u> • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms o Duration is recommended to be 10 days • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features o Duration is recommended to be 10 to 14 days • Infections caused by *S. aureus* or gram-negative bacilli o Duration is recommended to be 10 to 14 days • Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy o It is recommended that therapy be continued for 10 to 14 days after the last positive culture
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations**	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol,

Clinical Guideline	Recommendation(s)
for Naturally Acquired Infections and Bioterrorism Response (2021)[7]	fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole. • For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Centers for Disease Control and Prevention: **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis—United States (2016)[8]**	• The Centers for Disease Control and Prevention recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in patients of all ages, including children aged <8 years, and should be initiated immediately in persons with signs and symptoms suggestive of rickettsial disease. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain Spotted Fever; however, epidemiologic studies in which Centers for Disease Control and Prevention case report data have been used suggested that patients with Rocky Mountain Spotted Fever treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline. • Chloramphenicol is associated with adverse hematologic effects, which have resulted in its limited use in the United States, and monitoring of blood indices is required if this drug is used. • If chloramphenicol is substituted for doxycycline in the empiric treatment of tickborne rickettsial diseases, ehrlichiosis and anaplasmosis will not be covered and Rocky Mountain Spotted Fever treatment might be suboptimal. • Rifampin could be an alternative for the treatment of mild illness due to anaplasmosis in the case of pregnancy or documented allergy to tetracycline-class drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for chloramphenicol are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for Chloramphenicol[1-3]

Indications	Chloramphenicol
Serious infections caused by susceptible strains, including *Salmonella* species, *Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents*	✔
Acute infections caused by *Salmonella typhi*†	✔
Cystic fibrosis regimens	✔

* In accord with the concepts in chloramphenicols Black Box Warning, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions listed is believed to be present; in vitro sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by in vitro studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in chloramphenicols Black Box Warning.
† It is not recommended for the routine treatment of the typhoid carrier state. In treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for eight to 10 days after the patient has become afebrile to lessen the possibility of relapse.

IV. Pharmacokinetics

The pharmacokinetic parameters for chloramphenicol are listed in Table 5.

Table 5. Pharmacokinetic Parameters for Chloramphenicol[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chloramphenicol	50 (intramuscular)	50 to 80	Liver (90)	Renal (5 to 15)	1.6 to 3.3 (highly variable in infants)

V. Drug Interactions

Major drug interactions with chloramphenicol are listed in Table 6.

Table 6. Major Drug Interactions with Chloramphenicol[2]

Generic Name(s)	Interaction	Mechanism
Chloramphenicol	Voriconazole	Concurrent use of chloramphenicol and voriconazole may result in increased voriconazole exposure and plasma concentrations.
Chloramphenicol	Citalopram	Concurrent use of chloramphenicol and citalopram may result in increased citalopram exposure and risk of QT interval prolongation.

VI. Adverse Drug Events

The most common adverse drug events reported with chloramphenicol are listed in Table 7. The boxed warning for chloramphenicol is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with Chloramphenicol[1-3]

Adverse Events	Chloramphenicol
Central Nervous System	
Confusion	✔
Delirium	✔
Depression	✔
Fever	✔
Headache	✔
Optic neuritis	✔
Peripheral neuritis	✔
Gastrointestinal	
Diarrhea	✔
Enterocolitis	✔
Glossitis	✔
Nausea	✔
Stomatitis	✔
Vomiting	✔

Adverse Events	Chloramphenicol
Hematologic	
Aplastic anemia	✔
Granulocytopenia	✔
Hypoplastic anemia	✔
Leukemia	✔
Leukopenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Other	
Anaphylaxis	✔
Angioedema	✔
Hypersensitivity reactions	✔
Gray Syndrome	✔
Rash	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Boxed Warning for Chloramphenicol[1]

WARNING
Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.* It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

VII. Dosing and Administration

The usual dosing regimens for chloramphenicol are listed in Table 9.

Table 9. Usual Dosing Regimens for Chloramphenicol[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chloramphenicol	Serious infections caused by susceptible strains, including *Salmonella* species, *Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other	Serious infections caused by susceptible strains, including *Salmonella* species, *Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by *Salmonella typhi*; Cystic fibrosis regimens for infants and children: Injection: 50 mg/kg/day in divided doses	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by *Salmonella typhi*; Cystic fibrosis regimens: Injection: 50 mg/kg/day intravenous in divided doses every six hours; patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible	every six hours; severe infections may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible Serious infections caused by susceptible strains, including Salmonella species, Haemophilus influenzae (specifically meningeal infections), Rickettsia, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by Salmonella typhi; Cystic fibrosis regimens for neonates: Injection: 25 mg/kg/day in divided doses every six hours; after the first two full weeks of life, 50 mg/kg/day in divided doses every six hours may be administered	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of chloramphenicol are summarized in Table 10.

Table 10. Comparative Clinical Trials with Chloramphenicol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bacterial Meningitis				
Shann et al.[9] (1985) Chloramphenicol 25 mg/kg IM every 6 hours vs chloramphenicol 25 mg/kg IV every 6 hours plus penicillin Once clinical improvement was observed patients received oral chloramphenicol palmitate 25 mg/kg every 6 hours for a total of 14 days.	MC, PRO, RCT Children with bacterial meningitis	N=367 14 days	Primary: Cumulative endpoint of mortality, brain damage, and persistent illness; death Secondary: Not reported	Primary: The cumulative outcome measure was poor (death, discharged with brain damage) in 38% of the patients receiving chloramphenicol alone compared to 40% of those receiving combination therapy. There was no significant difference in mortality between the chloramphenicol and the combination treatment groups (26 vs 27%). Secondary: Not reported
Nathan et al.[10] (2005) Chloramphenicol 100 mg/kg IM as a single dose vs ceftriaxone 100	MC, OL, RCT Patients >2 months of age with meningitis	N=510 1 month	Primary: Treatment failure at 72 hours Secondary: Mortality within 72 hours, clinical sequelae at 72 hours, clinical failure between 24	Primary: Both treatment groups exhibited a treatment failure rate of 9% (90% CI, -3.8 to 4.5). Secondary: There was no significant difference in the mortality rate at 72 hours between the chloramphenicol and ceftriaxone groups (5 vs 6%, respectively; 90% CI, -2.3 to 3.8). Clinical failure took place in 4% of the chloramphenicol-group survivors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IM as a single dose			and 48 hours requiring a second injection	and 3% of the ceftriaxone-treated patients (90% CI, -3.3 to 2.8). There was no significant difference in the re-injection rate between the chloramphenicol and ceftriaxone groups (8 vs 7%, respectively; 90% CI, -4.7 to 3.0). Neurologic sequelae occurred in 5% of patients on chloramphenicol and 7% of patients on ceftriaxone therapy (90% CI, -2.1 to 5.1).
Rodriguez et al.[11] (1986) Chloramphenicol 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 4 to 6 divided doses vs ampicillin 400 mg/kg/day IV in 4 to 6 divided doses plus sulbactam 50 mg/kg/day	MC, PRO, RCT Hospitalized patients 1 month to 14 years of age with meningitis	N=81 10 days	Primary: Mortality rate, resolution of symptoms, complications, adverse effects Secondary: Not reported	Primary: Of the patients with assessable CSF pathogens, the mortality rate was 3% in the ampicillin-sulbactam group and 18% in the chloramphenicol-ampicillin group. Neurologic sequelae occurred in 12% of patients on ampicillin-sulbactam and 18% of patients on chloramphenicol-ampicillin therapy. The mean time to resolution of symptoms was 4.4 days in the ampicillin-sulbactam group and 4.8 days in the chloramphenicol-ampicillin. Abnormal laboratory findings were found in 20% of the ampicillin-sulbactam group and 35% in the chloramphenicol-ampicillin group. Secondary: Not reported
Girgis et al.[12] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every 6 hours (AMCL) vs ceftriaxone 100	RCT Patients with bacterial meningitis	N=100 6 days	Primary: CSF leukocyte count, glucose, protein content, disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate Secondary:	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the CSF leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg once daily			Not reported	Secondary: Not reported
Girgis et al.[13] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every 6 hours (group 1) vs ceftriaxone 100 mg/kg IV once daily (group 2)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary: Not reported	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *S. pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively. Secondary: Not reported
Jacobs et al.[14] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50-100 mg/kg/dose IV every 6 hours vs cefotaxime 50 mg/kg/dose IV every 6 hours	PRO, RCT Patients 1 week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively). Secondary: Not reported
Rodriguez et al.[15] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided	OL, RCT Patients 1 month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses plus ampicillin 400 mg/kg/day IV in 6 divided doses vs ceftazidime 150 mg/kg/day IV divided into 3 doses, administered every 8 hours			sequelae, mean duration of therapy Secondary: Not reported	Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported
Marks et al.[16] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided doses plus ampicillin 300 to 400 mg/kg/day IV every 6 hours vs cefuroxime 225 mg/kg/day IV divided into 3 doses, administered every 8 hours	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, CSF sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the CSF sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported
Johansson et al.[17] (1982) Chloramphenicol and ampicillin IV every 6 hours for at least 5 days (A+C)	MC, RCT Patients with bacterial meningitis	N=67 ≥5 days	Primary: Efficacy and safety Secondary: Not reported	Primary: Complete resolution of symptoms was recorded in 18 of the 21 patients in the CXM group and in 14 of the 19 patients in the A+C group. Two patients died in each group. Adverse events were reported on eight occasions in seven patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefuroxime IV every 8 hours for at least 5 days (CXM)				CXM group and in four patients in the A+C group. Rashes developed in two CXM patients and three A+C patients. Fever was noted in two CXM patients. Moderately severe diarrhea which required symptomatic treatment developed in one patient in each group, and one CXM patient had repeated thrombophlebitis. Secondary: Not reported
Peltola et al.[18] (1989) Chloramphenicol 100 mg/kg/day in 4 divided doses vs ampicillin 250 mg/kg/day in 4 divided doses plus chloramphenicol (administered until bacterial strain was shown to be susceptible to ampicillin alone) vs cefotaxime 150 mg/kg/day in 4 divided doses vs ceftriaxone 100 mg/kg once daily	MC, RCT Children 3 months to 15 years of age with bacterial meningitis	N=220 7 days	Primary: CSF culture pathogens, time to sterile CSF culture Secondary: Not reported	Primary: The CSF became sterile significantly earlier in meningococcal meningitis compared to patients presenting with *H. influenzae* type b (P<0.01). At 24 hours, positive cultures were found only in patients receiving chloramphenicol. At 24 hours, the CSF was sterile in a greater proportion of patients treated with cephalosporins compared to those treated with ampicillin-chloramphenicol or chloramphenicol (P<0.05). On day four, CSF culture was positive in only one patient, who was treated with chloramphenicol. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Typhoid and Enteric Fever				
Tanaka-Kido et al.[19] (1990) Chloramphenicol 100 mg/kg/day in 4 divided doses, which was continued for 8 days after the last fever day vs aztreonam 150 mg/kg/day IV in 3 divided doses, which was continued for 8 days after the last fever day	RCT Patients 2 to 6 years of age with typhoid fever	N=36 1 month	Primary: Clinical cure rate, fever duration, relapse rate, adverse effects Secondary: Not reported	Primary: There was no significant difference between the chloramphenicol and aztreonam groups in clinical cure rate (94 vs 100%). There was no significant difference between the chloramphenicol and aztreonam groups in fever duration (4.1 vs 5.9 days, respectively; P>0.05). There were no relapses in either of the two groups. While there was no incidence of anemia in the aztreonam group, there were five cases of anemia in the chloramphenicol group (P<0.05). There was no difference in the incidence of leukopenia and neutropenia between the two treatment groups (P>0.05). The approximate mean duration of antibiotic therapy was 15 days in the aztreonam group and 13 days in the chloramphenicol group. Secondary: Not reported
Gotuzzo et al.[20] (1994) Chloramphenicol 50 mg/kg/day oral/IV in 4 divided doses for 14 days vs aztreonam 2 g IV every 8 hours for 10 days	MC, RCT Patients >14 years of age with typhoid fever	N=44 10 weeks	Primary: Clinical cure rate, fever duration, bacteremia Secondary: Not reported	Primary: There was a significant difference between the chloramphenicol and aztreonam groups in terms of clinical cure rates (100 vs 68%, respectively; P<0.01). Defervescence occurred more quickly in patients receiving chloramphenicol compared to patients on aztreonam therapy (4.5 vs 6.6 days, respectively; P<0.03). There were no relapses in either of the two groups. While 24-hour positive blood cultures occurred in 32% of patients on chloramphenicol therapy, none of the patients in the aztreonam group had positive blood cultures (P<0.05). Adverse reactions experienced by patients in each treatment group deemed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				unusual or mild with no statistical difference found between the two groups. Secondary: Not reported
Arjyal et al.[21] (2011) Chloramphenicol 75 mg/kg/day in four divided doses for 14 days vs gatifloxacin 10 mg/kg once daily for 7 days	OL, RCT Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR, 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of one month (P=0.12). At the end of three months, only one patient in the chloramphenicol group had a positive stool culture, and at six months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.

Drug regimen abbreviations: IM=intramuscular, IV=intravenous
Study abbreviations: CI=confidence interval, CSF=cerebrospinal fluid, MC=multicenter OL=open-label, PRO=prospective, RCT=randomized trial

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of Chloramphenicol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chloramphenicol	injection	N/A	N/A	$$$$

N/A=Not available

X. Conclusions

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] It is available in a generic formulation.

Guidelines recommend chloramphenicol as an alternative treatment option in patients with bacterial meningitis and Rocky Mountain spotted fever.[4-8] Clinical trials have demonstrated similar efficacy with chloramphenicol (as monotherapy or in combination with ampicillin) compared to broad-spectrum cephalosporins in patients with bacterial meningitis.[10-18]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after both short-term and prolonged therapy with chloramphenicol. It should only be used when less potentially dangerous drugs are ineffective or contraindicated.[1-3] To facilitate appropriate studies and observation during therapy, it is desirable that patients receiving chloramphenicol be hospitalized.

There is insufficient evidence to support that one brand chloramphenicol product is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand chloramphenicol products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand chloramphenicol product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Macrolides
AHFS Class 081212
May 3, 2023

I. Overview

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-9] Most of the agents bind to the 50S subunit of bacterial ribosomes, which inhibits bacterial protein synthesis.[10,11] Fidaxomicin has a unique mechanism of action; it inhibits ribonucleic acid synthesis by ribonucleic acid polymerases.[9]

Erythromycin is available in several different pharmaceutical preparations, which were developed to improve the absorption of erythromycin base. Azithromycin and clarithromycin are structural derivatives of erythromycin. They have a broader spectrum of activity, improved oral absorption, fewer gastrointestinal adverse events, and a more favorable pharmacokinetic profile than erythromycin.[10,11] Resistance to the macrolides is increasing and cross-resistance among the various agents has been documented. Fidaxomicin is a newer macrolide that is approved to treat *Clostridium difficile*-associated diarrhea. It is minimally absorbed after oral administration and has little or no activity against organisms other than clostridia.[9]

The macrolides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Several of the macrolides are available in a generic formulation, with the exception of erythromycin stearate and fidaxomicin. This class was last reviewed in May 2021.

Table 1. Macrolides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azithromycin	injection, powder for suspension, suspension, tablet	Zithromax®*	azithromycin
Clarithromycin	extended-release tablet, suspension, tablet	N/A	clarithromycin, clarithromycin ER
Erythromycin base	delayed-release capsule, delayed-release tablet, tablet	N/A	erythromycin base
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®*, E.E.S. 400®*, EryPed 200®*, EryPed 400®*	erythromycin ethylsuccinate
Erythromycin lactobionate	injection	Erythrocin Lactobionate®*	erythromycin lactobionate
Erythromycin stearate	tablet	Erythrocin Stearate®	none
Fidaxomicin	suspension, tablet	Dificid®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

The macrolides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the macrolides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Macrolides[1-9]

Organism	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Gram-Positive Aerobes				
Listeria monocytogenes			✔	
Staphylococcus aureus	✔	✔	✔	
Streptococcus agalactiae	✔			
Streptococcus pneumoniae	✔	✔	✔	
Streptococcus pyogenes	✔	✔	✔	
Gram-Negative Aerobes				
Bordetella pertussis			✔	
Haemophilus ducreyi	✔			
Haemophilus influenzae	✔	✔	✔	
Haemophilus parainfluenzae		✔		
Helicobacter pylori		✔		
Legionella pneumophila			✔	
Moraxella catarrhalis	✔	✔		
Neisseria gonorrhoeae	✔		✔	
Anaerobes				
Clostridium difficile				✔
Corynebacterium diphtheriae			✔	
Corynebacterium minutissimum			✔	
Miscellaneous Organisms				
Entamoeba histolytica			✔	
Chlamydia trachomatis	✔		✔	
Chlamydophila pneumoniae	✔	✔		
Mycobacterium avium	✔	✔		
Mycobacterium intracellulare	✔	✔		
Mycoplasma hominis	✔			
Mycoplasma pneumoniae	✔	✔	✔	
Treponema pallidum			✔	
Ureaplasma urealyticum			✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the macrolides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Macrolides

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[12]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for four weeks (in β-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial

Clinical Guideline	Recommendation(s)
	healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[13]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered.

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	• Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[14]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of

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	therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable.

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	○ For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. ○ For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. ○ If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[15] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered.

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	• *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[16]	<u>Impetigo and ecthyma</u> • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. <u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u> • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. <u>Recurrent skin abscesses</u> • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.

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	• Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. <u>Erysipelas and cellulitis</u> • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. <u>Necrotizing fasciitis</u> • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-

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	acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. <u>Pyomyositis</u> • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. <u>Clostridial gas gangrene or myonecrosis</u> • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. <u>Animal bites</u> • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure.

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	Bacillary angiomatosis and cat scratch disease
	• Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol:
	  o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days.
	  o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days.
	• Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis.
	
	Erysipeloid
	• Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid.
	
	Glanders
	• Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility.
	
	Bubonic plague
	• Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin.
	
	Tularemia
	• Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia.
	• Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults (2017)**[17]	Treatment of *Clostridium difficile* infections • Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of *Clostridium difficile* infections recurrence. • Antibiotic therapy for *Clostridium difficile* infections should be started empirically for situations where a substantial delay in laboratory confirmation is expected, or for fulminant *Clostridium difficile* infections. • Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of *Clostridium difficile* infections. The dosage is vancomycin 125 mg orally four times per day or fidaxomicin 200 mg twice daily for 10 days. • In settings where access to vancomycin or fidaxomicin is limited, use metronidazole for an initial episode of nonsevere *Clostridium difficile* infections only. The suggested dosage is metronidazole 500 mg orally three times per day for 10 days. Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity. • For fulminant *Clostridium difficile* infections, vancomycin administered orally is the regimen of choice. If ileus is present, vancomycin can also be administered per rectum. The vancomycin dosage is 500 mg orally four times per day and 500 mg in approximately 100 mL normal saline per rectum every six hours as a retention enema. Intravenously administered metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present. The metronidazole dosage is 500 mg intravenously every eight hours. • Fulminant *Clostridium difficile* infections, previously referred to as severe,

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	complicated *Clostridium difficile* infections, may be characterized by hypotension or shock, ileus, or megacolon. • If surgical management is necessary for severely ill patients, perform subtotal colectomy with preservation of the rectum. Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes. • Treat a first recurrence of *Clostridium difficile* infections with oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin, OR • Treat a first recurrence of *Clostridium difficile* infections with a 10-day course of fidaxomicin rather than a standard 10-day course of vancomycin, OR • Treat a first recurrence of *Clostridium difficile* infections with a standard 10-day course of vancomycin rather than a second course of metronidazole if metronidazole was used for the primary episode. • Antibiotic treatment options for patients with >1 recurrence of *Clostridium difficile* infections include oral vancomycin therapy using a tapered and pulsed regimen, a standard course of oral vancomycin followed by rifaximin, or fidaxomicin. • Fecal microbiota transplantation is recommended for patients with multiple recurrences of *Clostridium difficile* infections who have failed appropriate antibiotic treatments. • There are insufficient data at this time to recommend extending the length of anti–*C. difficile* treatment beyond the recommended treatment course or restarting an anti–*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of *Clostridium difficile* infections treatment, respectively. • Either metronidazole or vancomycin is recommended for the treatment of children with an initial episode or first recurrence of nonsevere *Clostridium difficile* infections. • For children with an initial episode of severe *Clostridium difficile* infections, oral vancomycin is recommended over metronidazole. • For children with a second or greater episode of recurrent *Clostridium difficile* infections, oral vancomycin is recommended over metronidazole. • Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of *Clostridium difficile* infections following standard antibiotic treatments.
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **2021 Focused Update Guidelines on Management of *Clostridium difficile* Infection in Adults (2021)**[18]	• For patients with an initial *Clostridium difficile* infection episode, using fidaxomicin rather than a standard course of vancomycin is suggested. This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative. • In patients with recurrent *Clostridium difficile* infection episodes, fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin is suggested. Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first *Clostridium difficile* infection recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin. • For patients with a recurrent *Clostridium difficile* infection episode within the last six months, using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone is suggested. This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. In settings where logistics is not an issue, patients with a primary *Clostridium difficile* infection episode and other risk factors for

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	Clostridium difficile infection recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe *Clostridium difficile* infection on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. The FDA warns that "in patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefit outweighs the risk."

World Gastroenterology Organization: **Acute Diarrhea (2012)**[19]	General considerations
	• Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known.
	• Consider antimicrobial treatment for:
	  ○ *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections.
	  ○ Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation.
	  ○ Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools.
	• Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria.
	
	Antimicrobial agents for the treatment of specific causes of diarrhea
	• Cholera
	  ○ First-line: doxycycline.
	  ○ Alternative: azithromycin or ciprofloxacin.
	• Shigellosis
	  ○ First-line: ciprofloxacin.
	  ○ Alternative: pivmecillinam or ceftriaxone.
	• Amebiasis
	  ○ First-line: metronidazole.
	• Giardiasis
	  ○ First-line: metronidazole.
	  ○ Alternative: tinidazole, omidazole or secnidazole.
	• *Campylobacter*
	  ○ First-line: azithromycin.
	  ○ Alternative: fluoroquinolones (e.g., ciprofloxacin).

American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)**[20]	Epidemiology • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. Diagnosis • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. Treatment of acute disease • The usage of balanced electrolyte rehydration over other oral rehydration

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	options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness. • In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. <u>Evaluation of persisting symptoms</u> • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. <u>Prevention</u> • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)**[21]	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more. • Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow

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	appropriate infection prevention and control measures. • Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified. • Recommended antimicrobial agents by pathogen: o *Campylobacter* ▪ First choice: Azithromycin ▪ Alternative: Ciprofloxacin o *Clostridium difficile* ▪ First choice: Oral vancomycin ▪ Alternative: Fidaxomicin ▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). o Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, TMP-SMX, or amoxicillin. o *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or TMP-SMX or azithromycin o *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: TMP-SMX or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 μg/ mL or higher even if the laboratory report identifies the isolate as susceptible. o *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone o Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside o *Yersinia enterocolitica* ▪ First choice: TMP-SMX ▪ Alternative: Cefotaxime or ciprofloxacin o *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response o *Cyclospora cayetanensis* ▪ First choice: TMP-SMX ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer

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	durations of TMP-SMX treatment o *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. o *Cystoisospora belli* ▪ First choice: TMP-SMX ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide o *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole ▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
American College of Gastroenterology: **Clinical Guideline on the Treatment of *Helicobacter pylori* Infection (2017)**[22]	<u>Evidence-based first-line treatment strategies for providers in North America</u> • Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen. • Clarithromycin triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason. • Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin. • Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. • Sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days is a suggested first-line treatment option. • Hybrid therapy consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for seven days is a suggested first-line treatment option. • Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10 to 14 days is a suggested first-line treatment option. • Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, fluoroquinolone, and nitroimidazole for five to seven days is a suggested first-line treatment option. <u>When first-line therapy fails, options for salvage therapy</u> • In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline). • Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.

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	• Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.
	• The following regimens can be considered for use as salvage treatment:
	  ○ Bismuth quadruple therapy for 14 days is a recommended salvage regimen.
	  ○ Levofloxacin triple regimen for 14 days is a recommended salvage regimen.
	  ○ Concomitant therapy for 10 to 14 days is a suggested salvage regimen.
	  ○ Clarithromycin triple therapy should be avoided as a salvage regimen.
	  ○ Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen.
	  ○ High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.

Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)[23]**	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori.* • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht VI/ Florence Consensus Report (2022)[24]**	Treatment • It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalized use of such a susceptibility-guided strategy in routine clinical practice remains to be established. • If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered. • The treatment duration of bismuth quadruple therapy should be 14 days, unless 10- days effective therapies are available. • In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies. • The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days. • In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally. • The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days. • The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies. • Potassium-Competitive Acid Blockers (P-CAB; vonoprazan where available) – antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections. • Empiric second line and rescue therapies should be guided by local resistance

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	patterns assessed by susceptibility testing and eradication rates in order to optimize treatment success. • After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option. • After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment. • After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high- dose dual therapy might also be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered. • After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin- containing regimen or a combination of bismuth with different antibiotics should be used. • In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options. Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth.
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[26]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and

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	use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when

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	symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days

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	○ famciclovir 500 mg orally twice daily for five to 10 days ○ valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: ○ acyclovir 400 mg orally three times daily ○ valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. Pediculosis pubis (pubic lice infestation) • Recommended regimens: ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off. ○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. ○ Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for

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	eradication.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	• Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed.
	• Infants and children aged <10 years should not be treated with lindane.
	• Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost.
	• Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined.
	• Permethrin is the preferred treatment for pregnant women.
	• Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies.
	• Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases.
	
	<u>Bacterial vaginosis</u>
	• Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic.
	• Treatment for BV is recommended for women with symptoms.
	• Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2.
	• Recommended regimens for bacterial vaginosis include:
	  ○ Metronidazole 500 mg orally twice daily for seven days.
	  ○ Metronidazole 0.75% gel 5 g intravaginally once daily for five days.
	  ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.
	• Alternative regimens include:
	  ○ Tinidazole 2 g orally once daily for two days.
	  ○ Tinidazole 1 g orally once daily for five days.
	  ○ Clindamycin 300 mg orally twice daily for seven days.
	  ○ Clindamycin 100 mg ovules intravaginally once at bedtime for three days.
	  ○ Secnidazole 2 g oral granules in a single dose
	• Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended.
	• Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing.
	• Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same

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	recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. Uncomplicated vulvovaginal candidiasis • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.

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	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: o Cryotherapy with liquid nitrogen.

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	○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal Intra-anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal. ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
American Academy of Pediatrics/ American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[26] Reaffirmed 2019	Observation option • Observation without use of antibacterial agents in a child with unilateral acute otitis media is an option for selected children based on age, illness severity, and assurance of follow-up after joint decision-making with the parent(s)/caregiver. The "observation option" for acute otitis media refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children six months and older without severe symptoms at presentation. Antibacterial options - temperature <39°C without severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial options - temperature ≥39°C and/or severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for three days.
American Academy of Pediatrics: **Red Book – Group A streptococcal infections (2021)**[27]	• Penicillin V is the drug of choice for Group A *Streptococci* pharyngitis. Prompt administration of penicillin shortens the clinical course, decreases risk of transmission and suppurative sequelae, and prevents acute rheumatic fever, even when administered up to nine days after illness onset. All patients with acute rheumatic fever should receive a complete course of penicillin or another appropriate antimicrobial agent for Group A *Streptococci* pharyngitis, even if group A streptococci are not recovered from the throat. • Amoxicillin, orally as a single daily dose (50 mg/kg; maximum, 1000 to 1200 mg) for 10 days, is as effective as penicillin V or amoxicillin administered orally multiple times per day for 10 days and is a more palatable suspension than penicillin

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	V. This regimen is endorsed by the American Heart Association and the Infectious Disease Society of America in its guidelines for the treatment of Group A *Streptococci* pharyngitis and the prevention of acute rheumatic fever. Adherence is particularly important for once-daily dosing regimens. • The dose of oral penicillin V is 400 000 U (250 mg), 2 to 3 times per day, for 10 days for children weighing <27 kg and 800 000 U (500 mg), 2 to 3 times per day, for those weighing ≥27 kg, including adolescents and adults. To prevent acute rheumatic fever, oral penicillin or amoxicillin should be taken for 10 full days, regardless of promptness of clinical recovery. Treatment failures occur more often with oral penicillin than with intramuscular penicillin G benzathine because of inadequate adherence. Notably, short-course treatment (<10 days) for Group A *Streptococci* pharyngitis, particularly with penicillin V, is associated with inferior bacteriologic eradication rates. • Intramuscular penicillin G benzathine is appropriate therapy, ensuring adequate blood concentrations and avoiding adherence issues, but administration may be painful. Discomfort is decreased if the preparation of penicillin G benzathine is brought to room temperature before intramuscular injection. Mixtures containing shorter-acting penicillins (e.g., penicillin G procaine) in addition to penicillin G benzathine are not more effective than penicillin G benzathine alone but are less painful. Although supporting data are limited, the combination of 900 000 U (562.5 mg) of penicillin G benzathine and 300 000 U (187.5 mg) of penicillin G procaine is satisfactory for most children; however, the efficacy of this combination for heavier patients has not been documented. • For patients who have a history of nonanaphylactic allergy to penicillin, a 10-day course of a narrow-spectrum (first-generation) oral cephalosporin (e.g., cephalexin) is indicated. Patients with immediate (anaphylactic) or type I hypersensitivity to penicillin should receive oral clindamycin (20 mg/kg per day in three divided doses; maximum, 900 mg/day for 10 days) rather than a cephalosporin. • An oral macrolide (e.g., erythromycin, azithromycin, or clarithromycin) also is acceptable for penicillin-allergic patients. This should not be used in patients who can take a beta-lactam agent. Therapy for 10 days is indicated, except for azithromycin, which is given for five days. Group A *Streptococci* strains resistant to macrolides have been highly prevalent in some countries and have resulted in treatment failures. In some areas in the United States, macrolide resistance rates of more than 20% have been reported. Testing for macrolide resistance may help to decide the best antimicrobial agent for specific penicillin-allergic patients. • Tetracyclines, sulfonamides, and fluoroquinolones should not be used for treating Group A *Streptococci* pharyngitis. • Children with recurrent Group A *Streptococci* pharyngitis shortly after a full course of a recommended oral agent can be retreated with the same antimicrobial agent (if it is a beta-lactam), an alternative beta-lactam oral drug (such as cephalexin or amoxicillin-clavulanate), or an intramuscular dose of penicillin G benzathine. Susceptibility testing should be performed when considering a macrolide or clindamycin.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[28]	<u>Symptomatic relief of viral rhinosinusitis</u> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies

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	supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. <u>Symptomatic relief of acute bacterial rhinosinusitis</u> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. <u>Initial management of acute bacterial rhinosinusitis</u> • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. <u>Choice of antibiotic for acute bacterial rhinosinusitis</u> • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. <u>Treatment failure for acute bacterial rhinosinusitis</u> • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)[29]**	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of

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	acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[30]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[31]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Center for Disease Control and Prevention: **Recommended Antimicrobial Agents for the**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants <1 month of age, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is sulfamethoxazole-trimethoprim. • The choice of antimicrobial should take into account effectiveness, safety,

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Treatment and Postexposure Prophylaxis of Pertussis (2005)[32] **(Was reviewed and deemed current as of August 2017)**	tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients >6 months of age, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (one to two doses per day) and shorter treatment regimens (five to seven days).
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)[33]** Reviewed and deemed current as of 04/2013	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and**	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or

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Treatment of Adults with Community-Acquired Pneumonia (2019)[34]	○ doxycycline 100 mg twice daily or ○ a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. ○ Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). ○ Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) <u>Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting</u>: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: ○ combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or ○ monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. <u>Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting</u>: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid. • Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)[35]**	<u>Empiric Therapy</u> • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known ○ Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in

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	intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant ○ It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem ○ In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available Pathogen-Specific Therapy • MRSA ○ Vancomycin or linezolid are recommended treatments • *P. aeruginosa* ○ It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy ○ In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli ○ Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species ○ Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens ○ If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin Duration of therapy • Seven day course of treatment
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (2022)**[36]	Prophylaxis to Prevent First Episode of Opportunistic Disease • Coccidioidomycosis ○ Preferred: Fluconazole 400 mg PO daily ○ Alternative: None listed • *Histoplasma capsulatum* infection ○ Preferred: Itraconazole 200 mg PO daily ○ Alternative: None listed • Malaria ○ Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region. Refer to the Centers for Disease Control and Prevention webpage for the most recent recommendations based on region and drug susceptibility • *Mycobacterium avium* Complex (MAC) Disease ○ Preferred: Azithromycin 1200 mg PO once weekly, or Clarithromycin 500 mg PO BID, or Azithromycin 600 mg PO twice weekly ○ Alternative: Rifabutin (dose adjusted based on concomitant ART); rule out active TB before starting rifabutin • *Pneumocystis* Pneumonia (PCP)

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	○ Preferred: TMP-SMX (trimethoprim-sulfamethoxazole) 1 double strength (DS) tablet PO daily, or TMP-SMX 1 SS tablet daily ○ Alternative: TMP-SMX 1 DS PO three times weekly, or Dapsone 100 mg PO daily or 50 mg PO BID, or Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or Aerosolized pentamidine 300 mg via Respigard II nebulizer every month, or Atovaquone 1500 mg PO daily, or (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily • Syphilis ○ Preferred: Benzathine penicillin G 2.4 million units IM for 1 dose ○ Alternative: *For penicillin-allergic patients*: ▪ Doxycycline 100 mg PO BID for 14 days, or ▪ Ceftriaxone 1 g IM or IV daily for eight to 10 days, or ▪ Azithromycin 2 g PO for 1 dose – not recommended for men who have sex with men or pregnant women • Talaromycosis (Penicilliosis) ○ Preferred: For persons who reside in endemic areas, itraconazole 200 mg PO once daily; For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily three days before travel, and continue for one week after leaving the endemic area ○ Alternative: For persons who reside in endemic areas, fluconazole 400 mg PO once weekly; For those traveling to the highly endemic regions, take the first dose of fluconazole 400 mg three days before travel, continue 400 mg once weekly, and take the final dose after leaving the endemic area • *Toxoplasma gondii* Encephalitis ○ Preferred: TMP-SMX 1 DS PO daily ○ Alternative: TMP-SMX 1 DS PO three times weekly, or TMP-SMX 1 SS PO daily, or Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly; or Atovaquone 1500 mg PO daily; or (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily <u>Treatment of AIDS-Associated Opportunistic Infections (only preferred therapy is summarized here, please see full guideline for alternative therapies and additional information)</u> • Empiric therapy pending definitive diagnosis of bacterial enteric infections ○ Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. If a pathogen is identified, antibiotic susceptibilities should be performed to confirm and inform antibiotic choices given increased reports of antibiotic resistance. Reflex culture for antibiotic susceptibilities should also be done if diagnosis is made using PCR-based methods. ○ Empiric antibiotic therapy may be indicated for patients with CD4 count 200 to 500 cells/mm^3 where diarrhea is severe enough to compromise quality of life or the ability to work and is indicated in patients with CD4 count <200 cells/mm^3 or concomitant AIDS-defining illness and with clinically severe diarrhea (≥6 stools per day or bloody stool) and/or accompanying fever or chills. ○ Empiric Therapy: Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h • Campylobacteriosis ○ For Mild Disease and If CD4 Count >200 cells/µL: ▪ No therapy unless symptoms persist for more than several days ○ For Mild-to-Moderate Disease (If Susceptible):

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	▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, or ▪ Azithromycin 500 mg PO daily (Note: Not for patients with bacteremia) o For Campylobacter Bacteremia: ▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h + an aminoglycoside o Duration of Therapy: ▪ Gastroenteritis: seven to 10 days (five days with azithromycin) ▪ Bacteremia: ≥14 days ▪ Recurrent bacteremia: two to six weeks • Clostridium difficile Infection (CDI) o Fidaxomicin 200 mg PO two times daily for 10 days o Vancomycin 125 mg (PO) QID for 10 days • Salmonellosis o All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20 to 100 fold) and mortality (by up to 7-fold) compared to HIV negative individuals o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, if susceptible • Shigellosis o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h o Note: Increased resistance of Shigella to fluoroquinolones is occurring in the United States. Avoid fluoroquinolones if ciprofloxacin MIC is ≥0.12 µg/mL, even if the laboratory identifies the isolate as sensitive. Many Shigella strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of Shigella isolates from HIV-infected individuals should be performed routinely. • Bartonellosis o For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis: Doxycycline 100 mg PO or IV q12h, or Erythromycin 500 mg PO or IV q6h o CNS Infections: (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h o Confirmed Bartonella Endocarditis: (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) for two weeks, then continue with doxycycline 100 mg IV or PO q12h o Other Severe Infections: (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) q12h, or (Erythromycin 500 mg PO or IV q6h) +/- RIF 300 mg PO or IV q12h o Duration of therapy: at least three months • Candidiasis (Mucocutaneous) o For Oropharyngeal Candidiasis; Initial Episodes (for 7 to 14 Days): ▪ Fluconazole 100 mg PO daily o For Esophageal Candidiasis (for 14 to 21 Days): ▪ Fluconazole 100 100 mg (up to 400 mg) PO or IV daily ▪ Itraconazole oral solution 200 mg PO daily o For Uncomplicated Vulvo-Vaginal Candidiasis: ▪ Oral fluconazole 150 mg for one dose ▪ Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for three to seven days o For Severe or Recurrent VulvoVaginal Candidiasis: ▪ Fluconazole 100 to 200 mg PO daily for ≥7 days ▪ Topical antifungal ≥7 days • Chagas Disease (American Trypanosomiasis) o For Acute, Early Chronic, and Reactivated Disease: ▪ Benznidazole 5 to 8 mg/kg/day PO in 2 divided doses for 30 to 60 days (not commercially available in the United States;

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	contact the CDC) • Coccidioidomycosis o Clinically Mild Infections (e.g., Focal Pneumonia): ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day o Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): ▪ Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily ▪ Lipid formulation amphotericin B 4 to 6 mg/kg IV daily ▪ Duration of therapy: continue until clinical improvement, then switch to an azole o Meningeal Infections: ▪ Fluconazole 400 to 800 mg IV or PO daily o Chronic Suppressive Therapy: ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day • Community-Acquired Pneumonia (CAP) o Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia o Empiric Outpatient Therapy: ▪ A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: High-dose amoxicillin or amoxicillin/clavulanate ▪ Alternative Beta-Lactams: Cefpodoxime or cefuroxime, or Levofloxacin 750 mg PO once daily, or moxifloxacin 400 mg PO once daily, especially for patients with penicillin allergies. o Empiric Therapy for Hospitalized Patients with Non-Severe CAP: ▪ An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam; Levofloxacin 750 mg IV once daily, or moxifloxacin, 400 mg IV once daily, especially for patients with penicillin allergies. o Empiric Therapy for Hospitalized Patients with Severe CAP: ▪ An IV beta-lactam plus IV azithromycin, or ▪ An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam o Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia: ▪ An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every eight to 12 hours or levofloxacin 750 mg IV once daily) ▪ Preferred Beta-Lactams: Piperacillin-tazobactam, cefepime, imipenem, or meropenem o Empiric Therapy for Patients at Risk for Methicillin-Resistant Staphylococcus aureus Pneumonia: ▪ Add vancomycin IV or linezolid (IV or PO) to the baseline regimen ▪ Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production • Cystoisosporiasis (Formerly Isosporiasis) o For Acute Infection:

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	▪ TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or ▪ TMP-SMX (160 mg/800 mg) PO (or IV) BID for seven to 10 days ▪ Can start with BID dosing first and increase daily dose and/ or duration (up to three to four weeks) if symptoms worsen or persist ▪ IV therapy may be used for patients with potential or documented malabsorption o Chronic Maintenance Therapy (Secondary Prophylaxis): ▪ In patients with CD4 count <200/µL, TMP-SMX (160 mg/ 800 mg) PO three times weekly • Mycobacterium avium Complex (MAC) Disease o At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance: ▪ Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO daily, or ▪ If drug interaction or intolerance precludes the use of clarithromycin, (azithromycin 500 to 600 mg + ethambutol 15 mg/kg) PO daily o Duration: At least 12 months of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART • Pneumocystis Pneumonia (PCP) o Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX o Duration of PCP treatment: 21 days • Syphilis o Early Stage (Primary, Secondary, and Early-Latent Syphilis): ▪ Benzathine penicillin G 2.4 million units IM for one dose o Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses o Late-Stage (Tertiary–Cardiovascular or Gummatous Disease): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses (Note: rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management) o Neurosyphilis (Including Otic or Ocular Disease): ▪ Aqueous crystalline penicillin G 18 to 24 million units per day (administered as 3 to 4 million units IV q4h or by continuous IV infusion) for 10 to 14 days +/- benzathine penicillin G 2.4 million units IM weekly for three doses after completion of IV therapy
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for**	<u>Common principles</u> • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly

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antimicrobial prophylaxis in surgery (2013)[37]	encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a

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	cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole.
	• For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin).
	
	<u>Small intestine procedures</u>
	• For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole.
	• For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin).
	
	<u>Hernia repair procedures</u>
	• For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.
	
	<u>Colorectal procedures</u>
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	<u>Head and neck procedures</u>
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.

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	Neurosurgery procedures • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). Cesarean delivery procedures • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. Hysterectomy procedures • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is

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	cefazolin. <u>Heart, lung, heart-lung, liver, pancreas, and kidney transplantation</u> • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. <u>Plastic surgery and breast procedures</u> • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the macrolides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Macrolides[1-9]

Indication	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Dermatological Infections				
Erythrasma			✔	
Skin and skin-structure infections	✔ †	✔ §	✔	
Gastrointestinal Infections				
Treatment of *Clostridium difficile*-associated diarrhea				✔
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with amoxicillin and lansoprazole or omeprazole as triple therapy)		✔ §		
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with omeprazole or ranitidine bismuth citrate as dual therapy)		✔ §		
Genitourinary Infections				
Genital ulcer disease in men (chancroid)	✔ †			
Pelvic inflammatory disease due to *Neisseria gonorrhoeae*			✔	
Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Mycoplasma hominis*	✔ *			
Syphilis			✔	
Urethral, endocervical, or rectal infections due to *Chlamydia trachomatis*			✔	
Urethritis/cervicitis (gonococcal)	✔ †			
Urethritis/cervicitis (non-gonococcal)	✔ †‖		✔	
Urogenital infections in pregnancy			✔	
Respiratory Infections				
Acute exacerbations of chronic bronchitis		✔ §δ		
Acute infective exacerbations of chronic obstructive pulmonary disease (mild to moderate)	✔ †			
Legionnaires' disease			✔	
Otitis media	✔ †	✔ §		
Pertussis			✔	
Pharyngitis and/or tonsillitis	✔ †	✔ §	✔	
Pneumonia (community-acquired)	✔ *†‡	✔ §δ	✔	
Pneumonia of infancy due to *Chlamydia trachomatis*			✔	

Indication	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Respiratory tract infections (lower)			✔	
Respiratory tract infections (upper)			✔	
Sinusitis	✔ †‡	✔ §δ		
Miscellaneous Infections				
Conjunctivitis of the newborn due to *Chlamydia trachomatis*			✔	
Diphtheria			✔	
Intestinal amebiasis			✔ †	
Listeriosis			✔	
Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment)		✔ §		
Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention)	✔ ‖	✔ §		
Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, treatment)	✔ ‖			
Rheumatic fever (prophylaxis)			✔	

δExtended-release formulation.
§Immediate-release formulations.
*IV formulation.
‡Suspension formulation (extended-release).
†Tablet formulation (250 and 500 mg) and suspension formulation (immediate-release).
‖Tablet formulation (600 mg) and suspension formulation (1 g packet).

IV. Pharmacokinetics

The pharmacokinetic parameters of the macrolides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Macrolides[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Azithromycin	38	7 to 50	Liver (35)	Renal (4 to 12) Biliary (>50)	11 to 68
Clarithromycin	50	42 to 50	Liver	Renal (20 to 40)	3 to 7
Erythromycin	Variable	High (% not specified)	Liver	Biliary	1.5 to 2.0
Fidaxomicin	Minimal	Not reported	Intestine	Feces (>92)	11.7

V. Drug Interactions

Major drug interactions with the macrolides are listed in Table 6.

Table 6. Major Drug Interactions with the Macrolides[2]

Generic Name(s)	Interaction	Mechanism
Macrolides (azithromycin, clarithromycin, erythromycin)	Antiarrhythmic agents	Co-administration may result in additive increase in the QT interval and increase risk of life-threatening cardiac arrhythmias, such as torsades de pointes.
Macrolides (azithromycin, clarithromycin, erythromycin)	Anticoagulants	Effects of oral anticoagulants may be potentiated. Bleeding may occur. Close monitoring of prothrombin time is recommended.
Macrolides (azithromycin, clarithromycin, erythromycin)	Quinolones	The risk of life-threatening cardiac arrhythmias, such as torsades de pointes may be increased.
Macrolides (azithromycin, clarithromycin, erythromycin)	Digoxin	Increases in serum digoxin concentrations have been observed, resulting in signs of digoxin toxicity.
Macrolides (azithromycin, clarithromycin, erythromycin)	Dronedarone	Co-administration may result in additive increase in the QT interval and increase risk of life-threatening cardiac arrhythmias, such as torsades de pointes. The metabolism of dronedarone may be inhibited. Co-administration is contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin)	Nilotinib	Increased plasma nilotinib concentrations resulting in increased risk of adverse reactions including life-threatening cardiac arrhythmias, such as torsades de pointes.
Macrolides (azithromycin, clarithromycin, erythromycin)	Pimozide	Cardiac arrhythmia, QT prolongation, and cardiac arrest are possible due to elevated serum pimozide concentrations. Co-administration is contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin)	Ergotamine and dihydroergotamine	Reports of acute ergot toxicity characterized by vasospasm and ischemia in the extremities and other tissues, including the central nervous system have been reported.
Macrolides (azithromycin, clarithromycin, erythromycin)	HMG-CoA reductase inhibitors	Increased concentrations of HMG-CoA reductase inhibitors have been observed. Rhabdomyolysis and liver dysfunction may occur.
Macrolides (azithromycin, clarithromycin, erythromycin)	Opioid analgesics	Opioid analgesic plasma concentrations may be elevated resulting in increased pharmacological effect and adverse reactions.
Macrolides	Carbamazepine	Increases in plasma carbamazepine concentrations

Generic Name(s)	Interaction	Mechanism
(clarithromycin, erythromycin)		have been observed.
Macrolides (azithromycin, clarithromycin, erythromycin)	Cisapride	Torsades des points, QT prolongation, and cardiac arrest are possible due to decreased cisapride metabolism.
Macrolides (clarithromycin, erythromycin)	Colchicine	Increases in colchicine concentration have been observed due to inhibition of CYP3A4 and P-glycoprotein.
Macrolides (azithromycin, clarithromycin, erythromycin)	Tacrolimus	Macrolides may increase gastrointestinal absorption and inhibit hepatic and gastrointestinal metabolism of tacrolimus via inhibition of cytochrome P450 3A4. Pharmacologic effects of macrolides and tacrolimus on myocardium may be additive
Macrolides (erythromycin)	Theophylline	Inhibition of cytochrome P450 1A2 isoenzymes by erythromycin may decrease the metabolic elimination of theophylline. Elevated theophylline plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Macrolides (clarithromycin, erythromycin)	Benzodiazepines	Central nervous system effects such as somnolence and confusion have been reported with the co-administration of these medications.
Macrolides (azithromycin, clarithromycin, erythromycin)	Phosphodiesterase-5 inhibitors	Co-administration may result in increased exposure to phosphodiesterase-5 inhibitors. Reduction of phosphodiesterase-5 inhibitor doses may be considered.
Macrolides (azithromycin, clarithromycin, erythromycin)	Tyrosine kinase inhibitors	Concurrent use of macrolides and tyrosine kinase inhibitors may result in an increased risk of QT interval prolongation.
Macrolides (azithromycin, clarithromycin, erythromycin)	Azole antifungals	Concurrent use of macrolides and azole antifungals may result in an increased risk of QT interval prolongation.
Macrolides (azithromycin, clarithromycin, erythromycin)	Protease inhibitors	Plasma concentrations of protease inhibitors and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin)	Dopamine antagonists	Plasma concentrations of dopamine antagonists and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin)	Antipsychotic agents	Plasma concentrations of antipsychotic agents and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin)	Tricyclic antidepressants	Plasma concentrations of tricyclic antidepressants and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin)	Selective serotonin inhibitors (dolasetron, granisetron, ondansetron)	Concurrent use of selective serotonin inhibitors and macrolides may result in an increased risk of QT interval prolongation.
Macrolides (clarithromycin, erythromycin)	Rifamycins	Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of macrolides. Inhibition of hepatic microsomal enzymes by macrolides may decrease the metabolic elimination

Generic Name(s)	Interaction	Mechanism
		of rifamycins.
Macrolides (clarithromycin, erythromycin)	Cilostazol	Increased cilostazol exposure has been reported with co-administration. Monitor blood pressure, heart rate, complete blood counts, bleeding time, routine chemistry, and blood glucose for signs of cilostazol toxicity.
Macrolides (clarithromycin)	Silodosin	Silodosin plasma concentrations may be elevated resulting in increased pharmacological effect and adverse reactions.

VI. Adverse Drug Events

The most common adverse drug events reported with the macrolides are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Macrolides[1-9]

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Cardiovascular				
Bradycardia	-	-	-	-
Chest pain	<1	-	✔	-
Hypotension	✔	-	-	-
Palpitations	<1	-	✔	-
Torsades de pointes	✔	✔	✔	-
Ventricular tachycardia	✔	✔	✔	-
Central Nervous System				
Aggressive reactions	✔	-	-	-
Agitation	✔	-	-	-
Anxiety	✔	✔	-	-
Asthenia	✔	-	-	-
Behavioral changes	-	✔	-	-
Confusion	-	✔	✔	-
Depersonalization	-	✔	-	-
Depression	-	✔	-	-
Disorientation	-	✔	-	-
Dizziness	<1	✔	✔	-
Fever	✔	-	✔	-
Hallucinations	-	✔	✔	-
Headache	<1	2	8	-
Hyperactivity	✔	-	-	-
Insomnia	✔	✔	-	-
Manic behavior	-	✔	-	-
Nervousness	✔	-	-	-
Nightmares	-	✔	-	-
Paresthesia	✔	-	-	-
Psychosis	-	✔	-	-
Seizures	✔	✔	✔	-
Somnolence	<1	-	-	-
Sweating	✔	-	-	-
Syncope	✔	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Tinnitus	-	✔	-	-
Tremor	-	✔	-	-
Vertigo	<1	✔	✔	-
Dermatological				
Desquamation	-	-	1 to 10	-
Dryness	-	-	1 to 10	-
Eczema	✔	-	-	-
Erythema	-	-	1 to 10	-
Erythema multiforme	✔	-	✔	-
Photosensitivity	<1	-	-	-
Pruritus	✔	-	1 to 10	<2
Rash	<1	3	3	<2
Skin eruptions	-	✔	✔	-
Stevens Johnson Syndrome	✔	✔	✔	-
Toxic epidermal necrolysis	✔	✔	✔	-
Urticaria	✔	✔	✔	-
Gastrointestinal				
Abdominal distension	-	-	-	<2
Abdominal pain	3	2 to 3	8	6
Abdominal tenderness	-	-	-	<2
Anorexia	✔	✔	✔	-
Cholestatic jaundice	<1	✔	✔	-
Constipation	✔	-	-	-
Cramping	-	-	✔	-
Diarrhea	5	3 to 6	7	-
Dyspepsia	<1	2	2	<2
Dysphagia	-	-	-	<2
Flatulence	<1	-	2	<2
Gastritis	✔	-	-	-
Gastrointestinal hemorrhage	-	-	-	4
Glossitis	-	✔	-	-
Hypertrophic pyloric stenosis	-	-	✔	-
Intestinal Obstruction	-	-	-	<2
Loose stools	5.0 to 11.6	-	-	-
Megacolon	-	-	-	<2
Melena	<1	-	-	-
Mucositis	<1	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Nausea	3 to 5	3	8	11
Oral candidiasis	✔	✔	✔	-
Pancreatitis	✔	✔	✔	-
Pseudomembranous colitis	✔	-	✔	-
Stomatitis	-	✔	-	-
Taste perversion	✔	3 to 7	1	-
Tongue discoloration	✔	✔	-	-
Tooth discoloration	-	✔	-	-
Vomiting	<2	6	3	7
Genitourinary				
Acute renal failure	✔	-	-	-
Interstitial nephritis	✔	✔	-	-
Monilia	<1	-	-	-
Nephritis	<1	-	-	-
Vaginitis	<1	-	-	-
Hematological				
Anemia	✔	-	-	2
Eosinophilia	-	-	1	-
Leukopenia	<1	✔	-	-
Neutropenia	<1	✔	-	2
Thrombocytopenia	<1	✔	-	<2
Hepatic				
Hepatic dysfunction	-	-	✔	-
Hepatic failure	✔	✔	-	-
Hepatic necrosis	✔	-	-	-
Hepatitis	✔	✔	✔	-
Jaundice	✔	-	✔	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	-	<1	-	<2
Bicarbonate decreased	-	-	-	<2
Bilirubin increased	<1	-	-	-
Blood urea nitrogen increased	<1	4	-	-
Creatine phosphokinase increased	1 to 2	-	-	-
Creatinine increased	<1	<1	-	-
Gamma-glutamyl transferase increased	1 to 2	<1	-	-
Hepatic enzymes increased	-	-	-	<2
Hyperglycemia	<1	-	-	<2

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin
Hyperkalemia	1 to 2	-	-	-
Hypoglycemia	-	✔	-	-
Lactic dehydrogenase increased	<1	<1	-	-
Metabolic acidosis	-	-	-	<2
Phosphate increased	<1	-	-	-
Prothrombin time increased	-	1	-	-
Serum glutamic oxaloacetic transaminase increased	1 to 2	<1	2	-
Serum glutamic pyruvic transaminase increased	1 to 2	<1	2	-
Musculoskeletal				
Arthralgia	✔	-	-	-
Weakness	-	-	2	-
Respiratory				
Bronchospasm	<1	-	-	-
Cough	✔	-	3	-
Dyspnea	-	-	1	-
Pharyngitis	✔	-	-	-
Rhinitis	✔	-	-	-
Other				
Allergic reactions	-	-	✔	-
Anaphylaxis	✔	✔	✔	-
Angioedema	<1	-	-	-
Deafness	✔	-	-	-
Edema	✔	-	-	-
Fatigue	<1	-	-	-
Hearing disturbances	✔	-	-	-
Hearing loss	-	✔	✔	-
Hypersensitivity reactions	-	-	✔	-
Malaise	✔	-	-	-
Olfactory perversion	-	✔	-	-
Pain	✔	-	2	-
Phlebitis	-	-	✔	-
Thrombophlebitis	-	-	✔	-
Tinnitus	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the macrolides are listed in Table 8.

Table 8. Usual Dosing Regimens for the Macrolides[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Azithromycin	Acute infective exacerbations of chronic obstructive pulmonary disease (mild to moderate): Immediate release suspension, tablet (250 mg, 500 mg): 500 mg once daily for three days or 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Genital ulcer disease (chancroid): Immediate release suspension, tablet (250 mg, 500 mg): 1 g as a single dose *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention): Tablet (600 mg): 1,200 mg once weekly *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, treatment): Tablet (600 mg): treatment: 600 mg daily Urethritis/cervicitis (gonococcal): Immediate release suspension, tablet (250 mg, 500 mg): 2 g as a single dose Urethritis/cervicitis (non-gonococcal): Immediate release suspension, tablet (250 mg, 500 mg): 1 g as a single dose Suspension (1 g): 1 g as a single dose Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Mycoplasma hominis*: Injection: 500 mg as a single daily dose for one to two days	Otitis media in patients ≥6 months of age: Immediate release suspension, tablet (250 mg, 500 mg): 30 mg/kg given as a single dose or 10 mg/kg once daily for three days or 10 mg/kg as a single dose on the first day, followed by 5 mg/kg/day on days two through five Pharyngitis and/or tonsillitis in patients ≥2 years of age: Immediate release suspension, tablet (250 mg, 500 mg): 12 mg/kg once daily for five days Pneumonia (community-acquired) in patients ≥6 months of age: Extended release suspension: 60 mg/kg as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 10 mg/kg on day one, followed by 5 mg/kg on days two to five Sinusitis in patients ≥6 months of age: Immediate release suspension, tablet (250 mg, 500 mg): 10 mg/kg once daily for three days	Immediate release suspension: 100 mg/5 mL 200 mg/5 mL Injection: 500 mg Packet for suspension: 1 g Tablet: 250 mg 500 mg 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pharyngitis and/or tonsillitis: Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Pneumonia (community-acquired): Extended release suspension: 2 g as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Injection: 500 mg as a single daily dose for at least two days Sinusitis: Extended release suspension: 2 g as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 500 mg once daily for three days Skin and skin-structure infections: Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five		
Clarithromycin	Acute exacerbations of chronic bronchitis: Extended release tablet: 1,000 mg once daily for seven days Immediate release tablet: 250 to 500 mg every 12 hours for seven to 14 days *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention): Immediate release tablet: 500 mg every 12 hours Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment): Immediate release tablet: 500 mg	Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention) in patients ≥6 months of age: Immediate release tablet, suspension: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment): Immediate release tablet, suspension: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Otitis media in patients ≥6	Extended release tablet: 500 mg Immediate release tablet: 250 mg 500 mg Suspension: 125 mg/5 mL 250 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	every 12 hours Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with amoxicillin and lansoprazole or omeprazole as triple therapy): Immediate release tablet: 500 mg every 12 hours for 10 to 14 days given with amoxicillin and either lansoprazole or omeprazole Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with omeprazole or ranitidine bismuth citrate as dual therapy): Immediate release tablet: 500 mg every eight to 12 hours for 14 days given with ranitidine bismuth citrate or omeprazole Pharyngitis and/or tonsillitis: Immediate release tablet: 250 mg every 12 hours for 10 days Pneumonia (community-acquired): Extended release tablet:1,000 mg once daily for seven days Immediate release tablet: 250 mg every 12 hours for seven to 14 days Sinusitis: Extended release tablet: 1,000 mg once daily for 14 days Immediate release tablet: 500 mg every 12 hours for 14 days Skin and skin-structure infections: Immediate release tablet: 250 mg every 12 hours for seven to 14 days	months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Pneumonia (community-acquired) in patients ≥6 months of age: Immediate release tablets, suspension: 15 mg/kg/day divided every 12 hours for 10 days Sinusitis in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Skin and skin-structure infections in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days	
Erythromycin base	Intestinal amebiasis: Delayed release capsule, delayed release tablet, tablet: 500 mg every 12 hours or 250 mg every six hours for 10 to 14 days Legionnaires' disease: Delayed release capsule, delayed release tablet, tablet: 1 to 4 g daily in divided doses Nongonococcal urethritis:	Intestinal amebiasis: Delayed release capsule, delayed release tablet, tablet: 30 to 50 mg/kg/day in divided doses for 10 to 14 days Unspecified infections: Delayed release capsule, delayed release tablet, tablet: 30 to 50 mg/kg/day in two to four divided doses	Delayed release capsule: 250 mg Delayed release tablet: 250 mg 333 mg 500 mg Tablet: 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Delayed release capsule, delayed release tablet, tablet: 500 mg four times daily for seven days Pelvic inflammatory disease: Delayed release capsule, delayed release tablet, tablet: 500 mg intravenous every six hours for three days followed by 500 mg orally every 12 hours for seven days Pertussis: Delayed release capsule, delayed release tablet, tablet: 40 to 50 mg/kg/day in divided doses for five to 14 days Pharyngitis and/or tonsillitis: Delayed release capsule, delayed release tablet, tablet: 250 mg four times daily or 500 mg every 12 hours for 10 days Syphilis: Delayed release capsule, delayed release tablet, tablet: 30 to 40 g given in divided doses over 10 to 15 days Unspecified infections: Delayed release capsule, delayed release tablet, tablet: 250 mg four times daily or 500 mg every 12 hours Urogenital infections in pregnancy: Delayed release capsule, delayed release tablet, tablet: 500 mg four times daily for seven days or either 250 mg four times daily or 500 mg every 12 hours for 14 days		500 mg
Erythromycin ethylsuccinate	Intestinal amebiasis: Suspension, tablet: 400 mg four times daily for 10 to 14 days Legionnaires' disease: Suspension, tablet: 1.6 to 4 g daily in divided doses Pertussis: Suspension, tablet: 40 to 50 mg/kg/day in divided doses for five to 14 days Syphilis:	Intestinal amebiasis: Suspension, tablet: 30 to 50 mg/kg/day in divided doses for 10 to 14 days Unspecified infections: Suspension, tablet: 30 to 50 mg/kg/day in two to four divided doses	Suspension: 200 mg/5 mL 400 mg/5 mL Tablet: 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension, tablet: 48 to 64 g in divided doses over 10 to 15 days Unspecified infections: Suspension, tablet: 400 mg every six hours, or total daily dose divided every eight or every 12 hours Urethritis: Suspension, tablet: 800 mg three times daily for seven days		
Erythromycin lactobionate	Unspecified infections: Injection: 15 to 20 mg/kg/day divided every six hours or 0.5 to 1 g every six hours or continuous infusion	Unspecified infections: Injection: 15 to 20 mg/kg/day divided every six hours	Injection: 500 mg
Erythromycin stearate	Unspecified infections: Tablet: 250 mg every six hours or 500 mg every 12 hours up to 4 g per day	Unspecified infections: Tablet: 30 to 50 mg/kg/day in two to four divided doses	Tablet: 250 mg
Fidaxomicin	*Clostridium difficile*-associated diarrhea: Tablet: 200 mg twice daily for 10 days	*Clostridium difficile*-associated diarrhea in patients six months of age and older: Tablet: for patients weighing at least 12.5 kg, 200 mg twice daily for 10 days; see labeling for oral suspension dosing for other pediatric patients	Suspension: 40 mg/mL Tablet: 200 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the macrolides are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Macrolides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Dey et al.[38] (2015) Azithromycin 2 g once vs azithromycin 500 mg once daily for five days	OL, PG, PRO, RCT Patients 12 years of age or older with an uncomplicated skin and skin structure infection	N=292 7 days	Primary: Clinical response (cessation of the spread of redness, edema, and induration around the lesion or reduction of the size of the lesion at 72 hours) Secondary: Clinical cure, adverse effects	Primary: The resolution of individual signs and symptoms was highly significant over seven days in both groups and remained comparable between the two dosing groups throughout. Secondary: At the end of study, cure was recorded in 145 subjects (97.97%) who received single dose azithromycin vs 144 (98.63%) subjects who received conventional five days azithromycin; the difference is statistically not significant. The differences in frequency of individual adverse events between the two groups were not statistically significant.
Wasilewski et al.[39] (2000) Dirithromycin 500 mg daily for five days vs erythromycin 250 mg every 6 hours for seven days	DB, DD, MC, PG, RCT Patients 12 years of age or older with a culturable bacterial infection of the skin and/or soft tissue	N=439 Treatment duration plus 10 to 14 days	Primary: Clinical response (cure defined as resolution of pre-treatment signs and symptoms), bacteriologic response (eradication of pathogen based on culture results) Secondary: Not reported	Primary: A favorable response was seen in 85.0% of patients in the dirithromycin group compared to 80.8% of patients in the erythromycin group. No significant differences were observed. A favorable bacteriologic response was seen in 66.4% of patients in the dirithromycin group and 63.5% in the erythromycin group. No significant differences were observed. Secondary: Not reported
Gastrointestinal Infections				
Kaushik et al.[40] (2010)	OL, RCT	N=180	Primary: Clinical success	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 20 mg/kg as a single dose vs azithromycin 20 mg/kg as a single dose	Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for Vibrio cholerae by hanging drop examination or culture of stool	3 days	(resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of Vibrio cholerae by day three) Secondary: Duration of diarrhea, duration of excretion of Vibrio cholerae in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	ciprofloxacin (RR, 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR, 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 vs 71.5 hours, respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of Vibrio cholerae than patients receiving ciprofloxacin (34.6 vs 52.1 hours; P<0.001). The amount of IV fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 vs 3,491.1 mL; P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Vukelic et al.[41] (2010) Azithromycin 20 mg/kg as a single oral dose vs azithromycin 30 mg/kg as a single oral dose vs	RCT, SC Children ≤12 years of age with *Campylobacter jejuni/coli* enterocolitis	N=120 Variable duration	Primary: Clinical cure rates achieved during the 144 hours study period and safety Secondary: Not reported	Primary: The incidence of clinically cured patients during the 144-hour study period was 50% in the control, 46.6% in the azithromycin 20 mg/kg group, 66.6% in the azithromycin 30 mg/kg group, and 83.3% in the erythromycin group. Only azithromycin 30 mg/kg was significantly more effective than no treatment (P=0.011). Azithromycin 30 mg/kg was also significantly more effective than erythromycin (P=0.006). There was no difference between the erythromycin and the control group. All treatments were well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erythromycin 50 mg/kg/day orally divided in three daily doses for five days vs no antibiotic (control group)				
Hsu et al.[42] (2015) Reverse hybrid therapy (pantoprazole 40 mg plus amoxicillin 1 g twice daily for 12 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the first seven days) vs standard triple therapy (pantoprazole 40 mg plus clarithromycin 500 mg and amoxicillin 1 g twice daily for	MC, RCT, SB Patients ≥20 years of age with diagnosis of *H pylori* based on at least two positive results of rapid urease test, histology, and culture and with endoscopically proven peptic ulcer diseases or gastritis	N=440 6 weeks after treatment	Primary: Eradication rate Secondary: Frequency of adverse events, drug compliance	Primary: Intent-to-treat eradication rates were 93.6 and 86.8% for reverse hybrid and standard triple therapies, respectively. Reverse hybrid therapy achieved a higher eradication rate than standard triple therapy (95% CI, 1.3 to 12.3%; P=0.016). The modified intent-to-treat (95.4 vs 88.4%) and per-protocol analyses (95.7 vs 88.3%) yielded similar results (P=0.008 and 0.005, respectively). Secondary: The incidences of adverse events in the participants receiving reverse hybrid and standard triple therapies were 14.1% (95% CI, 9.2 to 19.0%) and 9.5% (95% CI, 5.6 to 13.4%), respectively. The two therapies exhibited similar frequencies of overall adverse events (P=0.14). Reverse hybrid and standard triple groups displayed similar compliance rates (96.8%; 95% CI, 94.5 to 99.1% and 98.6%; 95% CI, 97.1 to 100.2%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 days).				
Molina-Infante et al.[43] (2013) Hybrid therapy (40 mg omeprazole and 1 g amoxicillin, twice daily for 14 days; 500 mg clarithromycin and 500 mg nitroimidazole were added, twice daily for the final seven days) vs concomitant therapy (same 4 drugs taken concurrently, twice daily for 14 days)	NI, PRO, RCT Consecutive adult patients with *H pylori* infection and dyspepsia, peptic ulcer disease, or familiar history of gastric cancer, who did not receive prior eradication therapy	N=343 8 weeks posttreatment	Primary: Eradication rates in the intent-to-treat population Secondary: Eradication rates in the per-protocol population, compliance	Primary: In the intent-to-treat analysis, eradication rates were 153 of 170 (90%; 95% CI, 86 to 93%) for hybrid and 156 of 170 (91.7%; 95% CI, 88 to 95%) for concomitant therapy (P=0.35). Secondary: Eradication rates in the per-protocol analysis were 150 of 163 (92%; 95% CI, 87 to 95%) for hybrid therapy and 150 of 156 (96.1%; 95% CI, 93 to 99%) for concomitant therapy (P=0.07). More patients were compliant (defined as compliance ≥80%) with hybrid therapy (98.8%) than concomitant therapy (95.2%; P=0.05).
Zhang et al.[44] (2015) Metronidazole 400 mg four times a day vs clarithromycin 500 mg twice a day	NI, OL, R Consecutive patients who presented with epigastric symptoms and had endoscopically proven functional dyspepsia or scarred peptic ulcers. *H pylori* infection was	N=215 6 weeks posttreatment	Primary: Eradication rates Secondary: Compliance, adverse events	Primary: In the per-protocol analysis, the lower bound of the 95% CI for difference between metronidazole and clarithromycin groups was greater than the pre-established non-inferiority margin of –10% (95% CI, −2.7 to 6.7%, P<0.0001). The same CI was derived with the intent-to-treat population. Secondary: Eight subjects in the metronidazole group and six subjects in the clarithromycin group failed to take at least 80% of the drugs due to adverse effects, including three subjects of each group that were withdrawn from the treatment because of nausea, drowsiness and skin allergy. Both regimens were well tolerated (92.6 vs 94.4%; P=0.593). Side

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Each treatment was taken in combination with lansoprazole 30 mg twice a day, bismuth potassium citrate 300 mg (220 mg elemental bismuth) twice a day, and amoxicillin 1000 mg twice a day for 14 days	diagnosed by positive rapid urease test and 13C-urea breath test or anti-*H pylori* antibody			effects were reported by 21.3% (23/108) in the metronidazole group vs 11.2% (12/107) in the clarithromycin group (P=0.045). Adverse effects included nausea, fatigue, bad taste, epigastric pain, skin rash, diarrhoea, dizziness, and fever. They all disappeared after cessation of medications. Adverse effects were more frequent in the metronidazole group than in the clarithromycin group (P=0.045). Nausea was the most frequent adverse event in the metronidazole group (P=0.031)
Ohlin et al.[45] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and lansoprazole 30 mg BID for 14 days (LAC) vs lansoprazole 30 mg BID and amoxicillin 1g BID for 14 days (LA) vs omeprazole 20 mg BID and amoxicillin 1g BID for 14 days (OA)	DB, MC, RCT Patients 18 to 80 years of age with *H pylori* infection and a present recurrent duodenal ulcer and/or previous recurrent duodenal ulcer	N=177 4 weeks posttreatment	Primary: Eradication of *H pylori* at least four weeks after the end of treatment period Secondary: Not reported	Primary: Triple therapy with LAC was significantly better than either dual therapy with OA or LA in ulcer healing and eradication of *H pylori* (P<0.001). There was no significant difference between dual therapy groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Uygun et al.[46] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Kearney et al.[47] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H2) vs tetracycline 500	OL Patients with peptic ulcer disease or prescribed H2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05). The per-protocol cure rates for BMT-H2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H2 and MLC groups, and between BMT-PPI and BMT-H2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H2 group (P=0.02). A

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)				significantly higher number of patients discontinued therapy due to adverse events in the BMT-H2 and BMT-PPI treatment groups than the MLC group (P=0.049).
Magaret et al.[48] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500	MC, RCT Patients failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 14 days				
Songür et al.[49] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[50] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported
Zheng et al.[51] (2010) Tetracycline 750	OL, RCT, SC Patients 18 to 70 years of age with	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	non-ulcer dyspepsia and *H pylori* infection		Secondary: Not reported	In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[52] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days				
Altintas et al.[53] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump inhibitor clarithromycin and amoxicillin for the treatment of *H pylori*	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).
Luther et al.[54] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)				The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Louie et al.[55] (2011) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *Clostridium difficile* infection, as well as the presence of *Clostridium difficile* toxin A, B, or both in the stool	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within four weeks after treatment)	Primary: Clinical cure rates in the modified intent to treat analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the per protocol analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin. Secondary: Recurrence in the modified intent to treat analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the per protocol analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.
Cornely, Crook et al.[56] (2012) Fidaxomicin 200	DB, MC, PRO, RCT Patients ≥16 years of age with	N=535 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further	Primary: In the per protocol population, clinical cure rates in the fidaxomicin group (91.7%) were non-inferior to the rates in the vancomycin group (90.6%; one-sided 97.5% CI, -4.3). In the modified intent to treat population, clinical cure rates in the fidaxomicin group (87.7%) were non-inferior to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg every 12 hours for 10 days vs vancomycin 125 mg orally every 6 hours daily for 10 days	*Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool		therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30days of treatment completion)	the rates in the vancomycin group (86.8%; treatment difference, 0.9; 95% CI, -4.9 to 6.7; P=0.754). Secondary: In the modified intent to treat population, significantly more patients in the vancomycin group had a recurrence compared to the fidaxomicin group (26.9 vs 12.7%; treatment difference, -14.2; 95% CI, -21.4 to -6.8; P=0.0002). In this population, there was a significantly higher rate of sustained clinical response in the fidaxomicin group compared to the vancomycin group (76.6 vs 63.4%; treatment difference, 13.2; 95% CI, 5.3 to 21.0; P=0.001).
Cornely, Miller et al.[57] (2012) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, PRO, RCT Patients >15 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=178 28 days posttreatment	Primary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30 days of treatment completion) Secondary: Not reported	Primary: In patients with no prior episode of *Clostridium difficile* infection, there was a significantly greater proportion of patients in the vancomycin group (24.8%) that had a recurrence compared to the fidaxomicin group (12.9%; treatment difference, -11.8; 95% CI, 17.1 to 6.5; P<0.001). In patients with one prior episode of *Clostridium difficile* infection, there was no significant difference in recurrence between the vancomycin and fidaxomicin groups (32.3 vs 20.3%; treatment difference -12.3; 95% CI, -25.4 to 1.5; P=0.08). Secondary: Not reported
Genitourinary Infections				
Tyndall et al.[58] (1994) Azithromycin 1 g as a single dose	RCT, SB Male patients 18 to 60 years of age with genital ulcers	N=204 21 days	Primary: Response to treatment (cure defined as epithelialization of	Primary: Complete ulcer resolution was observed in 89% of men in the azithromycin group and 91% of men in the erythromycin group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg QID or seven days			ulcer complete by day 21) Secondary: Not reported	Not reported
Hook et al.[59] (2002) Azithromycin 2 g as a single dose vs azithromycin 2 g as two doses given six to eight days apart vs penicillin benzathine G 2.4 million units IM as a single dose	RCT Patients 18 to 56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response Secondary: Not reported	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75). The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95). Secondary: Not reported
Hook et al.[60] (2010) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	MC, OL, RCT Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection Secondary: Not reported	Primary: In the intent to treat analysis at the six-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the per protocol analysis at the six-month follow-up visit, 77.5%) of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound, −7.9%). The efficacy of 2 g azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				syphilis in patients without human immunodeficiency virus infection. Secondary: Not reported
Bai et al.[61] (2008) Azithromycin vs penicillin G benzathine	MA Patients ≥18 years of age with early syphilis	N=476 (4 trials) Variable duration	Primary: Cure rates and adverse events Secondary: Not reported	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR, 1.37; 95% CI, 1.05 to 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09 to 1.61; P=0.38). There was no significant difference in the rate of adverse events between the treatment groups. Secondary: Not reported
Mena et al.[62] (2009) Doxycycline 100 mg BID for 7 days vs azithromycin 1 g as a single dose	RCT, SC Men with nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *Mycoplasma genitalium* infection Secondary: Not reported	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *Mycoplasma genitalium*. Of those testing positive at initial follow-up (10 to 17 days post therapy), 13% (95% CI, 3 to 35) were from the azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *Mycoplasma genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent two to six weeks. Secondary: Not reported
Adair et al.[63] (1998) Azithromycin 1 g as a single dose	OL, RCT Pregnant females with positive deoxyribonucleic	N=106 3 weeks posttreatment	Primary: Response to therapy (eradication determined by	Primary: There was no significant difference in treatment efficacy between groups (88.1% compared to 93.0% for azithromycin and erythromycin respectively, P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg every 6 hours for seven days	acid antigen assays for *Chlamydia trachomatis*		deoxyribonucleic acid assay probe) Secondary: Not reported	Secondary: Not reported
Mikamo et al.[64] (1999) Clarithromycin 400 mg BID for 5, 7, or 14 days (CAM) vs erythromycin 600 mg TID for 5, 7, or 14 days (EM)	RCT Female patients 17 to 56 years of age with cervicitis caused by *Chlamydia trachomatis*	N=96 6 weeks	Primary: Eradication of *Chlamydia trachomatis* Secondary: Not reported	Primary: Eradication rates were significantly higher in the seven-day CAM group compared to the seven-day EM group. Eradication rates were significantly higher in the 14-day CAM group compared to the 14-day EM group. Secondary: Not reported
Respiratory Infections				
Pichichero et al.[65] (2003) Azithromycin 10 mg/kg on day one, followed by 5 mg/kg on days two to five	OL Patients 6 months to 20 years of age with a diagnosis of pertussis	N=34 21 days posttreatment	Primary: Bacteriologic eradication Secondary: Not reported	Primary: Microbiological eradication was observed in 97% of patients at days two to three of treatment and in 100% of patients at the 14 to21 day post-treatment follow-up visit. Secondary: Not reported
Albert et al.[66] (2011) Azithromycin 250 mg daily for one year vs	MC, PC, RCT Patients ≥40 years of age with COPD who were either using continuous supplemental oxygen or had received systemic	N=1,142 13 months	Primary: Time to the first acute exacerbation of COPD Secondary: Quality of life and adherence	Primary: The median time to the first exacerbation of COPD was 266 days (95% CI, 227 to 313) with azithromycin compared to 174 days (95% CI, 143 to 215) with placebo (P<0.001). The HR of having an acute exacerbation of COPD per patient-year in the azithromycin group as compared to the placebo group was 0.73 (95% CI, 0.63 to 0.84; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	glucocorticoids within the previous year, who had gone to an emergency room or had been hospitalized for an acute exacerbation of COPD, who had not had an acute exacerbation of COPD for at least 4 weeks before enrollment			The rates of acute exacerbations of COPD per patient-year were 1.48 with azithromycin and 1.83 with placebo (P=0.01). The frequency of acute exacerbations was lower among patients receiving azithromycin than among those receiving placebo (P=0.008). Secondary: The total SGRQ scores recorded at one year decreased a mean of 2.8 units in the azithromycin group compared to a mean of 0.6 units in the placebo group (P=0.004). No consistent changes were seen in the scores on the SF-36. The mean rate of adherence to the study medication was 67.3% in the azithromycin group and 66.9% in the placebo group (P=0.84).
Bacharier et al.[67] (2015) Azithromycin 12 mg/kg/day for five days vs placebo	DB, PC, PG, RCT Children 12 to 71 months of age with recurrent severe wheezing in the context of clinically significant lower RTIs that required systemic corticosteroids, an unscheduled physician office visit, an urgent or emergency department visit, or hospitalization	N=607 18 months	Primary: Number of RTIs not progressing to a severe lower RTI Secondary: Numbers of urgent care visits, emergency department visits, and hospitalizations; respiratory-related symptoms	Primary: The azithromycin group experienced significantly lower risk of progressing to severe lower RTI than the placebo group (HR, 0.64; 95% CI, 0.41 to 0.98; P=0.04; absolute risk for first RTI, 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03; 95% CI, 0.00 to 0.06), after adjustment for study site, age, modified asthma predictive index status,18 season during which the RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks. Secondary: Urgent care and emergency department visits occurred in 3.6% of participants receiving azithromycin and 5.4% of participants receiving placebo. There were 28 participants hospitalized for respiratory illnesses (azithromycin group, 13; placebo group, 15) over the duration of the trial. Azithromycin therapy decreased the overall severity of symptoms during severe lower RTIs compared with placebo, as reflected by lower mean total symptom scores over the duration of RTI, but not during episodes not progressing to severe lower RTI.
Jorgensen et al.[68] (2009) Azithromycin ER 2 g as a single dose	DB, MC, RCT Patients ≥13 years of age with group A β-hemolytic	N=598 Up to 45 days	Primary: Bacteriological response at the test of cure visit (days 24 to 28) in the	Primary: Bacteriological eradication was achieved in 85.4% of the patients receiving AZ-ER and in 81.4% of patients receiving AZ-IR (95% CI, -3.1 to 11.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(AZ-ER) vs azithromycin IR 500 mg once daily for three days (AZ-IR)	streptococcal pharyngitis or tonsillitis		bacteriological protocol population Secondary: Clinical cure rates at the test of cure visit and long term follow up visit (days 38 to 45)	Secondary: Clinical cure at the test of cure visit was 99% in the AZ-ER group and 96.7% in the AZ-IR group. The continued clinical cure rates at long term follow up were 92.1% and 95.2% for patients in the AZ-ER and AZ-IR treatment groups, respectively. One hundred percent of patients in the AZ-ER group and 98% in the AZ-IR group complied with active treatment.
Morris et al.[69] (2010) Azithromycin 30 mg/kg as a single dose vs amoxicillin 50 mg/kg/day in two divided doses for a minimum of seven days	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days six to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days six to 11) Secondary: Clinical and microbiological outcomes	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *Streptococcus pneumoniae* compared to amoxicillin (P<0.001).
Henry et al.[70] (2003) Azithromycin 500	DB, DD, MC, RCT Patients 18 years of age or older with	N=936 28 days	Primary: Clinical success at end of study	Primary: Cure rates were 71.7% in the AZM-3 group, 73.4% in the AZM-6 group, and 71.3% in the AMC group. There was no significant difference between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 3 days (AZM-3) vs azithromycin 500 mg daily for 6 days (AZM-6) vs amoxicillin-clavulanate 500 mg TID for 10 days (AMC)	acute bacterial sinusitis		Secondary: Not reported	Secondary: Not reported
Klapan et al.[71] (1999) Azithromycin 500 mg daily for three days vs amoxicillin-clavulanate 625 mg every 8 hours for 10 days	OL, RCT Patients 15 to 50 years of age with sinusitis	N=100 4 weeks	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: Cure was established in 95% of patients in the azithromycin group and 74% of patients in the amoxicillin-clavulanate group at the end of therapy (day 10 to 12), and clinical improvement was seen in the remainder of patients in both groups (P=0.012 in favor of azithromycin). At the follow-up visit (four weeks), cure was established in 98% of patients in the azithromycin group and 91% in the amoxicillin-clavulanate group. No significant differences were observed between groups (P>0.05). There was no significant difference in bacteriologic response seen between groups (P=0.409). Secondary: Not reported
Marple et al.[72] (2010) Azithromycin ER 2 g as a single dose vs	MC, OL, RCT Patients ≥18 years of age with acute, uncomplicated, bacterial maxillary sinusitis based on	N=751 28 days	Primary: Symptom resolution at day five in the per protocol population Secondary:	Primary: At day five in the per protocol population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference, 10.8%; 95% CI, 3.1 to 18.4). At day five in the intent to treat population, a significantly greater percentage of patients in the azithromycin group met the primary end point

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin-clavulanate 875-125 mg every 12 hours for 10 days	signs and symptoms lasting for 7 to 30 days		Time to resolution of symptoms, sinusitis-related quality of life, resource use, treatment success, and treatment satisfaction	(20.0%) than in the amoxicillin-clavulanate group (13.2%; difference, 6.8%; 95% CI, 1.5 to 12.2). Secondary: Over the course of the trial, both treatments led to similar rates of symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared to 63.0% of patients receiving amoxicillin-clavulanate. In the per protocol population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%). A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the two treatment arms. Patients treated with azithromycin reported greater satisfaction with the convenience of the medication than did patients given amoxicillin-clavulanate (difference, 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference, −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76 vs 60.92%; P=0.02). There was no difference in the incidence of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[73] (2011) Azithromycin ER 60 mg/kg as a single dose	DB, MC, RCT Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test of cure visit (days 12 to 14) in the bacteriologic	Primary: Clinical response at the test of cure visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference, – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 45-3.2 mg/kg every 12 hours for 10 days			eligible population Secondary: Bacterial response at other visits, compliance, and safety	Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). All patients receiving treatment with azithromycin received their single dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared to 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in 8.2% of patients receiving amoxicillin-clavulanate.
Panpanich et al.[74] (2008) Azithromycin vs amoxicillin or amoxicillin-clavulanate	MA Patients with acute lower respiratory tract infections	N=2,601 (15 trials) 10 to 14 days	Primary: Clinical failure Secondary: Microbial eradication, and adverse events	Primary: The pooled analysis of all trials showed that the incidence of clinical failure on day 10 to 14 in azithromycin group was 10.1% compared to 10.3% in the amoxicillin or amoxicillin-clavulanate group (RR, 1.09; 95% CI 0.64 to 1.85). Subgroup analysis stratified by age groups showed no significant difference of treatment effects between the azithromycin group and the amoxicillin or amoxicillin-clavulanate group in either adults (RR, 1.15; 95% CI, 0.60 to 2.20) or children (RR, 0.93; 95% CI, 0.45 to 1.94). Secondary: The pooled analysis showed that the incidence of microbial eradication in azithromycin group was 66.4% compared to 67.6% in amoxicillin or amoxicillin-clavulanate group. (RR, 0.95; 95% CI, 0.87 to 1.03). The overall incidence of adverse events in azithromycin group was 17.9% compared to 23.6% in amoxicillin or amoxicillin-clavulanate group (RR, 0.76; 95% CI, 0.57 to 1.00).
Swanson et al.[75] (2005)	DB, DD, MC, RCT	N=322	Primary: Clinical response	Primary: No significant differences in the clinical cure rates were found between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Azithromycin 500 mg daily for three days vs clarithromycin 500 mg BID for 10 days	Patients with an acute exacerbation of chronic bronchitis	24 days	and bacteriologic response at the test of cure visit (21 to 24 days) Secondary: Not reported	groups at the test of cure visit (85% for azithromycin and 82% for clarithromycin). No significant differences in the bacteriologic response rates were found between groups at the test of cure visit. Secondary: Not reported
Venuta et al.[76] (1998) Azithromycin 10 mg/kg once daily for three days vs clarithromycin 7.5 mg/kg BID for 10 days	RCT, SB Patients 4 to 13 years of age diagnosed with streptococcal pharyngitis with a positive antigen test throat culture	N=174 20 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: Cure rates were 95.9% in the azithromycin group and 96.8% in the clarithromycin group. There was no significant difference between groups. There was no significant difference in bacteriologic eradication rates between groups. Secondary: Not reported
Drehobl et al.[77] (2005) Azithromycin 2 g single dose vs clarithromycin ER 100 mg daily for seven days	DB, MC, RCT Patients 16 years of age and older with a diagnosis of pneumonia and suitable for outpatient treatment	N=499 35 days	Primary: Clinical response at the test of cure visit (day 14 to 21), bacteriologic response Secondary: Not reported	Primary: The clinical response at the test of cure visit was 92.6% in the azithromycin group and 94.7% in the clarithromycin group. No significant difference was found between groups. Bacteriologic eradication occurred in 91.8% of azithromycin patients and 90.5% of clarithromycin patients, although most bacteriologic responded were based on clinical response rather than follow-up cultures. No significant differences were seen between groups. Secondary: Not reported
O'Doherty et al.[78] (1998)	MC, RCT Patients 12 to 75	N=203 19 to 23 days	Primary: Clinical response and bacteriologic	Primary: A satisfactory clinical response (judged as cured or improved) was observed in 94% of azithromycin patients and 95% of clarithromycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Azithromycin 500 mg daily for three days vs clarithromycin 250 mg BID for 10 days	years of age with clinically diagnosed community-acquired pneumonia		response Secondary: Not reported	patients (P=0.518). In the azithromycin patients, 97% of pathogens were considered eradicated and 91% of pathogens were considered eradicated in the clarithromycin group. Secondary: Not reported
Muller[79] (1993) Azithromycin 500 mg daily for three days vs clarithromycin 250 mg BID for 10 days	MC, OL, RCT Patients 12 years of age and older with acute upper respiratory infections	N=380 14 to 28 days	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: No significant difference was found between the two groups in clinical response for any diagnosis (P>0.05). Bacteriologic response was also similar between groups. Secondary: Not reported
Aoyama et al.[80] (1996) Azithromycin 10 mg/kg daily for five days vs clarithromycin 10 mg/kg/day in 2 divided doses for seven days vs	CS Patients with culture- positive pertussis; each patient was matched with 2 erythromycin-treated patients with culture-positive pertussis recruited from historical controls	N=17 2 weeks posttreatment	Primary: Eradication rates Secondary: Not reported	Primary: Eradication rates one week after treatment were 100% in the clarithromycin and 89% in the matched erythromycin group, and 100% in the azithromycin group and 81% in the matched erythromycin group. Eradication rates two weeks after treatment were 100% in all groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erythromycin standard regimens 40 to 50 mg/kg/day for 2 weeks				
Altunaiji et al.[81] (2007) Azithromycin vs clarithromycin vs erythromycin	MA Patients with pertussis	N=2,197 (13 trials) Variable duration	Primary: Clinical response rates Secondary: Not reported	Primary: Short-term antibiotics (azithromycin for three to five days, clarithromycin for seven days, or erythromycin for seven days) were as effective as long-term antibiotics (erythromycin for 10 to 14 days) in eradicating *Bordetella pertussis* from the nasopharynx (RR, 1.02; 95% CI, 0.98 to 1.05), but were associated with fewer adverse events (RR, 0.66; 95% CI, 0.52 to 0.83). Sulfamethoxazole-trimethoprim for seven days was also effective. There were no differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Secondary: Not reported
Castaldo et al.[82] (2003) Azithromycin 500 mg on day one, then 250 mg daily for days two to five vs dirithromycin 500 mg daily for five days	RCT, SB, PG, MC Patients 35 years of age and older who are smokers or ex-smokers with an acute exacerbation of chronic bronchitis	N=86 35 days	Primary: Clinical success rates at the early (seven to 10 days) and the late (25 to 35 days) posttreatment visits Secondary: Not reported	Primary: Clinical efficacy was observed in 84.8% of patients in the dirithromycin group and 75.7% in the azithromycin group at the early post-treatment visit. No significant difference was observed. Clinical efficacy was observed in 95.5% of patients in the dirithromycin group and 86.5% in the azithromycin group at the late post-treatment visit. No significant difference was observed. Secondary: Not reported
Schonwald et al.[83] (1990) Azithromycin 250 mg BID on day one and 250 mg daily on days two	MC, OL, RCT Patients 12 years of age and older with a diagnosis of atypical pneumonia	N=101 21 days posttreatment	Primary: Clinical response to treatment Secondary: Not reported	Primary: There was no significant difference between the azithromycin group and erythromycin group in clinical response to treatment. Very good efficacy was reported in 82% of azithromycin patients and 84% of erythromycin patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to five vs erythromycin 500 mg QID for 10 days				Good efficacy was reported in 18% of azithromycin patients and 16% of erythromycin patients. No clinical failures were reported in either group. Secondary: Not reported
Griffin et al.[84] (2010) Levofloxacin vs azithromycin or clarithromycin	RETRO Patients with Legionella pneumonia	N=39 Variable duration	Primary: Time to clinical stability and length of hospital stay Secondary: Not reported	Primary: The mean time to clinical stability for the macrolide group was 5.1 and 4.3 days for the levofloxacin group (P=0.43). The mean length of hospital stay for the macrolide group was 12.7 and 8.9 days for the levofloxacin group (P=0.10). Secondary: Not reported
Rechtweg et al.[85] (2004) Clarithromycin 500 mg BID for 14 days vs amoxicillin-clavulanate 500 mg TID for 14 days (A-C)	RCT, SB Patients with uncomplicated acute rhinosinusitis	N=22 4 weeks	Primary: Results of five surveys completed by the patients Secondary: Not reported	Primary: The allergy outcomes survey failed to demonstrate a significant improvement from baseline in any patient in either group (P>0.48). At day 28, the rhinoconjunctivitis quality of life questionnaire showed significant improvement in symptoms from baseline in both groups (P=0.003). The SF-36 failed to demonstrate a significant change in patients' global perception of their health at either day 14 or day 28 for all patients in both groups (P>0.25). The symptom severity survey indicated that there was a significant improvement in the clarithromycin patients at day 14 (P=0.02) and day 28 (P=0.03). The A-C patients demonstrated a significant improvement at day 28 (P=0.05), but not at day 14 (P=0.54). The visual analogue scale failed to demonstrate a significant improvement in symptoms at day 14 and day 28 in either group (P>0.30). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Gotfried et al.[86] (2005) Clarithromycin 500 mg BID for seven days vs clarithromycin ER 1,000 mg daily for five days	DB, MC, RCT Patients 40 years of age and older with a presumptive diagnosis of an acute exacerbation of chronic bronchitis	N=485 40 days	Primary: Clinical cure, bacteriologic cure, target pathogen eradication rates at test of cure visit (days 14 to 40) Secondary: Not reported	Primary: Clinical cure rates were similar between groups (84% for both groups). Bacteriologic cure rates were 89% in the regular release group and 87% in the extended-release group. The overall pathogen eradication rates were 89% in the regular release group and 88% in the extended-release group. Secondary: Not reported
Gotfried et al.[87] (2007) Clarithromycin ER 1,000mg once daily for five days vs clarithromycin IR 500 mg BID for seven days or telithromycin 800 mg once daily for five days	DB, MC, RCT Patients ≥35 years of age with a presumptive diagnosis of acute bacterial exacerbation of chronic bronchitis	N=818 8 to 40 days	Primary: Clinical bacteriological responses Secondary: Not reported	Primary: The clinical cure rate in clinically evaluable patients at the follow-up visit was 90% each for the clarithromycin ER group and the comparator group (95% CI, -4.4 to 4.3). No significant between-group differences were observed in clinically evaluable patients based on resolution or resolution/improvement at the follow-up visit of the most common pretreatment signs/symptoms. The overall target pathogen eradication rate was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –6.5 to 3.6). The bacteriological cure rate in clinically and bacteriologically evaluable patients was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –7.3 to 3.9). The study drugs were well tolerated, with 1.9% of clarithromycin ER-treated patients and 1.5% of comparator-treated patients prematurely discontinuing treatment due to a drug-related adverse event(s). The overall incidence of drug-related adverse events was 18% in the clarithromycin ER group and 24% in the comparator group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common drug-related adverse events (>2% of patients) or those with a statistically significant difference in incidence between groups were: abdominal pain (0.2 and 1.7% in the clarithromycin ER and comparator groups, respectively; P=0.037), diarrhea (2.4 and 4.7%, respectively; P=NS), nausea (2.7 and 4.4%, respectively; P=NS), and abnormal taste (2.4 and 4.7%, respectively; P=NS). Clarithromycin ER-treated patients reported fewer episodes of abdominal pain than did patients treated with a comparator agent (0.2 vs 1.7%, respectively; P=0.037). Secondary: Not reported
Lee et al.[88] (2008) Clarithromycin 15 mg/kg/day BID vs erythromycin 30-50 mg/kg/day QID	RCT Children <15 years of age with community-acquired pneumonia	N=97 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: All children with mycoplasma or chlamydia infections were cured clinically at the end of the study period. Delayed defervescence was observed in 18% of clarithromycin-treated children and in 20% of erythromycin-treated children (P>0.05). Secondary: Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 6% of children receiving clarithromycin and in 22% receiving erythromycin (P=0.039).
Esposito et al.[89] (1998) Erythromycin ethylsuccinate 15 mg/kg TID for 10 days vs cefaclor 25 mg/kg BID for 10 days	RCT Patients 2 to 12 years of age with acute pharyngotonsillitis	N=245 30 days	Primary: Clinical outcomes and bacteriologic outcomes Secondary: Not reported	Primary: On day 10, clinical cure and microbiologic eradication was observed in 91.9% of patients in the cefaclor group, 90.5% in the amoxicillin-clavulanate group, and 76.8% in the erythromycin group. At day 30, bacteriologic recurrence was observed in five patients in the cefaclor group, three in the amoxicillin-clavulanate group, and four in the erythromycin group. The clinical and bacteriologic cure rates were significantly higher in the cefaclor and amoxicillin-clavulanate groups compared to the erythromycin group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 15 mg/kg TID for 10 days				Secondary: Not reported
Macfarlane et al.[90] (1983) Erythromycin lactobionate 300 mg IV every 6 hours for 48 hours, followed by erythromycin stearate 500 mg orally QID for seven days vs ampicillin 500 mg IV every 6 hours for 48 hours, followed by amoxicillin 500 mg orally QID for seven days	DB, RCT Patients <80 years of age with primary pneumonia, including Legionnaires' disease	N=122 9 days	Primary: Clinical response to therapy (categorized as uncomplicated recovery, complicated recovery, or fatality) Secondary: Not reported	Primary: Clinical response to therapy in all categories was similar between the groups. Secondary: Not reported
Rodriguez et al.[91] (1985) Erythromycin-sulfisoxazole vs amoxicillin	CS, RCT Patients with acute otitis media	N=145 28 days	Primary: Cure rates Secondary: Cure rates based on organism, occurrence of middle ear effusions	Primary: Cure rates at 10 to 14 days for infections due to all organisms was 83% in the amoxicillin group and 89% in the erythromycin-sulfisoxazole group. Secondary: Cure rates in patients infected with *Haemophilus influenzae* were 84% in the amoxicillin group and 83% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with *Streptococcus pneumoniae* were 82%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the amoxicillin group and 98% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with ampicillin-resistant *Haemophilus* were 100% in the amoxicillin group (1/1) and 88% in the erythromycin-sulfisoxazole group (7/8), and one patient had persistent otitis media at day 10. By day 10 to 14, 38% of patients in the amoxicillin group had a middle ear effusion compared to 48% in the erythromycin-sulfisoxazole group. By day 28, 10% of patients in the amoxicillin group had a middle ear effusion compared to 16% in the erythromycin-sulfisoxazole group.
Van Rensburg et al.[92] (2005) Telithromycin 800 mg daily for seven days	OL Patients ≥13 years of age with community-acquired pneumonia	N=831 24 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: Clinical cure and bacteriologic eradication were seen in 15 of 16 patients infected with erythromycin-resistant *Streptococcus pneumonia* and/or penicillin- resistant *Streptococcus pneumonia*. The overall clinical cure rate was 89.3% and bacteriologic eradication was observed in 87.6% of patients. Secondary: Not reported
van Rensburg et al.[93] (2005) Telithromycin 800 mg daily for 5 to 10 days	MA Patients ≥18 years of age with community-acquired pneumonia	N=327 (9 trials) 24 to 28 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: The clinical cure rate with telithromycin was 91.2%. Thirty-five patients had infections caused by strains resistant to erythromycin and of these, clinical cure was established in 88.6%. Clinical failure was recorded in 4 patients with penicillin- and/or erythromycin-resistant pneumococci. Thirteen patients had penicillin- and/or erythromycin- resistant pneumococcal bacteremia. Clinical cure was established in 84.6% of resistant isolates compared to 90.2% of all pneumococcal bacteremia. The overall rate of satisfactory bacteriologic outcomes was 90.4%. In patients infected with isolates demonstrating reduced susceptibility to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				penicillin and/or erythromycin, eradication was achieved in 93.4%. Secondary: Not reported
Aubier et al.[94] (2002) Telithromycin 800 mg daily for five days vs amoxicillin-clavulanate 500 mg TID for 10 days	DB, PG, RCT Patients ≥18 years of age with an acute exacerbation of chronic bronchitis	N=325 31 to 36 days	Primary: Clinical cure rate at the test of cure visit (days 17 to 21) Secondary: Clinical cure rate at the late post-therapy visit (days 31 to 36), bacteriologic outcomes at the test of cure visit (days 17 to 21) and late post-therapy visit (days 31 to 36)	Primary: There was no significant difference in clinical cure rates between groups at the test of cure visit (86.1% for telithromycin and 82.1% for the amoxicillin-clavulanate group). Secondary: There was no significant difference in clinical cure rates at the late post-therapy visit between groups (78.1% for telithromycin and 75.0% for amoxicillin-clavulanate). Bacteriologic outcome was judged as satisfactory in 69.2% of patients in the telithromycin group and 70.0% of patients in the amoxicillin-clavulanate group.
Desrosiers et al.[95] (2008) Telithromycin 800 mg once daily for five days vs amoxicillin-clavulanate 875-125 mg BID for 10 days	MC, OL Patients ≥18 years old with clinical and radiological diagnosis of acute bacterial sinusitis	N=298 Up to 49 days	Primary: Clinical success, adverse events, and quality of life Secondary: Not reported	Primary: The PP clinical success rate measured at the test-of-cure visit was 88.6% with telithromycin compared to 88.8% in the amoxicillin-clavulanate treatment group (95% CI, -8.9 to 8.5). At the follow-up visit (days 41 to 49), 84.6% of patients in the telithromycin group achieved clinical success, compared to 84.8% of those in the amoxicillin–clavulanate group. Median times to reduction of total symptom scores were shorter for telithromycin vs amoxicillin–clavulanate (seven days vs eight days [75% reduction] and four days vs five days [50% reduction] with the difference being statistically significant for the 50% reduction (P=0.044). Treatment-emergent adverse events occurred in 20.7% of telithromycin-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients vs 31.8% of amoxicillin-clavulanate-treated patients (P=0.034). In the baseline SF-36 health questionnaire, 75.5% of patients (209/278) described themselves as feeling much or somewhat worse than a week earlier (telithromycin, 74.2% and amoxicillin–clavulanate, 76.6%). Secondary: Not reported
Siempos et al.[96] (2007) Quinolones vs amoxicillin-clavulanate vs macrolides	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37; 95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones. Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Miscellaneous Infections				
Dunne et al.[97] (2000) Azithromycin 250 mg daily vs azithromycin 600 mg daily vs clarithromycin 500 mg BID	DB, DD, MC, RCT Patients ≥13 years of age with a positive blood culture for *Mycobacterium avium* complex within the previous 2 months, infected with the human immunodeficiency virus and expected to survive for at least 2 months, and who had not received therapy for *Mycobacterium avium* complex since the positive blood culture	N=239 24 weeks of treatment with follow-up every 3 months	Primary: Sterilization (two consecutive negative blood cultures for *Mycobacterium avium* complex at week 24) Secondary: Time to sterilization, change from baseline in level of mycobacteremia, durability of sterilization, mortality, clinical response judged by the investigator, change in quality of life, and patient tolerance for each regimen	Primary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in the primary endpoint. Secondary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in any secondary endpoint. This study did not enroll the target of 200 participants; therefore, the power of the study to conclude equivalence between the two arms was only 61%.
Peirce et al.[98] (1996) Clarithromycin 500 mg BID vs	DB, MC, PC, RCT Patients >12 years of age with human immunodeficiency virus infection	N=682 10 months	Primary: Time from randomization to the detection of disseminated infection with *Mycobacterium avium* complex as	Primary: *Mycobacterium avium* complex infection developed in 19 of the 333 patients (6%) in the clarithromycin group and in 53 of the 334 patients (16%) in the placebo group (P<0.001). Secondary: During the follow-up period of 10 months, 32% of patients in the clarithromycin group died and 41% in the placebo group died (P=0.026).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			evidenced by a positive blood culture or positive culture at another usually sterile site Secondary: Effect of clarithromycin on survival	
Benson et al.[99] (2000) Clarithromycin 500 mg BID vs rifabutin 450 mg once daily vs combination therapy at the same doses	DB, MC, PC, RCT Patients 12 years of age and older with human immunodeficiency virus infection and no signs or symptoms of *Mycobacterium avium* complex disease	N=1,216 ~595 days	Primary: Development of *Mycobacterium avium* complex disease as evidenced by a positive blood culture or positive culture at another usually sterile site Secondary: Death, treatment-limiting adverse effects	Primary: Of those patients who developed *Mycobacterium avium* complex disease, 9% were in the clarithromycin group, 15% were in the rifabutin group, and 7% were in the combination group. Patients who received rifabutin were more likely to develop *Mycobacterium avium* complex compared to patients in the clarithromycin group (P=0.005) or the combination group (P=0.0003). There was no significant difference in the time to development of *Mycobacterium avium* complex disease for clarithromycin compared to combination therapy (P=0.36). Secondary: There were no differences between groups in survival rates (P>0.28). Patients in the combination therapy group were more likely to discontinue treatment compared to patients in the clarithromycin group and the rifabutin group (P<0.0001). There was no significant difference between the rifabutin and clarithromycin group (P=0.29).
Stenberg et al.[100] (1991) Erythromycin ethylsuccinate 200 mg divided into two doses for 10	RCT, SB Neonates and adults with chlamydial conjunctivitis	N=55 1 month posttreatment	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: All patients in the neonate and adult groups were cured except for one in the neonatal group and three in the adult group. There was no significant difference in the clinical cure rate between erythromycin and roxithromycin. Ten patients in the erythromycin group were still culture-positive at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days (neonates) or erythromycin stearate 1,000 mg divided into two doses for 10 days (adults) vs roxithromycin 50 mg divided into 2 doses for 10 days (neonates) or 300 mg divided into 2 doses for 10 days (adults)				follow-up compared to six patients in the roxithromycin group. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, ER=extended release, IM=intramuscular, IR=immediate release, IV=intravenous, QID=four times daily, TID=three times daily
Study abbreviations: CI=confidence interval, COPD=chronic pulmonary respiratory disease, CS=comparative study, DB=double blind, DD=double dummy, *H pylori=Helicobacter pylori*, HR=hazard ratio, MA=meta-analysis, MC=multi-center, NI=non-inferiority, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RTI=respiratory tract illness, SB=single blind, SC=single center, SF-36=short form-36, SGRQ=St. George's Respiratory Questionnaire

Additional Evidence

Dose Simplification:
Several studies have assessed the effects of dosing regimens on compliance with antibiotics. Adair et al. compared azithromycin as a single dose to erythromycin administered every six hours in the treatment of *Chlamydia* infections in pregnant females.[63] Significantly more patients were compliant with the azithromycin regimen compared to the erythromycin regimen; however, efficacy was similar among the treatment groups. Significantly fewer gastrointestinal side effects were noted in the azithromycin group compared to the erythromycin group. Dey et al. compared azithromycin as a single dose to azithromycin once daily for five days in the treatment of uncomplicated skin and skin structure infections. No significant difference was found between groups in frequency of clinical cure, clinical response, or adverse events.[38]

Lebel et al. compared clarithromycin administered twice daily to erythromycin administered three times daily in children with pertussis.[101] Efficacy was similar among the treatment groups; however, patients in the clarithromycin group experienced significantly fewer adverse events compared to patients in the erythromycin group (45 and 62%, respectively; P=0.035). Compliance was significantly higher in the clarithromycin group compared to the erythromycin group (98.5 vs 88.6%, respectively; P<0.001).[101]

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits:
Milstone et al. analyzed outcomes in patients with an acute exacerbation of chronic bronchitis receiving treatment with azithromycin for three days or usual care for five to 14 days.[102] The usual care group included quinolones, amoxicillin-clavulanate, clarithromycin, or β-lactams. Patients completed two quality-of-life questionnaires. Both groups recorded similar improvements in signs and symptoms of infection, absenteeism, use of concomitant respiratory medications, health care resource utilization, compliance, and treatment satisfaction.

Burgess et al. analyzed outcomes in patients with pneumonia who were initially treated with erythromycin, clarithromycin, azithromycin, and/or a non-pseudomonal third generation cephalosporin.[103] Results indicate no significant difference in patients who did or did not receive a macrolide in terms of comorbid illness, length of hospital stay, length of intravenous antibiotic therapy or mortality.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Macrolides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azithromycin	injection, powder for suspension, suspension, tablet	Zithromax®*	$$-$$$	$
Clarithromycin	extended-release tablet, suspension, tablet	N/A	N/A	$$$
Erythromycin base	delayed-release capsule, delayed-release tablet, tablet	N/A	N/A	$$$$$
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®*, E.E.S. 400®*, EryPed 200®*, EryPed 400®*	$$$$$	$$$$$
Erythromycin lactobionate	injection	Erythrocin Lactobionate®*	$$$$$	$$$$$
Erythromycin stearate	tablet	Erythrocin Stearate®	$$$$$	N/A
Fidaxomicin	suspension, tablet	Dificid®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as a variety of miscellaneous infections.[1-9] Several of the macrolides are available in a generic formulation, with the exception of erythromycin stearate and fidaxomicin.

There are many guidelines that define the appropriate place in therapy for the macrolides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the macrolide. The macrolides are recommended as specific therapy for the treatment of susceptible pathogens causing encephalitis, skin and soft-tissue infections, infectious diarrhea, *Helicobacter pylori* infections, *Clostridium difficile,* sexually transmitted diseases, pertussis, community-acquired pneumonia, as well as prophylaxis and treatment of disseminated *Mycobacterium avium* disease in patients with human immunodeficiency virus infection.[12-25,32-36] They are recommended as an alternative treatment option for otitis media, pharyngitis, sinusitis, infectious exacerbations of chronic obstructive pulmonary disease, as well as for the prophylaxis of rheumatic fever.[14,26-31] Clinical trials have demonstrated comparable efficacy among the macrolides for the treatment of genital ulcers, upper/lower respiratory tract infections, and disseminated *Mycobacterium avium* disease.[58,59,63,64,75-83,88,97] The macrolides have also been shown to be comparable in efficacy to antibacterial agents in other classes.[39,40,55-57,60-62,69-74,84,85,89-91,94-96,99,100]

Fidaxomicin (Dificid®) is a locally-acting macrolide antibiotic indicated for the treatment of *C. difficile*-associated diarrhea (CDAD).[1,2,9] According to the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) 2021 Focused Update Guidelines on Management of *Clostridium difficile* Infection in Adults, fidaxomicin is suggested rather than a standard course of vancomycin for patients with an initial or recurrent *Clostridium difficile* infection.[18]

There is insufficient evidence to support that one brand macrolide is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Fidaxomicin should be available for the treatment of *C. difficile*-associated diarrhea through the medical justification portion of the prior authorization process.

Therefore, all brand macrolides within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand macrolide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Penicillins
AHFS Class 081216
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I. Overview

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-7] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins.[8] Penicillins inhibit the synthesis of the bacterial peptidoglycan cell wall by binding to specific penicillin-binding proteins located inside the bacterial cell wall.

The natural penicillins (penicillin G and penicillin V) are active against many gram-positive and gram-negative cocci, gram-positive rods, and most anaerobes.[9] However, they are readily hydrolyzed by the enzyme penicillinase and are ineffective against most strains of *Staphylococcus aureus*. Penicillinase-resistant penicillins (dicloxacillin, nafcillin, and oxacillin) have a narrower spectrum of activity than the natural penicillins. They are primarily active against penicillinase-producing strains of gram-positive cocci, particularly *Staphylococcus* species. Aminopenicillins (amoxicillin and ampicillin) have an extended spectrum of activity compared to the natural penicillins and penicillinase-resistant penicillins.[9] They are active against gram-negative bacilli, but not against penicillinase-producing staphylococci. They are also inhibitors of β-lactamases of gram-negative bacilli. Piperacillin (ureidopenicillin) is active against *Pseudomonas aeroginosa*.[8] Its spectrum of activity is similar to the aminopenicillins; however, it has additional activity against gram-negative aerobic rods. It is susceptible to inactivation by β-lactamases.

Bacteria have developed several mechanisms to counter the effects of penicillins. The most significant is the production of β-lactamases, which are enzymes that hydrolytically disrupt the β-lactam ring of the penicillin, rendering the penicillin ineffective. Another mechanism of resistance includes alteration of the penicillin-binding proteins within the bacteria so that their affinity for penicillins is decreased. Due to increased bacterial resistance, penicillins are combined with β-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam.[9] The β-lactamase inhibitors have a high, irreversible binding affinity for the β-lactamase enzyme and prevent hydrolysis of the penicillin β-lactam ring. They also bind to the penicillin-binding proteins of the bacteria, increasing the effectiveness of penicillin. However, they possess minimal antimicrobial activity by themselves; therefore, they are not used as monotherapy.[9]

The penicillins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the penicillins are available in a generic formulation, with the exception of penicillin G benzathine (with or without penicillin G procaine). This class was last reviewed in May 2021.

Table 1. Penicillins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Amoxicillin	capsule, chewable tablet, suspension, tablet	N/A	amoxicillin
Ampicillin	capsule, injection	N/A	ampicillin
Dicloxacillin	capsule	N/A	dicloxacillin
Nafcillin	injection	N/A	nafcillin
Oxacillin	injection	N/A	oxacillin
Penicillin G benzathine	injection	Bicillin L-A®	none
Penicillin G potassium	injection	Pfizerpen®*	penicillin G potassium
Penicillin G procaine	injection	N/A	penicillin G procaine
Penicillin G sodium	injection	N/A	penicillin G sodium
Penicillin V potassium	solution, tablet	N/A	penicillin V potassium
Combination Products			

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*	amoxicillin and clavulanate
Ampicillin and sulbactam	injection	Unasyn®*	ampicillin and sulbactam
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	none
Piperacillin and tazobactam	injection	Zosyn®*	piperacillin and tazobactam

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

The penicillins have been shown to be active against the strains of microorganisms indicated in Tables 2 and 3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the penicillins that are noted in Tables 5 and 6. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Single Entity Penicillins[1-7]

Organism	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Gram-Positive Aerobes							
Bacillus anthracis						✔ §	
Corynebacterium diphtheriae						✔ §	
Enterococcus faecalis	✔ *						
Enterococcus species		✔					
Erysipelothrix insidiosa						✔ §	
Listeria monocytogenes		✔				✔ §	
Staphylococcus aureus		✔					
Staphylococcus species	✔ *	✔	✔	✔	✔	✔ †§	✔
Streptococcus pneumoniae	✔ *	✔					
Streptococcus species	✔ *	✔					✔
Gram-Negative Aerobes							
Alcaligenes faecalis						✔ §	
Enterobacter species						✔ §	
Escherichia coli	✔ *	✔				✔ §	
Haemophilus influenzae	✔ *	✔					
Helicobacter pylori	✔ *						
Neisseria gonorrhoeae		✔				✔ §	
Neisseria meningitidis		✔					
Pasteurella multocida						✔ §	
Proteus mirabilis	✔ *	✔				✔ §	
Salmonella species		✔				✔ §	
Salmonella typhosa		✔					
Shigella species		✔				✔ §	
Spirillum minus						✔ §	
Streptobacillus moniliformis						✔ §	
Anaerobes							
Actinomyces species						✔ §	
Clostridium species						✔ §	
Fusobacterium species						✔ §	✔
Treponema pallidum						✔ §	

*Immediate-release formulation.
†Intramuscular formulation.
§Intravenous formulation.

Table 3. Microorganisms Susceptible to the Combination Penicillins[1-7]

Organism	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Piperacillin and Tazobactam
Gram-Positive Aerobes			
Staphylococcus aureus		✔	✔
Staphylococcus epidermidis			
Streptococcus pneumoniae	✔ ‡		
Gram-Negative Aerobes			
Acinetobacter baumannii			✔
Acinetobacter calcoaceticus		✔	
Citrobacter species			
Enterobacter cloacae			
Enterobacter species	✔ *	✔	
Escherichia coli	✔ *	✔	✔
Haemophilus influenzae	✔ *‡		✔
Haemophilus parainfluenza	✔ ‡		
Klebsiella pneumoniae	✔ ‡	✔	✔
Klebsiella species	✔ *	✔	
Moraxella catarrhalis	✔ *‡		
Proteus mirabilis		✔	
Pseudomonas aeruginosa			✔
Pseudomonas species			
Serratia marcescens			
Anaerobes			
Bacteroides fragilis		✔	✔
Bacteroides species		✔	
Prevotella melaninogenicus			

*Immediate-release formulation.
‡Extended-release formulation.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the penicillins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Penicillins

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[10]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in β-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	○ Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: ○ Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. ○ Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: ○ Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: ○ *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. ○ *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ ○ *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. ○ *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. ○ *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. ○ *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): ○ Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). ○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[11]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered.

Clinical Guideline	Recommendation(s)
	• Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[12]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable;

Clinical Guideline	Recommendation(s)
	vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve

Clinical Guideline	Recommendation(s)
	endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[13]** **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or

Clinical Guideline	Recommendation(s)
	clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[14]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: Sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.

Clinical Guideline	Recommendation(s)
Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[15]	Empiric Therapy • Empiric therapy should be used when infection is suspected but cultures are not yet available. • Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended. • Choice of anti-pseudomonal β-lactam should be based on local resistance patterns. • In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 μg/mL • For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin • Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens Pathogen Specific Therapy • Methicillin-susceptible *S. aureus* o Recommended treatment includes nafcillin or oxacillin o In patients who cannot receive β-lactams, vancomycin is recommended • Methicillin-resistant *S. aureus* o Recommended treatment includes vancomycin • *P. acnes* o Recommended treatment includes penicillin G • *Pseudomonas* species o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone • Gram-negative bacilli o Recommended treatment includes ceftriaxone or cefotaxime • Extended-spectrum β-lactamase–producing gram-negative bacilli o Recommended treatment includes meropenem • *Acinetobacter* species o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B • *Candida* species o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine • *Aspergillus* or *Exserohilum* o Recommended treatment includes voriconazole • In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain o Use of rifampin as part of combination therapy is recommended Duration of Therapy • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms o Duration is recommended to be 10 days • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features o Duration is recommended to be 10 to 14 days • Infections caused by *S. aureus* or gram-negative bacilli o Duration is recommended to be 10 to 14 days • Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy • It is recommended that therapy be continued for 10 to 14 days after the last

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	positive culture
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[16]	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and

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	animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. <u>Necrotizing fasciitis</u> • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. <u>Pyomyositis</u> • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.

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	Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders

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	• Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. <u>Bubonic plague</u> • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. <u>Tularemia</u> • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)**[17]	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended.
	• Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost.
	• A course of antibiotic therapy of one to two weeks is usually adequate for most mild and moderate infections.
	  o For more serious skin and soft tissue infections, three weeks is usually sufficient.
	  o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed.
	• Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding.
	• For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity.
	• For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection.
	• For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.

American College of Gastroenterology: **Clinical Guideline on the Treatment of *Helicobacter pylori* Infection (2017)**[18]	<u>Evidence-based first-line treatment strategies for providers in North America</u> • Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen. • Clarithromycin triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason.

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	• Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin.
	• Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option.
	• Sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days is a suggested first-line treatment option.
	• Hybrid therapy consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for seven days is a suggested first-line treatment option.
	• Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10 to 14 days is a suggested first-line treatment option.
	• Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, fluoroquinolone, and nitroimidazole for five to seven days is a suggested first-line treatment option.
	
	<u>When first-line therapy fails, options for salvage therapy</u>
	• In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline).
	• Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.
	• Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.
	• The following regimens can be considered for use as salvage treatment:
	  ○ Bismuth quadruple therapy for 14 days is a recommended salvage regimen.
	  ○ Levofloxacin triple regimen for 14 days is a recommended salvage regimen.
	  ○ Concomitant therapy for 10 to 14 days is a suggested salvage regimen.
	  ○ Clarithromycin triple therapy should be avoided as a salvage regimen.
	  ○ Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen.
	  ○ High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.

Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)[19]**	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori.* • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of**	<u>Treatment</u> • It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to

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***Helicobacter pylori* Infection–The Maastricht VI/ Florence Consensus Report (2022)[20]**	antibiotic stewardship. However, the generalized use of such a susceptibility-guided strategy in routine clinical practice remains to be established. • If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered. • The treatment duration of bismuth quadruple therapy should be 14 days, unless 10-days effective therapies are available. • In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies. • The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days. • In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally. • The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days. • The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies. • Potassium-Competitive Acid Blockers (P-CAB; vonoprazan where available) – antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections. • Empiric second line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimize treatment success. • After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option. • After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment. • After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high- dose dual therapy might also be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered. • After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual

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	therapy, a rifabutin- containing regimen or a combination of bismuth with different antibiotics should be used. • In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options. Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth.
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[21]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons.

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	• Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated

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	pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body

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	weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.
	
	Pediculosis pubis (pubic lice infestation)
	• Recommended regimens:
	  ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes.
	  ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes.
	• Alternative regimens:
	  ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off.
	  ○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days.
	• Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide.
	
	Scabies
	• The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation.
	• Scabies among adults frequently is sexually acquired, although scabies among children usually is not.
	• Recommended regimens:
	  ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours.
	  ○ Ivermectin 200 µg/kg orally and repeated in two weeks.
	• Oral ivermectin has limited ovicidal activity; a second dose is required for eradication.
	• Alternative regimens:
	  ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
	• Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed.
	• Infants and children aged <10 years should not be treated with lindane.
	• Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost.
	• Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined.
	• Permethrin is the preferred treatment for pregnant women.
	• Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies.
	• Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases.

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	Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose. • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. Uncomplicated vulvovaginal candidiasis • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one

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	day. ○ Tioconazole 6.5% ointment 5 g single intravaginal application. ○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.

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	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
	
	Cervical warts
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	Intra-anal warts
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International**	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis

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Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)[22] Reviewed and deemed current as of 07/2013	do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute pyelonephritis</u> • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days. o Trimethoprim 100 mg twice daily for three days. o Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days.

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(2008)[23] Reaffirmed 2016	○ Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days. ○ Fosfomycin tromethamine, 3 g dose (powder) single dose.
American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in Women: Guideline (2022)[24]**	Evaluation • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. • Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy.
American Academy of Pediatrics/	Observation option • Observation without use of antibacterial agents in a child with unilateral acute otitis

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American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[25] Reaffirmed 2019	media is an option for selected children based on age, illness severity, and assurance of follow-up after joint decision-making with the parent(s)/caregiver. The "observation option" for acute otitis media refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children six months and older without severe symptoms at presentation. <u>Antibacterial options - temperature <39°C without severe otalgia</u> • For the initial treatment of otitis media, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. <u>Antibacterial options - temperature ≥39°C and/or severe otalgia</u> • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for three days.
American Academy of Pediatrics: **Red Book – Group A streptococcal infections (2021)**[26]	• Penicillin V is the drug of choice for Group A *Streptococci* pharyngitis. Prompt administration of penicillin shortens the clinical course, decreases risk of transmission and suppurative sequelae, and prevents acute rheumatic fever, even when administered up to nine days after illness onset. All patients with acute rheumatic fever should receive a complete course of penicillin or another appropriate antimicrobial agent for Group A *Streptococci* pharyngitis, even if group A streptococci are not recovered from the throat. • Amoxicillin, orally as a single daily dose (50 mg/kg; maximum, 1000 to 1200 mg) for 10 days, is as effective as penicillin V or amoxicillin administered orally multiple times per day for 10 days and is a more palatable suspension than penicillin V. This regimen is endorsed by the American Heart Association and the Infectious Disease Society of America in its guidelines for the treatment of Group A *Streptococci* pharyngitis and the prevention of acute rheumatic fever. Adherence is particularly important for once-daily dosing regimens. • The dose of oral penicillin V is 400 000 U (250 mg), 2 to 3 times per day, for 10 days for children weighing <27 kg and 800 000 U (500 mg), 2 to 3 times per day, for those weighing ≥27 kg, including adolescents and adults. To prevent acute rheumatic fever, oral penicillin or amoxicillin should be taken for 10 full days, regardless of promptness of clinical recovery. Treatment failures occur more often with oral penicillin than with intramuscular penicillin G benzathine because of inadequate adherence. Notably, short-course treatment (<10 days) for Group A *Streptococci* pharyngitis, particularly with penicillin V, is associated with inferior bacteriologic eradication rates. • Intramuscular penicillin G benzathine is appropriate therapy, ensuring adequate blood concentrations and avoiding adherence issues, but administration may be painful. Discomfort is decreased if the preparation of penicillin G benzathine is brought to room temperature before intramuscular injection. Mixtures containing shorter-acting penicillins (e.g., penicillin G procaine) in addition to penicillin G benzathine are not more effective than penicillin G benzathine alone but are less painful. Although supporting data are limited, the combination of 900 000 U (562.5 mg) of penicillin G benzathine and 300 000 U (187.5 mg) of penicillin G procaine is satisfactory for most children; however, the efficacy of this combination for heavier patients has not been documented.

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	• For patients who have a history of nonanaphylactic allergy to penicillin, a 10-day course of a narrow-spectrum (first-generation) oral cephalosporin (e.g., cephalexin) is indicated. Patients with immediate (anaphylactic) or type I hypersensitivity to penicillin should receive oral clindamycin (20 mg/kg per day in three divided doses; maximum, 900 mg/day for 10 days) rather than a cephalosporin. • An oral macrolide (e.g., erythromycin, azithromycin, or clarithromycin) also is acceptable for penicillin-allergic patients. This should not be used in patients who can take a beta-lactam agent. Therapy for 10 days is indicated, except for azithromycin, which is given for five days. Group A *Streptococci* strains resistant to macrolides have been highly prevalent in some countries and have resulted in treatment failures. In some areas in the United States, macrolide resistance rates of more than 20% have been reported. Testing for macrolide resistance may help to decide the best antimicrobial agent for specific penicillin-allergic patients. • Tetracyclines, sulfonamides, and fluoroquinolones should not be used for treating Group A *Streptococci* pharyngitis. • Children with recurrent Group A *Streptococci* pharyngitis shortly after a full course of a recommended oral agent can be retreated with the same antimicrobial agent (if it is a beta-lactam), an alternative beta-lactam oral drug (such as cephalexin or amoxicillin-clavulanate), or an intramuscular dose of penicillin G benzathine. Susceptibility testing should be performed when considering a macrolide or clindamycin.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[27]	<u>Symptomatic relief of viral rhinosinusitis</u> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. <u>Symptomatic relief of acute bacterial rhinosinusitis</u> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. <u>Initial management of acute bacterial rhinosinusitis</u> • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after

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	acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[28]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[29]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are

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	attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)**[30]	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole. • For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[31]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older**	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.

Clinical Guideline	Recommendation(s)
Than 3 Months of Age (2011)[32] Reviewed and deemed current as of 04/2013	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-Acquired Pneumonia (2019)[33]**	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) <u>Regimens recommended for empiric treatment of CAP in adults without risk factors for</u>

Clinical Guideline	Recommendation(s)

	methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting:
	• In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended:
	  o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or
	  o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily).
	• In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended.
	• Corticosteroid use is not recommended.
	• It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis.
	
	Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting:
	• It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present.
	• Empiric treatment options for MRSA include vancomycin or linezolid.
	• Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.

American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)**[34]	Empiric Therapy
	• It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities
	• In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended
	• Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known
	  o Standard therapy for MRSA coverage includes vancomycin or linezolid
	• Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant
	  o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem
	  o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage
	• One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available
	• Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available
	
	Pathogen-Specific Therapy
	• MRSA
	  o Vancomycin or linezolid are recommended treatments
	• *P. aeruginosa*
	  o It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy

Clinical Guideline	Recommendation(s)
	○ In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli ○ Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species ○ Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens ○ If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin <u>Duration of therapy</u> • Seven day course of treatment
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children (2010)[35]**	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups.

Clinical Guideline	Recommendation(s)
	• Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health care-associated infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology: **Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease (2020)**[36]	• Prophylactic antibiotic therapy is only recommended for adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal risk or low risk. If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high-risk only if it meets the following three criteria: the tick bite was from (a) an identified *Ixodes* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours. • For high-risk *Ixodes* spp. bites in all age groups, administer a single dose of oral doxycycline within 72 hours of tick removal over observation. • Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children. • For patients with erythema migrans, use oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil. For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin. • Patients with erythema migrans should be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses. If azithromycin is used, the indicated duration is five to 10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States.
Infectious Diseases Society of America: **Guideline on**	• Treat babesiosis with the combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine. Atovaquone plus azithromycin is the preferred antimicrobial combination for patients experiencing babesiosis, while

Clinical Guideline	Recommendation(s)
Diagnosis and Management of Babesiosis (2020)[37]	clindamycin plus quinine is the alternative choice. The duration of treatment is seven to 10 days in immunocompetent patients but often is extended when the patient is immunocompromised.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)[38]**	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for

Clinical Guideline	Recommendation(s)
	six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.

Clinical Guideline	Recommendation(s)
	○ Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. ○ For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess ○ Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. ○ Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus ○ Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. ○ Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. ○ Intravenous vancomycin is recommended in children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the penicillins are noted in Tables 5 and 6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Single Entity Penicillins[1-7]

Indication	Amoxi-cillin	Ampi-cillin	Dicloxa-cillin	Naf-cillin	Oxa-cillin	Penicillin G Benzathine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium
Central Nervous System Infections										
Chorea (prophylaxis)						✔				✔
Meningitis		✔ ‡§					✔	✔		
Neurosyphilis						✔	✔	✔	✔	
Dermatological Infections										
Bejel						✔			✔	
Erysipelas									✔	✔
Erysipeloid									✔	
Gas gangrene								✔		
Pinta						✔			✔	
Skin and skin-structure infections	✔ §								✔	✔
Yaws						✔			✔	
Gastrointestinal Infections										
Gastrointestinal infections		✔ ‡§								
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or one year history of a duodenal ulcer) to eradicate *Helicobacter pylori* (in combination with clarithromycin plus lansoprazole as triple therapy)	✔ §									
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or one year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected (in combination with lansoprazole delayed-release capsules as dual therapy)	✔ §									
Genitourinary Infections										
Genitourinary infections	✔ §	✔ §					✔	✔		
Gonococcal infections							✔	✔		
Gonorrhea	✔ §	✔ §								
Syphilis						✔	✔	✔	✔	
Urinary tract infections		✔ ‡								
Respiratory Infections										
Ear, nose, and throat infections	✔ §									
Diphtheria (prevention of carrier state)							✔		✔	
Diphtheria (adjunct to antitoxin and prevention of carrier state)								✔		
Otitis media										✔
Pharyngitis and/or tonsillitis									✔	✔

Indication	Amoxi-cillin	Ampi-cillin	Dicloxa-cillin	Naf-cillin	Oxa-cillin	Penicillin G Benzathine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium
Pneumonia							✔	✔	✔	
Respiratory tract infections		✔ ‡§							✔	✔
Respiratory tract infections (lower)	✔ §						✔	✔		
Respiratory tract infections (upper)						✔			✔	✔
Vincent's infection							✔	✔	✔	✔
Miscellaneous Infections										
Actinomycosis							✔	✔		
Anthrax							✔	✔	✔	
Bacteremia							✔	✔		
Botulism (adjunct to antitoxin)								✔		
Clostridial infections							✔	✔		
Empyema							✔	✔		
Endocarditis		✔ ‡					✔	✔	✔	✔
Fusospirochetosis							✔	✔		✔
Haverhill fever								✔		
Listeria infections							✔	✔		
Pasteurella infections							✔	✔		
Penicillinase-producing staphylococci			✔	✔	✔					
Pericarditis							✔	✔		
Rat-bite fever							✔	✔	✔	
Rheumatic fever (prophylaxis)						✔				✔
Scarlet fever									✔	✔
Septicemia		✔ ‡					✔	✔		
Staphylococcal infections							✔			
Streptococcal infections							✔		✔	
Tetanus (adjunct)								✔		

§Immediate-release oral formulations.
‡Injection formulation.

Table 6. FDA-Approved Indications for the Combination Penicillins[1-7]

Indication	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Dermatological Infections				
Abscesses (cutaneous)				✔
Cellulitis				✔
Diabetic foot infections				✔
Erysipelas			✔	
Skin and skin-structure infections	✔	✔	✔	✔
Genitourinary Infections				
Endometritis				✔
Gynecologic infections		✔		
Pelvic inflammatory disease				✔
Urinary tract infections	✔			
Respiratory Infections				
Otitis media	✔		✔	
Pneumonia			✔	

Indication	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Pneumonia (community-acquired)	✔			✔
Pneumonia (nosocomial)				✔
Respiratory tract infections (lower)	✔			
Respiratory tract infections (upper)			✔	
Sinusitis	✔			
Miscellaneous Infections				
Appendicitis				✔
Bone and/or joint infections				
Intra-abdominal infections		✔		
Peritonitis				✔
Scarlet fever			✔	
Septicemia				

IV. Pharmacokinetics

The pharmacokinetic parameters of the penicillins are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Penicillins[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Amoxicillin	89	20	Not reported	Renal (50 to 70)	1.0 to 1.3
Ampicillin	50	20	Not reported	Renal (34 to 92) Bile (not reported)	1.0 to 1.9
Dicloxacillin	60 to 80	88 to 98	Not reported	Renal (35 to 90) Feces (not reported)	0.6 to 0.8
Nafcillin	N/A	90	Liver (60 to 70)	Renal (31 to 38) Bile (8) Feces (not reported)	0.5 to 1.0
Oxacillin	N/A	94	Liver (75)	Renal (39 to 66)	20 to 60 minutes
Penicillin G	Oral: <30 IM: 72	65	Liver (30)	Renal (79 to 85)	20 to 50 minutes
Penicillin V	25 to 60	60 to 80	Not reported	Renal (20 to 40) Feces (32)	30 to 40 minutes
Combination Products					
Amoxicillin and clavulanate	Well absorbed	A: 18 C: 25	C: Liver	A: Renal (50 to 70) C: Renal (25 to 40)	A: 1.0 to 1.3 C: 1.0
Ampicillin and sulbactam	A: 92 (IM) S: 100 (IM)	A: 17 to 28 S: 38	Not reported	Renal (75 to 85)	A: 1.0 to 1.8 S: 1.0 to 1.3
Penicillin G benzathine and penicillin G procaine	IM: slowly	30 to 60	Liver (30)	Renal (60 to 90)	20 to 30 minutes
Piperacillin and tazobactam	IM: 71	30	Liver	P: Renal (68) T: Renal (80)	0.7 to 1.2

IM=intramuscular, N/A=not applicable

V. Drug Interactions

Major drug interactions with the penicillins are listed in Table 8.

Table 8. Major Drug Interactions with the Penicillins[2]

Generic Name(s)	Interaction	Mechanism
Penicillins	Anticoagulants	Plasma concentrations and anticoagulant effects of anticoagulants may be decreased by these agents.
Penicillins	Tetracyclines	The antimicrobial effectiveness of penicillins may be decreased by tetracyclines.
Penicillins	Methotrexate	Penicillins may increase the serum concentrations and pharmacologic effects of methotrexate. Toxicity may occur.
Amoxicillin	Venlafaxine	Concurrent use my result in an increased risk of serotonin syndrome.
Amoxicillin and clavulanate	Mycophenolate	Concurrent use of amoxicillin-clavulanic acid and mycophenolate mofetil may result in decreased mycophenolic acid plasma exposure.
Nafcillin	CYP3A4 substrates	Nafcillin is a moderate inducer of CYP3A4. Concurrent use may result in decreased concentrations.
Piperacillin	Vecuronium	Concurrent use of piperacillin and vecuronium may result in enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis.

VI. Adverse Drug Events

The most common adverse drug events reported with the penicillins are listed in Tables 9 and 10. The boxed warning for penicillin G benzathine and penicillin G benzathine-penicillin G procaine is listed in Table 11.

Table 9. Adverse Drug Events (%) Reported with the Single Entity Penicillins[1-7]

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Cardiovascular							
Chest pain	-	-	-	-	-	-	-
Cardiac arrest	-	-	-	-	-	✔	-
Myocardial infarction	-	-	-	-	-	✔	-
Myocarditis	-	-	-	-	-	✔	-
Central Nervous System							
Agitation	✔	-	-	-	-		-
Anxiety	✔	-	-	-	-	-	-
Behavioral changes	✔	-	-	-	-	-	-
Chills	-	-	-	-	-	-	-
Coma	-	-	-	-	-	✔	-
Confusion	✔	-	-	-	-	-	-
Dizziness	✔	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-
Fever	-	✔	-	-	✔	-	-
Headache	✔	-	-	-	-	-	-
Hyperactivity	✔	-	-	-	-	-	-
Hyperflexia	-	-	-	-	-	✔	-
Insomnia	✔	-	-	-	-	✔	-
Jarisch-Herxheimer reaction	-	-	-	-	-	✔	-
Myoclonus	-	-	-	-	-	-	-
Neurotoxicity	-	-	-	✔	-	-	-
Penicillin encephalopathy	-	✔	-	-	-	-	-
Seizure	✔	✔	<1	-	-	✔	<1
Dermatologic							
Acute exanthematous pustulosis	✔	-	-	-	-	-	-
Contact dermatitis	-	-	-	-	-	✔	-
Cutis laxa	-	-	-	-	-	✔	-
Diaper rash	-	-	-	-	-	-	-
Erythema	-	-	-	-	-	-	-
Erythema multiforme	✔	✔	-	-	-	-	-
Erythematous maculopapular rash	✔	-	-	-	-	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Erythroderma	-	✔	-	-	-	-	-
Exfoliative dermatitis	✔	✔	-	-	-	-	-
Facial swelling	-	-	-	-	-	-	-
Lipoatrophy	-	-	-	-	-	✔	-
Rash	-	✔	<1	-	✔	✔	-
Stevens-Johnson syndrome	✔	✔	-	-	-	-	-
Toxic epidermal necrolysis	✔	✔	-	-	-	-	-
Tissue necrosis	-	-	-	-	-	✔	-
Urticaria	✔	✔	-	-	-	✔	-
Gastrointestinal							
Abdominal distension	-	-	-	-	-	-	-
Abdominal pain	-	-	1 to 10	-	-	✔	-
Black hairy tongue	✔	✔	-	-	-	✔	✔
Clostridium difficile colitis	-	-	-	-	-	-	✔
Diarrhea	✔	✔	1 to 10	-	✔	-	>10
Enterocolitis	-	✔	-	-	-	-	-
Epigastric discomfort	-	-	-	-	-	-	✔
Flatulence	-	-	-	-	-	-	-
Gastritis	-	-	-	-	-	-	-
Glossitis	-	✔	-	-	-	-	-
Hemorrhagic colitis	✔	-	-	-	-	-	-
Indigestion	-	-	-	-	-	-	-
Loose stools	-	-	-	-	-	-	-
Mucocutaneous candidiasis	✔	-	-	-	-	-	-
Mucosal bleeding	-	-	-	-	-	-	-
Nausea	✔	✔	1 to 10	-	✔	✔	>10
Oral candidiasis	-	-	-	-	-	-	>10
Pseudomembranous colitis	✔	✔	<1	✔	-	✔	-
Sore mouth or tongue	-	✔	-	-	-	-	-
Stomatitis	-	✔	-	-	-	✔	-
Throat tightness	-	-	-	-	-	-	-
Tooth discoloration	✔	-	-	-	-	-	-
Vomiting	✔	✔	1 to 10	-	✔	✔	>10
Genitourinary							
Crystalluria	✔	-	-	-	-	-	-
Dysuria	-	-	-	-	-	-	-
Hematuria	-	-	-	-	✔	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Interstitial nephritis	-	✔	<1	✔	✔	✔	<1
Renal tubular damage	-	-	-	✔	-	✔	-
Urinary retention	-	-	-	-	-	-	-
Vaginal mycosis	-	-	-	-	-	-	-
Vaginitis	-	-	<1	-	-	-	-
Hematologic							
Agranulocytosis	✔	✔	<1	✔	✔	✔	-
Anemia	✔	✔	-	-	-	✔	-
Bone marrow depression	-	-	-	✔	-	-	-
Eosinophilia	✔	✔	<1	-	✔	✔	-
Hemolytic anemia	✔	✔	<1	-	-	✔	✔
Leukopenia	✔	✔	<1	-	✔	✔	-
Neutropenia	-	-	<1	✔	✔	✔	-
Prothrombin time increased	-	-	-	-	-	✔	-
Thrombocytopenia	✔	✔	<1	-	✔	-	-
Thrombocytopenia purpura	✔	✔	-	-	-	-	-
Thrombocytosis	-	-	-	-	-	-	-
Hepatic							
Acute cytolytic hepatitis	✔	-	-	-	-	-	-
Cholestatic jaundice	✔	-	-	-	-	✔	-
Hepatic cholestasis	✔	-	-	-	-	-	-
Hepatic dysfunction	-	-	-	-	-	-	-
Hepatitis	-	-	-	-	-	-	-
Hepatotoxicity	-	-	<1	-	✔	✔	-
Laboratory Test Abnormalities							
Alkaline phosphatase increased	-	-	-	-	-	-	-
Liver function tests increased	✔	✔	-	-	✔	-	-
Other							
Anaphylaxis	✔	✔	-	✔	-	✔	✔
Angioedema	-	-	-	-	-	-	-
Candidiasis	-	-	-	-	-	-	-
Edema	-	-	-	-	-	-	-
Epistaxis	-	-	-	-	-	-	-
Hypersensitivity reaction	-	✔	<1	✔	-	✔	✔
Hypersensitivity vasculitis	✔	-	-	-	-	-	-
Injection site reaction	-	-	-	✔	-	-	-
Laryngeal stridor	-	✔	-	-	-	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Malaise	-	-	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	-
Pain at injection site	-	-	-	✔	-	-	-
Pruritus	-	-	-	-	-	-	-
Serum sickness-like reaction	✔	✔	<1	✔	✔	✔	-
Substernal pain	-	-	-	-	-	-	-
Thrombophlebitis	-	-	-	✔	-	✔	-
Vasculitis	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Combination Penicillins[1-7]

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Cardiovascular				
Arrhythmia	-	-	-	≤1
Atrial fibrillation	-	-	-	≤1
Bradycardia	-	-	-	≤1
Cardiac arrest	-	-	✔	≤1
Cardiac failure	-	-	-	≤1
Chest pain	-	<1	-	≤1
Circulatory failure	-	-	-	≤1
Conduction disturbances	-	-	✔	-
Cyanosis	-	-	✔	-
Edema	-	-	-	≤1
Hypertension	-	-	-	2
Hypotension	-	-	✔	≤1
Myocardial depression	-	-	✔	-
Myocardial infarction	-	-	-	≤1
Myocarditis	-	-	-	-
Pallor	-	-	✔	-
Palpitations	-	-	✔	-
Syncope	-	-	✔	≤1
Tachycardia	-	-	✔	≤1
Vasodilation	-	-	✔	-
Vasospasm	-	-	✔	-
Vasovagal reaction	-	-	✔	-

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Ventricular fibrillation	-	-	-	≤1
Central Nervous System				
Agitation	✔	-	-	2
Anxiety	✔	-	✔	≤1
Cerebral vascular accident	-	-	✔	-
Central nervous system stimulation	-	-	✔	-
Coma	-	-	✔	-
Confusion	✔	-	✔	≤1
Depression	-	-	-	≤1
Dizziness	✔	-	✔	≤1
Drowsiness	-	-	✔	-
Euphoria	-	-	✔	-
Fatigue	-	✔	✔	-
Fever	-	-	-	2 to 5
Hallucination	-	-	-	≤1
Headache	✔	✔	✔	8
Hyperreflexia	-	-	-	-
Insomnia	✔	✔	-	7
Jarisch-Herxheimer reaction	-	-	✔	-
Myoclonus	-	-	-	-
Nervousness	-	-	✔	-
Numbness	-	-	✔	-
Seizures	-	✔	✔	≤1
Somnolence	-	-	✔	-
Tremor	-	-	✔	≤1
Vertigo	-	-	-	≤1
Dermatologic				
Acute exanthematous pustulosis	✔	-	-	-
Abscess	-	-	✔	2
Atrophy	-	-	✔	-
Bruising	-	-	✔	-
Cellulitis	-	-	✔	-
Contact dermatitis	-	-	-	-
Cutis laxa	-	-	-	-
Diaphoresis	-	✔	-	≤1
Edema	-	-	✔	-
Erythema multiforme	✔	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Flushing	-	-	-	≤1
Gangrene	-	-	✔	-
Hemorrhage	-	-	✔	-
Inflammation	-	-	✔	≤1
Lipoatrophy	-	-	-	-
Lump	-	-	✔	-
Necrosis	-	-	✔	-
Pain	-	-	✔	2
Photophobia	-	-	-	≤1
Pruritus	-	-	-	3
Purpura	-	-	-	≤1
Rash	1 to 10	1 to 10	-	4
Skin ulcer	-	-	✔	-
Stevens-Johnson syndrome	✔	-	-	≤1
Tissue necrosis	-	-	-	-
Toxic epidermal necrolysis	-	-	-	≤1
Urticaria	1 to 10	<1	-	-
Gastrointestinal				
Abdominal pain	1 to 10	-	-	1 to 2
Black hairy tongue	✔	<1	-	-
Bloody stool	-	-	✔	-
Clostridium difficile colitis	-	-	-	✔
Constipation	-	-	-	1 to 8
Diarrhea	3 to 34	1 to 10	-	7 to 11
Epigastric discomfort	✔	✔	-	-
Flatulence	✔	-	-	≤1
Gastritis	✔	✔	-	≤1
Ileus	-	-	-	≤1
Intestinal necrosis	-	-	✔	-
Nausea	1 to 10	✔	-	7
Oral candidiasis	-	-	-	-
Pseudomembranous colitis	✔	✔	✔	≤1
Stomatitis	✔	-	-	-
Stool changes	-	-	-	2
Taste perversion	-	-	-	≤1
Thirst	-	-	-	≤1
Ulcerative stomatitis	-	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Vomiting	1 to 10	<1	-	3 to 4
Genitourinary				
Dysuria	-	✔	-	≤1
Genital pruritus	-	-	-	≤1
Hematuria	✔	-	✔	≤1
Hemorrhagic cystitis	-	-	-	-
Impotence	-	-	✔	-
Incontinence	-	-	-	≤1
Interstitial nephritis	✔	✔	✔	≤1
Leukorrhea	-	-	-	≤1
Myoglobinuria	-	-	✔	-
Neurogenic bladder	-	-	✔	-
Oliguria	-	-	-	≤1
Priapism	-	-	✔	-
Proteinuria	-	-	✔	-
Renal failure	-	-	✔	≤1
Renal tubular damage	-	-	-	-
Urinary retention	-	✔	-	≤1
Vaginitis	1 to 10	-	-	≤1
Hematologic				
Agranulocytosis	✔	-	-	≤1
Anemia	✔	-	-	≤1
Bleeding	-	-	-	-
Eosinophilia	✔	-	-	-
Granulocytopenia	-	-	-	-
Hemolytic anemia	✔	-	✔	≤1
Leukopenia	✔	-	-	✔
Neutropenia	-	-	✔	✔
Pancytopenia	-	-	-	≤1
Positive Coombs' reaction	-	-	✔	-
Prothrombin time prolonged	✔	-	-	-
Thrombocytopenia	✔	✔	-	≤1
Thrombocytosis	✔	-	-	≤1
Hepatic				
Cholestatic jaundice syndrome	✔	-	-	-
Hepatitis	✔	-	-	≤1
Hepatotoxicity	✔	-	-	-

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Jaundice	-	-	-	≤1
Liver function tests increased	✔	<1	✔	1 to 10
Laboratory Test Abnormalities				
Blood urea nitrogen increased	-	-	✔	-
Electrolyte imbalance	-	-	-	-
Hypoglycemia	-	-	-	≤1
Serum creatinine increased	-	-	✔	-
Musculoskeletal				
Arthralgia	-	-	-	≤1
Arthritis exacerbation	-	-	✔	-
Back pain	-	-	-	≤1
Joint disorder	-	-	✔	-
Myalgia	-	-	-	≤1
Periostitis	-	-	✔	-
Rhabdomyolysis	-	-	✔	-
Traverse myelitis	-	-	✔	-
Weakness	-	-	✔	-
Respiratory				
Bronchospasm	-	-	-	≤1
Coughing	-	-	-	≤1
Dyspnea	-	-	-	3
Pharyngitis	-	-	-	2
Other				
Anaphylaxis	✔	✔	-	≤1
Blindness	-	-	✔	-
Blurred vision	-	-	✔	-
Candidiasis	-	<1	-	≤1
Diaphoresis	-	<1	✔	-
Epistaxis	-	-	-	≤1
Hemorrhage	-	-	-	≤1
Hiccough	-	-	-	≤1
Hypersensitivity reaction	-	1 to 10	✔	✔
Infection	-	-	-	2
Injection site reaction	-	-	-	≤1
Lymphadenopathy	-	-	✔	-
Malaise	-	-	-	≤1
Mesenteric embolism	-	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Moniliasis	-	-	-	2
Mottling	-	-	✔	-
Myoclonus	-	-	✔	-
Neurovascular damage	-	-	✔	-
Pseudoanaphylactic reaction	-	-	✔	-
Pulmonary edema	-	-	-	≤1
Pulmonary embolism	-	-	-	≤1
Rhinitis	-	-	-	≤1
Rigors	-	-	-	≤1
Sepsis	-	-	-	2
Serum sickness-like reaction	-	-	✔	-
Thrombophlebitis	-	1 to 10	✔	≤1
Tinnitus	-	-	-	≤1
Warmth	-	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Boxed Warning for the Penicillin G Benzathine and Penicillin G Benzathine/Penicillin G Procaine[1]

WARNING
Not for intravenous use. Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. Prior to administration of this drug, carefully read the warnings, adverse reactions, and dosage and administration sections of the labeling.

VII. Dosing and Administration

The usual dosing regimens for the penicillins are listed in Table 12.

Table 12. Usual Dosing Regimens for the Penicillins[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Amoxicillin	Ear, nose, and throat infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Ear, nose, and throat infections (severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Genitourinary tract infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Genitourinary tract infections (severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Gonorrhea (acute), anogenital infections (uncomplicated), urethral infections: Capsule, chewable tablet, suspension, tablet: 3 g as a single dose *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence: Dual therapy: Capsule, chewable tablet, suspension, tablet: 1 g	Ear, nose, and throat infections in patients >3 months of age (mild to moderate): Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Ear, nose, and throat infections in patients >3 months of age (severe): Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Genitourinary tract infections in patients >3 months of age (mild to moderate): Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Genitourinary tract infections in patients >3 months of age (severe): Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours	Capsule: 250 mg 500 mg Chewable tablet: 125 mg 250 mg Suspension: 125 mg/5 mL 200 mg/5 mL 250 mg/5 mL 400 mg/5 mL Tablet: 500 mg 875 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	amoxicillin and 30 mg lansoprazole given three times daily for 14 days Triple therapy: Capsule, chewable tablet, suspension, tablet: 1 g amoxicillin, 500 mg clarithromycin, and 30 mg lansoprazole given twice daily for 14 days Respiratory tract infections (lower) (mild to moderate or severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Skin and skin-structure infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Skin and skin-structure infections (severe): Severe: Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours	Gonorrhea (acute), anogenital infections (uncomplicated), urethral infections in prepubertal children (≥2 years of age): Capsule, chewable tablet, suspension, tablet: 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose Respiratory tract infections (lower) (mild to moderate or severe) in patients >3 months of age: Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Skin and skin-structure infections (mild to moderate) in patients >3 months of age: Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Skin and skin-structure infections (severe) in patients ≥3 months of age: Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Unspecified infections in patients ≤3 months of age: Capsule, chewable tablet, suspension, tablet: 30 mg/kg/day divided every 12 hours	
Ampicillin	Gastrointestinal and genitourinary tract infections: Injection: IM/IV 500 mg every six hours Capsule: 500 mg four times daily Gonorrhea (men and women):	Gastrointestinal and genitourinary tract infections: Injection: <40 kg, IM/IV 50 mg/kg/day in divided doses at six to eight hour intervals; ≥40 kg, IM/IV 500 mg every six hours	Capsule: 500 mg Injection: 125 mg 250 mg 500 mg 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: 3.5 g as a single dose administered simultaneously with 1 g of probenecid Meningitis: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Respiratory tract infections: Injection: IM/IV 250 to 500 mg every six hours Septicemia: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Soft tissue infections: Injection (IM/IV): 250 to 500 mg every six hours Urethritis (males): Injection: IM/IV two doses of 500 mg each at an interval of eight to 12 hours	Capsule: ≤20 kg, 100 mg/kg/day in divided doses administered four times daily; >20 kg: 500 mg four times daily Meningitis: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Respiratory tract infections: Injection: <40 kg, IM/IV 25 to 50 mg/kg/day in divided doses at six to eight hour intervals; ≥40 kg, IM/IV 250 to 500 mg every six hours Septicemia: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours. Soft tissue infections: Injection: <40 kg, IM/IV 25 to 50 mg/kg/day in divided doses at six- to eight- hour intervals; ≥40 kg, IM/IV 250 to 500 mg every six hours Oral formulations: ≤20 kg, 50 mg/kg/day in divided doses administered three to four times daily; >20 kg, 250 mg four times daily	2 g 10 g
Dicloxacillin	Unspecified infections: Capsule: 125 to 250 mg every six hours	Unspecified infections: Capsule: <40 kg, 12.5 to 25 mg/kg/day divided every six hours; ≥40 kg: 125 to 250 mg every six hours	Capsule: 250 mg 500 mg
Nafcillin	Unspecified infections (mild to moderate): Injection: 500 mg IM every four to six hours or 500 mg IV every four hours Unspecified infections (severe): Injection: 1 g IM/IV every four hours	Unspecified infections: Injection: neonates, 10 mg/kg IM twice daily; <40 kg, 25 mg/kg IM twice daily; ≥40 kg, 500 mg IM every four to six hours or 500 mg IV every four hours	Injection: 1 g 2 g 10 g
Oxacillin	Mild to moderate infections: Injection: 250 to 500 mg IM/IV every four to six hours	Mild to moderate infections: Injection: <40 kg, 50 mg/kg/day IM/IV in divided	Injection: 1 g 2 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Severe infections: Injection: 1 g IM/IV every four to six hours	doses every six hours; ≥40 kg, 250 to 500 mg IM/IV every four to six hours Severe infections: Injection: <40 kg, 100 mg/kg/day IM/IV in divided doses every four to six hours; ≥40 kg, 1 g IM/IV every four to six hours Unspecified infections in premature and neonates: Injection: 25 mg/kg/day IM/IV	10 g
Penicillin G benzathine	Prophylaxis (rheumatic fever and glomerulonephritis): Injection: 1,200,000 units IM once a month or 600,000 units IM every two weeks Streptococcal (group A) upper respiratory tract infections: Injection: 1,200,00 units IM as a single dose Syphilis (primary, secondary and latent): Injection: 2,400,000 units IM as a single dose Late and neurosyphilis: Injection: 2,400,000 units IM at seven-day intervals for three doses Yaws, Bejel, Pinta: Injection: 1,200,000 units IM as a single dose	Streptococcal (group A) upper respiratory tract infections: Injection: <60 lbs, 300,000 to 600,000 units IM as a single dose; ≥60 lbs, 900,000 units IM as a single dose Syphilis (congenital) in patients <2 years of age: Injection: 50,000 units/kg IM as a single dose Syphilis (congenital) in patients two to 12 years of age: Injection: Adjust dosage based on adult dosage schedule	Injection: 600,000 units/mL 1.2 million units/2 mL 2.4 million units/4 mL
Penicillin G (potassium and sodium)	Actinomycosis (cervicofacial): Injection: 1 to 6 million units/day Actinomycosis (thoracic and abdominal disease): Injection: 10 to 20 million units/day Anthrax: Injection: A minimum of 5 to 8 million units/day until cure is effected Clostridial infections: Injection: 20 million units/day as an adjunct to antitoxin	Diphtheria: Injection: 150,000 to 250,000 units/kg/day in divided doses every six hours for seven to 10 days Gonococcal infections (disseminated) (arthritis): Injection: <45 kg, 100,000 units/kg/day in four equally divided doses for seven to 10 days; ≥45 kg, 10 million units/day in four equally divided doses Gonococcal infections (disseminated) (meningitis): Injection: <45 kg, 250,000	Injection (potassium): 5 million units 20 million units Injection (sodium): 5 million units

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Diphtheria: Injection: 2 to 3 million units/day in divided doses for 10 to 12 days Erysipeloid endocarditis: Injection: 12 to 20 million units/day for four to six weeks Fusospirochetal infections (severe infections of oropharynx, lower respiratory tract and genital area): Injection: 5 to 10 million units/day Gonococcal infections (disseminated) (arthritis, meningitis, endocarditis): Injection: 10 million units/day Gram-negative bacillary infections (bacteremia): Injection: 20 to 80 million units/day Haverhill fever: Injection: 12 to 20 million units/day for three to four weeks Listeria infections (endocarditis): Injection: 15 to 20 million units/day for four weeks Listeria infections (meningitis): Injection: 15 to 20 million units/day for two weeks Meningococcal meningitis: Injection: 1 to 2 million units IM every two hours or 24 million units/day IV as 2 million units every two hours Pasteurella infections (bacteremia and meningitis): Injection: 4 to 6 million units/day for two weeks Rat-bite fever: Injection: 12 to 20 million units/day for three to four weeks Septicemia: Injection: 1 to 2 million units IM every two hours or 24 million	units/kg/day in equal doses every four hours for 10 to 14 days; ≥45 kg, 10 million units/day in four equally divided doses Gonococcal infections (disseminated) (endocarditis): Injection: <45 kg, 250,000 units/kg/day in equal doses every four hours for four weeks; ≥45 kg, 10 million units/day in four equally divided doses Haverhill fever: Injection: 150,000 to 250,000 units/kg/day in equal doses every four hours for four weeks Listeria infections in neonates: Injection: 500,000 to 1 million units/day Meningitis (pneumococcus and meningococcus): Injection: 250,000 units/kg/day divided in equal doses every four hours for seven to 14 days Rat-bite fever: Injection: 150,000 to 250,000 units/kg/day in equal doses every four hours for four weeks Serious infections (streptococci and meningococcus): Injection: 150,000 to 300,000 units/kg/day divided in equal doses every four to six hours Syphilis (congenital and neurosyphilis): Injection: 50,000 units/kg every four to six hours for 10 to 14 days	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	units/day IV as 2 million units every two hours Serious infections (streptococci, pneumococci, and staphylococci): Injection: 5 to 24 million units in divided doses every four to six hours Syphilis and neurosyphilis: Injection: 2 to 4 million units every four hours for 10 to 14 days		
Penicillin G procaine	Anthrax: Injection: 600,000 to 1 million units/day IM Anthrax, inhalational (postexposure): Injection: 1.2 million units IM every 12 hours Bacterial endocarditis: Injection: 600,000 to 1 million units/day IM Diphtheria (adjunctive therapy with antitoxin): Injection: 300,000 to 600,000 units/day IM Diphtheria (carrier state): Injection: 300,000 units/day IM for 10 days Erysipelas: Injection: 600,000 to 1 million units/day IM for at least 10 days Fusospirochetosis (Vincent's infection): Injection: 600,000 to 1 million units/day IM Pneumonia (moderately severe and uncomplicated): Injection: 600,000 to 1 million units/day IM Rat-bite fever: Injection: 600,000 to 1 million units/day IM Scarlet fever: Injection: 600,000 to 1 million	Anthrax, inhalational (postexposure): Injection: 25,000 units/kg every 12 hours Pneumonia: Injection: <60 lbs, 300,000 units/day IM Staphylococcal infections: Injection: <60 lbs, 300,000 units/day IM Streptococcal infections: Injection: <60 lbs, 300,000 units/day IM Syphilis (primary, secondary and latent) in patients >12 years of age: Injection: 600,000 units/day IM for eight days Syphilis (late) in patients >12 years of age: Injection: 600,000 units/day IM for 10 to 15 days Syphilis (congenital): Injection: <70 lbs, 50,000 units/kg/day for 10 days	Injection: 600,000 units 1.2 million units/2 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	units/day IM for at least 10 days Skin and soft-tissue infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Staphylococcal infections (moderately severe to severe): Injection: 600,000 to 1 million units/day IM Streptococcal infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Syphilis (primary, secondary and latent): Injection: 600,000 units/day IM for eight days Syphilis (late): Injection: 600,000 units/day IM for 10 to 15 days Tonsillitis (moderately severe to severe): Injection: 600,000 to 1 million units/day IM for at least 10 days Upper respiratory tract infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Yaws, Bejel, Pinta: Injection: Treatment as for syphilis in corresponding stage of disease		
Penicillin V potassium	Chorea (prophylaxis): Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Erysipelas: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Fusospirochetosis (Vincent's infection) of the oropharynx: Suspension, tablet: 250 to 500 mg every six to eight hours Pneumococcal infections: Suspension, tablet: 250 to 500 mg every six hours	Chorea (prophylaxis) in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Erysipelas in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Fusospirochetosis (Vincent's infection) of the oropharynx in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours	Solution: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Prophylaxis (procedures): Suspension, tablet: 2 g one hour before procedure and 1 g six hours later Otitis media: Suspension, tablet: 250 to 500 mg every six hours Rheumatic fever (prophylaxis): Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Scarlet fever: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Skin and soft-tissue infections: Suspension, tablet: 250 to 500 mg every six to eight hours Staphylococcal infections: Suspension, tablet: 250 to 500 mg every six to eight hours Streptococcal infections: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days	Fusospirochetosis (Vincent's infection) of the oropharynx in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Pneumococcal infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six hours Prophylaxis (procedures): Suspension, tablet: <60 lbs, 1 g one hour before procedure and 1 g six hours later Prophylaxis (procedures) in patients ≥12 years of age: Suspension, tablet: 2 g one hour before procedure and 1 g six hours later Otitis media in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six hours Otitis media in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Rheumatic fever (prophylaxis) in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Scarlet fever in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Scarlet fever in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Skin and soft-tissue infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Skin and soft-tissue infections in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Staphylococcal infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours Streptococcal infections in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days	
Combination Products			
Amoxicillin and clavulanate	Sinusitis: Extended-release tablet: Two tablets every 12 hours for 10 days Pneumonia (community-acquired): Extended-release tablet: Two tablets every 12 hours for seven to 10 days Unspecified infections: Chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours	Otitis media, sinusitis, respiratory tract infections (lower), more severe infections in patients >3 months of age: Chewable tablet, suspension: 45 mg/kg/day divided every 12 hours or 40 mg/kg/day divided every eight hours Sinusitis in patients ≥40 kg: Extended-release tablet: Two tablets every 12 hours for 10 days Less severe infections in patients >3 months of age: Chewable tablet, suspension: 25 mg/kg/day divided every 12 hours or 20 mg/kg/day divided every eight hours Pneumonia (community-acquired) in patients ≥40 kg: Extended-release tablet: Two tablets every 12 hours for seven to 10 days Severe infections and infections of the respiratory tract in patients ≥40 kg: Chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Unspecified infections in patients ≤3 months of age: Chewable tablet, suspension, tablet: 30 mg/kg/day divided	Chewable tablet: 200-28.5 mg 400-57 mg Suspension: 200-28.5 mg/5 mL 250-62.5 mg/5 mL 400-57 mg/5 mL 600-42.9 mg/5 mL Tablet: 250-125 mg 500-125 mg 875-125 mg Extended-release tablet: 1,000-62.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		every 12 hours Unspecified infections in patients >3 months of age: Chewable tablet, suspension, tablet: 200 to 400 mg every 12 hours or 125 to 250 mg every eight hours Unspecified infections in patients ≥40 kg: Chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours	
Ampicillin and sulbactam	Unspecified infections: Injection: 1.5 to 3 g IM/IV every six hours	Unspecified infections in patients ≥1 year of age: Injection: ≤40 kg, 300 mg/kg IV every six hours; >40 kg: 1.5 to 3 g IM/IV every six hours	Injection: 1.5 g 3 g 15 g
Penicillin G benzathine and penicillin G procaine	Erysipelas: Injection: 2,400,000 units IM as a single dose Pneumococcal infections (except pneumococcal meningitis): Injection: 1,200,000 units IM repeated every two to three days until the temperature is normal for 48 hours Scarlet fever: Injection: 2,400,000 units IM as a single dose Skin and skin-structure infections: Injection: 2,400,000 units IM as a single dose Respiratory tract infections (upper): Injection: 2,400,000 units IM as a single dose	Erysipelas: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a single dose Pneumococcal infections (except pneumococcal meningitis): Injection: 600,000 units IM repeated every two to three days until the temperature is normal for 48 hours Scarlet fever: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs 2,400,000 units IM as a single dose Skin and skin-structure infections: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a single dose Respiratory tract infections (upper): Injection: <30 pounds, 600,000 units IM as a single dose; 30 to	Injection: 900-300 units/2 mL 600-600 units/2 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a single dose	
Piperacillin and tazobactam	Pneumonia (nosocomial): Injection: 4.5 g IV every six hours with an aminoglycoside for seven to 14 days Unspecified infections: Injection: 3.375 g IV every six hours for seven to 10 days	Appendicitis and peritonitis in patients two to nine months of age: Injection: 80 mg piperacillin-10 mg tazobactam per kg IV every eight hours for seven to 10 days Appendicitis and peritonitis in patients ≥9 months of age (up to 40 kg): Injection: 100 mg piperacillin/12.5 mg tazobactam per kg IV every eight hours for seven to 10 days Appendicitis and peritonitis in patients >40 kg: Injection: 3.375 g every six hours for seven to 10 days Pneumonia (nosocomial) in patients two to nine months of age: Injection: 80 mg piperacillin-10 mg tazobactam per kg IV every six hours Pneumonia (nosocomial) in patients ≥9 months of age (up to 40 kg): Injection: 100 mg piperacillin/12.5 mg tazobactam per kg IV every six hours	Injection: 2.25 g 3.375 g 4.5 g 13.5 g 40.5 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the penicillins are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Penicillins

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dermatological Infections				
Dagan et al.[39] (1989) Amoxicillin 40 mg/kg/day in three divided doses for 10 days vs amoxicillin-clavulanate 40 mg/kg/day for 10 days	DB, PRO Children six months to nine years of age with culture-positive (*Staphylococcus aureus* or β-hemolytic *Streptococcus*) nonbullous impetigo	N=51 10 days	Primary: Impetigo markedly improved or cured Secondary: New lesions	Primary: Treatment with amoxicillin-clavulanate resulted in faster clinical improvement compared to amoxicillin (95 vs 68% at five days; P<0.05) and showed a trend toward more clinical improvement at 10 days (96 vs 80%; P=NS). Secondary: Amoxicillin-clavulanate resulted in fewer new lesions at 10 days (0 vs 20%; P<0.05).
Vick-Fragoso et al.[40] (2009) Moxifloxacin 400 mg IV once daily for at least 3 days followed by 400 mg orally for 7 to 21 days vs amoxicillin-clavulanate 1,000-200 mg IV TID for at least 3	MC, OL, RCT Patients ≥18 years of age with complicated skin or skin structure infections	N=804 21 days	Primary: Clinical response at test of cure for the per protocol population Secondary: Clinical response at test of cure for the intent to treat population and clinical response at test of cure by indication, bacteriological success at test of cure for the per	Primary: Clinical cure (success) rates at test of cure for the per protocol population were not significantly different between the treatment groups: 80.6% for moxifloxacin compared to 84.5% for amoxicillin-clavulanate. These efficacy findings were supported by results for the intent to treat population: 72.7% for moxifloxacin compared to 74.8% for amoxicillin/clavulanate. Moxifloxacin was not inferior to amoxicillin-clavulanate for complicated skin or skin structure infections. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days followed by 500 mg-125 mg orally TID for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.			protocol population	Among the per protocol population, 19.4% of moxifloxacin- treated and 15.5% of amoxicillin-clavulanate-treated patients were clinical failures at test of cure. There were no significant differences in bacteriological success rates at test of cure in the per protocol population between moxifloxacin-treated patients (76.0%) and amoxicillin-clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Stevens et al.[41] (2000) Oxacillin 2 g IV every six hours followed by dicloxacillin 500 mg orally every six hours vs linezolid 600 mg IV every 12 hours	DB, DD, MC, RCT Hospitalized patients ≥18 years of age with a suspected gram-positive complicated skin and soft tissue infection	N=819 10 to 21 days	Primary: Clinical outcome and microbiological outcome based on resolution or improvement of clinical signs/ symptoms of skin and soft tissue infections at the end of treatment compared to baseline Secondary: Not reported	Primary: Of clinically evaluable patients (N=600), clinical cure rate was 88.6% in the linezolid group compared to 85.8% in the oxacillin and dicloxacillin group (P=0.300). Of microbiologically evaluable patients (N=294), the cure rate was 88.1% in the linezolid group compared to 86.1% in the oxacillin and dicloxacillin group (P=0.606). No statistically significant differences were noted in the frequency of adverse events between treatment groups. Secondary: Not reported
Tong et al.[42] (2010) SMX-TMP 20 to 4 mg/kg BID for five days vs penicillin	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day seven after the commencement of treatment Secondary: Bacterial	Primary: Treatment was successful in all seven patients assigned to SMX-TMP, and five of six patients assigned to the penicillin group seven days after randomization (P=0.46). Secondary: By day four, microbiological clearance was documented in five of seven patients treated with SMX-TMP and in two of six patients treated with penicillin (P=0.28).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
benzathine 45 mg/kg IM as a single dose			resolution of sores at day four and day seven; successful treatment at day four	By day seven, microbiological clearance was documented in all seven patients treated with SMX-TMP and in three of six patients treatment with penicillin (P=0.07). Treatment was successful after four days in six of seven treated with SMX-TMP and three of six with penicillin (P=0.27).
Harkless et al.[43] (2005) Piperacillin-tazobactam 4-0.5 g every eight hours vs ampicillin-sulbactam 2-1 g every six hours	MC, OL, RCT Adult patients with moderate-to-severe infected diabetic foot ulcers	N=314 9 to 10 days	Primary: Clinical efficacy rates (cure or improvement) Secondary: Bacteriologic success rates, adverse events	Primary: Clinical success rates were similar for both treatment groups (71.2% for piperacillin-tazobactam vs 66.7% for ampicillin-sulbactam; P=NS). Secondary: Bacteriologic success rates were similar for both treatment groups (P=NS). Incidence and severity of adverse events were similar between the two treatment groups (P=NS).
Saltoglu et al.[44] (2010) Imipenem-cilastatin 0.5 g IV every six hours for 14 to 28 days vs piperacillin-tazobactam 4.5 g IV every eight hours for 14 to 28 days	OL, RCT, SC Patients ≥18 years of age with a diagnosis of moderate to severe diabetic lower extremity foot infection	N=64 2 months post-treatment	Primary: Clinical response Secondary: Relapse rate after two months	Primary: A successful clinical response was seen in 46.7% of patients in the piperacillin-tazobactam group and in 28.1% of patients in the imipenem group (RR, 1.6; 95% CI, 0.84 to 3.25; P=0.130). Secondary: During two months follow-up, two patients in the imipenem group and none in the piperacillin-tazobactam group relapsed (RR, 2; 95% CI, 0.94 to 4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the piperacillin-tazobactam and imipenem groups (60 vs 68.8%; P=0.739).
Tan et al.[45] (1993)	DB, MC, RCT Hospitalized	N=251 10 to 14 days	Primary: Clinical outcome	Primary: No significant difference in the overall clinical response was observed. The percentages of cured/improved/favorable outcomes were similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Piperacillin-tazobactam 3 g-375 mg every six hours vs ticarcillin-clavulanate 3 g-100 mg every six hours	patients with complicated skin and skin structure infections		Secondary: Bacteriological outcome	(61/15/76% for the piperacillin-tazobactam group vs 61/16/77% for the ticarcillin-clavulanate group; P=1.00). Secondary: No statistically significant differences in microbial eradication rates were observed between treatment groups for monomicrobial infections and polymicrobial infections.
Gesser et al.[46] (2004) Ertapenem 1 g IV daily vs piperacillin-tazobactam 13.5 grams IV divided every six hours Study medications were given as outpatient parenteral antimicrobial therapy or as inpatient therapy.	DB, MC, PRO, RCT Patients 18 years of age and older with skin and skin structure infections requiring parenteral therapy	N=146 10 to 21 days post-therapy	Primary: Clinical response, adverse events Secondary: Not reported	Primary: For patients receiving outpatient parenteral antimicrobial therapy, 83.3% in the ertapenem group and 82.0% in the piperacillin-tazobactam group had a clinical response to therapy and were considered cured (P=0.78). The only significant difference in adverse event between the two treatment groups was that 10.5% of patients in the piperacillin-tazobactam group experienced moderate-severe tenderness compared to 0% in the ertapenem group; P=0.006). Secondary: Not reported
Lipsky et al.[47] (2005) Ertapenem 1 g IV daily	DB, MC, RCT Adult patients with type 2 diabetes mellitus with a foot infection not	N=445 10 days after completion of antibiotic therapy	Primary: Proportion of patients with a favorable clinical response at the discontinuation of	Primary: At the discontinuation of IV therapy visit, 94% of patients in the ertapenem group and 92% in the piperacillin-tazobactam group had a favorable clinical response. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs piperacillin-tazobactam 3.375 g every six hours Investigators switched patients to oral therapy if appropriate after five days of IV therapy.	extending above the knees		IV therapy Secondary: Proportion of patients with a favorable clinical response at follow-up assessment	At the follow-up assessment visit, 87% of patients in the ertapenem group and 83% in the piperacillin-tazobactam group had a favorable clinical response.
Genitourinary Infections				
Brathwaite et al.[48] (1979) Amoxicillin 3 g as a single dose vs ampicillin 3 g as a single dose Both groups with probenecid 1 g pretreatment.	DB, PRO, RCT Men with uncomplicated gonorrhea	N=160 14 days	Primary: Cure rate (microbial and clinical resolution) Secondary: Adverse effects	Primary: Amoxicillin and ampicillin both had 98.6% cure rates (P=NS). Secondary: No adverse effects were reported.
Felman et al.[49] (1979) Amoxicillin 3 g for one dose vs ampicillin 3.5 g for one dose	PRO, RCT Adults with uncomplicated gonorrhea	N=115 1 week	Primary: Culture negativity one week post-treatment Secondary: Adverse effects	Primary: Amoxicillin and ampicillin were similarly curative (100 vs 96.2%; P=0.18). Secondary: Four patients on amoxicillin and two patients on ampicillin had mild adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tran et al.[50] (2001) SMX-TMP 40-80 mg/kg/day for one to three days (short-treatment course) vs SMX-TMP 40-80 mg/kg/day for 7 to 14 days (long-treatment course) or amoxicillin for one to three days (short-treatment course) vs amoxicillin for 7 to 14 days (long-treatment course)	MA Children <18 years of age with uncomplicated cystitis confirmed by urine culture	N=1,279 (22 trials) Up to 14 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: There was no difference between short- and long-courses of SMX-TMP in terms of cure rates (difference in cure rate, 6.24%; 95% CI, -3.74 to 16.2). The short-course amoxicillin therapy was less effective in curing the infection compared to the conventional length of therapy (difference in cure rate, 13%; 95% CI, 4 to 24). Consequently, eight patients would need to receive a conventional amoxicillin course of therapy to prevent one treatment failure that would have occurred with a shorter duration of treatment. Drug-related toxicity increased in proportion to the length of therapy. Secondary: Not reported
Latif et al.[51] (1984) Amoxicillin 3 g and clavulanate 250 mg for one dose vs	Unblinded Men with uncomplicated gonococcal urethritis	N=121 14 days	Primary: Microbial cure (culture negative two weeks post-treatment) Secondary: Infections due to penicillinase-	Primary: Treatment with amoxicillin resulted in a higher cure rate compared to penicillin (90.6 vs 73.7%; P=0.01). Secondary: The rate of infection due to penicillinase-producing *Neisseria* (7.8 vs 15.8%) and post-gonococcal urethritis (7.8 vs 14.0%) were not statistically different between the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
penicillin procaine 2.4 million units IM for one dose			producing *Neisseria*, post gonococcal urethritis	
Gallacher et al.[52] (1986) Amoxicillin-clavulanate 250-125 mg orally for five days vs amoxicillin 250 mg orally for five days	DB, RCT Elderly inpatients with urinary tract infections	N=67 5 days	Primary: Bacteriologic cure at end of treatment Secondary: Bacteriologic cure after conversion to amoxicillin-clavulanate	Primary: Treatment with amoxicillin-clavulanate was more effective than treatment with amoxicillin at achieving a negative urine culture (87.5 vs 43.0%; P<0.001). Secondary: Of the patients who failed amoxicillin, 62.5% responded to amoxicillin-clavulanate.
Karney et al.[53] (1974) Ampicillin 3.5 g orally with probenecid 1 g orally for one dose vs amoxicillin 3 g orally for one dose	DB, RCT Adults with uncomplicated gonorrhea	N=108 2 weeks	Primary: Bacteriologic culture negative at two weeks post-treatment Secondary: Not reported	Primary: Treatment with ampicillin and treatment with amoxicillin had similar bacteriologic cure rates at two weeks post-treatment (98.3 vs 95.8%) in anogenital gonorrhea. Secondary: Not reported
Hook et al.[54] (2002) Azithromycin 2 g as a single dose vs	RCT Patients 18 to 56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response Secondary: Not reported	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
azithromycin 2 g as two doses given six to eight days apart vs penicillin benzathine G 2.4 million units IM as a single dose				The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95). Secondary: Not reported
Hook et al.[55] (2010) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	MC, OL, RCT Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection Secondary: Not reported	Primary: In the intent to treat analysis at the six-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the per protocol analysis at the six-month follow-up visit, 77.5% of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound, −7.9%). The efficacy of 2 g azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early syphilis in patients without human immunodeficiency virus infection. Secondary: Not reported
Bai et al.[56] (2008) Azithromycin vs penicillin G benzathine	MA Patients ≥18 years of age with early syphilis	N=476 (4 trials) Variable duration	Primary: Cure rates and adverse events Secondary: Not reported	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR, 1.37; 95% CI, 1.05 to 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09 to 1.61; P=0.38). There was no significant difference in the rate of adverse events between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the treatment groups. Secondary: Not reported
Ryo et al.[57] (2005) Imipenem-cilastatin 500 mg IV BID for three days plus betamethasone 12 mg SC vs penicillin or a cephalosporin or no antibiotic treatment	RETRO Pregnant women admitted to hospital with preterm premature rupture of membranes at 24 weeks and 0 days to 31 weeks and 6 days gestation	N=140 1 year	Primary: Time from preterm premature rupture of membranes to delivery, prognosis of infants (death within one year, alive with or without handicap) Secondary: Sensitivity of imipenem-cilastatin to cultured bacteria obtained at admission compared to ampicillin	Primary: The mean time from preterm premature rupture of membranes to delivery was 11 days in the imipenem-cilastatin group and 6 days in the control group (P=0.016). Also 53% of women treated with imipenem-cilastatin were able to continue pregnancy for greater than one week after preterm premature rupture of membranes as opposed to 25% in the control group (P=0.0048). There were no infant deaths in the imipenem-cilastatin group but 12.5% of the infants died in the control group (P=0.002). There was no difference in the incidence of infants with handicaps between each group (P=0.3277). Secondary: All cultured bacteria specimens in 94% of the women in the study group were sensitive to imipenem-cilastatin while all specimens found in 25% of those in the control group were sensitive to ampicillin (P<0.0001).
Landis et al.[58] (1981) Piperacillin 2 g IM for one dose vs penicillin G 4.8 million units IM for one dose, with pre-administration of probenecid 1 g orally	PRO, RCT Men with uncomplicated gonococcal urethritis	N=127 7 to 10 days post-treatment	Primary: Clinical cure, bacteriologic cure Secondary: Not reported	Primary: A total of 100% of the patients in both groups were reported as clinically and bacteriologically cured. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Namias et al.[59] (2007) Piperacillin-tazobactam 3.375 grams IV every six hours vs ertapenem 1 g IV once daily	DB, MC, RCT Patients 18 to 90 years of age with presumptive (pre-operative) or confirmed complicated intra-abdominal infections	N=500 4 to 14 days	Primary: Clinical response rates Secondary: Microbiological efficacy, clinical failure, mortality	Primary: Favorable clinical responses were demonstrated for 82.1% of the patients in the ertapenem group and 81.7% of the patients in the piperacillin-tazobactam group (95% CI, -9.6 to 10.5). At the end of therapy, 89.6 and 86.2%, and at late follow-up assessment, 78.9 and 79.3%, of the microbiologically evaluable patients had favorable clinical responses in the ertapenem and piperacillin-tazobactam treatment groups, respectively. Clinical response rates of 63.2% for ertapenem and 60.9% were similar for piperacillin-tazobactam-treated patients in the modified intent-to-treat population at early follow-up assessment (95% CI, -7.5 to 12.0). Secondary: There were no clinically important differences in the response rates of gram-positive, gram-negative, or anaerobic pathogens in the ertapenem and piperacillin-tazobactam treatment groups. Favorable overall microbiological responses were demonstrated in 82.2% in the ertapenem group and 82.5% in the piperacillin-tazobactam group (95% CI, -10.1 to 9.8) at early follow-up assessment. The pathogens isolated most frequently were *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*. At the early follow-up assessment, there were 22 clinical failures (17.9%) in the ertapenem group and 20 (18.5%) in the piperacillin-tazobactam group. The incidence of adverse events and study discontinuations because of adverse events was similar in the two groups. During the study and post-treatment follow-up period, clinical adverse events resulted in 21 deaths, nine of which occurred in the ertapenem group (3.6%) and 12 in the piperacillin-tazobactam group (4.9%; RR, 0.75; 95% CI, 0.30 to 1.77; risk difference, -1.21; 95% CI, -5.08 to 2.53).
Seo et al.[60]	MC, OL, PRO,	N=66	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2017) Piperacillin-tazobactam 4.5 g every six hours vs ertapenem 1 g every 24 hours vs cefepime 2 g every 12 hours	RCT Hospitalized patients ≥ 19 years of age with healthcare-associated UTI caused by extended-spectrum β-lactamase-producing *Escherichia coli*	28 to 30 days	Clinical response at three to five days and microbiological response at 10 to 14 days Secondary: 28 day mortality rate	After recruitment of six participants to the cefepime treatment group, allocation to this treatment group was stopped due to an unexpectedly high treatment failure rate. Clinical success rate was 93.9% with piperacillin-tazobactam and 97.0% with ertapenem (P=0.500). Clinical success rate with cefepime was 33.3% (P<0.001) Microbiological success rates were 97.0% with both piperacillin-tazobactam and ertapenem, and 33.3% with cefepime. Secondary: The 28-day mortality rate was 6.1% with both piperacillin-tazobactam and ertapenem and 33.3% (two of six patients) with cefepime (P=0.108)
Kaye et al.[61] (2018) TANGO I Piperacillin-tazobactam 4.5 g IV every eight hours vs meropenem-vaborbactam 4 g IV infusion every eight hours Patients were treated for at least five days. After five days, patients could be switched to an oral	AC, DB, DD, MC, RCT Patients ≥18 years of age with cUTI or acute pyelonephritis	N=550 Mean study duration of 25 days	Primary: Overall success defined as a composite of clinical cure (complete resolution or significant improvement of baseline signs and symptoms of cUTI or acute pyelonephritis), and microbial eradication (baseline pathogens reduced to $<10^4$ CFU/mL urine) at the end of IV treatment visit for the microbiologic	Primary: Overall success at the end of the IV treatment in the microbiologic modified intent-to-treat population (n=545) was observed in 98.4% of patients in the meropenem-vaborbactam arm and 94.0% in the piperacillin-tazobactam arm (observed difference, -4.5%; 95% CI, 0.7 to 9.1%; P<0.001 for noninferiority). Secondary: Overall success at test-of-cure (TOC) in the meropenem-vaborbactam group was 74.5% compared to the piperacillin-tazobactam group of 70.3% (difference, 4.1%; 95% CI, -4.9 to 9.1%). In the microbiologic modified intent-to-treat population, clinical cure at the end of IV treatment was 98.4 and 95.6% in the meropenem-vaborbactam and piperacillin-tazobactam groups respectively (difference, 2.8%; 95% CI, -0.7 to 7.1%) and at TOC was 90.6 and 86.3% (difference, 4.4%; 95% CI, -2.2 to 11.1%). Microbial eradication at TOC in the microbiologic modified intent-to-treat was 74.2% in the meropenem-vaborbactam group and 63.4% in the piperacillin-tazobactam group (difference, 10.8%; 95% CI, -1.4 to 23.0%) in patients with acute pyelonephritis, 60.0 and 53.6% (difference, 7.4%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
antibiotic to complete a total of ten days of treatment.			modified intent-to-treat population Secondary: Proportion of patients with overall success at end of IV treatment and at test-of-cure visits, clinical cure at end of IV treatment and at test-of-cure visits, microbial eradication	95% CI, -15.4 to 29.3%) in patients with cUTI and a removable source of infection; and 48.6 and 48.8% (difference, -0.2%; 95% CI, -21.7 to 21.4%) in patients with cUTI and a nonremovable source of infection.
File et al.[62] (1985) Ticarcillin 80 to 160 mg/kg/day plus clavulanate 0.1 mg to 0.2 g every eight hours IV vs piperacillin 125 to 200 mg/kg/day every six to eight hours	RCT Adult patients with serious urinary tract infections	N=47 Mean 9.3 days	Primary: Clinical symptomatic response, bacterial response Secondary: Adverse events	Primary: Satisfactory symptomatic response was observed with all patients in the study. Bacteriologic eradication was achieved in 41% of patients in the ticarcillin-clavulanate group and 55% of patients in the piperacillin group. Secondary: Minimal adverse effects in two of ticarcillin-clavulanate-treated patients (rash and diarrhea).
Respiratory Infections				
Gillespie et al.[63] (2015) Amoxicillin (two 500 mg tablets	PC, RCT Patients ≥18 years of age with an acute uncomplicated	N=2061 28 days	Primary: Clinician-rated symptom severity between days two and four, new or	Primary: The adjusted between-group mean difference in symptom severity score on days two to four was slightly lower in the amoxicillin group than the placebo group (adjusted mean difference of −0.07; 95% CI, −0.15 to 0.01). The odds of developing new or worsening symptoms were 21% lower for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
three times daily for seven days) vs placebo	lower RTI in whom pneumonia was not suspected by the clinician		worsening symptoms and presence of side effects at 4-weeks, adherence Secondary: Not reported	participants who were prescribed amoxicillin than for those prescribed a matched placebo (OR, 0.79; 95% CI, 0.63 to 0.99). When the effectiveness analyses were only performed on participants for whom outcome and adherence data were available, there was a 19% decrease in the odds of developing new or worsening symptoms in participants prescribed amoxicillin (OR, 0.81; 95% CI, 0.64 to 1.03). Being prescribed amoxicillin was associated with a 28% increase in the odds of reporting non-respiratory symptoms (side effects) in the four weeks post-randomization (OR, 1.28; 95% CI, 1.03 to 1.59). Adjusting for adherence, a small increase in the between-group mean difference in symptom severity score for participants who complete their course of amoxicillin was found (−0.08; 95% CI, −0.17 to 0.01). The odds of developing new or worsening symptoms remained lower in participants who took their full course of amoxicillin (OR for 100% adherence to amoxicillin, 0.81; 95% CI, 0.66 to 0.98). Secondary: Not reported
Stenstrom et al.[64] (1991) Amoxicillin 20 mg/kg/day for 10 days vs amoxicillin-clavulanate 20 mg/kg/day for seven days	DB, PRO, RCT Children six months to 10 years of age with recurrent acute otitis media or failure of penicillin	N=102 30 days post-treatment	Primary: Clinical and bacteriological response at the last visit Secondary: Adverse effects	Primary: There was no significant difference between the amoxicillin-clavulanate and amoxicillin groups in clinical improvement rate (86.7 vs 86.1%). There was no significant difference between the elimination, persistence, or re-colonization rate between the two groups, except that amoxicillin-clavulanate eliminated β-lactamase-producing *Branhamella catarrhalis* more frequently than amoxicillin (67 vs 31%; P=0.02). Secondary: The two drugs were equally well-tolerated (24 vs 20% had adverse effects; one patient vs three patients discontinued therapy).
Chan et al.[65] (1988) Amoxicillin 30 mg/kg/day given	DB, MC, RCT Children seven months to 12 years of age with otitis	N=108 16 weeks after start of therapy for responders	Primary: Clinical response (no effusion) at day 10 and four weeks after start of	Primary: Treatment with amoxicillin-clavulanate showed a trend toward better resolution of the effusion at 10 days compared to amoxicillin (51.8 vs 32%; P=0.06), but not at four weeks (50 vs 51%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in three divided doses for 10 days vs amoxicillin-clavulanate 30 mg/kg/day given in three divided doses for 10 days	media with effusion (secretory otitis media) without symptoms of acute otitis media		therapy, recurrence of effusion up to 16 weeks post-therapy in responders at four weeks Secondary: Adverse effects	Treatment with amoxicillin-clavulanate showed a trend toward reduced recurrence of effusion during a 16-week follow-up (36.4 vs 63.2%), but the difference was not statistically significant (P=0.16). Secondary: The adverse effect rate was similar in both groups, and the adverse events were mainly gastrointestinal or dermatological.
Kuroki et al.[66] (2012) Amoxicillin 30 mg/kg/day in three divided doses for 10 days vs amoxicillin-clavulanate 96.4 mg/kg/day in two divided doses for three days	MC, OL, RCT Children ≤15 years of age with pharyngolaryngitis or tonsilliths who tested positive on the instantaneous Group A *Streptococcus* infection diagnosis kit	N=97 1 to 2 weeks after therapy completion	Primary: Clinical efficacy Secondary: Not reported	Primary: In the amoxicillin-clavulanate treatment group, treatment was rated as markedly effective in 92.6% of cases and effective in 5.6% of cases, yielding a clinical efficacy rate of 92.6% and a clinical response rate of 98.1%. In the amoxicillin treatment group, treatment was rated as markedly effective in 88.1% of cases and effective in 4.8% of cases, yielding a clinical efficacy rate of 88.1% and a clinical response rate of 92.9%. There was no significant different between treatment groups in terms of clinical efficacy or response rates. Secondary: Not reported
Jibril et al.[67] (1989) Amoxicillin 250 mg-500 mg TID vs amoxicillin 250-500 mg and clavulanate 62.5-125 mg TID	OL, PRO, RCT Children with bacterial pneumonia	N=100 Median 7 days	Primary: Clinical improvement Secondary: Time to clinical improvement, adverse reactions	Primary: Treatment with amoxicillin-clavulanate was more effective at achieving clinical improvement than amoxicillin (93.8 vs 60.4%; P<0.001). Secondary: Treatment with amoxicillin-clavulanate improved the symptoms more quickly than amoxicillin (2.92 vs 3.58 days). Mild rash or diarrhea was seen in two patients on amoxicillin-clavulanate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jensen et al.[68] (1988) Amoxicillin 50 mg/kg/day plus probenecid 250 to 750 mg/day for 14 days vs amoxicillin 50 mg/kg/day and clavulanate (4:1 ratio) plus probenecid 250 to 750 mg/day	SB Outpatient children and adults with COPD and ampicillin sensitive *Haemophilus influenzae*	N=71 2 week post-treatment	Primary: Clinical and microbial efficacy Secondary: Adverse events	Primary: No difference in clinical efficacy in symptomatic patients was observed (57% for amoxicillin vs 59% for amoxicillin-clavulanate). No difference in microbial eradication two weeks post-treatment between groups was observed (57% for amoxicillin vs 70% for amoxicillin-clavulanate). Treatment with amoxicillin-clavulanate was significantly better (P<0.05) than amoxicillin if more than one strain of *Haemophilus influenzae* was present. Beta-lactamase producing *Haemophilus influenzae* was detected at two weeks post-treatment in 29% of patients in the amoxicillin group and 23% of patients in the amoxicillin-clavulanate (P=NS). Secondary: Both groups experienced similar rates of adverse events (3%).
Morris et al.[69] (2010) Azithromycin 30 mg/kg as a single dose vs amoxicillin 50 mg/kg/day in two divided doses for a minimum of seven days	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days six to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days six to 11)	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *Streptococcus pneumoniae* compared to amoxicillin (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Clinical and microbiological outcomes	
Feder et al.[70] (1999) Amoxicillin 750 mg orally daily for 10 days vs penicillin V 250 mg orally TID for 10 days	PRO, RCT Children with group A β-hemolytic streptococcal pharyngitis	N=152 14 to 21 day follow-up	Primary: Clinical course, bacteriologic eradication within 18 to 24 hours, bacteriologic treatment failure rate at days four to six and days 14 to 21 Secondary: Not reported	Primary: No significant differences between clinical response (about 90% for both groups) or bacteriologic response at 18 to 24 hour follow-up visit. Treatment failure occurred in 5% of the patients in the amoxicillin group and 11% of the patients in the penicillin V group. Secondary: Not reported
Cohen et al.[71] (1996) Amoxicillin 50 mg/kg/day in two divided doses for six days vs penicillin V 45 mg/kg/day in three divided doses for 10 days	MC, OL, RCT Children with group A β-hemolytic streptococcal pharyngitis	N=318 1 month	Primary: Bacteriologic eradication at four days Secondary: Clinical efficacy, adverse events	Primary: Bacteriologic eradication at four days was similar between the amoxicillin and penicillin groups (83.7 vs 85.3%; P=0.71). Secondary: No significant differences in clinical efficacy were observed (clinical cure rate of 90.8% for amoxicillin vs 89% for penicillin). No serious adverse events were reported. Only three patients in the penicillin group discontinued treatment due to side effects.
Gopichand et al.[72] (1998) Amoxicillin 40 mg/kg/day TID for 10 days	PRO, RCT, SB Pediatric patients with group A streptococcal pharyngitis	N=113 10 days	Primary: Culture negativity at end of treatment Secondary: Resolution of	Primary: Treatment with amoxicillin was more likely to eradicate group A streptococcus compared to penicillin V (79.3 vs 54.5%; P=0.005). Secondary: Treatment with amoxicillin was more likely to resolve the symptoms

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs penicillin V 125 mg to 250 mg TID for 10 days			symptoms, adverse effects	compared to penicillin V (87.9 vs 70.9%; P=0.025). Two patients developed hives requiring discontinuation of penicillin V.
Addo-Yobo et al.[73] (2004) Amoxicillin 45 mg/kg orally in three divided doses vs penicillin G 200,000 units/kg/day in four divided doses	MC, OL, RCT Children 3 to 59 months of age who were hospitalized for severe pneumonia	N=1,702 Duration not specified	Primary: Treatment failure at 48 hours (clinical signs such as tachypnea, lower chest in-drawing) Secondary: Cumulative treatment failure at five and 14 days	Primary: The treatment failure rate for both groups was 19% at 48 hours. Secondary: The cumulative treatment failure rate was 22% for both groups at five days and was 27% in the amoxicillin group and 26% in the penicillin group at 14 days (95% CI, -5 to 5).
Atkinson et al.[74] (2007) Amoxicillin 8 mg/kg orally three times a day (children six months to 12 years) or 500 mg three times a day (children 12 to 16 years) vs penicillin benzyl 25 mg/kg IV four times a day (six	MC, RCT Children with community-acquired pneumonia	N=246 Variable duration	Primary: Time for the temperature to be <38 degrees C for 24 continuous hours and oxygen requirement to cease Secondary: Time in hospital, complications, duration of oxygen requirement and time to resolution of illness.	Primary: The time for temperature to settle and oxygen requirement to cease for those needing oxygen was similar in the two groups (1.3 and 1.2 days in the IV and oral groups, respectively; P=0.03). Secondary: The median length of hospital stay was significantly shorter in the oral group than in the IV group (1.77 and 2.1 days, respectively; P<0.001). The duration of oxygen requirement was significantly longer in the IV group than in the oral group (median 20.5 vs 11.0 hours; P=0.04). Three children in the oral group were changed to IV antibiotics and seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was nine days in both groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
months to 16 years) Children in the IV group were changed to oral amoxicillin after a median of six IV doses and received seven days of antibiotics in total.				
Lennon et al.[75] (2008) Amoxicillin 1,500 mg orally once daily (or 750 mg if <30 kg) for 10 days vs penicillin V 500 mg orally BID (or 250 mg if <20 kg) for 10 days	RCT Children with group A β-hemolytic streptococcal pharyngitis	N=353 36 days	Primary: Eradication of group A β-hemolytic streptococcal Secondary: Not reported	Primary: At visit two (days three to six), the between-treatment difference in the incidence of positive cultures was 0.3% with a bacteriological failure of 5.8% for amoxicillin and 6.2% for penicillin. At visit three (days 12 to 16), bacteriological failure was similar between groups (12.7 and 11.9% for amoxicillin and penicillin, respectively). At visit four (days 26 to 36), the incidence of positive cultures had increased with a between-treatment difference of 1.9% but bacteriological failure decreased slightly (10.7% for amoxicillin and 11.3% for penicillin V). There was no evidence of inferiority of amoxicillin to penicillin V at any time period. No significant differences in resolution of symptoms were noted between treatment groups. Secondary: Not reported
Sachs et al.[76] (1995) SMX-TMP 800-160 mg BID for	DB, RCT Patients ≥18 years of age with asthma or COPD	N=195 14 days	Primary: Peak expiratory flow Secondary:	Primary: Peak expiratory flow percent predicted assessed during an exacerbation improved significantly in all three groups over the 14-day observation period (P<0.001), ranging from 0.34 to 0.78% predicted per day, finally returning to baseline value. No statistically significant difference was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
seven days in addition to oral corticosteroids vs amoxicillin 500 mg TID for seven days in addition to oral corticosteroids vs oral corticosteroids			Not reported	observed between the groups. There was no statistically significant difference between the groups in symptom scores, expressed as slopes or absolute values from days one to 14. The decrease in the symptom severity scores was significant in all three groups (P<0.001). There was no statistically significant difference between the three groups in terms of treatment failure rate. Secondary: Not reported
Garau et al.[77] (2003) Amoxicillin-clavulanate extended-release tablets 2,000-125 mg BID for 7 to 10 days vs amoxicillin-clavulanate 875-125 mg TID for 7 to 10 days	DB, DD, MC, RCT Patients ≥ 18 years of age with radiologically confirmed community-acquired pneumonia	N=230 7 to 10 days	Primary: Clinical response at follow-up (days 28 to 35) Secondary: Clinical response at end of therapy (days nine to 14), bacteriological response at end of therapy and at follow-up, radiological response at end of therapy and at follow-up, adverse events	Primary: Clinical success rate was higher in the amoxicillin-clavulanate extended-release group compared to the amoxicillin-clavulanate group (94.7 vs 88.8%; 95% CI, 1.1 to 13.0). Secondary: Radiological efficacy at follow-up was higher in the amoxicillin-clavulanate extended-release group compared to the amoxicillin-clavulanate group (94.7 vs 87.9%). Radiological success rates at the end of therapy were similar for both treatment groups (88.1 vs 86.7%; 95% CI, -6.8 to 9.5). Bacteriological success rate at follow-up was higher in the amoxicillin-clavulanate extended-release group compared to the amoxicillin-clavulanate group (85.0 vs 77.3%; 95% CI, 15.8 to 31.2). Adverse events were similar in both treatment groups.
File et al.[78] (2004) Amoxicillin-clavulanate	DB, MC, PG, RCT Patients ≥ 16 years of age with a clinical and	N=633 7 days	Primary: Clinical response (sufficient improvement in the signs and	Primary: Clinical success rates were similar for both treatment groups (90.3% for amoxicillin-clavulanate extended-release vs 87.6% for amoxicillin-clavulanate; 95% CI, -3.0 to 8.3).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
extended-release 2,000-125 mg BID for seven days vs amoxicillin-clavulanate 875-125 mg BID for seven days	radiological diagnosis of community-acquired pneumonia		symptoms of pneumonia) at follow-up (days 28 to 35) Secondary: Radiological outcome, bacterial response, adverse events	Secondary: Bacteriological response rates were similar for both treatment groups at the end of therapy (90.5% for amoxicillin-clavulanate extended-release vs 82.5% for amoxicillin-clavulanate; 95% CI, -3.8 to 20.0) and at follow-up (86.6 vs 78.4%; 95% CI, -5.8 to 22.1). Radiological response rates at follow-up were also similar for both treatment groups (93.1 vs 90.3%; 95% CI, -2.1 to 7.8). Rates of adverse events reported were similar in both treatment groups (40.4% in the amoxicillin-clavulanate extended-release group vs 42.1% in the amoxicillin-clavulanate group).
Matho et al.[79] (2018) Standard-dose immediate-release amoxicillin-clavulanate 875-125 mg BID (total daily dose, 1,750 mg) vs high-dose extended-release amoxicillin-clavulanate (initially [Time Period 1] 1,000-62.5 mg ER BID which became a discontinued product, then [Time Period 2] 875-125 mg IR	DB, RCT Patients ≥18 years of age with acute bacterial sinusitis, as defined by the 2012 IDSA clinical guidelines: 1) persistent symptoms and not improving (lasting for ≥ 10 days); 2) severe symptoms or signs of fever ≥ 102 degrees F and nasal discharge or facial pain (lasting for ≥ 3 to 4 days); or 3) worsening symptoms or signs characterized by new onset of fever, headache, or increase in nasal discharge following	N=315 10 days	Primary: Percent of patients in each group who gave a global rating of 5 or 6 after three days of treatment (1 = a lot worse, 2 = a little worse, 3 = the same, 4 = a little better, 5 = a lot better, and 6 = no symptoms) Secondary: Percent that gave a global rating of 5 or 6 at Day 10 and the average changes in the ratings on the Sinonasal Outcome Test-16 questions at Day 3 and Day 10	Primary: The primary outcome was reported overall by 36.4% of standard-dose vs 44.8% of high-dose participants (P=0.15); during Time Period 1 by 37.9% of standard-dose vs 38.8% of ER high-dose participants (P=0.91); and during Time Period 2 by 34.4% of standard-dose vs. 52.4% of IR high-dose participants. Secondary: The secondary efficacy outcomes did not differ significantly. Most patients in both arms reported major improvement at Day 10 regardless of time period. The mean Sinonasal Outcome Test-16 item scores from Day 0 did not improve significantly at either Day 3 or Day 10.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and amoxicillin 875 mg IR BID was used; total daily dose was 4,000 mg then 3,500 mg)	a typical viral URI that lasted 5 to 6 days and was initially improving		compared to baseline ratings (with a minimally important difference of 0.5 units)	
Hazir et al.[80] (2008) Amoxicillin 80 mg to 90 mg/kg/day in two divided doses for five days (at home) vs ampicillin 100 mg/kg per day in four doses for 48 hours (inpatient), followed by three days of oral amoxicillin 80 mg to 90 mg/kg/day	OL, RCT Children 3 to 59 months of age with severe pneumonia	N=2037 14 days	Primary: Treatment failure by day six Secondary: Not reported	Primary: There were 87 (8.6%) treatment failures in the hospitalized group and 77 (7.5%) in the ambulatory group (95% CI, -1.3 to 3.5) by day six. Five (0.2%) children died within 14 days of enrollment, one in the ambulatory group and four in the hospitalized group. In each case, treatment failure was declared before death and the antibiotic had been changed. None of the deaths were considered to be associated with treatment allocation. There were no serious adverse events reported in the trial. Secondary: Not reported
Marple et al.[81] (2010) Azithromycin ER 2 g as a single dose vs amoxicillin-clavulanate 875-125 mg every 12 hours for 10 days	MC, OL, RCT Patients ≥18 years of age with acute, uncomplicated, bacterial maxillary sinusitis based on signs and symptoms lasting for 7 to 30 days	N=751 28 days	Primary: Symptom resolution at day five in the per protocol population Secondary: Time to resolution of symptoms, sinusitis-related quality of life,	Primary: At day five in the per protocol population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference, 10.8%; 95% CI, 3.1 to 18.4). At day five in the intent to treat population, a significantly greater percentage of patients in the azithromycin group met the primary end point (20.0%) than in the amoxicillin-clavulanate group (13.2%; difference, 6.8%; 95% CI, 1.5 to 12.2). Secondary: Over the course of the trial, both treatments led to similar rates of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			resource use, treatment success, and treatment satisfaction	symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared to 63.0% of patients receiving amoxicillin-clavulanate. In the per protocol population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%). A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the two treatment arms. Patients treated with azithromycin reported greater satisfaction with the convenience of the medication than did patients given amoxicillin-clavulanate (difference, 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference, −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76 vs 60.92%; P=0.02). There was no difference in the incidence of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[82] (2011) Azithromycin ER 60 mg/kg as a single dose vs amoxicillin-clavulanate	DB, MC, RCT Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test of cure visit (days 12 to 14) in the bacteriologic eligible population Secondary: Bacterial response at other visits,	Primary: Clinical response at the test of cure visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference, – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate. Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). All patients receiving treatment with azithromycin received their single

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
45-3.2 mg/kg every 12 hours for 10 days			compliance, and safety	dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared to 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in 8.2% of patients receiving amoxicillin-clavulanate.
Noel et al.[83] (2008) Levofloxacin 10 mg/kg BID vs amoxicillin-clavulanate (amoxicillin 45 mg/kg) BID	MC, RCT, SB Children six months to five years of age with recurrent and/or persistent acute otitis media that was unchanged or worsened after ≥three days of treatment with an antimicrobial regimen used to treat acute otitis media	N=1,650 27 days	Primary: Clinical cure rates at visit three (two to five days post-therapy) Secondary: Clinical cure rate at visit four (10 to 17 days post therapy), clinical success (cured or improved) at visits three and four, safety	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9 vs 66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9 vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit four were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit three were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit four were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Thomsen et al.[84] (1997)	DB, PRO, RCT Children 1 to 10	N=360 2 months after	Primary: Improved tympanometric	Primary: Amoxicillin-clavulanate treatment for 28 days was significantly more efficacious than amoxicillin-clavulanate for 14 days (P=0.07), penicillin V

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amoxicillin-clavulanate 12.5-3.125 mg orally BID for 14 days vs amoxicillin-clavulanate 12.5-3.125 mg orally BID for 28 days vs penicillin V 25 mg orally BID for 14 days vs penicillin V 25 mg orally BID for 28 days	years of age with secretory otitis media of at least three months duration	initiation of therapy	findings at 14 and 28 days after start of therapy Secondary: Not reported	for 14 days (P=0.005), and penicillin V for 28 days (P<0.001) at improving tympanometric testing (44, 31, 23, and 19%, respectively). Secondary: Not reported
Brook et al.[85] (1989) Amoxicillin-clavulanate 40 mg/kg/day in four divided doses for 10 days vs penicillin VK 40 mg/kg/day in four divided doses for	DB, PRO, RCT Children 4 to 16 years of age with acute recurrent group A β-hemolytic streptococcal tonsil-litis (>2 episodes per year) despite prior treatment with antibiotics for 10 days (penicillin or erythromycin)	N=43 Up to 1 year	Primary: Group A β-hemolytic streptococcal eradication 10 days post-therapy Secondary: Recurrence of tonsillitis in one year	Primary: Treatment with amoxicillin-clavulanate eradicated group A β-hemolytic streptococcal more effectively than penicillin VK (100 vs 70%; P<0.001). Secondary: Treatment with amoxicillin-clavulanate prevented recurrent tonsillitis more effectively than penicillin VK (89 vs 42%; P< 0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
10 days				
Siempos et al.[86] (2007) Quinolones vs amoxicillin-clavulanate vs macrolides	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37; 95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones. Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Feder et al.[87] (1982) SMX-TMP 37.5-	DB, RCT Patients two months to seven years of	N=282 14 days	Primary: Premature discontinuation of therapy due to ≥5	Primary: Therapy was discontinued in significantly more ampicillin-treated patients compared to amoxicillin-treated patients (P<0.01) or SMX-TMP-treated patients (P<0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
7.5 mg/kg/day divided into two doses for 14 days vs ampicillin 70 mg/kg/day divided into four doses for 14 days vs amoxicillin 30 mg/kg/day divided into three doses for 14 days	age with signs/symptoms of otitis media in addition to a bulging tympanic membrane with decreased mobility		watery stools per day, diarrhea Secondary: Not reported	Among patients who completed a full course of therapy, significantly more ampicillin-treated patients developed diarrhea compared to amoxicillin-treated patients (P<0.04) or SMX-TMP-treated patients (P<0.02). Initial symptom resolution occurred after approximately two days of treatment in all three groups. Secondary: Not reported
Mackay et al.[88] (1980) Ampicillin 250 mg orally TID for seven days vs ampicillin 500 mg orally TID for seven days vs amoxicillin 250 mg orally TID for seven days vs	DB, MC, RCT Patients with acute exacerbations of chronic bronchitis	N=199 7 days	Primary: Clinical response (no indication for continued antibiotics), days for sputum to become mucoid Secondary: Not reported	Primary: There was no significant difference between any of the treatment groups in clinical response (70, 74, 62, and 74%) or in days for sputum to become mucoid (5.1, 5.2, 5.0, and 5.0). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amoxicillin 500 mg orally TID for seven days				
Chodosh et al.[89] (1982) SMX-TMP 800-160 mg BID for 14 days vs ampicillin 500 mg, one capsule QID for 14 days	DB, RCT, XO Patients ≥18 years of age with chronic bronchitis who developed an acute bronchial infectious exacerbation within two weeks of the study *Pseudomonas, Klebsiella*, or *Staphylococcus aureus* were isolated	N=21 14 days	Primary: Chest symptoms, physical findings, vital signs, pulmonary function, laboratory values, sputum analysis, time to recurrence of exacerbation Secondary: Not reported	Primary: Patients in the ampicillin group experienced a longer recurrence-free time compared to patients in the SMX-TMP group (P<0.05). Sputum volumes decreased significantly in each treatment group, starting on day three of the study (P<0.05). While none of the patients in the ampicillin group discontinued therapy due to adverse effects, three patients in the SMX-TMP group discontinued treatment. There were no significant differences noted between the two study drugs in all other outcome measures. Secondary: Not reported
Macfarlane et al.[90] (1983) Erythromycin lactobionate 300 mg IV every 6 hours for 48 hours, followed by erythromycin stearate 500 mg orally QID for seven days vs ampicillin 500 mg IV every 6 hours	DB, RCT Patients <80 years of age with primary pneumonia, including Legionnaires' disease	N=122 9 days	Primary: Clinical response to therapy (categorized as uncomplicated recovery, complicated recovery, or fatality) Secondary: Not reported	Primary: Clinical response to therapy in all categories was similar between the groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 48 hours, followed by amoxicillin 500 mg orally QID for seven days				
Aubier et al.[91] (2002) Telithromycin 800 mg daily for five days vs amoxicillin-clavulanate 500 mg TID for 10 days	DB, PG, RCT Patients ≥18 years of age with an acute exacerbation of chronic bronchitis	N=325 31 to 36 days	Primary: Clinical cure rate at the test of cure visit (days 17 to 21) Secondary: Clinical cure rate at the late post-therapy visit (days 31 to 36), bacteriologic outcomes at the test of cure visit (days 17 to 21) and late post-therapy visit (days 31 to 36)	Primary: There was no significant difference in clinical cure rates between groups at the test of cure visit (86.1% for telithromycin and 82.1% for the amoxicillin-clavulanate group). Secondary: There was no significant difference in clinical cure rates at the late post-therapy visit between groups (78.1% for telithromycin and 75.0% for amoxicillin-clavulanate). Bacteriologic outcome was judged as satisfactory in 69.2% of patients in the telithromycin group and 70.0% of patients in the amoxicillin-clavulanate group.
Seki et al.[92] (2009) Ampicillin-sulbactam 3 g IV BID for 7 to 14 days vs piperacillin 2 g IV BID for 7 to 14 days	RCT Patients with mild to severe community-acquired pneumonia	N=109 7 to 14 days	Primary: Efficacy and safety Secondary: Not reported	Primary: The total efficacy rate was 77.4% in the piperacillin group and 67.3% in the ampicillin-sulbactam group. There was no significant difference among the treatment groups. There was a significant difference in efficiency between piperacillin and ampicillin-sulbactam treatments in male patients (79.4 vs 55.6%, respectively; P<0.046), patients with underlying disease (83.3 vs 57.6%, respectively; P<0.019), and in respiratory disease patients (84.6 vs 28.6%, respectively; P<0.022). There was also a significant difference in efficiency among ampicillin-sulbactam groups dependent on age. In the piperacillin group, adverse reactions were seen in 5.4% of patients and the major adverse reactions were diarrhea and hepatic dysfunction. In

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the ampicillin-sulbactam group, adverse reactions were seen in 9.4% of the patients, with the major adverse reactions being diarrhea and hepatic dysfunction. No significant differences were found between the groups. All reactions were mild or moderate and transient. Secondary: Not reported.
Allewelt et al.[93] (2004) Ampicillin-sulbactam vs clindamycin with or without cephalosporin Dosing varied per patient	MC, OL, PRO, RCT Patients with aspiration pneumonia and lung abscess	N=70 Mean 23.4 days	Primary: Clinical response Secondary: Not reported	Primary: Clinical response at end of therapy in the ampicillin-sulbactam group was 73.0 vs 66.7% in the clindamycin group (P=0.06 and P=0.02, respectively). Clinical response at seven to 14 days after therapy was 65.7% in the ampicillin-sulbactam group vs 63.5% in the clindamycin group (P=0.10 and P=0.04). Duration of therapy was 22.7 days in the ampicillin-sulbactam group vs 24.1 days in the clindamycin group. Secondary: Not reported
Yanagihara et al.[94] (2006) Imipenem-cilastatin 0.5 g BID vs ampicillin-sulbactam 3 g BID	PRO, RCT Elderly patients >65 years of age with moderate-to-severe community-acquired pneumonia	N=67 7 to 14 days	Primary: Clinical efficacy Secondary: Bacteriological efficacy, adverse events	Primary: Overall clinical efficacy of ampicillin-sulbactam therapy was 91.4% compared to 87.5% for imipenem-cilastatin therapy (P=NS). Secondary: The eradication rate was 100% in both treatment arms (P=NS). The overall eradication rate for the pathogenic microorganism was 84% in the ampicillin-sulbactam group and 80%in the imipenem-cilastatin group (P=NS). All adverse reactions were mild or moderate and transient in both treatment groups.
Peyramond et al.[95] (1996)	MC, OL, PRO, RCT	N= 234 1 month	Primary: Group A β-hemolytic	Primary: Successful group A β-hemolytic streptococcal eradication was similar between the two treatment groups at end of treatment (92% for amoxicillin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Penicillin V 1 million units TID for 10 days vs amoxicillin 1 g BID for six days	Patients with group A β-hemolytic streptococcal acute tonsillitis	posttreatment follow-up	streptococcal eradication Secondary: Clinical efficacy, adverse effects	vs penicillin V 92.7%; P=0.95) and at one month post-treatment (90.8 vs 92.6%; P=0.85). Secondary: Clinical response rates were similar between the two groups at end of treatment (96% for amoxicillin vs 95.4% for penicillin; P=0.92) and at one month (91.7 vs 94.7%; P=0.59). Adverse effects occurred in 3% of patients in the amoxicillin group and 5.2% of the patients in the penicillin group, with three patients in the penicillin group requiring discontinuation of treatment.
Curtin-Wirt et al.[96] (2003) Penicillin V 35 mg/kg/day in two divided doses vs amoxicillin 35 mg/kg/day in two divided doses	OL, OS, PRO Children with group A β-hemolytic streptococcal tonsillo-pharyngitis	N=276 6 to 14 day posttreatment	Primary: Bacteriologic cure rate Secondary: Clinical cure rate	Primary: Bacteriologic cure rate was 76% in the amoxicillin group vs 64% in the penicillin group (P=0.04). Secondary: Clinical cure rate was 84% in the amoxicillin group vs 73% in the penicillin group (P=0.03).
Réa-Neto et al.[97] (2008) Doripenem 500 mg IV every eight hours vs piperacillin-tazobactam 4.5 grams IV every six hours	MC, OL, PRO, RCT Patients aged 18 years or older with signs and symptoms of nosocomial pneumonia, including non-ventilated patients and those with early-onset ventilator-associated	N=448 7 to 14 days	Primary: Clinical cure rate in the clinically evaluable population and in the clinically evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the end of IV therapy and at	Primary: The clinical cure rates in clinically evaluable patients at the test-of-cure visit were 81.3% in the doripenem arm and 79.8% in the piperacillin-tazobactam arm (95% CI, -9.1 to 12.1). In the clinically evaluable-modified intent-to-treat population, the clinical cure rates in the doripenem and piperacillin-tazobactam arms were 69.5 and 64.1%, respectively (95% CI, -4.1 to 14.8). Secondary: Clinical response rates at the end of IV study drug therapy in clinically evaluable patients were 87% in both treatment arms (95% CI, -9.2 to 9.2%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pneumonia		the late follow-up visit, clinical and microbiological cure rates in the microbiologically evaluable patients at the test-of-cure visit and in the microbiologically evaluable-modified intent-to-treat population, clinical and microbiological cure rates at the test-of-cure visit in microbiologically evaluable patients with early-onset ventilator-associated pneumonia, and all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population.	Clinical relapse rates at the late follow-up visits were low for both the doripenem (3%) and piperacillin-tazobactam (4%) treatment arms. The clinical cure rates in microbiologically evaluable patients at the test-of-cure visit were 82.1 and 78.3% (95% CI, -9.4 to 17.1) in the doripenem and piperacillin-tazobactam arms, respectively. In the microbiologically evaluable-modified intent-to-treat population, clinical cure rates were 67.6 and 67.4%, respectively (95% CI, -11.4 to 11.9). Microbiological responses in the microbiologically evaluable patients at the test-of-cure visit were achieved in 84.5% of patients in the doripenem arm and 80.7% of patients in the piperacillin-tazobactam arm (95% CI, -8.9 to 16.5). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 13.8% with doripenem and 14.6% with piperacillin-tazobactam (95% CI, -7.9 to 6.3). A Kaplan-Meier analysis found no difference in cumulative mortality rate between the two treatment arms.
Ito et al.[98] (2010) Imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days vs	OL, RCT, SC Patients aged ≥15 years of age with a risk for aspiration who had been hospitalized after developing moderate-to-severe	N=469 30 days	Primary: Clinical response rate at the end of treatment in validated per protocol population Secondary:	Primary: At the end-of-treatment visit, the clinical effective rate for the validated per protocol population was 83% for piperacillin-tazobactam and 82% for imipenem-cilastatin (P=0.92). Secondary: There were no significant differences between the groups in any of the secondary outcome measures.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
piperacillin-tazobactam 5 g IV every 12 hours for 7 to 14 days	pneumonia in the community or nursing home		Clinical response during treatment (days four and seven) and at the end of study in validated per protocol population, and survival at day 30 in modified intention-to-treat population	Mortality rate within 30 days of admission in modified intention-to-treat population was 15% in the piperacillin-tazobactam group and 24% in the imipenem-cilastatin group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving piperacillin-tazobactam and 31% of patients receiving imipenem-cilastatin.
Schmitt et al.[99] (2006) Imipenem-cilastatin 4 g-500 mg every eight hours vs piperacillin-tazobactam 1 g-1 g every eight hours Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present.	DB, MC, RCT Hospitalized patients with nosocomial pneumonia	N=221 5 to 21 days	Primary: Clinical response at the end of the treatment period Secondary: Clinical responses on the last day of treatment or on day 21 and on day 14±7 days after treatment, bacteriological responses, safety	Primary: Therapeutic response was seen in 66% [95% CI, 56.5 to 75] of patients receiving piperacillin-tazobactam and in 70% [95% CI, 60.4 to 78.2] of patients receiving imipenem-cilastatin. Failure rates were similar at 18.7 and 18.2%, respectively. On the last day of treatment or on day 21, therapeutic responses were higher and seen in 71% [95% CI, 61.3 to 79.2] and 77.3% [95% CI, 68.1 to 84.5] of patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. Failure rates were 17.8 and 16.4% respectively. Secondary: At the second follow-up (14±4 days after the end of treatment) clinical responses were 59.8% [95% CI, 49.9 to 69] and 66.4% [95% CI, 56.6 to 74.9] and failure rates were 19.6 and 15%, in patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. The majority of patients in both groups responded to treatment and the overall response rate was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods. Eradication immediately after treatment with piperacillin-tazobactam or imipenem-cilastatin was 45.7 and 52.7%, respectively compared to 40.3 and 50% at the first follow-up and 34.6 and 42.2% at the second follow-up, respectively. Overall, 74.5 and 64.9% of patients receiving piperacillin-tazobactam and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				imipenem-cilastatin, respectively reported adverse events, the majority of which were of mild intensity. The most common related adverse events were diarrhea and fever in the piperacillin-tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem-cilastatin group.
Joshi et al.[100] (2006) Imipenem-cilastatin 500 mg IV every six hours vs piperacillin-tazobactam 4.5 grams IV every six hours Patients also received aminoglycoside therapy.	DB, MC, RCT Hospitalized patients with acute nosocomial pneumonia	N=437 21 days	Primary: Clinical cure and microbiological response rates; pathogen eradication rates; length of hospital stay; hospital readmissions; adverse events Secondary: Not reported	Primary: The overall clinical cure rate was 68% in piperacillin-tazobactam patients and 61% in imipenem patients in the efficacy evaluable population (P=0.256). Microbiological response rates were comparable among efficacy evaluable patients treated with piperacillin-tazobactam and those treated with imipenem. Microbiological responses for piperacillin-tazobactam and imipenem patients were: eradication, 64 vs 59%; persistence, 29 vs 21%; relapse, 0 vs 5%; and superinfection, 7 vs 15%, respectively. Gram-positive isolates were eradicated in 83% of piperacillin-tazobactam patients and 75% of imipenem patients; Gram-negative pathogens were eradicated in 72% of piperacillin-tazobactam patients and 77% of imipenem patients. Piperacillin-tazobactam and imipenem patients had similar hospital and intensive care unit length of stay. Hospital readmission rates in both groups were small and were not significantly different. There were no significant differences in adverse events between the two treatment groups. Secondary: Not reported
Miscellaneous Infections				
Kacmar et al.[101] (2001) Amoxicillin 500 mg TID for seven days	RCT, SB Women with *Chlamydia trachomatis* in pregnancy before 33	N=39 4 to 6 weeks post-therapy	Primary: Clinical response Secondary: Not reported	Primary: No statistically significant differences in side effects, compliance, or efficacy were observed between the two treatment groups. Secondary: Not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs azithromycin 1 g single dose	weeks gestation			
Smith et al.[102] (2021) SCAMP Ampicillin, gentamicin, and metronidazole (group 1) vs ampicillin, gentamicin, and clindamycin (group 2) vs piperacillin-tazobactam and gentamicin (group 3) Doses stratified by postmenstrual age; Additional gram-positive therapy (e.g., vancomycin, nafcillin, oxacillin, linezolid) was permitted at the discretion of the	MC, OL, RCT Infants ≤33 weeks gestational age at birth with a postnatal age <121 days, who demonstrated physical, radiologic, and/or bacteriologic findings consistent with complicated intra-abdominal infection (cIAI) Due to slow enrollment, a protocol amendment allowed eligible infants already receiving study regimens to enroll without randomization	N=180 (128 randomized [R], 52 non-randomized [NR]) 30 days	Primary: Mortality within 30 days of study drug completion Secondary: Adverse events, outcomes of special interest, and therapeutic success (absence of death, negative cultures, and clinical cure score >4) 30 days after study drug completion	Primary: Twenty-nine (16%) infants were transferred or discharged before the 30-day safety and overall therapeutic success evaluations. Thirty-day mortality was 8%, 7%, and 9% in groups 1, 2, and 3, respectively. Secondary: There were no differences in safety outcomes between antibiotic regimens. After adjusting for treatment group and gestational age, mortality rates through end of follow-up were 4.22 (95% CI, 1.39 to 12.13), 4.53 (95% CI, 1.21 to 15.50), and 4.07 (95% CI, 1.22 to 12.70) for groups 1, 2, and 3, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treating physician				
Hsu et al.[103] (2015) Reverse hybrid therapy (pantoprazole 40 mg plus amoxicillin 1 g twice daily for 12 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the first seven days) vs standard triple therapy (pantoprazole 40 mg plus clarithromycin 500 mg and amoxicillin 1 g twice daily for 12 days).	MC, RCT, SB Patients ≥20 years of age diagnosis of *H pylori* was based on at least two positive results of rapid urease test, histology, and culture and with endoscopically proven peptic ulcer diseases or gastritis	N=440 6 weeks after treatment	Primary: Eradication rate Secondary: Frequency of adverse events, drug compliance	Primary: Intent-to-treat eradication rates were 93.6 and 86.8% for reverse hybrid and standard triple therapies, respectively. Reverse hybrid therapy achieved a higher eradication rate than standard triple therapy (95% CI, 1.3 to 12.3%; P=0.016). The modified intent-to-treat (95.4 vs 88.4%) and per-protocol analyses (95.7 vs 88.3%) yielded similar results (P=0.008 and 0.005, respectively). Secondary: The incidences of adverse events in the participants receiving reverse hybrid and standard triple therapies were 14.1% (95% CI, 9.2 to 19.0%) and 9.5% (95% CI, 5.6 to 13.4%), respectively. The two therapies exhibited similar frequencies of overall adverse events (P=0.14). Reverse hybrid and standard triple groups displayed similar compliance rates (96.8%; 95% CI, 94.5 to 99.1% and 98.6%; 95% CI, 97.1 to 100.2%, respectively).
Molina-Infante et al.[104] (2013) Hybrid therapy (40 mg omeprazole and 1 g amoxicillin, twice	NI, PRO, RCT Consecutive adult patients with *H pylori* infection and dyspepsia, peptic ulcer disease, or familiar history of	N=343 8 weeks posttreatment	Primary: Eradication rates in the intent-to-treat population Secondary: Eradication rates in the per-protocol	Primary: In the intent-to-treat analysis, eradication rates were 153 of 170 (90%; 95% CI, 86 to 93%) for hybrid and 156 of 170 (91.7%; 95% CI, 88 to 95%) for concomitant therapy (P=0.35). Secondary: Eradication rates in the per-protocol analysis were 150 of 163 (92%; 95% CI, 87 to 95%) for hybrid therapy and 150 of 156 (96.1%; 95% CI, 93 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily for 14 days; 500 mg clarithromycin and 500 mg nitroimidazole were added, twice daily for the final seven days) vs concomitant therapy (same four drugs taken concurrently, twice daily for 14 days)	gastric cancer, who did not receive prior eradication therapy		population, compliance	99%) for concomitant therapy (P=0.07). More patients were compliant (defined as compliance ≥80%) with hybrid therapy (98.8%) than concomitant therapy (95.2%; P=0.05).
Ohlin et al.[105] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and lansoprazole 30 mg BID for 14 days (LAC) vs lansoprazole 30 mg BID and amoxicillin 1g BID for 14 days (LA) vs	DB, MC, RCT Patients 18 to 80 years of age with *H pylori* infection and a present recurrent duodenal ulcer and/or previous recurrent duodenal ulcer	N=177 4 weeks posttreatment	Primary: Eradication of *H pylori* at least four weeks after the end of treatment period Secondary: Not reported	Primary: Triple therapy with LAC was significantly better than either dual therapy with OA or LA in ulcer healing and eradication of *H pylori* (P<0.001). There was no significant difference between dual therapy groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
omeprazole 20 mg BID and amoxicillin 1g BID for 14 days (OA)				
Magaret et al.[106] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	MC, RCT Patients years of age failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[107] (2003) Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14	RCT, XO Patients 18 to 80 years of age with at least one previous failure of *H pylori* therapy documented by confirmatory examinations and antimicrobial	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated 13C-urea breath test to confirm successful treatment	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	resistance to both metronidazole and clarithromycin		Secondary: Not reported	Secondary: Not reported
Perri et al.[108] (2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID,	OL, PRO, RCT Patients with *H pylori* infection confirmed by 13C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative 13C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups ($P<0.025$). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, ($P<0.0001$), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)				
Katelaris et al.[109] (2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days (BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and	MC, OL, PG, RCT Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and 13C-urea breath test	N=405 8 weeks	Primary: At week eight, ^{13}C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analyses, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clarithromycin 500 mg BID (PAC7)				
Uygun et al.[110] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[111] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and amoxicillin)	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary: Not reported	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95% CI, 74 to 92; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)				Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[112] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[113] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported
Zheng et al.[114] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The H pylori primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[115] (1998)	OL, PG, RCT Patients with upper	N=168 8 weeks	Primary: Endoscopy performed six	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days	gastrointestinal symptoms and infected with *H pylori*		weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Luther et al.[116] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)				Secondary: Not reported
Henry et al.[117] (2003) Azithromycin 500 mg daily for 3 days (AZM-3) vs azithromycin 500 mg daily for 6 days (AZM-6) vs amoxicillin-clavulanate 500 mg TID for 10 days (AMC)	DB, DD, MC, RCT Patients 18 years of age or older with acute bacterial sinusitis	N=936 28 days	Primary: Clinical success at end of study Secondary: Not reported	Primary: Cure rates were 71.7% in the AZM-3 group, 73.4% in the AZM-6 group, and 71.3% in the AMC group. There was no significant difference between groups. Secondary: Not reported
Klapan et al.[118] (1999) Azithromycin 500 mg daily for three days vs amoxicillin-clavulanate 625	OL, RCT Patients 15 to 50 years of age with sinusitis	N=100 4 weeks	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: Cure was established in 95% of patients in the azithromycin group and 74% of patients in the amoxicillin-clavulanate group at the end of therapy (day 10 to 12), and clinical improvement was seen in the remainder of patients in both groups (P=0.012 in favor of azithromycin). At the follow-up visit (four weeks), cure was established in 98% of patients in the azithromycin group and 91% in the amoxicillin-clavulanate group. No significant differences were observed between groups (P>0.05). There was no significant difference in bacteriologic response seen between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg every 8 hours for 10 days				groups (P=0.409). Secondary: Not reported
Gupta et al.[119] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg once daily as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy	OL, RCT, SC Pediatric patients two to 15 years of age with low-risk febrile neutropenia	N=88 (123 episodes) Variable duration	Primary: Treatment success Secondary: Not reported	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported
Desrosiers et al.[120] (2008) Telithromycin 800 mg once daily for five days vs amoxicillin-clavulanate 875-125 mg BID for 10 days	MC, OL Patients ≥18 years old with clinical and radiological diagnosis of acute bacterial sinusitis	N=298 Up to 49 days	Primary: Clinical success, adverse events, and quality of life Secondary: Not reported	Primary: The per protocol clinical success rate measured at the test-of-cure visit was 88.6% with telithromycin compared to 88.8% in the amoxicillin-clavulanate treatment group (95% CI, -8.9 to 8.5). At the follow-up visit (days 41 to 49), 84.6% of patients in the telithromycin group achieved clinical success, compared to 84.8% of those in the amoxicillin–clavulanate group. Median times to reduction of total symptom scores were shorter for telithromycin vs amoxicillin–clavulanate (seven days vs eight days [75% reduction] and four days vs five days [50% reduction] with the difference being statistically significant for the 50% reduction (P=0.044).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Treatment-emergent adverse events occurred in 20.7% of telithromycin-treated patients vs 31.8% of amoxicillin-clavulanate-treated patients (P=0.034). In the baseline SF-36 health questionnaire, 75.5% of patients (209/278) described themselves as feeling much or somewhat worse than a week earlier (telithromycin, 74.2% and amoxicillin–clavulanate, 76.6%). Secondary: Not reported
Ziogos et al.[121] (2010) Cefuroxime 1.5 g IV as a single dose vs ampicillin-sulbactam 3 g IV as a single dose	RCT Women scheduled for cesarean delivery	N=176 30 days	Primary: Development of an infection Secondary: Not reported	Primary: Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses six or more vaginal examinations prior to the operation (P=0.004), membrane rupture for more than six hours (P=0.08) and blood loss greater than 500 mL (P=0.018) were associated with developing a postoperative surgical site infection. In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative surgical site infection (OR, 6.8; 95% CI, 1.4 to 33.4; P=0.019). Regular prenatal follow-up was associated with a protective effect (OR, 0.04; 95% CI, 0.005 to 0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of five vs four days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported. Secondary: Not reported
McKinnon et al.[122] (1999) Ampicillin-	OL, MC, RETRO Patients with skin and soft tissue,	N=890 Duration not specified	Primary: Clinical response rate	Primary: Rate of satisfactory clinical response was highest with ampicillin-sulbactam 1.5 g (85.9 vs 82.5% for ampicillin-sulbactam 3.0 g vs 77.5% for ticarcillin-clavulanate; P=0.044).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sulbactam 1.5 or 3.0 g every 6 hours vs ticarcillin-clavulanate 3.1 g every six hours	intraabdominal, gynecologic, respiratory, urinary tract, or other infections requiring parenteral antibiotic therapy		Secondary: Bacteriologic cure rate	Secondary: Overall bacteriologic efficacy of ampicillin-sulbactam and ticarcillin-clavulanate were not statistically different, with the exception of a higher bacteriologic eradication rate for ticarcillin-clavulanate against *Pseudomonas* species (P=0.013).
Tanaka-Kido et al.[123] (1990) Chloramphenicol 100 mg/kg/day in 4 divided doses, which was continued for 8 days after the last fever day vs aztreonam 150 mg/kg/day IV in 3 divided doses, which was continued for 8 days after the last fever day	RCT Patients 2 to 6 years of age with typhoid fever	N=36 1 month	Primary: Clinical cure rate, fever duration, relapse rate, adverse effects Secondary: Not reported	Primary: There was no significant difference between the chloramphenicol and aztreonam groups in clinical cure rate (94 vs 100%). There was no significant difference between the chloramphenicol and aztreonam groups in fever duration (4.1 vs 5.9 days, respectively; P>0.05). There were no relapses in either of the two groups. While there was no incidence of anemia in the aztreonam group, there were five cases of anemia in the chloramphenicol group (P<0.05). There was no difference in the incidence of leukopenia and neutropenia between the two treatment groups (P>0.05). The approximate mean duration of antibiotic therapy was 15 days in the aztreonam group and 13 days in the chloramphenicol group. Secondary: Not reported
Gotuzzo et al.[124] (1994) Chloramphenicol 50 mg/kg/day oral/IV in 4 divided doses for 14 days	MC, RCT Patients >14 years of age with typhoid fever	N=44 10 weeks	Primary: Clinical cure rate, fever duration, bacteremia Secondary: Not reported	Primary: There was a significant difference between the chloramphenicol and aztreonam groups in terms of clinical cure rates (100 vs 68%, respectively; P<0.01). Defervescence occurred more quickly in patients receiving chloramphenicol compared to patients on aztreonam therapy (4.5 vs 6.6 days, respectively; P<0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs aztreonam 2 g IV every 8 hours for 10 days				There were no relapses in either of the two groups. While 24-hour positive blood cultures occurred in 32% of patients on chloramphenicol therapy, none of the patients in the aztreonam group had positive blood cultures (P<0.05). Adverse reactions experienced by patients in each treatment group deemed unusual or mild with no statistical difference found between the two groups. Secondary: Not reported
Rodriguez et al.[125] (1986) Chloramphenicol 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 4-6 divided doses vs ampicillin 400 mg/kg/day IV in 4-6 divided doses plus sulbactam 50 mg/kg/day	MC, PRO, RCT Hospitalized patients 1 month to 14 years of age with meningitis	N=81 10 days	Primary: Mortality rate, resolution of symptoms, complications, adverse effects Secondary: Not reported	Primary: Of the patients with assessable CSF pathogens, the mortality rate was 3% in the ampicillin-sulbactam group and 18% in the chloramphenicol-ampicillin group. Neurologic sequelae occurred in 12% of patients on ampicillin-sulbactam and 18% of patients on chloramphenicol-ampicillin therapy. The mean time to resolution of symptoms was 4.4 days in the ampicillin-sulbactam group and 4.8 days in the chloramphenicol-ampicillin. Abnormal laboratory findings were found in 20% of the ampicillin-sulbactam group and 35% in the chloramphenicol-ampicillin group. Secondary: Not reported
Girgis et al.[126] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every	RCT Patients with bacterial meningitis	N=100 6 days	Primary: Cerebrospinal fluid leukocyte count, glucose, protein content, disappearance of meningeal	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the cerebrospinal fluid leukocyte count, glucose or protein content at baseline,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
six hours (AMCL) vs ceftriaxone 100 mg/kg once daily			irritation, fever defervescence, patient alertness, mortality rate Secondary: Not reported	as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%. Secondary: Not reported
Girgis et al.[127] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every six hours (group 1) vs ceftriaxone 100 mg/kg IV once daily (group 2)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary: Not reported	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *Streptococcus pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively. Secondary: Not reported
Jacobs et al.[128] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50 to 100 mg/kg/dose IV every six hours vs cefotaxime 50 mg/kg/dose IV every six hours	PRO, RCT Patients one week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rodriguez et al.[129] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 400 mg/kg/day IV in six divided doses vs ceftazidime 150 mg/kg/day IV divided into three doses, administered every eight hours	OL, RCT Patients one month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological sequelae, mean duration of therapy Secondary: Not reported	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime. Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported
Marks et al.[130] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 300 to 400 mg/kg/day IV every six hours vs cefuroxime 225 mg/kg/day IV divided into three doses, administered every	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, cerebrospinal fluid sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the cerebrospinal fluid sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eight hours				
Babinchak et al.[131] (2005) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	MA Adults with complicated intra-abdominal infections	N=1,642 (2 trials) 47 to 56 days	Primary: Clinical response (infection and associated signs and symptoms resolved) Secondary: Safety	Primary: Clinical cure rates were 86.1% for patients in the tigecycline group, vs 86.2% for patients in the imipenem-cilastatin group (P<0.0001 for non-inferiority). Secondary: Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [P=0.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [P=0.008]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [P=0.719]) were the most frequently reported adverse events.
Fomin et al.[132] (2008) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1,259 5 to 14 days	Primary: Clinical response at the test-of-cure visit in the microbiologically evaluable and microbiological modified intent-to-treat populations Secondary: Safety	Primary: Clinical cure rates at the test-of-cure visit were 92.4% for tigecycline vs 88.8% for imipenem-cilastatin in the microbiologically evaluable population (95% CI, 2.2 to 9.4). Clinical cure rates for the modified intent-to-treat populations were 87.3% for tigecycline vs 83.5% for imipenem-cilastatin (95% CI, -2.5 to 10.0) at the test-of-cure visit. Secondary: The most commonly reported treatment emergent adverse events for tigecycline and imipenem-cilastatin were nausea (14.7 and 11.8%, respectively; P=0.267) and vomiting (10.7 and 7.3%, respectively; P=0.146). The imipenem-cilastatin group had significantly higher treatment emergent adverse events of fever, hyperglycemia, and dyspnea (P=0.017, P=0.031, and P=0.011, respectively) compared to tigecycline. The tigecycline treatment group had significantly higher treatment emergent adverse events of amylase and blood urea nitrogen increase (P=0.011 and P=0.003, respectively).
Mallick et al.[133]	DB, RCT	N=1005	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2007) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	(pooled analysis) Adults with complicated intra-abdominal infections	5 to 14 days	Clinical response, safety, and health care resource utilization Secondary: Not reported	Clinical cure rates were 88.1% for tigecycline and 87.0% for imipenem–cilastatin (P=0.59). Treatment-emergent adverse events, regardless of study drug causality or severity, occurred in 73.8% of tigecycline- and 71.6% of imipenem–cilastatin-treated patients (P=0.346). Of the three most frequently reported adverse events, tigecycline was associated with a significantly higher rate of nausea (24.4%) relative to imipenem–cilastatin (19.0%; P<0.010) and a significantly higher rate of vomiting (19.2% relative to imipenem–cilastatin (14.3%; P<0.008). There were no significant differences between the groups in terms of occurrence of diarrhea (13.8% with tigecycline; 13.2% with imipenem–cilastatin; P=0.719). There were no significant differences between the tigecycline and the imipenem– cilastatin groups for any health resource utilization, clinical outcome, or antibiotic discontinuation rates.
Gentry et al.[134] (1997) Nafcillin vs vancomycin	RETRO Patients with staphylococcal endocarditis	N=56 Duration not specified	Primary: Clinical response Secondary: Not reported	Primary: In patients with methicillin-sensitive *Staphylococcus aureus* infection, complete response rate was 74% in the nafcillin group compared to 50% in the vancomycin group (P=0.12); however these differences were not statistically significant. Mortality rate was 22% in the nafcillin group and 28% in the vancomycin group (P=0.73). Secondary: Not reported
Fang et al.[135] (1998) Piperacillin 4 g-tazobactam 500 mg every eight hours by IV infusion	OL, RCT Hospitalized patients 16 years and older with lower respiratory tract infections or urinary tract	N=124 7 to 14 days	Primary: Overall clinical efficacy rates, bacterial eradication rates Secondary: Adverse events	Primary: No statistical differences were observed between the two groups. Overall efficacy rates for the treatment of all infections was 90.5% in the piperacillin-tazobactam group compared to 88.5% in the ticarcillin-clavulanate group (P>0.05). Bacterial clearance rates for the piperacillin-tazobactam group were 90.2 vs 92.0% for the ticarcillin-clavulanate group (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ticarcillin 3 g-clavulanate 200 mg every eight hours by IV infusion	infections			Secondary: Adverse drug reactions were similar in both groups (7.69% for ticarcillin-clavulanate vs 8.06% for piperacillin-tazobactam; P=0.938).
Kobayashi et al.[136] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into four doses Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success Secondary: Not reported	Primary: Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively (P≥0.05). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <0.5x10^9/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported
Uygun et al.[137] (2009)	RCT, OL	N=70 (131 episodes)	Primary: Success	Primary: Success without modification was similar between the two groups (60.0 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cefepime 50 mg/kg IV every eight hours (CEF) vs piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every six hours (PIP/TAZO)	Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and had febrile neutropenia	Variable duration	without modification Secondary: Not reported	61.3% for PIP/TAZO and CEF, respectively; P>0.05). Success without modification was 84.8 and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin episodes. Success without modification was 29.2 and 12.5% in microbiologically documented infection episodes (P>0.05). Modifications were done with only glycopeptides in eight episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in two episodes. Duration of fever and neutropenia was similar in both groups. There was no significant difference in the duration of hospitalization between the treatment groups. No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF). Secondary: Not reported
Gómez et al.[138] (2010) Cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a single dose (C-A) vs piperacillin-tazobactam 4 g/500 mg IV every	OL, RCT Patients >18 years of age with an episode of febrile neutropenia	N=190 (317 episodes) Variable duration	Primary: Clinical efficacy and toxicity Secondary: Not reported	Primary: The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group. The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eight hours plus amikacin 15 mg/kg/day as a single dose (PT-A)				A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group. Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group. Secondary: Not reported
Vural et al.[139] (2010) Imipenem-cilastatin 60 mg/kg/day IV in four divided doses vs piperacillin-tazobactam 360 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate Secondary: Not reported	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71 and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62 and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects. Secondary: Not reported
Yellin et al.[140] (2007) Ertapenem 1 g IV once daily (13 to 17 years of age) or 15 mg/kg (2 to 12 years of age) vs ticarcillin-	MC, OL, RCT Children aged 3 months to 17 years of age with complicated intra-abdominal infections or acute pelvic infections	N=105 3 to 9 days	Primary: Incidence of any serious drug-related clinical and/or laboratory adverse experiences Secondary: Overall response rates, drug-related clinical and/or	Primary: Forty-six percent of patients had one or more clinical adverse event as assessed by the investigator: 39% in the ertapenem group and 67% in the comparator group. Eleven patients (14%; 95% CI, 7.0 to 23.0) in the ertapenem group and eight patients (33%; 95% CI, 15.6 to 55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion site pain was the most common drug-related adverse event in both groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clavulanate 50 mg/kg four to six times daily (<60 kg) or 3.1 grams four to six times daily (≥60 kg)			laboratory adverse experiences, incidence of moderate-to-severe administration site reactions	Secondary: Overall response rates were 89% for ertapenem and 73% for the comparator. Comparable rates were seen across each of the age groups studied. In the modified intent-to-treat analysis, the age-adjusted posttreatment clinical response rates were 87 and 100% in the complicated intra-abdominal infections and acute pelvic infection patients, respectively, for ertapenem and 73and 100%, respectively, for ticarcillin-clavulanate. Overall age-adjusted response rates were 91% for ertapenem and 83% for the comparator. Eleven percent (95% CI, 5.2 to 20.0) in the ertapenem group and 25% (95% CI, 9.8 to 46.7) in the comparator group experienced ≥1 local reactions of any intensity at the infusion/injection site.
Falagas et al.[141] (2008) Ertapenem vs piperacillin-tazobactam, ceftriaxone plus metronidazole, or ticarcillin-clavulanic acid	MA Patients with complicated intra-abdominal infections or acute pelvic infections	7 trials 4 to 14 days	Primary: Clinical success Secondary: Mortality, laboratory adverse events, patient withdrawals because of adverse events	Primary: No difference was found regarding clinical success in patients treated with ertapenem, compared to those treated with other antibiotics (OR, 1.11; 95% CI, 0.89 to 1.39). There was no difference in microbiological success of adult patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with comparator antibiotics (OR, 1.19, 95% CI, 0.83 to 1.71). Microbiological or clinical success did not differ between compared treatments for the subsets of patients infected with either *Pseudomonas aeruginosa* (OR, 1.00; 95% CI, 0.41 to 2.45) or *Enterococcus* spp. (OR, 1.19; 95% CI, 0.60 to 2.39). Secondary: There was no difference in mortality between adult patients with complicated intra-abdominal infections treated with ertapenem or comparator antibiotics (OR, 1.14; 95% CI, 0.72 to 1.83). No difference was found regarding clinical adverse events between adult

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with other antibiotics (OR, 0.86; 95% CI, 0.61 to 1.20). Significantly more laboratory adverse events were noted in patients with complicated intra-abdominal infections, treated with ertapenem compared to patients treated with other antibiotics (OR, 1.73; 95% CI, 1.14 to 2.61). No difference was found regarding withdrawals from the included studies because of adverse events, between patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with other antibiotics (OR, 0.94; 95% CI, 0.47 to 1.87).

Drug regimen abbreviations: BID=twice daily, ER=extended release, IM=intramuscular, IV=intravenous, QID=four times daily, SC=subcutaneous, TID=three times daily,
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SC=single center, XO=cross over
Other abbreviations: COPD=chronic obstructive pulmonary disease, *H pylori=Helicobacter pylori*, SMX-TMP=sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification
Previous analyses have demonstrated that oral antibiotics given once or twice daily are associated with higher adherence rates than antibiotics given three times daily.[142,143] Thanaviratananich et al. conducted a systematic review to evaluate clinical cure rates with amoxicillin (with or without clavulanate) administered once or twice daily compared to three times daily.[144] Five studies involving 1,601 patients were included. All studies were found to be at moderate to high risk for bias; therefore, the investigators did not perform a pooled data meta-analysis. The clinical cure rates at the end of therapy and at the follow-up periods of each study were shown to be comparable between the two groups.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Penicillins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Amoxicillin	capsule, chewable tablet, suspension, tablet	N/A	N/A	$
Ampicillin	capsule, injection	N/A	N/A	$
Dicloxacillin	capsule	N/A	N/A	$$
Nafcillin	injection	N/A	N/A	$$$$$
Oxacillin	injection	N/A	N/A	$$$$$
Penicillin G benzathine	injection	Bicillin L-A®	$$$$$	N/A
Penicillin G potassium	injection	Pfizerpen®*	$$$$	$$$$$
Penicillin G procaine	injection	N/A	N/A	$
Penicillin G sodium	injection	N/A	N/A	$$$$$
Penicillin V potassium	solution, tablet	N/A	N/A	$
Combination Products				

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*	N/A	$
Ampicillin and sulbactam	injection	Unasyn®*	$$$$-$$$$$	$$$$
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	$$	N/A
Piperacillin and tazobactam	injection	Zosyn®*	$$$$-$$$$$	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-7] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins. The majority of the penicillins are available in a generic formulation, with the exception of penicillin G benzathine (with or without penicillin G procaine).

There are many guidelines that define the appropriate place in therapy for the penicillins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the penicillin. The penicillins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, *Helicobacter pylori* infections, syphilis, pyelonephritis, otitis media, pharyngitis, sinusitis, anthrax, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, Lyme disease, as well as for the prophylaxis for rheumatic fever.[10-15,18-21,25-36] They are recommended as an alternative treatment option for pelvic inflammatory disease and cystitis.[21,22]

Clinical trials have demonstrated comparable efficacy among the penicillins for the treatment of skin and soft-tissue infections, genitourinary infections, upper/lower respiratory tract infections, as well as several miscellaneous infections.[43,45,48,49,53,61,64,65,70,71,73-75,84,92,134,135,144] The penicillins have also been shown to be comparable in efficacy to antibacterial agents in other classes.[40-42,44,46,47,54,55,69,80,82,83,88,93,96,98,101,119,121,122,137,138,139] Clinical data from published studies supports similar safety profiles among the penicillins.

There is insufficient evidence to support that one brand of penicillin is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand penicillins within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand penicillin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Quinolones
AHFS Class 081218
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I. Overview

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] They are broad-spectrum agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[7-8]

The quinolones are most active against gram-negative bacilli and gram-negative cocci.[8] Ciprofloxacin has the most potent activity against gram-negative bacteria. Levofloxacin and moxifloxacin have greater potency against gram-positive cocci, and moxifloxacin has enhanced activity against anaerobic bacteria.[7-8] Levofloxacin and moxifloxacin are considered respiratory fluoroquinolones. They possess enhanced activity against *Streptococcus pneumoniae* while maintaining efficacy against *Haemophilus influenzae, Moraxella catarrhalis,* and atypical pathogens. Resistance to the quinolones is increasing and cross-resistance among the various agents has been documented. Two mechanisms of bacterial resistance have been identified. These include mutations in chromosomal genes (DNA gyrase and/or topoisomerase IV) and altered drug permeability across the bacterial cell membranes.[7-8] Delafloxacin (Baxdela®) was approved in 2017 for the treatment of acute bacterial skin and skin structure infections caused by designated susceptible bacteria.[6] Delafloxacin remains active against most otherwise fluoroquinolone-resistant *Staphylococcus aureus* isolates.[7]

In May 2016 the FDA released a Safety Alert advising restricted use of quinolones for certain uncomplicated infections, including acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[9] For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options. The FDA safety review found that systemic quinolone use is associated with serious side effects affecting the tendons, muscles, joints, nerves, and central nervous system.[9] In June 2016 the FDA approved an updated Boxed Warning for the quinolones, advising that the serious side effects associated with quinolones generally outweigh the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections who have other treatment options.[10] In July 2018 the FDA released a safety alert strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects.[11] In December 2018 the FDA warned of ruptures or tears in the aorta blood vessel with fluoroquinolone use in certain patients.[12]

The quinolones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in a generic formulation. This class was last reviewed in May 2021.

Table 1. Quinolones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ciprofloxacin	extended-release tablet, suspension, tablet, injection	Cipro®*, Cipro XR®*	ciprofloxacin, ciprofloxacin ER
Delafloxacin	injection, tablet	Baxdela®	none
Levofloxacin	injection, solution, tablet	N/A	levofloxacin
Moxifloxacin	tablet, injection	N/A	moxifloxacin
Ofloxacin	tablet	N/A	ofloxacin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

The quinolones have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the quinolones that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Quinolones[1-6]

Organism	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Gram-Positive Aerobes					
Bacillus anthracis	✔		✔		
Enterococcus faecalis	✔	✔	✔	✔	
Staphylococcus aureus	✔	✔	✔	✔	✔
Staphylococcus epidermidis	✔		✔		
Staphylococcus haemolyticus		✔			
Staphylococcus lugdunensis		✔			
Staphylococcus saprophyticus	✔		✔		
Streptococcus agalactiae		✔			
Streptococcus anginosus		✔		✔	
Streptococcus constellatus		✔		✔	
Streptococcus intermedius		✔			
Streptococcus pneumoniae	✔		✔	✔	✔
Streptococcus pyogenes	✔	✔	✔	✔	✔
Gram-Negative Aerobes					
Campylobacter jejuni	✔				
Citrobacter divs	✔				✔
Citrobacter freundii	✔				
Enterobacter aerogenes					✔
Enterobacter cloacae	✔	✔	✔	✔	
Escherichia coli	✔	✔	✔	✔	✔
Haemophilus influenzae	✔		✔	✔	✔
Haemophilus parainfluenzae	✔		✔	✔	
Klebsiella pneumoniae	✔	✔	✔	✔	✔
Legionella pneumophila			✔		
Moraxella catarrhalis	✔		✔	✔	
Morganella morganii	✔				
Neisseria gonorrhoeae	✔				✔
Proteus mirabilis	✔		✔	✔	✔
Proteus vulgaris	✔				
Providencia rettgeri	✔				
Providencia stuartii	✔				

Organism	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Pseudomonas aeruginosa	✔	✔	✔		✔
Salmonella typhi	✔				
Serratia marcescens	✔		✔		
Shigella boydii	✔				
Shigella dysenteriae	✔				
Shigella flexneri	✔				
Shigella sonnei	✔				
Yersinia pestis	✔		✔	✔	
Anaerobes					
Bacteroides fragilis				✔	
Bacteroides thetaiotaomicron				✔	
Clostridium perfringens				✔	
Peptostreptococcus species				✔	
Miscellaneous Organisms					
Chlamydia pneumoniae			✔	✔	
Chlamydia trachomatis					✔
Mycoplasma pneumoniae			✔	✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the quinolones are summarized in Table 3.

Table 3. Treatment Guidelines Using the Quinolones

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[13]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in β-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	○ Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: ○ Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. ○ Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: ○ Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: ○ *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. ○ *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ ○ *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. ○ *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. ○ *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. ○ *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): ○ Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). ○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[14]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered.

Clinical Guideline	Recommendation(s)
	• Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[15]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable;

Clinical Guideline	Recommendation(s)
	vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve

Clinical Guideline	Recommendation(s)
	endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[16]** **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or

Clinical Guideline	Recommendation(s)
	clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[17]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: Sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.

Clinical Guideline	Recommendation(s)
Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[18]	Empiric Therapy • Empiric therapy should be used when infection is suspected but cultures are not yet available. • Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended. • Choice of anti-pseudomonal β-lactam should be based on local resistance patterns. • In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 μg/mL • For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin • Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens Pathogen Specific Therapy • Methicillin-susceptible *S. aureus* o Recommended treatment includes nafcillin or oxacillin o In patients who cannot receive β-lactams, vancomycin is recommended • Methicillin-resistant *S. aureus* o Recommended treatment includes vancomycin • *P. acnes* o Recommended treatment includes penicillin G • *Pseudomonas* species o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone • Gram-negative bacilli o Recommended treatment includes ceftriaxone or cefotaxime • Extended-spectrum β-lactamase–producing gram-negative bacilli o Recommended treatment includes meropenem • *Acinetobacter* species o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B • *Candida* species o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine • *Aspergillus* or *Exserohilum* o Recommended treatment includes voriconazole • In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain o Use of rifampin as part of combination therapy is recommended Duration of Therapy • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms o Duration is recommended to be 10 days • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features o Duration is recommended to be 10 to 14 days • Infections caused by *S. aureus* or gram-negative bacilli o Duration is recommended to be 10 to 14 days • Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy • It is recommended that therapy be continued for 10 to 14 days after the last

Clinical Guideline	Recommendation(s)
	positive culture
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[19]	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and

Clinical Guideline	Recommendation(s)
	animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. <u>Necrotizing fasciitis</u> • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. <u>Pyomyositis</u> • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.

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	Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid. Glanders

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	• Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)**[20]	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended. • Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost. • A course of antibiotic therapy of one to two weeks is usually adequate for most mild and moderate infections. o For more serious skin and soft tissue infections, three weeks is usually sufficient. o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed. • Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding. • For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity. • For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection. • For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.
World Gastroenterology Organization: **Acute Diarrhea (2012)**[21]	General considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with

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	bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)**[22]	<u>Epidemiology</u> • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. <u>Diagnosis</u> • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. <u>Treatment of acute disease</u> • The usage of balanced electrolyte rehydration over other oral rehydration options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness. • In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is

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	viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. <u>Evaluation of persisting symptoms</u> • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. <u>Prevention</u> • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)**[23]	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more. • Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures. • Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified. • Recommended antimicrobial agents by pathogen: o *Campylobacter* ▪ First choice: Azithromycin ▪ Alternative: Ciprofloxacin o *Clostridium difficile* ▪ First choice: Oral vancomycin ▪ Alternative: Fidaxomicin ▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). o Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased

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	risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, TMP-SMX, or amoxicillin. o *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or TMP-SMX or azithromycin o *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: TMP-SMX or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. o *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone o Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside o *Yersinia enterocolitica* ▪ First choice: TMP-SMX ▪ Alternative: Cefotaxime or ciprofloxacin o *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response o *Cyclospora cayetanensis* ▪ First choice: TMP-SMX ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer durations of TMP-SMX treatment o *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. o *Cystoisospora belli* ▪ First choice: TMP-SMX ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide o *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole

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	▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[24]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily.

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	• Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent

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	sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. <u>Pediculosis pubis (pubic lice infestation)</u> • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off.

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	○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. ○ Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: ○ Metronidazole 500 mg orally twice daily for seven days. ○ Metronidazole 0.75% gel 5 g intravaginally once daily for five days. ○ Clindamycin 2% cream 5 g intravaginally at bedtime for seven days.

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	• Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose. • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida*

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	albicans respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy. • Recommended regimens for external anogenital warts (patient-applied): o Podofilox 0.5% solution or gel. o Imiquimod 3.75% or 5% cream. o Sinecatechins 15% ointment. • Recommended regimens (provider administered): o Cryotherapy with liquid nitrogen or cryoprobe. o Trichloroacetic acid or bichloracetic acid 80 to 90% solution o Surgical removal • Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.

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	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal Intra-anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal. ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)**[25] Reviewed and deemed current as of 07/2013	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be

Clinical Guideline	Recommendation(s)
	used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute pyelonephritis</u> • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)[26]** Reaffirmed 2016	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: ○ Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days. ○ Trimethoprim 100 mg twice daily for three days. ○ Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days. ○ Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days. ○ Fosfomycin tromethamine, 3 g dose (powder) single dose.
American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in Women: Guideline (2022)[27]**	<u>Evaluation</u> • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each

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	symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. • Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)**[28]	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole.

Clinical Guideline	Recommendation(s)
	• For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)**[29]	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole. • For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[30]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in**	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-

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Infants and Children Older Than 3 Months of Age (2011)[31] Reviewed and deemed current as of 04/2013	acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-acquired Pneumonia (2019)[32]**	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy)

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	Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting:
	• In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended:
	  o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or
	  o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily).
	• In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended.
	• Corticosteroid use is not recommended.
	• It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis.
	
	Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting:
	• It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present.
	• Empiric treatment options for MRSA include vancomycin or linezolid.
	• Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.

American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)[33]**	Empiric Therapy
	• It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities
	• In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended
	• Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known
	  o Standard therapy for MRSA coverage includes vancomycin or linezolid
	• Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant
	  o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem
	  o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage
	• One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available
	• Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available
	
	Pathogen-Specific Therapy
	• MRSA
	  o Vancomycin or linezolid are recommended treatments
	• *P. aeruginosa*

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	○ It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy ○ In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli ○ Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species ○ Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens ○ If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin <u>Duration of therapy</u> • Seven day course of treatment
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children (2010)**[34]	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms.

Clinical Guideline	Recommendation(s)
	Community-acquired infection in pediatric patients • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health care-associated infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[35]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options

Clinical Guideline	Recommendation(s)
	include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results.

Clinical Guideline	Recommendation(s)
	• For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppressio**	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with

Clinical Guideline	Recommendation(s)
n (2018)[36]	solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir). • Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)[37]**	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one):

Clinical Guideline	Recommendation(s)
	○ Cefepime. ○ Imipenem-cilastatin. ○ Meropenem. ○ Piperacillin-tazobactam. ○ Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: ○ Ciprofloxacin plus amoxicillin-clavulanate. ○ Moxifloxacin. ○ Levofloxacin ○ Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): ○ Intravenous antibiotic monotherapy is preferred. ○ Intravenous combination therapy could be considered especially in cases of resistance. <u>Antibacterial agents: empiric gram-positive activity</u> • Vancomycin ○ Gram-positive organisms with the exception of VRE and a number of rare organisms. ○ Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. ○ Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin ○ Has in vitro activity against VRE but is not FDA-approved for this indication. ○ Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. ○ Not indicated for pneumonia due to inactivation by pulmonary surfactant. ○ Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid ○ Gram-positive organisms including VRE. ○ Hematologic toxicity (typically with prolonged cases over two weeks) may occur. ○ Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. ○ Treatment option for VRE and MRSA. ○ Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime ○ Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever. ○ Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime ○ Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem

Clinical Guideline	Recommendation(s)
	○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. ○ Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. ○ Use for suspected intra-abdominal source. ○ Meropenem is preferred over imipenem for suspected/proven CNS infection. ○ Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. ○ Empiric therapy for neutropenic fever. ○ Data are limited, but it is expected that doripenem, like meropenem, would be efficacious. • Piperacillin-tazobactam ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Use for suspected intra-abdominal source. ○ Not recommended for meningitis. ○ Empiric therapy for neutropenic fever. <u>Antibacterial agents: other</u> • Aminoglycosides ○ Activity primarily against gram-negative organisms. ○ Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate ○ Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. ○ Ciprofloxacin alone has no activity against anaerobes. ○ Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes. ○ Oral combination therapy in low-risk patients. ○ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. ○ Increasing Gram-negative resistance in many centers. ○ Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered. • Levofloxacin/ moxifloxacin ○ Good activity against gram-negative and atypical organisms. ○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. ○ Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole ○ Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. ○ Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. ○ Interactions with methotrexate.
American Society of Health-System Pharmacists/ Infectious Diseases	<u>Common principles</u> • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these

Clinical Guideline	Recommendation(s)
Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)[38]**	agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. <u>Cardiac procedures</u> • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. <u>Thoracic procedures</u> • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. <u>Gastroduodenal procedures</u> • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. <u>Biliary tract procedures</u> • A single dose of cefazolin should be administered in patients undergoing open

Clinical Guideline	Recommendation(s)
	biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. <u>Appendectomy procedures</u> • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Small intestine procedures</u> • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). <u>Hernia repair procedures</u> • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. <u>Colorectal procedures</u> • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation. • Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity. <u>Head and neck procedures</u> • Clean procedures: o Antimicrobial prophylaxis is not required. • Clean-contaminated procedures:

Clinical Guideline	Recommendation(s)
	○ Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures. ○ The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam. ○ Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. <u>Neurosurgery procedures</u> • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). <u>Cesarean delivery procedures</u> • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. <u>Hysterectomy procedures</u> • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. <u>Ophthalmic procedures</u> • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. <u>Orthopedic procedures</u> • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. <u>Urologic procedures</u> • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the

Clinical Guideline	Recommendation(s)
	procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. <u>Vascular procedures</u> • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. <u>Heart, lung, heart-lung, liver, pancreas, and kidney transplantation</u> • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. <u>Plastic surgery and breast procedures</u> • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the quinolones are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Quinolones[1-6]

Indication	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Dermatological Infections					
Skin and skin-structure infections	✔ §*	✔	✔	✔	✔
Gastrointestinal Infections					
Infectious diarrhea	✔ §				
Genitourinary Infections					
Cystitis	✔ §				✔
Pelvic inflammatory disease					✔
Prostatitis	✔ §*		✔		✔
Pyelonephritis	✔ §†*		✔		
Urethritis/cervicitis (gonococcal)	✔ §				✔
Urethritis/cervicitis (non-gonococcal)					✔
Urinary tract infections	✔ §†*		✔		✔
Respiratory Infections					
Acute exacerbations of chronic bronchitis			✔	✔	✔
Inhalation anthrax (post-exposure)	✔ §*		✔		
Pneumonia (community-acquired)		✔	✔	✔	✔
Pneumonia (nosocomial)	✔ *		✔		
Respiratory tract infections (lower)	✔ §*				
Sinusitis	✔ §*		✔	✔	
Miscellaneous Infections					
Bone and/or joint infections	✔ §*				
Empiric therapy for febrile neutropenic patients	✔ *				
Intra-abdominal infections	✔ §*			✔	
Plague	✔ §*		✔	✔	
Typhoid fever	✔ §				

§Immediate-release formulation.
†Extended-release formulation.
*IV formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the quinolones are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Quinolones[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ciprofloxacin	60 to 80	20 to 40	Liver	Renal (30 to 57) Feces (20 to 35)	IR: 3 to 6 ER: 6 to 7
Delafloxacin	59	84	Glucuronidation	Renal (50) Feces (48)	IR: 4.2 to 8.5 IV: 3.7
Levofloxacin	99	24 to 38	Liver	Renal (61 to 87) Feces (<4)	6 to 8
Moxifloxacin	90	30 to 50	Liver (52)	Renal (20) Feces (25)	8 to 16
Ofloxacin	90 to 98	20 to 32	Liver	Renal (65 to 80) Feces (4 to 8)	5.0 to 7.5

ER=extended-release, IR=immediate-release

V. Drug Interactions

Major drug interactions with the quinolones are listed in Table 6.

Table 6. Major Drug Interactions with the Quinolones[2]

Generic Name(s)	Interaction	Mechanism
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Antiarrhythmic agents	Both quinolones and antiarrhythmics can cause prolongation of the QT interval. Additive prolongation may occur.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Warfarin	The effect is an increased anticoagulant effect of warfarin. The mechanism is unknown.
Quinolones (ciprofloxacin, ofloxacin)	Methadone	Methadone inhibits cardiac potassium channels and prolongs QT interval. This may become significant with larger doses and in combination with other drugs that also prolong QT interval.
Quinolones (ciprofloxacin, levofloxacin)	Theophylline	Inhibition of hepatic metabolism of theophylline leads to increased theophylline levels and toxicity can occur.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Butyrophenones	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Macrolides and detolides	Pharmacologic effects of macrolides/ketolides and quinolones on the cardiac conduction system and QT interval may be additive.
Quinolones (ciprofloxacin, levofloxacin, ofloxacin)	Phenothiazines	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Sulfonylureas	The hypoglycemic effect of sulfonylureas may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, ofloxacin)	Arsenic	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Cisapride	The risk of cardiovascular side effects may be increased. The mechanism is unknown.

Generic Name(s)	Interaction	Mechanism
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Crizotinib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Halofantrine	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Nilotinib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Pimozide	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tacrolimus	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Toremifene	Pharmacologic effects of toremifene and quinolones on electrical conduction of the heart may be additive.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Vandetanib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Ziprasidone	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Tizanidine	Quinolones may inhibit tizanidine metabolism (CYP1A2). Tizanidine plasma concentrations may be elevated, increasing the pharmacologic and adverse effects (e.g., dizziness, hypotension).
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Chloroquine	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin)	Aluminum salts	Gastrointestinal absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones. Reduced gastrointestinal acidity may be an additional mechanism.
Quinolones (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin)	Calcium salts	Gastrointestinal absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones.
Quinolones (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin)	Iron salts	The formation of insoluble chelates with iron decreases gastrointestinal absorption of quinolones.
Quinolones (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin)	Magnesium salts	The gastrointestinal absorption of quinolones may be decreased due to formation of poorly soluble chelates with magnesium. Reduced gastrointestinal acidity may be an additional mechanism.
Quinolones (ciprofloxacin)	Alfuzosin	Concurrent use of alfuzosin and ciprofloxacin may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Amoxapine	Concurrent use of amoxapine and quinolones may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin)	Artemether-lumefantrine	Concurrent use of artemether-lumefantrine and quinolones may result in an increased risk of QT-interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Asenapine	Concurrent use of asenapine and quinolones may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Azole antifungals	Concurrent use of quinolones and azole antifungals may result in an increased risk of QT interval

Generic Name(s)	Interaction	Mechanism
		prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Citalopram, escitalopram	Concurrent use of quinolones and citalopram may result in increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Clozapine	Inhibition of cytochrome P450 1A2 isoenzymes by ciprofloxacin may decrease the metabolic elimination of clozapine. This may increase clozapine blood levels, leading to increased risk of clozapine's adverse effects.
Quinolones (ciprofloxacin, ofloxacin)	Dasatinib	Concurrent use of quinolones and dasatinib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Erlotinib	Concurrent use of ciprofloxacin and erlotinib may result in increased erlotinib exposure.
Quinolones (ciprofloxacin, ofloxacin)	Iloperidone	Concurrent use of quinolones and iloperidone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Lapatinib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Mifepristone	Concurrent use of quinolones and mifepristone may result in increased risk of QT-interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, ofloxacin)	Ondansetron	Concurrent use of quinolones and ondansetron may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Pirfenidone	Concurrent use of ciprofloxacin and pirfenidone may result in increased pirfenidone exposure.
Quinolones (ciprofloxacin, ofloxacin)	Quinidine	Concurrent use of quinolones and quinidine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Quinine	Concurrent use of quinolones and quinine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Ranolazine	Concurrent use of quinolones and ranolazine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Mefloquine	Concurrent use of quinolones and mefloquine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Octreotide	Concurrent use of quinolones and octreotide may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Paliperidone	Concurrent use of quinolones and paliperidone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Pazopanib	Concurrent use of quinolones and pazopanib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Simvastatin	Concurrent use of ciprofloxacin and simvastatin may result in an increased risk of myopathy or rhabdomyolysis.
Quinolones (ciprofloxacin, ofloxacin)	Solifenacin	Concurrent use of quinolones and solifenacin may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Sorafenib	Concurrent use of quinolones and sorafenib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Sunitinib	Concurrent use of quinolones and sunitinib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tetrabenazine	Concurrent use of quinolones and tetrabenazine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Trazodone	Concurrent use of ciprofloxacin and trazodone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tricyclic antidepressants	Concurrent use of quinolones and tricyclic antidepressants may result in an increased risk of QT interval prolongation.

Generic Name(s)	Interaction	Mechanism
Quinolones (ciprofloxacin, ofloxacin)	Vardenafil	Concurrent use of quinolones and vardenafil may result in an increased risk of vardenafil adverse effects and an increased risk of QT interval prolongation.

VI. Adverse Drug Events

The most common adverse drug events reported with the quinolones are listed in Table 7. The boxed warning for the quinolones is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with the Quinolones[1-6]

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Cardiovascular					
Angina pectoris	<1	-	-	0.1 to 1.0	-
Atrial fibrillation	-	-	-	0.1 to 1.0	-
Atrial flutter	<1	-	-	-	-
Bradycardia	-	<2	-	0.1 to 1.0	-
Cardiac arrest	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Cerebral thrombosis	<1	<2	-	-	-
Congestive heart failure	-	-	-	0.1 to 1.0	-
Hypertension	<1	<2	-	0.1 to 1.0	<1
Hypotension	<1	<2	-	0.1 to 1.0	<1
Myocardial infarction	<1	-	-	-	-
Palpitations	<1	<2	0.1 to 1.0	0.1 to 1.0	<1
QT prolongation	✔	-	✔	0.1 to 1.0	-
Syncope	<1	<2	0.1 to 1.0	0.1 to 1.0	<1
Tachycardia	<1	<2	✔	0.1 to 1.0	-
Ventricular arrhythmia	-	-	0.1 to 1.0	✔	-
Ventricular ectopy	<1	-	-	-	-
Ventricular tachycardia	-	-	0.1 to 1.0	✔	-
Central Nervous System					
Abnormal dreaming	-	<2	0.1 to 1.0	-	<1
Abnormal gait	<1	-	0.1 to 1.0	✔	-
Agitation	✔	-	0.1 to 1.0	0.1 to 1.0	-
Anosmia	✔	-	✔	-	-
Anxiety	-	<2	0.1 to 1.0	0.1 to 1.0	<1
Asthenia	-	-	-	0.1 to 1.0	<1
Ataxia	<1	-	-	-	-
Chills	<1	-	-	0.1 to 11	<1
Confusion	✔	-	0.1 to 1.0	0.1 to 1.0	<1
Delirium	✔	-	-	-	-
Depersonalization	<1	-	-	-	-
Depression	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Dizziness	<1	<2	0.3 to 3.0	3	1 to 5

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Drowsiness	<1	-	-	-	-
Encephalopathy	-	-	✔	-	-
Fatigue	-	-	<1	0.1 to 1.0	1 to 3
Fever	<1	-	✔	1.1	1 to 3
Hallucinations	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Headache	<1	<2	0.3 to 6.0	4.2	1 to 9
Hyperkinesias	-	-	0.1 to 1.0	-	-
Hypertonia	-	-	0.1 to 1.0	-	-
Insomnia	<1	<2	4	1.9	3 to 7
Irritability	<1	-	-	-	-
Lethargy	<1	-	<1	0.1 to 1.0	1 to 3
Lightheadedness	<1	-	-	✔	-
Malaise	<1	-	<1	0.1 to 1.0	1 to 3
Manic reaction	<1	-	-	-	-
Migraine	<1	-	-	-	-
Nightmares	<1	-	0.1 to 1.0	-	-
Paranoia	-	-	✔	-	-
Paresthesia	<1	<2	0.1 to 1.0	0.1 to 1.0	<1
Peripheral neuropathy	✔	-	✔	✔	✔
Phobia	<1	-	-	-	-
Psychotic reactions	<1	-	✔	✔	-
Restlessness	<1	-	-	0.1 to 1.0	<1
Seizures	<1	-	0.1 to 1.0	✔	<1
Sleep disorder	-	-	0.1 to 1.0	-	-
Somnolence	<1	-	0.1 to 1.0	0.1 to 1.0	1 to 3
Suicide attempt or ideation	-	-	✔	-	-
Tinnitus	<1	-	✔	0.1 to 1.0	<1
Tremor	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Weakness	<1	-	-	-	-
Vertigo	-	<2	0.1 to 1.0	0.1 to 1.0	<1
Dermatological					
Cutaneous candidiasis	<1	-	-	-	-
Dermatitis	-	<2	-	0.1 to 1.0	-
Erythema multiform	-	<2	✔	-	-
Erythema nodosum	<1	-	-	-	-
Flushing	<1	<2	-	-	-
Hyperpigmentation	<1	-	-	-	-

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Night sweats	-	-	-	0.1 to 1.0	-
Petechia	<1	-	-	-	-
Photosensitivity	<1	-	✔	✔	✔
Pruritus	<1	<2	1	0.1 to 1.0	1 to 3
Rash	1	<2	1	0.1 to 1.0	1 to 3
Stevens-Johnson syndrome	✔	-	✔	✔	-
Sweating	<1	-	-	0.1 to 1.0	<1
Toxic epidermal necrolysis	✔	-	✔	✔	-
Urticaria	<1	<2	0.1 to 1.0	0.1 to 1.0	<1
Gastrointestinal					
Abdominal pain/discomfort	<1	<2	≤2	1.5	1 to 3
Anorexia	<1	-	0.1 to 1.0	0.1 to 1.0	-
Clostridium difficile infection	-	<2	-	-	-
Constipation	✔	-	3	<1	1 to 3
Diarrhea	1.6	8	5	6	1 to 4
Dry mouth	<1	-	<1	0.1 to 1.0	1 to 3
Dyspepsia	✔	<2	2	1	<1
Dysphagia	<1	-	-	-	-
Esophagitis	-	-	0.1 to 1.0	-	-
Flatulence	<1	-	-	0.1 to 1.0	1 to 3
Gastritis	-	-	0.1 to 1.0	-	-
Gastroenteritis	-	-	0.1 to 1.0	0.1 to 1.0	-
Gastroesophageal reflux disease	-	-	-	0.1 to 1.0	-
Gastrointestinal bleeding	<1	-	-	0.1 to 1.0	-
Glossitis	-	-	0.1 to 1.0	-	-
Intestinal perforation	<1	-	-	-	-
Nausea	2.5	8	0.6 to 7.0	6.9	3 to 10
Oral candidiasis	<1	<2	1	0.1 to 1.0	-
Painful oral mucosa	<1	-	-	-	-
Pancreatitis	-	-	0.1 to 1.0	-	-
Pseudomembranous colitis	✔	-	0.1 to 1.0	-	✔
Taste alterations	<1	-	✔	0.1 to 1.0	-
Vomiting	1	<2	0.5 to 3.0	2.4	1 to 4
Genitourinary					
Albuminuria	✔	-	-	-	≥1
Breast pain	<1	-	-	-	-
Candiduria	✔	-	-	-	-

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Crystalluria	✔	-	-	-	-
Cylindruria	✔	-	-	-	-
Dysuria	-	-	-	0.1 to 1.0	<1
Genital irritation (pain or rash)	-	-	-	-	<1
Genital moniliasis	-	-	0.1 to 1.0	-	-
Glucosuria	-	-	-	-	≥1
Hematuria	✔	-	-	-	≥1
Interstitial nephritis	<1	-	✔	✔	-
Nephritis	<1	-	-	-	-
Polyuria	<1	-	-	-	<1
Proteinuria	-	-	-	-	≥1
Pyuria	-	-	-	-	≥1
Renal failure	<1	<2	0.1 to 1.0	0.1 to 1.0	-
Renal function abnormal (non-specific)	-	-	0.1 to 1.0	✔	-
Urethral bleeding	<1	-	-	-	-
Urinary retention	<1	-	-	-	<1
Vaginitis	<1	-	<2	<1	1 to 5
Vulvovaginal candidiasis	-	<2	-	-	-
Hematologic					
Acidosis	<1	-	-	-	-
Agranulocytosis	✔	-	-	✔	-
Anemia	<0.1	-	0.1 to 1.0	-	≥1
Aplastic anemia	-	-	✔	-	-
Eosinophilia	0.6	-	✔	0.1 to 1.0	≥1
Granulocytopenia	-	-	0.1 to 1.0	-	-
Hematocrit decreased	<0.1	-	-	0.1 to 1.0	-
Hemoglobin decreased	<1	-	-	0.1 to 1.0	-
Hemolytic anemia	-	-	✔	-	-
Leukocytosis	<0.1	-	<1	0.1 to 1.0	≥ 1
Leukopenia	0.4	-	✔	0.1 to 1.0	≥1
Lymphocytosis	-	-	-	-	≥1
Monocytes increased	<0.1	-	-	-	-
Neutropenia	-	-	-	0.1 to 1.0	≥1
Neutrophils increased	-	-	-	≥2	-
Pancytopenia	0.1	-	✔	✔	-
Platelets decreased	0.1	-	-	-	-
Platelets increased	0.1	-	-	0.1 to 1.0	-

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Prothrombin time increased	<1	-	✔	0.1 to 1.0	-
Red blood cell decreased	-	-	-	≥2	-
Thrombocytosis	<1	-	-	0.1 to 1.0	≥1
Thrombocytopenia	<1	-	0.1 to 1.0	0.1 to 1.0	≥1
Hepatic					
Hepatic failure	✔	-	✔	✔	-
Hepatic function abnormal	-	-	0.1 to 1.0	0.1 to 1.0	-
Hepatitis	<1	-	✔	✔	-
Jaundice	<1	-	✔	✔	-
Laboratory Test Abnormalities					
Albumin decreased	-	-	-	≥2	-
Alkaline phosphatase increased	0.8	<2	0.1 to 1.0	0.1 to 1.0	≥1
Alanine aminotransferase increased	1.9	<2	-	1.1	≥1
Aspartate aminotransferase increased	1.7	<2	-	1.1	≥1
Bilirubin abnormalities	0.3	-	-	0.1 to 1.0	-
Blood urea nitrogen increased	0.9	-	-	0.1 to 1.0	≥1
Calcium decreased	-	-	-	≥2	-
Cholesterol increased	✔	-	-	-	-
Creatinine phosphokinase increased	-	<2	✔	-	-
Gamma-glutamyl transferase increased	-	-	-	1.1	-
Glucose abnormalities	<1	-	2	-	≥1
Hyperglycemia	-	<2	0.1 to 1.0	0.1 to 1.0	≥1
Hyperkalemia	-	-	0.1 to 1.0	-	-
Hypoglycemia	<0.1	<2	0.1 to 1.0	0.1 to 1.0	-
Hypokalemia	-	-	-	1	-
Lactic acid dehydrogenase increased	0.4	-	<1	0.1 to 1.0	-
Liver enzymes increased	-	-	0.1 to 1.0	0.1 to 1.0	-
Serum amylase increased	<1	-	-	0.1 to 1.0	-
Serum creatinine increased	1.1	<2	-	0.1 to 1.0	≥1
Serum lipase increased	<1	-	-	0.1 to 1.0	-
Triglycerides increased	✔	-	-	0.1 to 1.0	-
Uric acid increased	<0.1	-	-	0.1 to 1.0	-
Musculoskeletal					
Achiness or myalgia	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Arthralgia or back pain	<1	-	0.1 to 1.0	0.1 to 1.0	<1
Joint stiffness	<1	-	-	-	-
Muscle injury	-	-	✔	-	-

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Muscle spasms	-	-	-	0.1 to 1.0	-
Myalgia	-	<2	-	-	-
Neck or chest pain	<1	-	1	0.1 to 1.0	-
Rhabdomyolysis	-	-	✔	-	-
Skeletal pain	-	-	0.1 to 1.0	0.1 to 1.0	-
Tendinitis/tendon rupture	✔	-	0.1 to 1.0	✔	-
Respiratory					
Bronchospasm	<1	-	-	0.1 to 1.0	-
Cough	-	-	-	-	<1
Dyspnea	<1	-	1	0.1 to 1.0	-
Epistaxis	<1	-	0.1 to 1.0	-	<1
Hemoptysis	<1	-	-	-	-
Hiccough	<1	-	-	-	-
Laryngeal or pulmonary edema	<1	-	-	-	-
Pneumonitis	-	-	✔	-	-
Pulmonary embolism	<1	-	-	-	-
Rhinorrhea	-	-	-	-	<1
Wheezing	-	-	-	0.1 to 1	-
Other					
Allergic reaction	<1	-	0.1 to 1.0	-	-
Anaphylactic reactions	✔	-	✔	✔	-
Angioedema	<1	-	✔	✔	<1
Dehydration	-	-	-	0.1 to 1.0	-
Edema	<1	<2	1	0.1 to 1.0	<1
Eye Pain	<1	-	-	-	-
Foot Pain	<1	-	-	-	-
Fungal Infection	-	<2	-	0.1 to 1.0	-
Gout	<1	-	-	-	-
Hearing loss	<1	-	-	-	<1
Hypersensitivity	<1	<2	✔	✔	✔
Injection site reaction	<1	<2	1	0.1 to 1.0	-
Leukocytoclastic vasculitis	-	-	✔	-	<1
Lymphadenopathy	<1	-	-	-	-
Myasthenia gravis exacerbation	✔	-	✔	✔	-
Multi-organ failure	-	-	✔	-	-
Pain	<1	<2	-	0.1 to 1.0	<1
Pain in extremities	<1	-	-	0.1 to 1.0	<1

Adverse Events	Ciprofloxacin	Delafloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Phlebitis	<1	<2	0.1 to 1.0	0.1 to 1.0	-
Serum sickness-like reaction	-	-	✔	-	-
Tinnitus	-	<2	-	-	-
Vasodilation	-	-	✔	-	<1
Visual disturbances	<1	<2	✔	0.1 to 1.0	1 to 3

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Boxed Warning for the Quinolones[1-76]

WARNING
WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS • Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including: o Tendinitis and tendon rupture o Peripheral neuropathy o Central nervous system effects • Discontinue immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid in patients with known history of myasthenia gravis. • Because fluoroquinolones have been associated with serious adverse reactions, reserve for use in patients who have no alternative treatment options for the following indications: o Acute exacerbation of chronic bronchitis o Acute uncomplicated cystitis o Acute sinusitis

VII. Dosing and Administration

The usual dosing regimens for the quinolones are listed in Table 9.

Table 9. Usual Dosing Regimens for the Quinolones[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ciprofloxacin	Bone and joint infections (mild to moderate): Injection: 400 mg every 12 hours for ≥four to six weeks Suspension, tablet immediate-release: 500 mg every 12 hours for ≥ four to six weeks Bone and joint infections (severe or complicated): Injection: 400 mg every eight hours for ≥ four to six weeks Suspension, tablet immediate-release: 750 mg every 12 hours for ≥ four to six weeks Empiric therapy for febrile neutropenic patients: Injection: 400 mg every eight hours for five to seven days in combination with piperacillin Urethritis/cervicitis (gonococcal): Suspension, tablet immediate-release: 250 mg in a single dose Infectious diarrhea: Suspension, tablet immediate-release:	Inhalational anthrax (post-exposure) in patients one to 17 years of age: Injection: 10 mg/kg every 12 hours for 60 days Suspension, tablet immediate-release: 15 mg/kg every 12 hours for 60 days Plague in patients from birth to 17 years of age: Injection: 10 mg/kg every eight to 12 hours for 10 to 21 days Suspension, tablet immediate-release: 15 mg/kg every eight to 12 hours for 10 to 21 days Urinary tract infections or pyelonephritis in patients one to 17 years of age: Injection: 6 to 10 mg/kg every eight hours for 10	Suspension: 250 mg/5 mL 500 mg/5 mL Tablet (extended-release): 500 mg 1,000 mg Tablet (immediate-release): 100 mg 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	500 mg every 12 hours for five to seven days Inhalational anthrax: Injection: 400 mg every 12 hours for 60 days Suspension, tablet immediate-release: 500 mg every 12 hours for 60 days Intra-abdominal infections: Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days Plague: Injection: 400 mg every eight to 12 hours for 14 days Suspension, tablet immediate-release: 500 to 750 mg every 12 hours for 14 days Pneumonia (nosocomial): Injection: 400 mg every eight hours for 10 to 14 days Prostatitis: Injection: 400 mg every 12 hours for 28 days Suspension, tablet immediate-release: 500 mg every 12 hours for 28 days Pyelonephritis: Suspension, tablet immediate-release: 500 mg every 12 hours for seven days Tablet extended-release: 1,000 mg every 24 hours for seven days Respiratory tract infections (lower) (mild to moderate): Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days Respiratory tract infections (lower) (sever to complicated): Injection: 400 mg every eight hours for seven to 14 days	to 21 days Suspension, tablet immediate-release: 10 to 20 mg/kg every 12 hours for 10 to 21 days	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension, tablet immediate-release: 750 mg every 12 hours for seven to 14 days Sinusitis: Injection: 400 mg every 12 hours for 10 days Suspension, tablet immediate-release: 500 mg every 12 hours for 10 days Skin and skin-structure infections (mild to moderate): Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 to 750 mg every 12 hours for seven to 14 days Skin and skin-structure infections (severe/complicated): Injection: 400 mg every eight hours for seven to 14 days Suspension, tablet immediate-release: 750 mg every 12 hours for seven to 14 days Typhoid fever: Suspension, tablet immediate-release: 500 mg every 12 hours for 10 days Urinary tract infections (acute uncomplicated): Tablet extended-release: 500 mg every 24 hours for three days Suspension, tablet immediate-release: 250 mg every 12 hours for three days Urinary tract infections (mild/moderate): Injection: 200 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 250 mg every 12 hours for seven to 14 days Urinary tract infections (severe/ complicated): Injection: 400 mg every 12 hours for seven to 14 days Tablet extended-release: 1,000 mg every		

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	24 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days		
Delafloxacin	Pneumonia (community-acquired): Injection: 300 mg IV every 12 hours for five to 10 days Tablet: 450 mg every 12 hours for five to 10 days Skin and skin structure infections: Injection: 300 mg IV every 12 hours for five to 14 days Tablet: 450 mg every 12 hours for five to 14 days	Safety and efficacy in children have not been established.	Injection: 300 mg Tablet: 450 mg
Levofloxacin	Acute exacerbations of chronic bronchitis: Injection, solution, tablet: 500 mg once daily for seven days Inhalational anthrax (post-exposure): Injection, solution, tablet: 500 mg once daily for 60 days Plague: Injection, solution, tablet: 500 mg once daily for 10 to 14 days Pneumonia (community-acquired): Injection, solution, tablet: 500 mg once daily for seven to 14 days or 750 mg once daily for five days Pneumonia (nosocomial): Injection, solution, tablet: 750 mg once daily for seven to 14 days Prostatitis: Injection, solution, tablet: 500 mg once daily for 28 days Pyelonephritis: Injection, solution, tablet: 750 mg once daily for five days or 250 mg once daily for 10 days Sinusitis: Injection, solution, tablet: 750 mg once daily for five days or 500 mg once daily for 10 to 14 days Skin and skin-structure infections (complicated):	Inhalational anthrax (post-exposure) for patients ≥6 months of age: Injection, solution, tablet: >50 kg, 500 mg once daily for 60 days; <50 kg, 8 mg/kg every 12 hours for 60 days Plague for patients ≥6 months of age: Injection, solution, tablet: >50 kg, 500 mg once daily for 10 to 14 days; <50 kg, 8 mg/kg every 12 hours for 10 to 14 days	Injection: 25 mg/mL Solution: 250 mg/10 mL Tablet: 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection, solution, tablet: 750 mg once daily for seven to 14 days Skin and skin-structure infections (uncomplicated): Injection, solution, tablet: 500 mg once daily for seven to 10 days Urinary tract infections (complicated): Injection, solution, tablet: 750 mg once daily for five days or 250 mg once daily for 10 days Urinary tract infections (uncomplicated): Injection, solution, tablet: 250 mg once daily for three days		
Moxifloxacin	Acute exacerbations of chronic bronchitis: tablet: 400 mg once daily for five days Intra-abdominal infections: Injection, tablet: 400 mg once daily for five to 14 days Plague: Tablet: 400 mg once daily for 10 to 14 days Pneumonia (community-acquired): Injection, tablet: 400 mg once daily for seven to 14 days Sinusitis: Injection, tablet: 400 mg once daily for 10 days Skin and skin-structure infections (complicated): Injection, tablet: 400 mg once daily for seven to 21 days Skin and skin-structure infections (complicated): Injection, tablet: 400 mg once daily for seven days	Safety and efficacy in children have not been established.	Tablet: 400 mg
Ofloxacin	Acute exacerbations of chronic bronchitis: Tablet: 400 mg every 12 hours for 10 days Cystitis: Tablet: 200 mg every 12 hours for three to seven days Urethritis/cervicitis (gonococcal): Tablet: 400 mg in a single dose for one	Safety and efficacy in children have not been established.	Tablet: 300 mg 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	day Urethritis/cervicitis (non-gonococcal): Tablet: 300 mg every 12 hours for seven days Pelvic inflammatory disease: Tablet: 400 mg every 12 hours for 10 to 14 days Pneumonia (community-acquired): Tablet: 400 mg every 12 hours for 10 days Prostatitis: Tablet: 300 mg every 12 hours for six weeks Skin and skin-structure infections: Tablet: 400 mg every 12 hours for 10 days Urinary tract infections: Tablet: 200 mg every 12 hours for 10 days		

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the quinolones are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Quinolones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Nicodemo et al.[39] (1998) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Adult patients with uncomplicated skin and skin structure infections	N=272 7 to 10 days	Primary: Clinical success rate (defined as cure or improvement in signs and symptoms) Secondary: Microbiological eradication rate	Primary: Clinical success was achieved in 96.1% of those on levofloxacin and 93.5% on ciprofloxacin (95% CI, –8.4 to 3.3). Secondary: Eradication was achieved in 93.0% of those on levofloxacin and 89.7% on ciprofloxacin (95% CI, –11.7 to 5.1). An adverse event related to the study medication was reported in 8.9% of the patients on levofloxacin and 8.2% of patients taking ciprofloxacin. Discontinuation due to an adverse event occurred in five patients taking levofloxacin and two patients taking ciprofloxacin.
Nichols et al.[40] (1997) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for seven days	MC, OL, RCT Adult patients with uncomplicated skin and skin structure infections	N=469 7 to 10 days	Primary: Clinical success rate (defined as cured or improvement in signs and symptoms) Secondary: Microbiological eradication rate by patient and by pathogen	Primary: Clinical success was achieved in 98% of those on levofloxacin and 94% on ciprofloxacin (95% CI, –7.7 to 0.7). Secondary: Eradication was achieved in 98% of those on levofloxacin and 89% on ciprofloxacin (95% CI, –14.5 to –2.7). The eradication rate of the most prevalent pathogen, Staphylococcus aureus, was 100% with levofloxacin and 87% with ciprofloxacin (95% CI, –20.2 to –5.1). The eradication rate of the second most prevalent pathogen, Streptococcus pyogenes, was 100% with levofloxacin and 90% with ciprofloxacin (95% CI, –26.7 to 6.7). An adverse event related to the study medication was reported in 6% of the patients on levofloxacin and 5% of patients taking ciprofloxacin.
Gentry et al.[41]	PRO, RCT	N=51	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1989) Ceftazidime 2 g IV every 8 eight hours vs ciprofloxacin 200 mg IV every 12 hours, then ciprofloxacin 750 mg by mouth every 12 hours	Patients with serious infections of the skin and skin structures caused by gram-negative organisms	19 to 25 days	Cure rate Secondary: Adverse events	Cure rate was reported as 75 and 58% in patients treated with ciprofloxacin and ceftazidime, respectively (P<0.05). Bacteriologic cure was reported as 78 and 72% in patients treated with ciprofloxacin and ceftazidime, respectively. Superinfection was reported as 28 and 11% in patients treated with ciprofloxacin and ceftazidime, respectively (0.01<P<0.05). Secondary: Adverse events were reported in 6 and 5% of patients treated with ciprofloxacin and ceftazidime, respectively.
Gentry et al.[42] (1989) Cefotaxime 2 g IV TID and one placebo tablet by mouth BID vs ciprofloxacin 750 mg by mouth BID and placebo IV over 30 minutes TID	DB, MC, PRO, RCT Patients with culture-confirmed skin or skin structure infections requiring hospitalization	N=461 4 to 34 days	Primary: Clinical response, bacteriologic response, overall response rate Secondary: Adverse events	Primary: For patients treated with cefotaxime, clinical response was reported as 74, 20, and 6% characterized as resolution, improvement, and failure, respectively. For patients treated with ciprofloxacin, clinical response was reported as 81, 16, and 3% characterized as resolution, improvement, and failure, respectively. For all comparisons; P=NS. Bacteriologic eradication was reported as 87 and 84% for patients treated with ciprofloxacin and cefotaxime, respectively (P=0.0123). Overall efficacy rate was reported as 76 and 75% for patients treated with ciprofloxacin and cefotaxime, respectively. Overall failure rate was higher in patients treated with cefotaxime compared to ciprofloxacin (8 vs 2%, respectively; P=0.0081). Secondary: There was no statistically significant difference in adverse events for treatment groups. However, there was a higher incidence of metabolic and nutritional systems-related events in patients treated with ciprofloxacin (0.01<P<0.05).
O'Riordan et al.[43] (2018) Delafloxacin 300	DB, MC, RCT Patients ≥18 years of age with	N=850 Variable duration	Primary: Objective response at 48 to 72 hours (±2 hours)	Primary: The percentage of responders at the 48 to 72 hours objective response assessment in the intent-to-treat analysis population (N=552) was 83.7% for delafloxacin and 80.6% for vancomycin plus aztreonam (difference,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV every 12 hours for three days and then 450 mg PO every 12 hours vs aztreonam 2 g IV every 12 hours plus vancomycin 15 mg/kg IV	ABSSSI		following treatment initiation Secondary: Investigator-assessed response of signs and symptoms of infection at follow-up in the intent-to-treat population, microbiological response in the microbiological intent-to-treat population, safety	3.1%; 95% CI, -2.0 to 8.3%), which met non-inferiority criteria. Secondary: The cure rate at follow-up in the intent-to-treat population was 57.7 and 59.7% for the delafloxacin and vancomycin plus aztreonam groups, respectively (difference, -2.0%; 95% CI, -8.6 to 4.6%). In the modified intent-to-treat population at follow-up, overall pathogen eradication rates were documented in 97.8% of patients treated in the delafloxacin group and 97.6% of patients treated with vancomycin pus aztreonam (difference, 0.2%; 95% CI, -2.9 to 3.5%). Treatment-emergent adverse events were observed in 43.6% in the delafloxacin group and 39.3% in the vancomycin plus aztreonam group. Treatment-emergent adverse events leading to drug discontinuation were higher in the vancomycin plus aztreonam group compared with the delafloxacin group, 2.8 and 2.4%, respectively.
Pullman et al.[44] (2017) Delafloxacin 300 mg IV every 12 hours vs aztreonam 2 g IV every 12 hours plus vancomycin 15 mg/kg IV	AC, DB, MC, RCT Patients ≥18 years of age with ABSSSI	N=660 28 days	Primary: Objective response at 48 to 72 hours (± 2 hours) following treatment initiation Secondary: Microbiological response in the microbiological intent-to-treat and microbiologically evaluable populations, safety	Primary: The percentage of responders at the 48 to 72 hours objective response assessment in the intent-to-treat population was 78.2% for delafloxacin and 80.9% for vancomycin plus aztreonam (difference, -2.6%; 95% CI, -8.78 to 3.57), which met non-inferiority criteria. Secondary: In the microbiologically evaluable population at follow-up, microbiological responses were documented in 97.8 and 98.4% of patients treated with delafloxacin and vancomycin plus aztreonam, respectively. Treatment-emergent adverse events were observed in 47.5% in the delafloxacin group and 59.2% in the vancomycin plus aztreonam group. Treatment-emergent adverse events leading to drug discontinuation were higher in the vancomycin plus aztreonam group compared with the delafloxacin group, 4.3 and 0.9%, respectively.
Vick-Fragoso et al.[45] (2009)	MC, OL, RCT Patients ≥18 years of age with	N=804 21 days	Primary: Clinical response at test of cure for the per protocol	Primary: Clinical cure (success) rates at test of cure for the per protocol population were not significantly different between the treatment groups: 80.6% for moxifloxacin compared to 84.5% for amoxicillin-clavulanate. These

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Moxifloxacin 400 mg IV QD for at least 3 days followed by 400 mg orally for 7 to 21 days vs amoxicillin-clavulanate 1,000-200 mg IV TID for at least 3 days followed by 500 mg-125 mg orally TID for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.	complicated skin or skin structure infections		population Secondary: Clinical response at test of cure for the intent to treat population and clinical response at test of cure by indication, bacteriological success at test of cure for the per protocol population	efficacy findings were supported by results for the intent to treat population: 72.7% for moxifloxacin compared to 74.8% for amoxicillin-clavulanate. Moxifloxacin was not inferior to amoxicillin-clavulanate for complicated skin or skin structure infections. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections. Among the per protocol population, 19.4% of moxifloxacin- treated and 15.5% of amoxicillin-clavulanate-treated patients were clinical failures at test of cure. There were no significant differences in bacteriological success rates at test of cure in the per protocol population between moxifloxacin-treated patients (76.0%) and amoxicillin-clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Gastrointestinal Infections				
Kaushik et al.[46] (2010) Ciprofloxacin 20 mg/kg as a single dose vs azithromycin 20 mg/kg as a single dose	OL, RCT Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for Vibrio cholerae by hanging drop examination or culture of stool	N=180 3 days	Primary: Clinical success (resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of Vibrio cholerae by day three) Secondary: Duration of	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with ciprofloxacin (RR, 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR, 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 vs 71.5 hours, respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			diarrhea, duration of excretion of Vibrio cholerae in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	Vibrio cholerae than patients receiving ciprofloxacin (34.6 vs 52.1 hours; P<0.001). The amount of IV fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 vs 3,491.1 mL; P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Genitourinary Infections				
Sandberg et al.[47] (2012) Ciprofloxacin 500 mg BID for seven days, followed by placebo for seven days vs ciprofloxacin 500 mg BID for 14 days	DB, MC, OL, PC, RCT Adult, non-pregnant female patients diagnosed with acute pyelonephritis	N=248 14 days	Primary: Clinical and bacteriological efficacy Secondary: Long-term cumulative efficacy	Primary: The cure rate for the ciprofloxacin seven-day treatment group was 97% (N=71/73) compared to 96% (N=80/83) for the 14-day treatment group. This showed statistical non-inferiority of the seven-day treatment group to the 14-day treatment group (-0.9; 90% CI, -6.5 to 4.8; P=0.004). Secondary: The cumulative efficacy rate for the ciprofloxacin seven-day treatment group was 93% (N=68/73) compared to 93% (N=78/84) for the 14-day treatment group. The seven-day treatment was shown to be non-inferior to the 14-day treatment (-0.3%; 90% CI, -7.4 to 7.2; P=0.015).
Fourcroy et al.[48] (2005) Ciprofloxacin immediate-release 250 mg BID for three days vs ciprofloxacin	DB, MC, RCT Adult female patients with uncomplicated urinary tract infections	N=1,037 3 days	Primary: Bacteriological eradication rates defined as $<10^4$ CFU/mL at four to 11 days Secondary: Bacteriological eradication rates at 28 to 42 days and	Primary: Eradication at four to 11days was observed in 93.4% of patients on the extended-release formulation compared to 89.6% in the immediate-release formulation (95% CI, –0.99 to 8.59). Secondary: Eradication at 28 to 42 days was observed in 82.4% of patients on the extended-release formulation compared to 83.2% in the immediate-release formulation (95% CI, –8.00 to 6.40). Clinical cure at four to 11 days was observed in 85.7% of patients on the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
extended-release 500 mg QD for three days			clinical cure rates at four to 11days and at 25 to 50 days after therapy	extended-release formulation compared to 86.1% in the immediate-release formulation (95% CI, –6.37 to 5.57). Clinical cure at 28 to 42 days was observed in 75.7% of patients on the extended-release formulation compared to 78.8% in the immediate-release formulation (95% CI, –10.60 to 4.40). Adverse events were reported in 12.7% of patients on the extended-release formulation and 14.7% on the immediate-release formulation (P=not specified). Seven patients on the extended-release formulation and three patients on the immediate-release formulation withdrew due to an adverse event.
Talan et al.[49] (2004) Ciprofloxacin immediate-release 500 mg BID for 7 to 10 days vs ciprofloxacin extended-release 1,000 mg QD for 7 to 10 days	DB, MC, RCT Adult patients with complicated urinary tract infections or acute uncomplicated pyelonephritis	N=1,035 7 to 14 days	Primary: Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at five to 11 days and at 28 to 42 days after therapy Secondary: Adverse events	Primary: Eradication at five to 11 days was observed in 89% of patients on the extended-release formulation compared to 85% in the immediate-release formulation (95% CI, –2.4 to 10.3). Eradication at 28 to 42 days was observed in 69.3% of patients on the extended-release formulation compared to 61.2% in the immediate-release formulation (95% CI, –0.8 to 18.6). Clinical cure at five to 11 days was observed in 97% of patients on the extended-release formulation compared to 94% in the immediate-release formulation (95% CI, –1.2 to 6.9). Clinical cure at 28 to 42 days was observed in 82.9% of patients on the extended-release formulation compared to 80.7% in the immediate-release formulation (95% CI, –5.4 to 10.4). Secondary: Drug-related adverse events were reported in 13.2% of patients on the extended-release formulation and 13.5% on the immediate-release formulation. The most commonly reported adverse reactions were nausea, diarrhea, vaginal moniliasis, headache and dizziness. Sixteen patients on the extended-release formulation and 12 on the immediate-release formulation withdrew due to an adverse event.
Henry et al.[50]	DB, MC, RCT	N=891	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Ciprofloxacin immediate-release 250 mg BID for three days vs ciprofloxacin extended-release 500 mg QD for three days	Adult female patients with uncomplicated urinary tract infections	3 days	Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at four to 11 days and at 25 to 50 days after therapy Secondary: Adverse events	Eradication at four to 11 days was observed in 94.5% of patients on the extended-release formulation compared to 93.7% in the immediate-release formulation (95% CI, –3.5 to 5.1). Eradication at 28 to 42 days was observed in 85.8% of patients on the extended-release formulation compared to 81.3% in the immediate-release formulation (95% CI, –1.9 to 12.2). Clinical cure at four to 11 days was observed in 95.5% of patients on the extended-release formulation compared to 92.7% in the immediate-release formulation (95% CI, –1.6 to 7). Clinical cure at 28 to 42 days was observed in 89.0% of patients on the extended-release formulation compared to 86.6% in the immediate-release formulation (95% CI, –3.1 to 8.8). Secondary: Drug-related adverse events were reported in 10.4% of patients on the extended-release formulation and 9.2% on the immediate-release formulation.
Richard et al.[51] (1998) Ciprofloxacin 500 mg BID vs levofloxacin 250 mg QD vs lomefloxacin 400 mg QD	MA Adult patients with acute uncomplicated pyelonephritis	N=186 (2 trials) 7 to 14 days	Primary: Eradication rates, defined as $<10^4$ CFU/mL at five to nine days Secondary: Clinical cure rate, defined as complete resolution of symptoms	Primary: Eradication was observed in 95% of the patients on levofloxacin, 94% in patients on ciprofloxacin, and 95% in patients on lomefloxacin. Secondary: Clinical cure was observed in 92% of the patients on levofloxacin, 88% in patients on ciprofloxacin, and 80% in patients on lomefloxacin. An adverse event related to the study medication was reported in 2% of the patients on levofloxacin, 8% of patients taking ciprofloxacin, and 5% of patients taking lomefloxacin. One patient taking lomefloxacin withdrew due to an adverse event.
Bundrick et al.[52] (2003)	DB, MC, RCT	N=377	Primary: Clinical success	Primary: Clinical success was observed in 75.0% of patients taking levofloxacin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 500 mg BID vs levofloxacin 500 mg QD	Adult male patients with a history of chronic prostatitis	28 days	and microbiological eradication rates Secondary: Adverse events	and 72.8% of those taking ciprofloxacin (95% CI, –13.27 to 8.87). Eradication was observed in 75.0% of patients taking levofloxacin and 76.8% of those taking ciprofloxacin (95% CI, –8.98 to 12.58). Secondary: Drug-related adverse effects were reported in 44.2% of patients taking levofloxacin and 37.2% taking ciprofloxacin. The most frequently reported adverse reaction was gastrointestinal in nature.
Schaeffer et al.[53] (1992) Ciprofloxacin 500 mg BID vs norfloxacin 400 mg BID	OL, PRO, RCT Adult patients with complicated urinary tract infection	N=72 10 to 21 days	Primary: Clinical cure rates, defined as complete resolution of symptoms and eradication of the infecting organism(s) after two to four days and five to nine days of therapy Secondary: Not reported	Primary: Clinical cure rates were 72% for those on norfloxacin and 79% on ciprofloxacin (P=0.56). Secondary: Not reported
Auquer et al.[54] (2002) Ciprofloxacin 500 mg once vs norfloxacin 400 mg BID for three days	DB, MC, RCT Adult female patients with uncomplicated urinary tract infection	N=226 3 days	Primary: Clinical cure and bacterial eradication (defined as $<10^5$ CFU/mL of a gram-negative bacteria or $<10^4$ CFU/mL of a gram-positive bacteria) at day seven	Primary: After seven days of treatment, clinical cure were observed in 91.2% of patients on ciprofloxacin and 93.8% in patients on norfloxacin. After seven days of treatment, eradication was observed in 91.2% of patients on ciprofloxacin and 92.0% in patients on norfloxacin. Statistical analysis yielded significant results in favor of the hypothesis of equivalence between the two treatment groups (P=0.0062). Drug-related adverse effects were reported in 17 patients taking ciprofloxacin and 13 taking norfloxacin. The most frequently reported adverse reaction was gastrointestinal in nature.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Perea et al.[55] (1989) Ciprofloxacin 500 mg BID vs ofloxacin 200 mg BID	DB, RCT Adult patients with nongonococcal urethritis	N=95 7 days	Primary: Clinical cure rates, defined as lack of symptoms and fewer than five polymorphonuclear leukocytes in a Gram-stained urethral smear Secondary: Not reported	Primary: Clinical cure rates two weeks after treatment was observed in 75% of patients on ciprofloxacin and 74% of those on ofloxacin. Secondary: Not reported
Raz et al.[56] (2000) Ciprofloxacin 250 mg BID vs ofloxacin 200 mg BID	DB, MC, RCT Adult female patients with complicated lower urinary tract infection	N=465 7 days	Primary: Bacteriological success, defined as sterile urine culture at five to nine days Secondary: Bacteriological success at 28 to 42 days and clinical resolution after five to nine days and at 28 to 42 days	Primary: Bacteriological success at five to nine days was observed in 87.2% of the patients taking ofloxacin and 90.1% of patients taking ciprofloxacin (95% CI, –4.4 to 10.0). Secondary: Bacteriological success at 28 to 42 days was observed in 76.1% of the patients taking ofloxacin and 77.1 % of patients taking ciprofloxacin (95% CI, –9.2 to 10.5). Clinical cure at five to nine days was observed in 97.2% of the patients taking ofloxacin and 97.2% of patients taking ciprofloxacin (95% CI, –3.8 to 3.9). Clinical cure at 28 to 42 days was observed in 87.3% of the patients taking ofloxacin and 87.4% of patients taking ciprofloxacin (95% CI, –8.1 to 7.4). Drug-related adverse effects were reported in 10.9% of the women taking ciprofloxacin and 13.4% taking ofloxacin. The most frequently reported adverse reaction was gastrointestinal in nature. Thirteen women on ciprofloxacin and 16 on ofloxacin withdrew from the study due to adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				effects.
McCarty et al.[57] (1999) SMX-TMP 800-160 mg BID for three days vs ciprofloxacin 100 mg BID for three days vs ofloxacin 200 mg BID for three days	MC, RCT Women ≥18 years of age with primary urinary tract infection, confirmed by a positive urine culture obtained within 48 hours of study onset, presenting with signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration	N=688 Up to 6 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events Secondary: Not reported	Primary: End-of-study evaluation revealed a lack of statistically significant difference in the pre-treatment pathogen eradication rate between the study groups. Pathogen eradication occurred in 94% of ciprofloxacin, 93% of SMX-TMP, and 97% of ofloxacin-treated patients. At the four to six week follow-up evaluation, recurrence rates were 11% in the ciprofloxacin, 16% in the SMX-TMP, and 13% in the ofloxacin-treated group. Clinical success at the end of therapy was 31% in the ciprofloxacin, 41% in the SMX-TMP, and 39% in the ofloxacin-treated group. The frequency of adverse effects was 93% in the ciprofloxacin, 95% in the SMX-TMP, and 96% in the ofloxacin-treated group (P=0.03). Premature discontinuation of the study drug due to side effects was more common in the SMX-TMP group, compared to the ciprofloxacin and ofloxacin groups (P=0.02). Secondary: Not reported
Peterson et al.[58] (2008) Levofloxacin 750 mg IV/by mouth QD for five days vs ciprofloxacin 400 mg IV or 500 mg orally BID for 10 days	DB, MC, RCT Patients with complicated urinary tract infection	N=1,109 45 days	Primary: Microbiological eradication and clinical cure Secondary: Not reported	Primary: At end of therapy, eradication rates in the intent to treat population were 79.8% for levofloxacin and 77.5% for ciprofloxacin-treated patients (95% CI, -8.8 to 4.1). In the microbiological eradication population, eradication rates were 88.3% for levofloxacin and 86.7% for ciprofloxacin-treated patients (95% CI, -7.4 to 4.2). Clinical success at the end-of-therapy was 91.3 and 87.1% for levofloxacin-treated and ciprofloxacin-treated patients, respectively (95% CI, -9.6 to 1.2). At the post-therapy assessment, clinical response was 86.4% for

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				levofloxacin-treated and 88.4% for ciprofloxacin-treated patients (95% CI, -3.9 to 7.8). Clinical success rates for complicated urinary tract infections (78.9 vs 79.9%) were similar for levofloxacin and ciprofloxacin, respectively.
Klausner et al.[59] (2007) Levofloxacin 750 mg IV/by mouth QD for 5 days vs ciprofloxacin 400 mg IV and/or 500 mg orally BID for 10 days	DB, RCT Adult male and female patients with clinical signs and symptoms of complicated urinary tract infections	N=311 45 days	Primary: Microbiologic eradication post-therapy (study days 15 to 22) Secondary: Clinical response, safety, tolerability	Primary: In the intent to treat population, 83% of levofloxacin-treated and 79.6% of ciprofloxacin-treated patients achieved microbiological eradication (95% CI, -14.4 to 7.6). In the microbiologic eradication population 92.5% of levofloxacin-treated vs 93.4% of ciprofloxacin-treated patients achieved microbiologic eradication (95% CI, -7.1 to 8.9). Secondary: Clinical success was achieved in 86.2 vs 80.6% (intent to treat) and in 92.5 vs 89.5% (microbiologic eradication) of levofloxacin-treated and ciprofloxacin-treated patients, respectively. Escherichia coli was the most commonly uropathogen that was isolate. Few (2.1%) of the pathogens were fluoroquinolone-resistant. Adverse events were similar to those seen previously with both agents.
Wagenlehner et al.[60] (2015) ASPECT-cUTI Ceftolozane sulfate/ tazobactam sodium 1.5 gm IV every eight hours for seven days (doses were adjusted on the basis of creatinine clearance) vs	DB, DD, MN, NI, RCT Adults ≥ 18 years of age with pyuria (WBC count > 0.01x109/L in unspun urine or 0.01x109/L or more WBCs per high-power field in spun urine) with a diagnosis of pyelonephritis or	N=1,083 (MITT: N=1,068 mMITT: N=800) 7 days	Primary: Composite cure (i.e., achieving clinical cure and microbiological eradication of all baseline uropathogens) at the test-of-cure visit Secondary: Clinical cure (defined as	Primary: Ceftolozane/tazobactam was noninferior to levofloxacin for composite cure in the mMITT and per-protocol populations and achieved a significantly greater percentage of patients compared to levofloxacin for composite cure in both populations. For composite cure in the mMITT group, a total of 76.9% of patients in the ceftolozane sulfate/tazobactam group vs 68.4% in the levofloxacin group achieved the outcome, corresponding to an 8.5% between-group difference (95% CI, 2.3 to 14.6; P value not reported). Among the per-protocol population, the composite cure was achieved by 83.3% in the ceftolozane sulfate/tazobactam group and 75.4% in the levofloxacin group, corresponding to an 8.0% between-group difference

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levofloxacin 750 mg IV QD for seven days	complicated lower UTI infections, admitted to the hospital for IV antibiotic therapy, and a pretreatment baseline urine culture specimen obtained within 36 hours before the first dose of study drug Two identical studies conducted and results pooled together.		complete resolution, substantial improvement [i.e., reduction in severity of all baseline signs and symptoms and no worsening], or return to preinfection signs and symptoms of complicated lower UTI infections or pyelonephritis without the need for additional antibiotic therapy) and microbiological eradication (defined as a test-of-cure urine culture with $<10^4$ CFU/mL of the baseline uropathogen) at the TOC visit five to nine days after the last dose of study drug was administered, safety outcomes	(95% CI, 2.0 to 14.0; P value not reported). Secondary: Ceftolozane/tazobactam achieved higher overall microbiological eradication compared to levofloxacin for in the mMITT and per-protocol populations. Ceftolozane sulfate/tazobactam was also achieved greater microbiological eradication than levofloxacin for in patients in the per-protocol population who had *Enterobacteriaceae* species infections at baseline and showed higher per-pathogen microbiological eradication in patients infected with *P aeruginosa.* Clinical cure in the mMITT population was achieved by 92.0% of those treated with ceftolozane sulfate/tazobactam and 88.6% treated with levofloxacin, corresponding to a between-group difference of 3.4% (95% CI, -0.7 to 7.6; P value not reported). Among the per-protocol population, clinical cure was achieved by 95.9% of those treated with ceftolozane sulfate/tazobactam and 93.2% treated with levofloxacin, representing a between-group difference of 2.7% (95% CI, -0.8 to 6.2; P value not reported). Microbiologic eradication in the mMITT population was achieved by 80.4% of those treated with ceftolozane sulfate/tazobactam and 72.1% treated with levofloxacin, representing a between-group difference of 8.3% (95% CI, 2.4 to 14.1; P value not reported). Among the per-protocol population, microbiological eradication was achieved by 86.2 vs 77.6% of those treated with ceftolozane sulfate/tazobactam and levofloxacin, respectively, corresponding to a between-group difference of 8.6% (95% CI, 2.9 to 14.3; P value not reported). The incidence of adverse events, including serious adverse events, was similar in the two treatment groups with 34.7% reported in the ceftolozane sulfate/tazobactam and 34.4% reported in the levofloxacin group. Most events were mild to moderate in severity, with the most commonly reported events being headache and gastrointestinal symptoms.

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Redman et al.[61] (2010) Study 1 Doripenem 500 mg IV every eight hours vs levofloxacin 250 mg IV QD Study 2 Doripenem 500 mg IV every eight hours After a minimum of three days of IV therapy, investigators could switch patients from IV therapy to oral levofloxacin 250 mg daily.	DB, RCT Patients ≥18 years of age with complicated urinary tract infections and pyelonephritis	N=1,179 42 days after the last dose	Primary: Microbiological response at the test-of-cure visit (five to 11 days after the last dose); clinical cure rates Secondary: Not reported	Primary: Microbiological eradication rates in the microbiologically evaluable patient population at the test-of-cure visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin. Microbiological eradication rates in the microbiologically evaluable-modified intent-to-treat population at the test-of-cure visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the evaluable-modified intent-to-treat population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the test-of-cure and end-of-treatment visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2 to 15.6). These results suggest that the eradication preceded a switch from IV to oral levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the test-of-cure visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the test-of-cure and end-of-treatment visits showed that clinical improvement preceded a switch to oral levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2. Secondary: Not reported
Naber et al.[62] (2009) Doripenem 500 mg IV every eight hours	DB, MC, RCT Patients ≥18 years of age with complicated urinary tract	N=753 Up to 14 days	Primary: Microbiological cure rate in the microbiologically evaluable and microbiologically	Primary: The microbiologically evaluable population achieved microbiological cure rates of 82.1 and 83.4% with doripenem and levofloxacin, respectively. Patients in the microbiologically evaluable-modified intent-to-treat population achieved microbiological cure rates of 79.2 and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levofloxacin 250 mg IV QD Patients in both treatment arms were eligible to switch to oral levofloxacin after three days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological improvements.	infections or pyelonephritis who required initial treatment with a parenterally administered antibacterial agent		evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the test-of-cure visit for the clinically evaluable population and the microbiological cure rate for the microbiologically evaluable patients infected with Escherichia coli	for the treatment of complicated urinary tract infections or pyelonephritis. In the microbiologically evaluable population, the microbiological cure rates at the end-of-treatment were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the test-of-cure visit could be attributed to the IV portion of the therapeutic regimen, independently of a switch to oral levofloxacin. Secondary: In the clinically evaluable population, the clinical cure rates at end-of-treatment were 98.3 and 93.2% in the doripenem and levofloxacin arms, respectively. At the test-of-cure visit, the clinical cure rates were 95.1 and 90.2%, respectively (95% CI, 0.2 to 9.6). Clinical cure rates at the late follow-up visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were clinically evaluable were sustained. For the patients who received the IV study drug only, the clinical cure rates at the test-of-cure visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for Escherichia coli infections of microbiologically evaluable patients at the test-of-cure visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Heystek et al.[63] (2009) Moxifloxacin 400 mg QD for 14 days vs doxycycline 100 mg BID for 14 days, metronidazole 400	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=434 14 days	Primary: Clinical success two to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate at two to 14 days	Primary: Clinical success rates two to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the per protocol population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the intent to treat population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At two to 14 days posttreatment, clinical cure rates were 81.5% with moxifloxacin and 83.2% with the comparator regimen in the per protocol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg TID for 14 days, ciprofloxacin 500 mg as a single dose			posttreatment, clinical success rate at 21 to 35 days posttreatment (clinical failures at day two to 14 posttreatment carried forward for follow-up), bacteriological response	population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the intent to treat population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the per protocol population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the intent to treat (95% CI, -5.8 to 9.1).
Judlin et al.[64] (2010) Moxifloxacin 400 mg QD for 14 days vs levofloxacin 500 mg QD and metronidazole 500 mg BID for 14 days All patients positive for *Neisseria gonorrhoeae* also received ceftriaxone 250 mg IM as a single dose.	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=460 6 weeks	Primary: Clinical cure at test of cure visit (seven to 14 days after last dose of study drug) in the per protocol population Secondary: Clinical response during therapy and at the four week follow-up, microbiological response at test of cure, safety	Primary: The clinical cure rate at the test of cure visit was 78.4% with moxifloxacin and 81.6% with levofloxacin-metronidazole (P=0.460). Moxifloxacin was found to be non-inferior to levofloxacin-metronidazole. Secondary: In the intent to treat analysis 56.6% of patients receiving moxifloxacin and 56.9% of patients receiving levofloxacin-metronidazole experienced adverse events. A total of 4% of patients receiving moxifloxacin and 5.2% of patients receiving levofloxacin-metronidazole experienced at least one drug-related adverse event that resulted in premature termination of the study drug.
Ross et al.[65] (2006) Moxifloxacin 400 mg QD for 14 days vs	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=741 14 days	Primary: Clinical resolution rates at five to 24 days post-therapy Secondary: Clinical resolution	Primary: Clinical resolution was observed in 90.2% of patients on moxifloxacin and 90.7% of patients on ofloxacin and metronidazole (95% CI, –5.7 to 4.0). Secondary: Clinical resolution at 28 to 42 days was observed in 85.8% of patients on moxifloxacin and 87.9% of patients on ofloxacin and metronidazole (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ofloxacin 400 mg BID in combination with metronidazole 500 mg BID			at 28 to 42 days post-therapy and bacteriological response at five to 24 days	CI, –8.0 to 3.1). Bacteriological response at 5 to 24 days was observed in 87.5% of patients on moxifloxacin and 82.1% of patients on ofloxacin and metronidazole (95% CI, –8.3 to 8.8). Significantly more patients taking ofloxacin and metronidazole reported a drug-related adverse event (30.9%) than those taking moxifloxacin (22.5%; P=0.01). Most commonly reported adverse events were gastrointestinal in nature. Withdrawals due to a drug-related adverse event occurred in 6.3% of patients receiving moxifloxacin compared to 5.0% in the ofloxacin/metronidazole group (P=0.41).
Boothby et al.[66] (2010) Moxifloxacin 400 mg QD for 14 days vs ofloxacin 400 mg BID and metronidazole 400 mg BID	RETRO Women with uncomplicated pelvic inflammatory disease	N=741 14 days	Primary: Clinical response (significant improvement or response, marginal improvement, or no change/worse) Secondary: Tolerability	Primary: There was no significant difference in clinical response rates with moxifloxacin compared to ofloxacin-metronidazole (significant improvement/resolved: 70 and 77%, respectively; marginal improvement: 11 and 3%, respectively; no change/worse: 18 and 20%; P=0.14). Secondary: For those patients who attended clinic for follow-up, adverse events occurred in 16% of patients receiving moxifloxacin and in 19% of patients receiving ofloxacin-metronidazole. Most were gastrointestinal in nature.
Rafalsky et al.[67] (2006) Quinolones (ciprofloxacin, ciprofloxacin extended-release, fleroxacin, gemifloxacin, levofloxacin, norfloxacin, ofloxacin, pefloxacin, or	MA Women with uncomplicated acute cystitis	N=7,535 (11 Trials) Variable duration	Primary: Clinical response, bacteriological eradication, and clinical success (cure or improvement) and bacteriological eradication Secondary: Not reported	Primary: For all primary endpoint measures in all 11 trials, there were no significant differences in clinical or microbiological efficacy between the quinolones. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rufloxacin)				
Respiratory Infections				
Nouira et al.[68] (2010) SMX-TMP 800-160 mg BID for 10 days vs ciprofloxacin 750 mg BID for 10 days	DB, RCT Patients ≥40 years of age with an acute exacerbation of COPD requiring mechanical ventilation	N=170 10 days	Primary: Hospital death and need for an additional course of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-free interval	Primary: Combined hospital death and additional antibiotic prescription rates were similar in the two groups (16.4 vs 15.3% in the SMX-TMP vs ciprofloxacin group; 95% CI, -9.8% to 12.0; P=0.832). During the study, 15 patients died in the hospital, eight (8.2%) in the SMX-TMP group and eight (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean exacerbation-free interval was similar in both treatment groups (83 vs 79 days in the SMX-TMP vs ciprofloxacin group; P=0.41). Of 38 patients initially receiving noninvasive ventilation in the SMX-TMP group, 17 (45%) were secondarily intubated vs 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the two study groups. Adverse events were minor and comparably distributed in both treatment groups.
Sethi et al.[69] (2004) Gemifloxacin 320 mg QD for five days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Patients >40 years of age with acute exacerbation of chronic bronchitis	N=360 5 days	Primary: Clinical success rate (defined as resolution or significant improvement of symptoms) at days 14 to 21 Secondary: Clinical success rate at days nine to 11 and at 28 to 35 days, bacteriologic	Primary: Clinical success at 14 to 21 days was observed in 88.2% of patients treated with gemifloxacin and 85.1% in those treated with levofloxacin (95% CI, –4.67 to 10.72). Secondary: Clinical success at nine to 11 days was observed in 97.5% of patients treated with gemifloxacin and 93.5% in those treated with levofloxacin (95% CI, –0.61 to 8.51). Clinical success at 28 to 35 days was observed in 83.7% of patients treated with gemifloxacin and 78.4% in those treated with levofloxacin (95% CI, –3.83 to 14.34). Eradication at nine to 11 days was observed in 87.5% of patients treated with gemifloxacin and 90.4% in those treated with levofloxacin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eradication rate at nine to 11, 14 to 21 and at 28 to 35 days	Eradication at 14 to 21 days was observed in 78.4% of patients treated with gemifloxacin and 85.7% in those treated with levofloxacin. Eradication at 28 to 35 days was observed in 77.8% of patients treated with gemifloxacin and 70.5% in those treated with levofloxacin. Adverse events were reported in 39.6% of patients taking gemifloxacin and 33.7% of patients taking levofloxacin. Withdrawals due to adverse events occurred in four patients on gemifloxacin and 10 patients taking levofloxacin.
Blasi et al.[70] (2013) Prulifloxacin 600 mg QD for seven days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Patients at least 40 years of age with severe COPD, smokers or ex-smokers with > 10 pack years, diagnosed with an acute exacerbation of chronic bronchitis	N=346 7 days	Primary: Clinical assessment at the test of cure visit. Secondary: Clinical efficacy at visit four (six-week follow-up), clinical efficacy at visit five (six-month follow-up) and microbiological efficacy	Primary: At the test of cure visit, 92.5% (N=161/174) of patients treated with prulifloxacin in the intent to treat population were cured. 96.5% (N=166/172) of patients treated with levofloxacin in the intent to treat population were cured. The difference in the percentage of cured patients was -3.98 (95% CI, -8.76 to 0.79), which demonstrates non-inferiority of prulifloxacin to levofloxacin. Secondary: At visit four, patients cured by prulifloxacin had a treatment success rate of 96.8% (N=150/155), as defined by patients with mild relapse plus persistent resolution. Patients cured by levofloxacin had a treatment success rate of 98.1% (N=153/156) at visit four. At visit five, patients cured by prulifloxacin had a treatment success rate of 95.7% (N=135/141). Patients cured by levofloxacin had a treatment success rate of 98.6% (N=140/142) at visit five. Success rate for microbiological efficacy was defined as eradication plus presumed eradication. The success rate for patients treated with prulifloxacin was 83.3% (N=70/84) in the intent to treat population compared to 89.5% (N=68/76) in patients treated with levofloxacin.
Noel et al.[71] (2008) Levofloxacin 10 mg/kg BID	MC, RCT, SB Children six months to five years of age with recurrent and/or	N=1,650 27 days	Primary: Clinical cure rates at visit three (two to five days post-therapy)	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9 vs

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vs amoxicillin-clavulanate (amoxicillin 45 mg/kg) BID	persistent acute otitis media that was unchanged or worsened after ≥three days of treatment with an antimicrobial regimen used to treat acute otitis media		Secondary: Clinical cure rate at visit four (10 to 17 days post therapy), clinical success (cured or improved) at visits three and four, safety	66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9 vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit four were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit three were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit four were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Griffin et al.[72] (2010) Levofloxacin vs azithromycin or clarithromycin	RETRO Patients with Legionella pneumonia	N=39 Variable duration	Primary: Time to clinical stability and length of hospital stay Secondary: Not reported	Primary: The mean time to clinical stability for the macrolide group was 5.1 and 4.3 days for the levofloxacin group (P=0.43). The mean length of hospital stay for the macrolide group was 12.7 and 8.9 days for the levofloxacin group (P=0.10). Secondary: Not reported
Mokabberi et al.[73] (2010) Levofloxacin 500 mg IV QD vs doxycycline 100 mg IV BID	DB, PRO, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 two months	Primary: Response to treatment, failure to treatment and complications, length of stay Secondary: Not reported	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893). Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73

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Patients were allowed to switch from IV to oral therapy at the discretion of the physician.				and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001). Secondary: Not reported
Anzueto et al.[74] (2006) Levofloxacin 500 mg IV then by mouth for 7 to 14 days vs moxifloxacin 400 mg IV then by mouth for 7 to 14 days All patients received IV study medications and were converted to oral therapy after ≥ two days if they exhibited response to therapy and were able to tolerate oral food and medications.	DB, PRO, RCT Patients ≥65 years of age with community-acquired pneumonia	N=394 7 to 14 days	Primary: Clinical cure rate (defined as disappearance of symptoms or improvement that additional/ alternative therapy was not necessary) at five to 21 days after therapy Secondary: Clinical recovery (defined as disappearance to acute symptoms or reduction in severity or number of symptoms) during therapy (three to five days after start or therapy), bacteriologic eradication, and health resource utilization	Primary: Clinical cure was observed in 92.9% of the patients taking moxifloxacin and 87.9% of those on levofloxacin (95% CI, –1.9 to 11.9, P=0.2). Secondary: Significantly more patients taking moxifloxacin (97.9%) exhibited clinical recovery at three to five days than those on levofloxacin (90.0%, 95% CI: 1.7 to 14.1; P=0.01). Bacteriologic eradication was observed in 81.0% of patients taking moxifloxacin and 75.0% in patients taking levofloxacin (P=0.9). The total duration of hospital stay was 7.5±4.2 days on moxifloxacin compared to 7.5±4.6 days with levofloxacin (P=0.95). For patients in the intensive care unit, total duration of stay was similar between treatment groups. The rate of drug-related and serious adverse events was comparable between the two treatments. Ten patients on moxifloxacin and 7 taking levofloxacin withdrew due to a drug-related adverse event. There was no difference in mortality in the two treatment groups (P=0.5).
Tanaseanu et al.[75] (2008)	DB, MC, RCT	N=891	Primary: Clinical response	Primary: At the test of cure assessment in the clinically evaluable and clinical

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Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV BID Patients were allowed to switch to oral levofloxacin after 3 days if specific criteria were met.	Patients >18 years of age hospitalized with community-acquired pneumonia	7 to 14 days	in clinically evaluable and clinical modified intent to treat populations at test of cure Secondary: Health care resource utilization, safety	modified intent to treat populations, there were no significant differences in the clinical cure rates for tigecycline as compared to levofloxacin. Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1; P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of patients who switched to oral therapy (tigecycline, 89.9%; levofloxacin, 87.8%) or in the median duration of oral therapy in either group (3.9 days for tigecycline vs 3.32 for levofloxacin). In the clinical modified intent to treat population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1, P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the two treatment groups in hospital length of stay during the primary hospitalization (tigecycline: mean [SD], 9.8 [6.0] days; levofloxacin, 9.8 [6.0] days; P=0.883). There was no difference in mean duration of study antibiotic therapy (tigecycline, 9.8 [3.1] days; levofloxacin, 10.0 [3.2] days; P=0.453). There were no significant differences between the treatment groups in the rate of rehospitalization, admission for intensive care unit care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More tigecycline-treated patients than levofloxacin-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for tigecycline versus levofloxacin (P<0.001). Discontinuations for adverse events were low (tigecycline, 6.1% and levofloxacin, 8.1%).
Tanaseanu et al.[76]	DB, MC, RCT	N=428	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	Patients ≥18 years of age with a community-acquired pneumonia	7 to 14 days	Clinical response in the clinically evaluable population and clinical modified intent to treat populations at the test of cure visit (10 to 21days posttreatment) Secondary: Microbiologic eradication rates	In the clinically evaluable population, clinical cure rates at the test of cure visit were 88.9% for tigecycline and 85.3% for levofloxacin (P=0.4025). In the clinical modified intent to treat population, clinical cure rates were 83.7% for tigecycline and 81.5% for levofloxacin (P<0.6269). Tigecycline was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable population, eradication rates at the test of cure visit were similar among the treatment groups for common pathogens. The most common isolate was *Streptococcus pneumoniae*, with similar eradication for tigecycline (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *Mycoplasma pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of tigecycline patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
File et al.[77] (2019) LEAP 1 Lefamulin 150 mg IV every 12 hours vs moxifloxacin 400 mg IV every 24 hours Patients could be switched from IV to PO study drug (lefamulin 600 mg PO q12h or moxifloxacin 400 mg PO every 24h)	AC, DB, DD, MC, PG Patients ≥18 years fulfilled the FDA entry criteria for CABP; having radiographic findings suggestive of pneumonia, PORT risk classes ≥III[†], acute illness ≤7 days, and ≥3 CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain)	N=551 10 days	Primary: Early clinical response (ECR) responder rate in the ITT population at 96 ± 24 hours after the first study drug dose Secondary: IACR at TOC (test of cure, 5 to 10 days after the last dose of the study drug) in mITT and CE populations, ECR in the microITT analysis set, IACR at TOC in the microITT	Primary: Lefamulin was non-inferior to moxifloxacin with or without adjunctive linezolid for ECR responder rate (87.3% vs 90.2%; 95% CI, −8.5 to 2.8). Secondary: Lefamulin was non-inferior to moxifloxacin with or without adjunctive linezolid for IACR success rate. For IACR at TOC in the mITT population, IACR success rate was 81.7% in the lefamulin group and 84.2% in the moxifloxacin ± linezolid group (treatment difference, −2.6%; 95% CI, −8.9 to 3.9). For IACR at TOC in CE population, the IACR success rate was 86.9% in the lefamulin group and 89.4% in the moxifloxacin ± linezolid group (treatment difference, −2.5%; 95% CI, −8.4 to 3.4). The ECR rate in the microITT analysis set was 87.4% in the lefamulin group and 93.1% in the moxifloxacin ± linezolid group (treatment difference, −5.7%; 95% CI, −12.8 to 1.5). The IACR success rate at TOC in the microITT analysis set was 79.9% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
at the investigator's discretion after six doses (≥3 days) of IV treatment if predefined criteria were met If MRSA was suspected, either linezolid or placebo was added to moxifloxacin or lefamulin, respectively			and ME-TOC analysis sets, by-pathogen microbiological response at TOC in the microITT set and safety and tolerability	the lefamulin group and 85.5% in the moxifloxacin ± linezolid group (treatment difference, −5.7%; 95% CI, −14.1 to 2.8). The IACR success rate in the ME-TOC analysis set (which included all patients who met the criteria for inclusion in both the microITT and CE sets), was 83.9% in the lefamulin group and 90.1% in the moxifloxacin ± linezolid group (treatment difference, −6.2%; 95% CI, −14.3 to 1.9). ECR responder rates by baseline pathogen were generally high and similar between groups. ECR responder rates for the most frequently identified baseline pathogens in the microITT analysis set were *S. pneumoniae* (88.2% for lefamulin vs 93.8% for moxifloxacin ± linezolid), *H. influenzae* (92.2% for lefamulin vs 94.7% for moxifloxacin ± linezolid), *M. pneumoniae* (84.2% for lefamulin vs 90.0% for moxifloxacin ± linezolid), *M. catarrhalis* (92.0% for lefamulin vs 100.0% for moxifloxacin ± linezolid), *L. pneumophila* (88.9% for lefamulin vs 85.7% for moxifloxacin ± linezolid), and *C. pneumoniae* (90.9% for lefamulin vs 94.7% for moxifloxacin ± linezolid). Responder rates for *S. aureus* were 100.0% in both groups. Overall, the rate of TEAEs was similar for the 2 treatment groups (38.1% and 37.7% for lefamulin and moxifloxacin ± linezolid, respectively), as was the rate of study drug-related TEAEs (15.0% and 14.3%, respectively). The most common study drug-related TEAEs in the lefamulin group were general disorders and administration site conditions (6.6%), while the most common study drug-related TEAEs in the moxifloxacin ± linezolid group were GI disorders (8.1%).
Alexander et al.[78] (2019) LEAP 2 Lefamulin 600 mg PO every 12 hours for five days vs	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age, acute illness of ≤7 days' duration with ≥3 symptoms of lower respiratory tract infection (dyspnea,	N=738 7 days	Primary: Clinical response at 96 hours (within a 24-hour window) after the first dose of either study drug in the ITT population Secondary:	Primary: ECR rates were 90.8% with lefamulin and 90.8% with moxifloxacin (difference, 0.1%; 1-sided 97.5%CI, –4.4% to ∞). Secondary: Rates of IACR success were 87.5% with lefamulin and 89.1% with moxifloxacin in the mITT population (difference, –1.6% [1-sided 97.5%CI, –6.3% to ∞and 89.7% and 93.6%, respectively]), and in the CE population (difference, –3.9%; 1-sided 97.5% CI, –8.2% to ∞) at TOC.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
moxifloxacin 400 mg PO every 24 hours for seven days	new or increased cough, purulent sputum production, and chest pain due to pneumonia), ≥2 vital sign abnormalities (fever or hypothermia, hypotension, tachycardia, tachypnea), ≥1 other clinical sign or laboratory finding of CABP (hypoxemia, auscultatory and/or percussion findings consistent with pneumonia, WBC count >10,000 cells/mm3 or <4,500 cells/mm3 or >15% immature neutrophils regardless of total WBC count), radiographically document pneumonia within 48 hours before enrollment, PORT Risk Class of II to IV†, and an appropriate		IACR at TOC in the mITT population and in the CE population, ECR in the microITT analysis set, IACR at TOC in the microITT and ME-TOC analysis sets, by-pathogen microbiological response at TOC in the microITT and ME-TOC analysis sets and safety and tolerability	The ECR responder rate in the microITT analysis set was 90.7% in the lefamulin group and 93.0% in the moxifloxacin group (treatment difference, −2.3%; 95% CI, −8.2 to 3.6). the IACR success rate at TOC in the microITT analysis set was 85.9% in the lefamulin group and 87.6% in the moxifloxacin group (treatment difference −1.8%; 95% CI: −8.7 to 5.1) The IACR success rate at TOC in the ME-TOC analysis set was 88.5% in the lefamulin group and 91.5% in the moxifloxacin group (treatment difference −3.0%; 95% CI: −9.4, 3.7). ECR responder rates by baseline pathogen were generally high and similar between groups. ECR responder rates for the most frequently identified baseline pathogens in the microITT analysis set were *S. pneumoniae* (89.4% for lefamulin vs 91.3% for moxifloxacin), *H. influenzae* (89.3% for lefamulin vs 91.7% for moxifloxacin), *M. pneumoniae* (100% in both groups), *M. catarrhalis* (85.7% for lefamulin vs 100% for moxifloxacin), *L. pneumophila* (81.3% for lefamulin vs 94.1% for moxifloxacin), and *C. pneumoniae* (93.8% for lefamulin vs 100% for moxifloxacin). Responder rates for *S. aureus* were 100% in both groups. Overall, the rate of TEAEs was higher in the lefamulin group than in the moxifloxacin group (32.6% vs 25.0%, respectively), as was the rate of study drug-related TEAEs (15.8% vs 7.9%, respectively). At least one serious TEAE occurred in 17 (4.6%) and 18 (4.9%) patients in the lefamulin and moxifloxacin groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	candidate for oral antibiotic therapy.			
Ramirez et al.[79] (2019) OPTIC Omadacycline 100 mg IV every 12 hours for two doses on Day 1, followed by 100 mg IV daily OR 300 mg orally daily vs moxifloxacin 400 mg IV or orally daily	DB, DD, MC, NI, RCT Adults with qualifying CABP. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=774 Total treatment duration was 7 to 14 days with follow-up of 72 to 120 hours after the first dose for the primary endpoint and follow-up of 5 to 10 days after last dose of study drug for the secondary endpoints	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement 72 to 120 hours after the first dose of study drug [ECR window], no use of rescue antibiotics, and patient survival) Secondary: Number of participants with investigator assessment of clinical success at the post therapy evaluation visit.	Primary: Omadacycline was noninferior to moxifloxacin for percentage of patients with early clinical response (81.1% vs 82.7%; 95% CI, -7.1 to 3.8). Secondary: Clinical success at post therapy evaluation was high and similar between omadacycline and moxifloxacin (87.6% vs 85.1%; 95% CI, -2.4 to 7.4).
Siempos et al.[80] (2007) Quinolones vs amoxicillin-clavulanate vs	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
macrolides				95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones. Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Miscellaneous Infections				
Metallidis et al.[81] (2008) Ceftriaxone 4 g IV every 24 hours plus ciprofloxacin 400 mg IV BID vs ceftazidime 2 g IV every eight hours plus amikacin 500 mg IV every eight hours or 20 mg/kg	RCT Patients with febrile neutropenia	N=95 ≥3 days	Primary: Microbiologically and clinically documented infections and adverse events Secondary: Not reported	Primary: The overall incidence of microbiologically and clinically documented infections was 81.3% (80.85% in the ceftriaxone-ciprofloxacin group and 82.14% in the ceftazidime-amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone-ciprofloxacin group and 37% in the ceftazidime-amikacin group; P=0.011). The ceftriaxone-ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime-amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided in three doses				There was a low incidence of adverse events in both groups. Secondary: Not reported
Keramat et al.[82] (2009) Ciprofloxacin 15 mg/kg BID plus rifampin 15 mg/kg QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group) vs doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group)	PRO, RCT Patients ≥18 years of age with acute brucellosis	N=178 8 to 12 weeks	Primary: Response and relapse rates Secondary: Not reported	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all three groups (DR, 96.7%; CR, 95.2%; CD, 87.3%). There were no significant differences among the treatment groups (P=0.09). Therapeutic failure was seen in 12 cases, though no significant differences were noted among the three groups (P=0.88). After six months, 12 patients relapsed (DR, 7.7%; CR, 8.3%; CD, 17.5%; P=0.35).
GIMEMA Infection Program[83] (1991) Ciprofloxacin 500 mg BID vs norfloxacin 400 mg BID	MC, RCT, SB Patients ≥14 years of age with neutropenia with hematologic malignancies or had bone marrow transplantation or chemotherapy-induced neutropenia	N=801 Mean 29 days	Primary: Number of patients with febrile episodes, the number of days with a fever, the number of days parenteral antibiotics were used, interval to first febrile episode or infection,	Primary: Significantly less patients on ciprofloxacin (34%) developed fevers than norfloxacin 25% (P=0.01). The number of days with a fever did not differ significantly between treatment groups. Mean duration of parenteral antibiotic use was significantly shorter with ciprofloxacin (10.1 days) vs norfloxacin (12.0 days; P=0.02). The interval to first febrile episode was longer with ciprofloxacin (8.3 days) compared to norfloxacin (7.2 days; P=0.055).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	expected to last >10 days		compliance, classification of febrile episodes or infection, discontinuation due to adverse reactions and mortality Secondary: Not reported	Patients with ciprofloxacin had a lower rate of microbiologically documented infections (17% vs 24%; P=0.058). Differences among other febrile classifications (clinically documented infection, fever of unknown origin, or bacteremia) were not significant. Compliance was >90% and comparable between treatment groups. Discontinuation due to adverse events occurred in 2% of patients on norfloxacin and 4% of patients on ciprofloxacin. The mortality rate during neutropenic episodes was 13% with norfloxacin and 14% with ciprofloxacin.
Arjyal et al.[84] (2011) Gatifloxacin 10 mg/kg QD for 7 days vs chloramphenicol 75 mg/kg/day in four divided doses for 14 days	OL, RCT Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR, 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of one month (P=0.12). At the end of three months, only one patient in the chloramphenicol group had a positive stool culture, and at six months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.
Solomkin et al.[85] (2009)	DB, MC, RCT Patients ≥18 years	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ceftriaxone 2 g IV QD plus metronidazole 500 mg IV BID for three to 14 days vs moxifloxacin 400 mg IV QD for three to 14 days	of age with community-origin complicated intra-abdominal infections with an expected duration of treatment with IV antimicrobials of 3 to 14 days		cure visit (10 to 14 days after the end of therapy) Secondary: Clinical and bacteriological success rates on days three and five during treatment and at the end-of-therapy; bacteriological success rate at the test-of-cure visit; and clinical success rate at the test-of-cure visit in patients with bacteriologically proven complicated intra-abdominal infections	intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-to-treat populations. Secondary: During treatment, clinical improvement occurred in similar proportions of per protocol patients in the moxifloxacin group (31.0%) and the ceftriaxone plus metronidazole group (28.1%). In the intention-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole. In the per protocol population, clinical resolution at end-of-therapy occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at end-of-therapy occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Gupta et al.[86] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg QD as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12	OL, RCT, SC Pediatric patients two to 15 years of age with low-risk febrile neutropenia	N=88 (123 episodes) Variable duration	Primary: Treatment success Secondary: Not reported	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy				

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, COPD=chronic obstructive pulmonary disease, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MITT=modified intention to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind, SC=single center, SD=standard deviation, SMX-TMP=sulfamethoxazole-trimethoprim, UTI=urinary tract infection, WBC=white blood cell

Additional Evidence

Dose Simplification
Three clinical trials directly compared ciprofloxacin extended-release tablets (dosed once daily) with the immediate-release formulation (dosed twice daily). Fourcroy et al. and Henry et al. evaluated women with uncomplicated urinary tract infections receiving treatment for three days.[48,50] Talan et al. evaluated men and women with complicated urinary tract infections or uncomplicated pyelonephritis receiving treatment for seven to 14 days.[49] In all three trials, patients receiving the extended-release formulation demonstrated similar clinical cure rates, bacteriological eradication rates, and adverse event rates compared to patients receiving the immediate-release formulation.[48-50]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Quinolones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ciprofloxacin	extended-release tablet, suspension, tablet, injection	Cipro®*, Cipro XR®*	$$$$$	$
Delafloxacin	injection, tablet	Baxdela®	$$$$$	N/A
Levofloxacin	injection, solution, tablet	N/A	N/A	$
Moxifloxacin	tablet, injection	N/A	N/A	$
Ofloxacin	tablet	N/A	N/A	$$$-$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the quinolones. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the quinolone. The quinolones are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, diabetic foot infections, infectious diarrhea, chancroid, pyelonephritis, anthrax, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, and febrile neutropenia.[13-16,20-25,28,30,31-34,36] They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections, sexually transmitted diseases, and cystitis.[17-19,24,25]

Clinical trials have demonstrated comparable efficacy among the quinolones for the treatment of skin and soft-tissue infections, genitourinary infections, and respiratory tract infections.[39,40,51-59,64-67,69,74] Data from published studies supports similar safety profiles among the quinolones. There's an increased risk of tendinitis and tendon rupture with the use of quinolones. This risk is further increased in older patients, patients taking corticosteroid drugs, and patients with kidney, heart, or lung transplants.[1] Because of this risk, the use of quinolones has been limited in the pediatric population. The quinolones may also exacerbate muscle weakness in patients with myasthenia gravis. In May 2016 the FDA released a Safety Alert advising restricted use of quinolones for certain uncomplicated infections, including acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[9] For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options. The FDA safety review found that systemic quinolone use is associated with serious side effects affecting the tendons, muscles, joints, nerves, and central nervous system.[9] In June 2016 the FDA approved an updated Boxed Warning for the quinolones, advising that the serious side effects associated with quinolones generally outweigh the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections who have other treatment options.[10] In July 2018 the FDA released a safety alert strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects.[11] In December 2018 the FDA warned of ruptures or tears in the aorta blood vessel with fluoroquinolones in certain patients.[12]

There is insufficient evidence to support that one brand quinolone is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand quinolones within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand quinolone is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sulfonamides
AHFS Class 081220
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I. Overview

Sulfadiazine and sulfamethoxazole-trimethoprim are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-4] These agents are bacteriostatic and interfere with bacterial growth by inhibiting the synthesis of dihydrofolic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Due to synergism, the combination of sulfamethoxazole-trimethoprim is often bactericidal and active against a variety of organisms. Resistance to sulfonamides is widespread and cross-resistance among the various sulfonamides is common.

The sulfonamides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2021.

Table 1. Sulfonamides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Sulfadiazine	tablet	N/A	sulfadiazine
Combination Products			
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*	sulfamethoxazole and trimethoprim

*Generic is available in at least one dosage form or strength.
N/A=Not available
PDL=Preferred Drug List

The sulfonamides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the sulfonamides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Sulfonamides[1-4]

Organism	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Gram-Positive Aerobes		
Nocardia species	✔	
Staphylococcus aureus	✔	
Streptococcus pneumoniae		✔
Gram-Negative Aerobes		
Chlamydia trachomatis	✔	
Enterobacter species	✔	✔
Escherichia coli	✔	✔
Haemophilus influenzae	✔	✔
Klebsiella species	✔	✔
Morganella morganii		✔
Proteus mirabilis	✔	✔
Proteus vulgaris	✔	✔
Shigella flexneri		✔

Organism	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Shigella sonnei		✔
Protozoan Parasites		
Plasmodium falciparum	✔	
Toxoplasma gondii	✔	
Miscellaneous Organisms		
Pneumocystis jirovecii		✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the sulfonamides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Sulfonamides

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[5]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to

Clinical Guideline	Recommendation(s)
	temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered. • Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[6]** **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative.

Clinical Guideline	Recommendation(s)
	Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)**[7]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid

Clinical Guideline	Recommendation(s)
	should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[8]	Empiric Therapy • Empiric therapy should be used when infection is suspected but cultures are not yet available. • Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended. • Choice of anti-pseudomonal β-lactam should be based on local resistance patterns. • In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 μg/mL • For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin • Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens Pathogen Specific Therapy • Methicillin-susceptible *S. aureus* o Recommended treatment includes nafcillin or oxacillin o In patients who cannot receive β-lactams, vancomycin is recommended • Methicillin-resistant *S. aureus* o Recommended treatment includes vancomycin • *P. acnes* o Recommended treatment includes penicillin G • *Pseudomonas* species o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone • Gram-negative bacilli o Recommended treatment includes ceftriaxone or cefotaxime • Extended-spectrum β-lactamase–producing gram-negative bacilli o Recommended treatment includes meropenem • *Acinetobacter* species o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B • *Candida* species o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine • *Aspergillus* or *Exserohilum* o Recommended treatment includes voriconazole • In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain o Use of rifampin as part of combination therapy is recommended Duration of Therapy • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms o Duration is recommended to be 10 days • Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features o Duration is recommended to be 10 to 14 days

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	• Infections caused by *S. aureus* or gram-negative bacilli o Duration is recommended to be 10 to 14 days • Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy • It is recommended that therapy be continued for 10 to 14 days after the last positive culture

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[11]	<u>Impetigo and ecthyma</u>
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	<u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u>
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	<u>Recurrent skin abscesses</u>
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated.
	• Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection.
	• Adult patients should be evaluated for neutrophil disorders if recurrent

Clinical Guideline	Recommendation(s)
	abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.

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	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. <u>Clostridial gas gangrene or myonecrosis</u> • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. <u>Animal bites</u> • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options o Amoxicillin-clavulanate is recommended. o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. <u>Bacillary angiomatosis and cat scratch disease</u> • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two

Clinical Guideline	Recommendation(s)
	weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.

International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)[10]**	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended.
	• Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost.
	• A course of antibiotic therapy of one to two weeks is usually adequate for most mild and moderate infections.
	  o For more serious skin and soft tissue infections, three weeks is usually sufficient.
	  o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed.
	• Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding.
	• For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity.
	• For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection.
	• For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.

World Gastroenterology	General considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea

Clinical Guideline	Recommendation(s)
Organization: **Acute Diarrhea (2012)[11]**	and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)[12]**	<u>Epidemiology</u> • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. <u>Diagnosis</u> • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. <u>Treatment of acute disease</u> • The usage of balanced electrolyte rehydration over other oral rehydration options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness.

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	• In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. <u>Evaluation of persisting symptoms</u> • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. <u>Prevention</u> • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.

Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)**[13]	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more.
	• Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures.
	• Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified.
	• Recommended antimicrobial agents by pathogen:
	  ○ *Campylobacter*
	  ▪ First choice: Azithromycin
	  ▪ Alternative: Ciprofloxacin
	  ○ *Clostridium difficile*
	  ▪ First choice: Oral vancomycin
	  ▪ Alternative: Fidaxomicin

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	▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). o Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, TMP-SMX, or amoxicillin. o *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or TMP-SMX or azithromycin o *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: TMP-SMX or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. o *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone o Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside o *Yersinia enterocolitica* ▪ First choice: TMP-SMX ▪ Alternative: Cefotaxime or ciprofloxacin o *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response o *Cyclospora cayetanensis* ▪ First choice: TMP-SMX ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer durations of TMP-SMX treatment o *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available

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	but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. ○ *Cystoisospora belli* ▪ First choice: TMP-SMX ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide ○ *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole ▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[14]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: ○ acyclovir 400 mg orally three times daily for seven to 10 days ○ famciclovir 250 mg orally three times daily for seven to 10 days ○ valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral

Clinical Guideline	Recommendation(s)
	therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes: o acyclovir 800 mg orally twice daily for five days o acyclovir 800 mg orally three times daily for two days o famciclovir 1,000 mg orally twice daily for one day o famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days o famciclovir 125 mg orally twice daily for five days o valacyclovir 500 mg orally twice daily for three days o valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to

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	decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease

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	involving the CNS. Pediculosis pubis (pubic lice infestation) • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. o Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: o Malathion 0.5% lotion applied for eight to 12 hours and washed off. o Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: o Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. o Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 µg/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally

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	representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose. • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application.

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	○ Terconazole 0.4% cream 5 g intravaginally daily for seven days. ○ Terconazole 0.8% cream 5 g intravaginally daily for three days. ○ Terconazole 80 mg vaginal suppository one suppository daily for three days. ○ Fluconazole 150 mg oral tablet in single dose. Complicated vulvovaginal candidiasis • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Severe vulvovaginal candidiasis • Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. Non-albicans vulvovaginal candidiasis • The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended. • If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks. Genital warts • Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. • There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. • Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. • Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy. • In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. • The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. • Most genital warts respond within three months of therapy.

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	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
	
	Cervical warts
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.
	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	Intra-anal warts
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice**	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible.

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Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)[15] Reviewed and deemed current as of 07/2013	• Fosfomycin (3 g in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute pyelonephritis</u> • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral Sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 g or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results. Compared to
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)[16]**	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows: o Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days. o Trimethoprim 100 mg twice daily for three days. o Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days. o Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven

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Reaffirmed 2016	days, or nitrofurantoin monohydrate 100 mg twice daily for seven days. ○ Fosfomycin tromethamine, 3 g dose (powder) single dose.
American Urological Association/ Canadian Urological Association/ Society of Urodynamics: **Recurrent Uncomplicated Urinary Tract Infections in Women: Guideline (2022)**[17]	Evaluation • Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with recurrent urinary tract infections (rUTIs). • To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. • Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. • Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. • Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. • Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. Asymptomatic Bacteriuria • Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. • Clinicians should not treat asymptomatic bacteriuria in patients. Antibiotic Treatment • Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. • Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. • In patients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. Antibiotic Prophylaxis • Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. Non–Antibiotic Prophylaxis • Clinicians may offer cranberry prophylaxis for women with rUTIs. Follow–up Evaluation • Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. • Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. Estrogen • In peri– and post–menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy.
American Academy of Pediatrics/American	Observation option • Observation without use of antibacterial agents in a child with unilateral acute otitis media is an option for selected children based on age, illness severity, and

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Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[18] Reaffirmed 2019	assurance of follow-up after joint decision-making with the parent(s)/caregiver. The "observation option" for acute otitis media refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children six months and older without severe symptoms at presentation. <u>Antibacterial options - temperature <39°C without severe otalgia</u> • For the initial treatment of otitis media, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. <u>Antibacterial options - temperature ≥39°C and/or severe otalgia</u> • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for three days.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[19]	<u>Symptomatic relief of viral rhinosinusitis</u> • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. <u>Symptomatic relief of acute bacterial rhinosinusitis</u> • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. <u>Initial management of acute bacterial rhinosinusitis</u> • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after

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	acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[20]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[21]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose.

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	• Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[22]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.
Center for Disease Control and Prevention: **Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis (2005)**[23] **(Was reviewed and deemed current as of August 2017)**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants <1 month of age, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is sulfamethoxazole-trimethoprim. • The choice of antimicrobial should take into account effectiveness, safety, tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients >6 months of age, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (one to two doses per day) and shorter treatment regimens (five to seven days).

National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of**	<u>Prophylaxis to Prevent First Episode of Opportunistic Disease</u>
	• Coccidioidomycosis
	  ○ Preferred: Fluconazole 400 mg PO daily
	  ○ Alternative: None listed
	• *Histoplasma capsulatum* infection
	  ○ Preferred: Itraconazole 200 mg PO daily
	  ○ Alternative: None listed
	• Malaria
	  ○ Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region. Refer to the Centers for Disease Control and Prevention webpage for the most recent recommendations based on region and drug susceptibility

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Opportunistic Infections in Adults and Adolescents with HIV (2022)[24]	• *Mycobacterium avium* Complex (MAC) Disease o Preferred: Azithromycin 1200 mg PO once weekly, or Clarithromycin 500 mg PO BID, or Azithromycin 600 mg PO twice weekly o Alternative: Rifabutin (dose adjusted based on concomitant ART); rule out active TB before starting rifabutin • *Pneumocystis* Pneumonia (PCP) o Preferred: TMP-SMX (trimethoprim-sulfamethoxazole) 1 double strength (DS) tablet PO daily, or TMP-SMX 1 SS tablet daily o Alternative: TMP-SMX 1 DS PO three times weekly, or Dapsone 100 mg PO daily or 50 mg PO BID, or Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or Aerosolized pentamidine 300 mg via Respigard II nebulizer every month, or Atovaquone 1500 mg PO daily, or (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily • Syphilis o Preferred: Benzathine penicillin G 2.4 million units IM for 1 dose o Alternative: *For penicillin-allergic patients*: ▪ Doxycycline 100 mg PO BID for 14 days, or ▪ Ceftriaxone 1 g IM or IV daily for eight to 10 days, or ▪ Azithromycin 2 g PO for 1 dose – not recommended for men who have sex with men or pregnant women • Talaromycosis (Penicilliosis) o Preferred: For persons who reside in endemic areas, itraconazole 200 mg PO once daily; For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily three days before travel, and continue for one week after leaving the endemic area o Alternative: For persons who reside in endemic areas, fluconazole 400 mg PO once weekly; For those traveling to the highly endemic regions, take the first dose of fluconazole 400 mg three days before travel, continue 400 mg once weekly, and take the final dose after leaving the endemic area • *Toxoplasma gondii* Encephalitis o Preferred: TMP-SMX 1 DS PO daily o Alternative: TMP-SMX 1 DS PO three times weekly, or TMP-SMX 1 SS PO daily, or Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly; or Atovaquone 1500 mg PO daily; or (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily <u>Treatment of AIDS-Associated Opportunistic Infections (only preferred therapy is summarized here, please see full guideline for alternative therapies and additional information)</u> • Empiric therapy pending definitive diagnosis of bacterial enteric infections o Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. If a pathogen is identified, antibiotic susceptibilities should be performed to confirm and inform antibiotic choices given increased reports of antibiotic resistance. Reflex culture for antibiotic susceptibilities should also be done if diagnosis is made using PCR-based methods. o Empiric antibiotic therapy may be indicated for patients with CD4 count 200 to 500 cells/mm^3 where diarrhea is severe enough to compromise quality of life or the ability to work and is indicated in patients with CD4 count <200 cells/mm^3 or concomitant AIDS-defining illness and with clinically severe diarrhea (≥6 stools per day or bloody stool) and/or

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	accompanying fever or chills. o Empiric Therapy: Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h • Campylobacteriosis o For Mild Disease and If CD4 Count >200 cells/µL: ▪ No therapy unless symptoms persist for more than several days o For Mild-to-Moderate Disease (If Susceptible): ▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, or ▪ Azithromycin 500 mg PO daily (Note: Not for patients with bacteremia) o For Campylobacter Bacteremia: ▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h + an aminoglycoside o Duration of Therapy: ▪ Gastroenteritis: seven to 10 days (five days with azithromycin) ▪ Bacteremia: ≥14 days ▪ Recurrent bacteremia: two to six weeks • Clostridium difficile Infection (CDI) o Fidaxomicin 200 mg PO two times daily for 10 days o Vancomycin 125 mg (PO) QID for 10 days • Salmonellosis o All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20 to 100 fold) and mortality (by up to 7-fold) compared to HIV negative individuals o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, if susceptible • Shigellosis o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h o Note: Increased resistance of Shigella to fluoroquinolones is occurring in the United States. Avoid fluoroquinolones if ciprofloxacin MIC is ≥0.12 µg/mL, even if the laboratory identifies the isolate as sensitive. Many Shigella strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of Shigella isolates from HIV-infected individuals should be performed routinely. • Bartonellosis o For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis: Doxycycline 100 mg PO or IV q12h, or Erythromycin 500 mg PO or IV q6h o CNS Infections: (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h o Confirmed Bartonella Endocarditis: (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) for two weeks, then continue with doxycycline 100 mg IV or PO q12h o Other Severe Infections: (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) q12h, or (Erythromycin 500 mg PO or IV q6h) +/- RIF 300 mg PO or IV q12h o Duration of therapy: at least three months • Candidiasis (Mucocutaneous) o For Oropharyngeal Candidiasis; Initial Episodes (for 7 to 14 Days): ▪ Fluconazole 100 mg PO daily o For Esophageal Candidiasis (for 14 to 21 Days): ▪ Fluconazole 100 100 mg (up to 400 mg) PO or IV daily ▪ Itraconazole oral solution 200 mg PO daily o For Uncomplicated Vulvo-Vaginal Candidiasis: ▪ Oral fluconazole 150 mg for one dose ▪ Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for three to seven days o For Severe or Recurrent VulvoVaginal Candidiasis:

Clinical Guideline	Recommendation(s)
	▪ Fluconazole 100 to 200 mg PO daily for ≥7 days ▪ Topical antifungal ≥7 days • Chagas Disease (American Trypanosomiasis) o For Acute, Early Chronic, and Reactivated Disease: ▪ Benznidazole 5 to 8 mg/kg/day PO in 2 divided doses for 30 to 60 days (not commercially available in the United States; contact the CDC) • Coccidioidomycosis o Clinically Mild Infections (e.g., Focal Pneumonia): ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day o Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): ▪ Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily ▪ Lipid formulation amphotericin B 4 to 6 mg/kg IV daily ▪ Duration of therapy: continue until clinical improvement, then switch to an azole o Meningeal Infections: ▪ Fluconazole 400 to 800 mg IV or PO daily o Chronic Suppressive Therapy: ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day • Community-Acquired Pneumonia (CAP) o Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia o Empiric Outpatient Therapy: ▪ A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: High-dose amoxicillin or amoxicillin/clavulanate ▪ Alternative Beta-Lactams: Cefpodoxime or cefuroxime, or Levofloxacin 750 mg PO once daily, or moxifloxacin 400 mg PO once daily, especially for patients with penicillin allergies. o Empiric Therapy for Hospitalized Patients with Non-Severe CAP: ▪ An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam; Levofloxacin 750 mg IV once daily, or moxifloxacin, 400 mg IV once daily, especially for patients with penicillin allergies. o Empiric Therapy for Hospitalized Patients with Severe CAP: ▪ An IV beta-lactam plus IV azithromycin, or ▪ An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam o Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia: ▪ An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every eight to 12 hours or levofloxacin 750 mg IV once daily) ▪ Preferred Beta-Lactams: Piperacillin-tazobactam, cefepime, imipenem, or meropenem o Empiric Therapy for Patients at Risk for Methicillin-Resistant Staphylococcus aureus Pneumonia: ▪ Add vancomycin IV or linezolid (IV or PO) to the baseline

Clinical Guideline	Recommendation(s)
	regimen ▪ Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production • Cystoisosporiasis (Formerly Isosporiasis) o For Acute Infection: ▪ TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or ▪ TMP-SMX (160 mg/800 mg) PO (or IV) BID for seven to 10 days ▪ Can start with BID dosing first and increase daily dose and/ or duration (up to three to four weeks) if symptoms worsen or persist ▪ IV therapy may be used for patients with potential or documented malabsorption o Chronic Maintenance Therapy (Secondary Prophylaxis): ▪ In patients with CD4 count <200/µL, TMP-SMX (160 mg/ 800 mg) PO three times weekly • Mycobacterium avium Complex (MAC) Disease o At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance: ▪ Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO daily, or ▪ If drug interaction or intolerance precludes the use of clarithromycin, (azithromycin 500 to 600 mg + ethambutol 15 mg/kg) PO daily o Duration: At least 12 months of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART • Pneumocystis Pneumonia (PCP) o Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX o Duration of PCP treatment: 21 days • Syphilis o Early Stage (Primary, Secondary, and Early-Latent Syphilis): ▪ Benzathine penicillin G 2.4 million units IM for one dose o Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses o Late-Stage (Tertiary–Cardiovascular or Gummatous Disease): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses (Note: rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management) o Neurosyphilis (Including Otic or Ocular Disease): ▪ Aqueous crystalline penicillin G 18 to 24 million units per day (administered as 3 to 4 million units IV q4h or by continuous IV infusion) for 10 to 14 days +/- benzathine penicillin G 2.4 million units IM weekly for three doses after completion of IV therapy
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-**	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of

Clinical Guideline	Recommendation(s)
Resistant *Staphylococcus Aureus* (2011)[25]	systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to

Clinical Guideline	Recommendation(s)
	six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.

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	• Septic thrombosis of cavernous or dural venous sinus
	  ○ Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  ○ Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  ○ Intravenous vancomycin is recommended in children.

American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression (2018)**[26]	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir). • Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)**[27]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.

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	Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate. o Moxifloxacin. o Levofloxacin o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): o Intravenous antibiotic monotherapy is preferred. o Intravenous combination therapy could be considered especially in cases of resistance. Antibacterial agents: empiric gram-positive activity • Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. o Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. Antibacterial agents: anti-pseudomonal • Cefepime

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	○ Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever. ○ Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime ○ Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). ○ Use for suspected/proven CNS infection with susceptible organism. ○ Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. ○ Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. ○ Use for suspected intra-abdominal source. ○ Meropenem is preferred over imipenem for suspected/proven CNS infection. ○ Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. ○ Empiric therapy for neutropenic fever. ○ Data are limited, but it is expected that doripenem, like meropenem, would be efficacious. • Piperacillin-tazobactam ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Use for suspected intra-abdominal source. ○ Not recommended for meningitis. ○ Empiric therapy for neutropenic fever. <u>Antibacterial agents: other</u> • Aminoglycosides ○ Activity primarily against gram-negative organisms. ○ Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate ○ Good activity against gram-negative and atypical organisms. Less active than “respiratory” fluoroquinolones against gram-positive organisms. ○ Ciprofloxacin alone has no activity against anaerobes. ○ Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes. ○ Oral combination therapy in low-risk patients. ○ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. ○ Increasing Gram-negative resistance in many centers. ○ Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered. • Levofloxacin/ moxifloxacin ○ Good activity against gram-negative and atypical organisms. ○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas.

Clinical Guideline	Recommendation(s)
	○ Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole ○ Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. ○ Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. ○ Interactions with methotrexate.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonamides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Sulfonamides[1-4]

Indication	Single Entity Agents	Combination Products
	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Central Nervous System Infections		
Haemophilus influenzae meningitis (adjunctive therapy with parental streptomycin)	✔	
Meningococcal meningitis	✔	
Toxoplasmic encephalitis (adjunctive therapy with pyrimethamine)	✔	
Gastrointestinal Indications		
Shigellosis		✔
Traveler's diarrhea		✔
Genitourinary Infections		
Chancroid	✔	
Urinary tract infections	✔	✔
Respiratory Infections		
Acute exacerbations of chronic bronchitis		✔
Otitis media		✔
Otitis media (adjunctive therapy with penicillin)	✔	
Pneumocystis jirovecii pneumonia		✔
Miscellaneous Infections		
Adjunctive treatment of malaria due to chloroquine-resistant strains of *Plasmodium falciparum*	✔	
Inclusive conjunctivitis	✔	
Nocardiosis	✔	
Rheumatic fever (prophylaxis)	✔	
Trachoma	✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the sulfonamides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Sulfonamides[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Sulfadiazine	Well absorbed	38 to 48	Liver	Renal (45 to 84)	7.0 to 16.8
Combination Products					
Sulfamethoxazole and trimethoprim	90 to 100	Sulfa-methoxazole: 70 Trimethoprim: 44 to 62	Liver	Sulfa-methoxazole: Renal (84.5) Trimethoprim: Renal (66.8)	Sulfa-methoxazole: 8 to 11 Trimethoprim: 6 to 17

V. Drug Interactions

Major drug interactions with the sulfonamides are listed in Table 6.

Table 6. Major Drug Interactions with the Sulfonamides[2]

Generic Name(s)	Interaction	Mechanism
Sulfonamides	Methenamine	Methenamine is contraindicated for use with sulfonamides due to the potential for formation of insoluble precipitates in the urine. Methenamine is broken down in acidic urine to formaldehyde. Insoluble precipitates may form when certain sulfonamides are exposed to formaldehyde.
Sulfamethoxazole and trimethoprim	Anticoagulants	Sulfamethoxazole-trimethoprim may increase the hypoprothrombinemic effects of anticoagulants, possibly with bleeding. Inhibition of the hepatic metabolism of the S(-) warfarin enantiomorph appears to be the primary mechanism.
Sulfamethoxazole and trimethoprim	Methotrexate	The pharmacologic effects of methotrexate may be increased. Sulfonamides may displace methotrexate from plasma protein binding sites, competitively inhibit renal tubular secretion of methotrexate, and exert additive antifolate activity.
Sulfamethoxazole and trimethoprim	Tricyclic antidepressants	Concurrent use of sulfamethoxazole-trimethoprim and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Sulfamethoxazole and trimethoprim	Antiarrhythmic agents	Concurrent use of sulfamethoxazole-trimethoprim and antiarrhythmic agents may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Sulfamethoxazole and trimethoprim	Leucovorin	Concurrent use of leucovorin calcium and sulfamethoxazole-trimethoprim may result in an increased rate of treatment failure.
Sulfamethoxazole and trimethoprim	Pyrimethamine	Concurrent use of sulfamethoxazole-trimethoprim and pyrimethamine may result in an increased risk of megaloblastic anemia and pancytopenia.
Sulfamethoxazole and trimethoprim	Gemifloxacin	Concurrent use of gemifloxacin and sulfamethoxazole-trimethoprim may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonamides are noted in Table 7. The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.[1-4]

Table 7. Adverse Drug Events (%) Reported with the Sulfonamides[1-4]

Adverse Events	Single Entity Agents	Combination Products
	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Cardiovascular		
Polyarteritis nodosa	-	✔
Central Nervous System		
Apathy	-	✔
Aseptic meningitis	-	✔
Ataxia	✔	✔
Chills	✔	✔
Depression	✔	✔
Dizziness	✔	-
Fatigue	-	✔
Fever	✔	✔
Hallucinations	✔	✔
Headache	✔	✔
Insomnia	✔	✔
Kernicterus	-	✔
Nervousness	-	✔
Peripheral neuritis	✔	✔
Seizures	✔	✔
Tinnitus	✔	✔
Vertigo	✔	✔
Dermatological		
Erythema multiforme	✔	✔
Exfoliative dermatitis	✔	✔
Henoch-Schonlein purpura	-	✔
Lyell's syndrome	✔	-
Photosensitivity	✔	✔
Pruritus	✔	✔
Rash	✔	✔
Skin eruption	✔	✔
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	✔	✔
Endocrine and Metabolic		
Goiter production	✔	-
Thyroid function disturbance	✔	-
Gastrointestinal		
Abdominal pain	✔	✔
Anorexia	✔	✔
Clostridium difficile diarrhea	-	✔
Diarrhea	✔	✔
Glossitis	-	✔
Loss of appetite	-	✔
Nausea	✔	✔
Pancreatitis	✔	✔
Pseudomembranous colitis	-	✔
Stomatitis	✔	✔
Vomiting	✔	✔
Genitourinary		
Acute nephropathy	✔	-
Anuria	✔	✔
Crystalluria	✔	✔
Diuresis	✔	✔

Adverse Events	Single Entity Agents	Combination Products
	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Hematuria	✔	-
Interstitial nephritis	✔	✔
Nephrotoxicity	-	✔
Oliguria	✔	✔
Periarteritis nodosa	✔	✔
Renal failure	-	✔
Stone formation	✔	-
Toxic nephrosis	✔	✔
Hematologic		
Agranulocytosis	✔	✔
Aplastic anemia	✔	✔
Eosinophilia	-	✔
Granulocytopenia	✔	-
Hemolysis	-	✔
Hemolytic anemia	✔	✔
Hypoprothrombinemia	✔	✔
Leukopenia	✔	✔
Megaloblastic anemia	-	✔
Methemoglobinemia	✔	✔
Neutropenia	-	✔
Purpura	✔	-
Thrombocytopenia	✔	✔
Hepatic		
Hepatic necrosis	-	✔
Hepatitis	✔	-
Hepatotoxicity	-	✔
Jaundice	✔	-
Transaminases increased	-	✔
Laboratory Test Abnormalities		
Blood urea nitrogen increased	-	✔
Hyperbilirubinemia	-	✔
Hyperkalemia	-	✔
Hypoglycemia	✔	✔
Hyponatremia	-	✔
Serum creatinine increased	-	✔
Musculoskeletal		
Arthralgia	✔	✔
Myalgia	-	✔
Rhabdomyolysis	-	✔
Weakness	-	✔
Respiratory		
Cough	-	✔
Dyspnea	-	✔
Pulmonary infiltrates	-	✔
Other		
Allergic reaction	-	✔
Allergic myocarditis	✔	✔
Anaphylactoid reactions	✔	-
Anaphylaxis	✔	✔
Angioedema	-	✔
Conjunctival injection	✔	-
Drug fever	✔	-

Adverse Events	Single Entity Agents	Combination Products
	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Lupus-like symptoms	-	✔
Periorbital edema	✔	-
Scleral injection	✔	-
Serum sickness-like reactions	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the sulfonamides are listed in Table 8.

Table 8. Usual Dosing Regimens for the Sulfonamides[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Sulfadiazine	Unspecified infections: Tablet: Initial, 2 to 4 g; maintenance, 2 to 4 g, divided into three to six doses, every 24 hours	Rheumatic fever prophylaxis for patients ≥2 months of age: Tablet: <30 kg, 500 mg every 24 hours; ≥30 kg, 1 g every 24 hours Unspecified infections ≥2 months of age: Tablet: Initial, one-half the 24-hour dose; maintenance, 150 mg/kg or 4 g/m^2, divided into four to six doses, every 24 hours	Tablet: 500 mg
Combination Products			
Sulfamethoxazole and trimethoprim	Acute exacerbations of chronic bronchitis: Suspension, tablet: 800-160 mg every 12 hours for 14 days *Pneumocystis jirovecii* pneumonia prophylaxis: Suspension, tablet: 800-160 mg daily *Pneumocystis jirovecii* pneumonia treatment: Injection, tablet, suspension: 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per day given in equally divided doses every six hours for 14 to 21 days Shigellosis: Injection, suspension, tablet: 800-160 mg every 12 hours for five to seven days Traveler's diarrhea: Suspension, tablet: 800-160	Acute otitis media in patients ≥2 months of age: Suspension, tablet: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for 10 days *Pneumocystis jirovecii pneumonia* prophylaxis in patients ≥4 weeks of age: Suspension, tablet: 750 mg/m^2/day sulfamethoxazole and 150 mg/m^2/day trimethoprim given in equally divided doses twice daily on three consecutive days per week *Pneumocystis jirovecii* pneumonia treatment in patients ≥2 months of age: Injection, tablet, suspension: 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per day given in equally divided doses every six hours for 14 to 21 days	Injection: 80-16 mg/mL Suspension: 200-40 mg/5 mL 800-160 mg/20 mL Tablet: 400-80 mg 800-160 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg every 12 hours for five days Urinary tract infections: Suspension, tablet: 800-160 mg every 12 hours for 10 to 14 days	 Shigellosis in patients ≥2 months of age: Injection, tablet, suspension: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for five days Urinary tract infections in patients ≥2 months of age: Injection, tablet, suspension: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for 10 days	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sulfonamides are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Sulfonamides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Central Nervous System Infections				
Torre et al.[28] (1998) Sulfadiazine 60 mg/kg/day, pyrimethamine 50 mg QD, folinic acid 10 mg QD for four weeks, followed by three months maintenance therapy at half of the original dosage vs SMX-TMP 50 to 10 mg/kg/day for four weeks, followed by three months maintenance therapy at half of the original dosage	MC, PRO, RCT Patients >18 years of age with AIDS and toxoplasmic encephalitis	N=77 4 months	Primary: Clinical efficacy, radiologic efficacy, death, adverse events Secondary: Not reported	Primary: There was no statistically significant difference in complete clinical response rate between the sulfadiazine-pyrimethamine and the SMX-TMP groups at the end of acute therapy (65.7 vs 62.1%, respectively). A complete resolution of radiologic lesions was noted in 39.3% of patients in the sulfadiazine and pyrimethamine group compared to 62.1% patients in the SMX-TMP group (P=0.0478). There was no significant difference in survival between the two groups. Adverse effects occurred more frequently in the sulfadiazine and pyrimethamine treatment group compared to the SMX-TMP group (37.8 vs 12.5%, respectively; P=0.0162). Skin rashes were observed only in the sulfadiazine-pyrimethamine group. Secondary: Not reported
Chirgwin et al.[29] (2002) Sulfadiazine 1,500 mg QID and atovaquone suspension 1,500 mg QD for six	OL, RCT Patients with either presumptive or definitive toxoplasmic encephalitis, either acute or relapsed,	N=49 48 weeks	Primary: Clinical and radiographic response to treatment for acute disease and as maintenance therapy, adverse	Primary: Out of patients assigned to atovaquone and pyrimethamine, 75% experienced an overall response to treatment for acute disease compared to 82% in the atovaquone and sulfadiazine group. All patients demonstrated complete resolution of lesions on radiologic examinations performed at weeks 12 and 16 during the maintenance therapy phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks of acute treatment and 42 week maintenance period vs atovaquone suspension 1,500 mg QD and pyrimethamine 200 mg on day one, followed by 75 mg QD for six weeks of acute treatment and 42 week maintenance period	HIV-positive or diagnosed with AIDS		effects Secondary: Not reported	Adverse events requiring treatment discontinuation occurred in 32% of patients receiving pyrimethamine and 17% of those on sulfadiazine regimen. Secondary: Not reported
Dermatological Infections				
Talan et al.[30] (2016) SMX-TMP 1600-320 mg BID for seven days vs placebo	DB, MC, RCT Patients >12 years of age had a cutaneous lesion that was suspected to be an abscess	N=1247 Test-of-cure: 14 to 21 days Extended follow-up: 49 to 63 days	Primary: Clinical cure at test-of-cure visit Secondary: Composite cure (resolution of all symptoms and signs of infection, or improvement such that no additional antibiotic therapy or surgical drainage procedure was necessary), surgical drainage procedures, changes in abscess,	Primary: The abscess cure rate was 80.5% in the SMX-TMP group and 73.6% in the placebo group in the modified ITT population (difference, 6.9 percentage points; 95% CI, 2.1 to 11.7; P=0.005). Secondary: SMX-TMP achieved more favorable responses compared to placebo in most secondary outcomes, resulting in lower rates of subsequent surgical drainage procedures (3.4 vs 8.6%; difference, −5.2 percentage points; 95% CI, −8.2 to −2.2), skin infections at a new site (3.1 vs 10.3%; difference, −7.2 percentage points; 95% CI, −10.4 to −4.1), and infections among household members (1.7 vs 4.1%; difference, −2.4 percentage points; 95% CI, −4.6 to −0.2) through the test-of-cure visit. SMX-TMP was associated with slightly more gastrointestinal side effects (mostly mild) than placebo. At seven to 14 days after the treatment period, invasive infections had developed in two of 524 participants (0.4%) in the SMX-TMP group and in two of 533 participants (0.4%) in the placebo group; at 42 to 56 days after the treatment period, an invasive infection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			invasive infections, hospitalizations, days missed	had developed in one participant (0.2%) in the SMX-TMP group.
Tong et al.[31] (2010) SMX-TMP 20-4 mg/kg BID for five days vs penicillin benzathine 45 mg/kg IM as a single dose	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day seven after the commencement of treatment Secondary: Bacterial resolution of sores at day four and day seven; successful treatment at day four	Primary: Treatment was successful in all seven patients assigned to SMX-TMP, and five of six patients assigned to the penicillin group seven days after randomization (P=0.46). Secondary: By day four, microbiological clearance was documented in five of seven patients treated with SMX-TMP and in two of six patients treated with penicillin (P=0.28). By day seven, microbiological clearance was documented in all seven patients treated with SMX-TMP and in three of six patients treatment with penicillin (P=0.07). Treatment was successful after four days in six of seven treated with SMX-TMP and three of six with penicillin (P=0.27).
Khawcharoenporn et al.[32] (2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs clindamycin 300 mg QID	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety Secondary: Not reported	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91 vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001). Secondary: Not reported
Moran et al.[33] (2017) Cephalexin 500 mg four times daily, plus trimethoprim-sulfamethoxazole, 320 mg-1600 mg twice daily, for seven days vs cephalexin plus placebo for seven days	DB, MC, RCT Outpatients >12 years of age with cellulitis and no wound, purulent drainage, or abscess	N=500 9 weeks	Primary: Clinical cure [absence of these clinical failure criteria at follow-up visits: fever; increase in erythema (>25%), swelling, or tenderness (days 3 to 4); no decrease in erythema, swelling, or tenderness (days 8 to 10); and more than minimal erythema, swelling, or tenderness (days 14 to 21)] of cellulitis at the test-of-clinical-cure visit, 14 to 21 days after enrollment Secondary:	Primary: Among 500 randomized participants, 496 (99%) were included in the modified intention-to-treat analysis and 411 (82.2%) in the per-protocol analysis (median age, 40 years [range, 15 to 78 years]; 58.4% male; 10.9% had diabetes). Clinical cure occurred at 14 to 21 days after enrollment in 83.5% of participants in the cephalexin plus trimethoprim-sulfamethoxazole group and 85.5% of participants in the cephalexin group in the per-protocol population (difference, −2.0%; 95% CI, −9.7 to 5.7%; P=0.50). In the modified intention-to-treat population, clinical cure occurred in 76.2% of participants in the cephalexin plus trimethoprim-sulfamethoxazole group vs 69.0% of in the cephalexin group (difference, 7.3%; 95% CI, -1.0 to 15.5%; P=0.07). Secondary: Secondary outcomes were not significantly different between treatment groups, including drainage procedures, changes in erythema size and swelling/induration and tenderness, invasive infections, new skin infections at same or different site, overnight hospitalizations, similar infections in household contacts, days missed of normal activities and work/school, and analgesic use.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Surgical drainage procedures, changes in erythema size, presence of swelling/induration and tenderness, invasive infections, skin infections at the same or different site, hospitalizations, similar infections in household contacts, days missed from normal activities and work/school, and days of analgesic use	
Gastrointestinal Infections				
Ericsson et al.[34] (1990) SMX-TMP 1,600-320 mg given as one dose vs SMX-TMP 800-160 mg given orally BID for three days vs loperamide 4 mg	DB, PC, RCT Patients with >3 unformed stools within 24 hours of study entry in addition to another symptom of enteric disease, such as abdominal cramps, nausea, or vomiting	N=227 3 days	Primary: Duration of diarrhea, failure rate Secondary: Not reported	Primary: Patients treated with the combination therapy had the shortest duration of diarrhea (one hour) compared to the placebo group (59 hours) and the three-day SMX-TMP therapy (34 hours; P<0.005 compared to placebo). The proportion of treatment failures was significantly lower in all treatment groups compared to the placebo group (P<0.005). Patients presenting with mild diarrhea at baseline randomized to the loperamide group exhibited shorter duration of diarrhea (18 hours) compared to the placebo group (96 hours; P=0.02). Patients treated solely with loperamide exhibited longer diarrhea duration compared to patients on combination therapy (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
given as a loading dose, followed by 2 mg after each loose stool movement (maximum dose 16 mg) vs SMX-TMP 800-160 mg given orally BID for three days, in addition to loperamide, 4 mg given as a loading dose, followed by 2 mg after each loose stool movement (maximum dose 16 mg) vs placebo				Not reported
Genitourinary Infections				
Tran et al.[35] (2001) SMX-TMP 40-8 mg/kg/day for one to three days (short-treatment course) vs SMX-TMP 40-8 mg/kg/day for 7 to	MA Children <18 years of age with uncomplicated cystitis confirmed by urine culture	N=1,279 (22 trials) Up to 14 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: There was no difference between short- and long-courses of SMX-TMP in terms of cure rates (difference in cure rate, 6.24%; 95% CI, -3.74 to 16.2). The short-course amoxicillin therapy was less effective in curing the infection compared to the conventional length of therapy (difference in cure rate, 13%; 95% CI, 4 to 24). Consequently, eight patients would need to receive a conventional amoxicillin course of therapy to prevent one treatment failure that would have occurred with a shorter duration of treatment. Drug-related toxicity increased in proportion to the length of therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
14 days (long-treatment course) or amoxicillin for one to three days (short-treatment course) vs amoxicillin for 7 to 14 days (long-treatment course)				Secondary: Not reported
Mårild et al.[36] (2009) SMX-TMP 15-3 mg/kg oral suspension BID for 10 days vs ceftibuten 9 mg/kg oral suspension QD for 10 days	MC, OL, RCT Patients 1 month to 12 years of age with a first-time febrile UTI	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes Secondary: Not reported	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients treated with ceftibuten and SMX-TMP were 93 and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93 and 90%, respectively (P=NS). Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the SMX-TMP group (P=NS). Gastrointestinal symptoms were reported most frequently. There were no serious adverse events reported. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McCarty et al.[37] (1999) SMX-TMP 800-160 mg BID for three days vs ciprofloxacin 100 mg BID for three days vs ofloxacin 200 mg BID for three days	MC, RCT Women ≥18 years of age with primary UTI, confirmed by a positive urine culture obtained within 48 hours of study onset, presenting with signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration	N=688 Up to 6 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events Secondary: Not reported	Primary: End-of-study evaluation revealed a lack of statistically significant difference in the pre-treatment pathogen eradication rate between the study groups. Pathogen eradication occurred in 94% of ciprofloxacin, 93% of SMX-TMP, and 97% of ofloxacin-treated patients. At the four to six week follow-up evaluation, recurrence rates were 11% in the ciprofloxacin, 16% in the SMX-TMP, and 13% in the ofloxacin-treated group. Clinical success at the end of therapy was 31% in the ciprofloxacin, 41% in the SMX-TMP, and 39% in the ofloxacin-treated group. The frequency of adverse effects was 93% in the ciprofloxacin, 95% in the SMX-TMP, and 96% in the ofloxacin-treated group (P=0.03). Premature discontinuation of the study drug due to side effects was more common in the SMX-TMP group, compared to the ciprofloxacin and ofloxacin groups (P=0.02). Secondary: Not reported
Gupta et al.[38] (2007) SMX-TMP 800-160 mg tablets BID for three days vs nitrofurantoin 100 mg BID for five days	OL, RCT Women18 to 45 years of age who had symptoms of acute cystitis (dysuria, frequency, and/or urgency)	N=338 35 days	Primary: Clinical cure rate at the end of the entire study period (30 days after therapy) Secondary: Clinical and microbiological cure rates at the early follow-up visit (five to nine days after therapy)	Primary: Clinical cure was achieved in 79% of the SMX-TMP group and in 84% of the nitrofurantoin group (95% CI, -13 to 4; P=0.25). Secondary: Clinical and microbiological cure rates at the first follow-up visit were similar in the SMX-TMP group and the nitrofurantoin group. Among women treated with SMX-TMP, there was a statistically significant decrease in clinical cure in women who had a SMX-TMP–non-susceptible uropathogen compared to women who had a susceptible isolate. Overall, 84% of SMX-TMP–treated women with a SMX-TMP–susceptible uropathogen had a clinical cure compared to 41% with a SMX-TMP–non-susceptible uropathogen (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Microbiological cure was achieved in 97% of SMX-TMP–treated women with a SMX-TMP–susceptible isolate vs 65% of women with a SMX-TMP–non-susceptible isolate (P<0.001).
Buckwold et al.[39] (1982) SMX-TMP 800-160 mg two tablets as a single dose vs SMX-TMP 1,600-320 mg four tablets as a single dose vs sulfisoxazole 1 g two tablets as a single dose vs sulfisoxazole 2 g two tablets as a single dose	MC, RCT Women with symptoms suggestive of acute cystitis (dysuria, frequency of urination, suprapubic discomfort)	N=117 Up to 4 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events Secondary: Not reported	Primary: Overall cure rates varied from 85 to 95%, but there was no statistically significant difference between the study groups (P>0.05). SMX-TMP regimens were associated with a significantly greater minimum inhibitory concentration at 24 hours postdose compared to the sulfisoxazole group (P<0.001). None of the regimens predisposed patients to re-infection (P>0.05). Secondary: Not reported
Varde et al.[40] (1981) SMX-TMP 400-80 mg two tablets BID for 14 days vs trimethoprim-	RCT Patients 11 to 66 years of age with an uncomplicated UTI confirmed by urine culture	N=37 14 days	Primary: Microbiological and clinical response, adverse events Secondary: Not reported	Primary: The number of patients exhibiting good response (defined as symptomatic improvement with sterile urine culture after three days of treatment) was greater in the trimethoprim-sulfadiazine group compared to the SMX-TMP group (74 vs 61%, respectively). While 37% of patients in the trimethoprim-sulfadiazine group exhibited clinical response (defined as being asymptomatic on the first day of treatment with significant bacteriuria), 44% of patients in the SMX-TMP group exhibited a clinical response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfadiazine 75-225 mg two tablets BID for 14 days				Only one patient in the trimethoprim-sulfadiazine group developed a macular rash, which was the only adverse event observed during the study period. Secondary: Not reported
Respiratory Infections				
Chintu et al.[41] (2004) SMX-TMP 240 mg suspension daily (children <5 years of age); 480 mg suspension daily (children ≥5 years of age) vs placebo	DB, RCT Children 1 to 14 years of age with a positive HIV antibody test and, for those younger than 18 months of age, clinical features suggestive of an HIV infection	N = 534 19 months	Primary: Mortality, hospitalization, adverse events, PCP Secondary: Not reported	Primary: The study was conducted in an area of high SMX-TMP resistance (60 to 80%). A 33% reduction in mortality was seen in the SMX-TMP group compared to placebo (RR, 0.67; 95% CI, 0.53 to 0.85). SMX-TMP was associated with a statistically significant reduction in hospitalization rate compared to placebo (RR, 0.77; 95% CI, 0.62 to 0.96). There was no significant difference in adverse effects between the two groups (P=0.06). This benefit applied across all ages (test for heterogeneity P=0.82) and baseline CD4 counts (test for heterogeneity P=0.36). *Pneumocystis carinii* was identified in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia. Secondary: Not reported
Toma et al.[42] (1998) SMX-TMP 1,600-320 mg (≥60 kg) or 1,200-240 mg (<60 mg) QID for 21 days	DB, MC, RCT Patients ≥16 years of age with HIV-related PCP	N=116 21 days	Primary: Treatment success (>2-point improvement in the PCP score, calculated on the basis of body temperature,	Primary: There was no statistically significant difference in the duration of therapy between the treatment groups (P=0.68). The treatment success rates for SMX-TMP and clindamycin-primaquine were 76% and 74%, respectively. There were no statistically significant differences between the treatment regimens with respect to dyspnea scores, PCP scores and lactate dehydrogenase values at any time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clindamycin 450 mg QID and primaquine 15 mg QD for 21 days			respiratory rate, cough, chest tightness, dyspnea, supplemental oxygen requirements, and chest radiograph), steroid use, duration of therapy, adverse events Secondary: Not reported	There was no statistically significant difference between treatment groups with respect to the use of steroids (12 patients per group; P=0.74). There was no significant difference in the rate of PCP recurrence between the two treatment arms (P=0.99). There was no significant difference in the rate of adverse effects experienced by the two treatment groups (P=0.57). Rash was the most frequent side effect in both groups. The incidence of rash was similar in both groups (P=0.78). Secondary: Not reported
Klein et al.[43] (1992) SMX-TMP 100-20 mg/kg/day IV divided into four doses vs pentamidine 4 mg/kg/day IV administered over one hour	DB, PRO, RCT Patients with PCP, confirmed by either a bronchoalveolar lavage or lung biopsy	N=163 21 days	Primary: Treatment failure (defined as persistent fever, worsening hypoxemia, and/or progressive roentgenographic deterioration), change in therapy due to toxicity, five-day mortality rate, survival rate, adverse effects Secondary: Not reported	Primary: Slightly more patients in the SMX-TMP group (42%) experienced treatment failure compared to the pentamidine group (40%; P=0.733). Slightly more patients in the SMX-TMP group (34%) had to discontinue therapy due to toxicity compared to the pentamidine group (25%; P=0.235). The mortality rate during the first five days of therapy was 4% in each of the two treatment groups (P=0.984). The overall survival rates were similar in the SMX-TMP (67%) and pentamidine groups (74%; P=0.402). The survival rates for patients requiring a change in therapy because of failure to respond was 46% for the SMX-TMP group compared to 56% for the pentamidine group. When a change in therapy was made because of toxicity, survival rates were 97% for those receiving SMX-TMP vs 94% for those receiving pentamidine. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Bucher et al.[44] (1997) SMX-TMP 800-160 mg daily to three times weekly vs pentamidine 300 to 400 mg monthly to 300 mg bimonthly vs dapsone 50 mg QD to 100 mg twice weekly or dapsone-pyrimethamine 350-50 mg weekly	MA Patients with HIV receiving antiretroviral treatment	N=4,832 (22 trials) Mean 13.2 months	Primary: PCP events, all-cause mortality, toxoplasmosis events, drug-related toxicity Secondary: Not reported	Primary: The risk ratio of dapsone-pyrimethamine compared to pentamidine in terms of PCP infection was 0.90 (95% CI, 0.71 to 1.15), 0.72 for toxoplasma encephalitis (95% CI, 0.54 to 0.97), and 1.07 (95% CI, 0.90 to 1.27) for mortality. Patients with higher CD4 counts at baseline (>100 cells/mm3) were found to be at a higher risk for experiencing drug-related toxicity compared to those with lower CD4 cell counts (P=0.01). High-dose dapsone-pyrimethamine regimens (≥200/50 mg) were more effective compared to the low-dose regimens. Compared to aerosolized pentamidine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.59; 95% CI, 0.45 to 0.76). However the difference in the risk of toxoplasma encephalitis (RR, 0.78; 95% CI, 0.55 to 1.11) and mortality (RR, 0.88; 95% CI, 0.74 to 1.06) was not statistically significant. SMX-TMP was more effective at preventing PCP infections in patients with higher CD4 counts at baseline (>100 cells/mm^3) compared to those with lower CD4 cell counts (P=0.02). Compared to dapsone-pyrimethamine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.49; 95% CI, 0.26 to 0.92). However the difference in the risk of toxoplasma encephalitis (RR, 1.17; 95% CI, 0.26 to 2.18), mortality (RR, 0.98; 95% CI, 0.80 to 1.08), and drug-limiting toxicity (RR, 1.08; 95% CI, 0.88 to 1.25) was not statistically significant. The reduction of mortality risk due to SMX-TMP treatment was greater among patients with lower CD4 counts at baseline (<100 cells/mm3) compared to those with higher CD4 cell counts (P=0.03). Drug limiting toxicity was experienced by 31.5%, 29.7%, and 6.8% of patients treated with SMX-TMP, dapsone-pyrimethamine, and aerosolized

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pentamidine, respectively. Compared to aerosolized pentamidine, SMX-TMP administered to 100 patients will prevent three to seven cases of PCP at a risk of 21 additional patients experiencing toxicity. Secondary: Not reported.
Ioannidis et al.[45] (1996) SMX-TMP vs pentamidine vs dapsone-based regimen vs placebo	MA Patients ≥18 years of age with HIV	N=6,583 (35 trials) Up to 2 years	Primary: PCP events, PCP-related mortality, all-cause mortality, toxoplasmosis events Secondary: Not reported	Primary: SMX-TMP was effective in preventing PCP infection; the failure rate was close to zero (0.5%). Patients randomized to SMX-TMP exhibited less prophylactic failures (42% reduction; 95% CI, 24 to 55) compared to patients receiving aerosolized pentamidine. The overall rate of treatment-limiting adverse events (per 100 patient-years) was 19 (95% CI, 18 to 21) for SMX-TMP and 15 (95% CI, 14 to 17) for dapsone-based regimens. The risk of adverse effects requiring SMX-TMP discontinuation decreased by 43% in patients taking SMX-TMP three times weekly as opposed to QD (95% CI, 30 to 54). Secondary: Not reported
Sachs et al.[46] (1995) SMX-TMP 800-160 mg BID for seven days in addition to oral corticosteroids vs amoxicillin 500 mg TID for seven days	DB, RCT Patients ≥18 years of age with asthma or COPD	N=195 14 days	Primary: PEF Secondary: Not reported	Primary: PEF percent predicted assessed during an exacerbation improved significantly in all three groups over the 14-day observation period (P<0.001), ranging from 0.34 to 0.78% predicted per day, finally returning to baseline value. No statistically significant difference was observed between the groups. There was no statistically significant difference between the groups in symptom scores, expressed as slopes or absolute values from days one to 14. The decrease in the symptom severity scores was significant in all three groups (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in addition to oral corticosteroids vs oral corticosteroids				There was no statistically significant difference between the three groups in terms of treatment failure rate. Secondary: Not reported
Nouira et al.[47] (2010) SMX-TMP 800-160 mg BID for 10 days vs ciprofloxacin 750 mg BID for 10 days	DB, RCT Patients ≥40 years of age with an acute exacerbation of COPD requiring mechanical ventilation	N=170 10 days	Primary: Hospital death and need for an additional course of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-free interval	Primary: Combined hospital death and additional antibiotic prescription rates were similar in the two groups (16.4 vs 15.3% in the SMX-TMP vs ciprofloxacin group; 95% CI, -9.8% to 12.0; P=0.832). During the study, 15 patients died in the hospital, eight (8.2%) in the SMX-TMP group and eight (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean exacerbation-free interval was similar in both treatment groups (83 vs 79 days in the SMX-TMP vs ciprofloxacin group; P=0.41). Of 38 patients initially receiving noninvasive ventilation in the SMX-TMP group, 17 (45%) were secondarily intubated vs 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the two study groups. Adverse events were minor and comparably distributed in both treatment groups.
Chodosh et al.[48] (1982) SMX-TMP 800-160 mg BID for 14 days vs ampicillin 500 mg, one capsule QID for	DB, RCT, XO Patients ≥18 years of age with chronic bronchitis who developed an acute bronchial infectious exacerbation within two weeks	N=21 14 days	Primary: Chest symptoms, physical findings, vital signs, pulmonary function, laboratory values, sputum analysis, time to recurrence of exacerbation	Primary: Patients in the ampicillin group experienced a longer recurrence-free time compared to patients in the SMX-TMP group (P<0.05). Sputum volumes decreased significantly in each treatment group, starting on day three of the study (P<0.05). While none of the patients in the ampicillin group discontinued therapy due to adverse effects, three patients in the SMX-TMP group discontinued treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
14 days	of the study *Pseudomonas, Klebsiella*, or *Staphylococcus aureus* were isolated		Secondary: Not reported	There were no significant differences noted between the two study drugs in all other outcome measures. Secondary: Not reported
Feder et al.[49] (1982) SMX-TMP 37.5-7.5 mg/kg/day divided into two doses for 14 days vs ampicillin 70 mg/kg/day divided into four doses for 14 days vs amoxicillin 30 mg/kg/day divided into three doses for 14 days	DB, RCT Patients two months to seven years of age with signs/symptoms of otitis media in addition to a bulging tympanic membrane with decreased mobility	N=282 14 days	Primary: Premature discontinuation of therapy due to ≥5 watery stools per day, diarrhea Secondary: Not reported	Primary: Therapy was discontinued in significantly more ampicillin-treated patients compared to amoxicillin-treated patients (P<0.01) or SMX-TMP-treated patients (P<0.03). Among patients who completed a full course of therapy, significantly more ampicillin-treated patients developed diarrhea compared to amoxicillin-treated patients (P<0.04) or SMX-TMP-treated patients (P<0.02). Initial symptom resolution occurred after approximately two days of treatment in all three groups. Secondary: Not reported
Miscellaneous				
Soheilian et al.[50] (2005) <u>Regimen A:</u> Sulfadiazine 2 g for two days, followed by sulfadiazine 500 mg every six hours, pyrimethamine 100	AC, PRO, RCT, SB Patients with ocular toxoplasmosis	N=59 24 months	Primary: Changes in retinochoroidal lesion size at six weeks, difference in visual acuity, adverse events, rate of recurrence	Primary: Active toxoplasmosis retinochoroiditis resolved in all patients over the treatment phase of the study. There was no significant difference in mean reduction of retinochoroidal lesion size between the patients randomized to receive regimens A and B (61 vs 59% reduction, respectively; P=0.75). No significant difference in visual acuity between the regimen A and B groups (P=0.56).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD for two days, followed by 25 mg QD, and folinic acid 5 mg QD for six weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over two weeks vs Regimen B: SMX-TMP 400-80 mg two tablets every 12 hours for six weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over two weeks			Secondary: Not reported	Adverse effects were similar in both groups with only one patient in each group experiencing rash as the only significant drug-related side effect. There was no significant difference in the rate of recurrence between the regimen A and B groups after 24 months of follow-up (10.3 vs 10.0%, respectively; P=0.64). Secondary: Not reported
Bosch-Driessen et al.[51] (2002) Regimen A: Sulfadiazine 4 g QD, pyrimethamine 100 mg on day one, followed by 50 mg QD, and folinic acid 15 mg QD for four weeks; prednisone	AC, MC, OL, RCT Patients, 16 to 80 years of age with an active toxoplasmic retinochoroidal lesion located centrally within the major temporal vascular arcades or a juxtapapillary	N=46 24 months	Primary: Time of intraocular inflammation resolution, size of the retinochoroidal lesion, difference in visual acuity, side effects Secondary: Not reported	Primary: There was no significant difference in the duration of intraocular inflammation between the regimen A and B groups (P=0.96). There was no significant difference in the decrease in size of the retinochoroidal lesion between the regimen A and B groups three months after study onset (P=0.32). There was no significant difference in the decrease in visual acuity between the regimen A and B groups (P=0.72). There was no significant difference in the rate of recurrence between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg QD was started from the third day of therapy and tapered off after 10 days vs Regimen B: Pyrimethamine 100 mg on day one, followed by 50 mg QD, azithromycin 250 mg QD or 500 mg QOD, and folinic acid 15 mg QD for four weeks; prednisone 40 mg QD was started from the third day of therapy and tapered off after 10 days	lesion			regimen A and B groups during the 24 months of follow-up (56 vs 33%, respectively; P=0.10). Adverse effects were more frequent in the sulfadiazine group compared to the azithromycin group (64 vs 33%; P<0.04). Thrombocytopenia as well as an elevation in serum creatinine and liver enzymes was observed in both groups. Secondary: Not reported
van Rossum et al.[52] (2007) Sulfasalazine 50 mg/kg/day vs placebo	PRO, SB Patients 2 to 18 years of age, with onset of JIA before the age of 16, at least one joint with active arthritis, and an insufficient response to NSAID drug therapy	N=61 7 to 10 years	Primary: Disease outcomes over time Secondary: Not reported	Primary: Active joints were present in 74% of the patients, including 30% with active polyarthritis. Compared to the end of the trial, follow-up of both groups combined showed a significant increase in joint limitation, but a stable situation in clinical parameters and acute phase reactants. The median C-HAQ for the whole group was 0.25 (range 0 to 2). None to mild disability was reported by 74% of the patients, moderate disability by 20% and severe disability by 6% of the patients. At follow up, 53% of patients in the sulfasalazine group were on DMARDs, including four still on sulfasalazine. The median duration of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sulfasalazine treatment was 2.5 years. Over the follow-up period, 50% of sulfasalazine patients were switched to another DMARD treatment, including methotrexate in 47%. The median duration of methotrexate treatment was three years. The median number of DMARDs used in the follow-up period was 1.5 (range one to five). At follow-up, 72% of patients in the placebo group were on DMARDs, including four patients on sulfasalazine. The median duration of sulfasalazine treatment in the placebo group was significantly longer than in the sulfasalazine group (5.2 years). Over the follow-up period, 64% of the placebo group switched to other DMARDs, including methotrexate (55% of the patients). The median duration of methotrexate treatment was four years. The median number of DMARDs used in the follow-up period by the placebo group was two (range zero to five). At follow-up, 47% of the sulfasalazine patients were classified as ACR Pedi 30 responders compared to the placebo patients (P=0.02). Secondary: Not reported
Braun et al.[53] (2011) Sulfasalazine titrated to a maximum of 3 g/day for 16 weeks vs etanercept 50 mg once weekly for 16 weeks	DB, MC, RCT Patients with active ankylosing spondylitis	N=566 16 weeks	Primary: Proportion of patients who achieved the Assessment of SpondyloArthritis international Society criteria for 20% improvement at 16 weeks Secondary: Proportion of responders	Primary: A total of 75.9% patients receiving etanercept achieved an Assessment of SpondyloArthritis international Society criteria for 20% response at week 16, compared to 52.9% of the patients in the sulfasalazine group (P<0.0001). Secondary: A significantly greater proportion of patients in the etanercept group than in the sulfasalazine group achieved an Assessment of SpondyloArthritis international Society criteria for 20% response as early as week two of treatment (P<0.0001); this difference was sustained through week 16. The proportions of patients receiving etanercept who achieved Assessment of SpondyloArthritis international Society criteria for 40% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			according to the Assessment of SpondyloArthritis international Society criteria for 20% response criteria at prespecified visits up to week 16, as well as the proportion of patients meeting the Assessment of SpondyloArthritis international Society criteria for 40% improvement criteria and the proportion achieving Assessment of SpondyloArthritis international Society criteria for 20% improvement in five of six domains at prespecified visits up to week 16	Assessment of SpondyloArthritis international Society criteria for improvement in five of six domains at responses were significantly higher at all time points, as early as week two and through week 16, when compared to the proportions of patients receiving sulfasalazine who achieved these end points (P<0.0001). An Assessment of SpondyloArthritis international Society criteria for 40% response was achieved by 59.8% of etanercept-treated patients compared to 32.6% of sulfasalazine-treated patients at week 16 (P<0.0001). The percentage of patients achieving an Assessment of SpondyloArthritis international Society criteria for improvement in five of six domains at response after 16 weeks was significantly greater in the etanercept group (45.5%) compared to the sulfasalazine group (21.2%; P<0.0001). The percentage of patients achieving partial remission was significantly higher in the group receiving etanercept compared to the group receiving sulfasalazine, as early as week two through week 16 (P<0.001). At week 16, 33.3% of patients in the etanercept group and 15.5% of patients in the sulfasalazine group achieved partial remission (P<0.0001). Treatment-emergent adverse events were reported in 55.3% of patients in the study. The proportions of patients who reported a treatment-emergent adverse event or an adverse event of special interest were similar in the etanercept group and the sulfasalazine group. A significantly greater number of patients in the etanercept group than in the sulfasalazine group reported experiencing injection-site reactions (10.8 vs 1.6%, respectively; P<0.001. Other common adverse events reported in the etanercept and sulfasalazine groups were upper respiratory tract infection (8.2% and 9.1%, respectively), headache (7.7 and 11.2%, respectively), and nausea (6.6 and 9.6%, respectively).
Song et al.[54] (2011) Sulfasalazine 2 to 3 g per day	MC, OL, RCT Patients 18 to 50 years of age with NSAID-refractory axial	N=76 48 weeks	Primary: Change of active inflammatory lesions in the sacroiliac joints and spine on	Primary: At week 48, the reduction of the sacroiliac joint score from 7.7 at baseline to 2.0 with etanercept was significantly larger than the sulfasalazine group (decrease from 5.4 at baseline to 3.5; P=0.02). Secondary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>vs

etanercept 25 mg SC twice weekly

Sulfasalazine patients could be switched to methotrexate (15 to 20 mg weekly).</td><td>spondyloarthritis with a symptom duration of <5 years</td><td></td><td>magnetic resonance imaging

Secondary:
Reduction of active inflammatory lesions on the posterior elements of the spine and a reduction of peripheral enthesitis on magnetic resonance imaging</td><td>At week 48, the reduction of inflammation in the spine from 2.2 at baseline to 1.0 in the etanercept group was significantly larger than the sulfasalazine group (decrease from 1.4 at baseline to 1.3; P=0.01).

The number of enthesitic sites improved significantly from 26 to 11 in the etanercept group vs 24 to 26 in the sulfasalazine group (P=0.04).

At week 48, 50% of patients reached clinical remission in the etanercept group vs 19% in the sulfasalazine group.</td></tr>
<tr><td>Hissink Muller et al.[55]
(2017)
BeSt-for-kids

DMARD-monotherapy (sulfasalazine or methotrexate) (arm 1)

vs

methotrexate / prednisolone-bridging (arm 2)

vs

etanercept and methotrexate combination (arm 3)</td><td>MC, SB, RCT

Patients two to 16 years of age diagnosed as DMARD-naive JIA, either rheumatoid factor negative polyarticular, oligoarticular JIA, or juvenile psoriatic arthritis, in need of systemic DMARD therapy according to treating physician</td><td>N=94

3 months</td><td>Primary:
Percentage inactive disease, adjusted ACR Pedi30, 50 and 70 and Juvenile Arthritis Disease Activity Score after six and 12 weeks of treatment

Secondary:
Adverse effects</td><td>Primary:
<table>
<tr><th></th><th>Etanercept + methotrexate</th><th>DMARD monotherapy</th><th>methotrexate + prednisone</th><th>P-value</th></tr>
<tr><td>Inactive disease 6-weeks (%)</td><td>3</td><td>0</td><td>13</td><td>0.25</td></tr>
<tr><td>Inactive disease 3-months (%)</td><td>17</td><td>25</td><td>9</td><td>Not reported</td></tr>
<tr><td>aACR Pedi 30 6-weeks (%)</td><td>57</td><td>47</td><td>56</td><td>0.68</td></tr>
<tr><td>aACR Pedi 30 3-months (%)</td><td>73</td><td>50</td><td>53</td><td>0.13</td></tr>
<tr><td>aACR Pedi 50 6-weeks (%)</td><td>37</td><td>28</td><td>44</td><td>0.56</td></tr>
<tr><td>aACR Pedi 50 3-months (%)</td><td>53</td><td>31</td><td>38</td><td>0.19</td></tr>
<tr><td>aACR Pedi 70 6-weeks (%)</td><td>20</td><td>9</td><td>25</td><td>0.25</td></tr>
<tr><td>aACR Pedi 70 3-months (%)</td><td>47</td><td>25</td><td>19</td><td>0.04</td></tr>
<tr><td>JADAS 6-weeks (median)</td><td>12.4</td><td>13.9</td><td>9.6</td><td>0.12</td></tr>
<tr><td>JADAS 3-months (median)</td><td>8.2</td><td>9.0</td><td>11.5</td><td>0.25</td></tr>
</table>
Secondary:</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Gastrointestinal symptoms were most frequently reported and were observed 7/32 (22%), 14/32 (44%) and 9/30 (28%) in arm 1, 2 and 3, respectively. Second most reported were mild infectious complications (25% in arm 1, 19% in arm 2 and 43% in arm 3) with eight upper respiratory tract infections documented in arm 3.

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily
Study design abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, PG=parallel group, PRO=prospective, RCT=randomized trial, RETRO=retrospective, RR=relative risk, XO=crossover
Other abbreviations: ACR=American College of Rheumatology, AIDS=acquired immunodeficiency syndrome, C-HAQ=childhood health assessment questionnaire, COPD=chronic obstructive pulmonary disease, DAS=disease activity score, DMARD=disease modifying antirheumatic drug, EULAR=European League Against Rheumatism, HIV=human immunodeficiency virus, ITT=intention to treat, IV=intravenous, JIA=juvenile idiopathic arthritis, MRSA=methicillin resistant Staphylococcus aureus, NSAID=nonsteroidal antiinflammatory drug, PCP=pneumocystis pneumonia, PEF=peak expiratory flow, RA=rheumatoid arthritis, SMX-TMP=sulfamethoxazole-trimethoprim, UTI=urinary tract infection

Additional Evidence

Dose Simplification
In a meta-analysis of 22 studies, Tran et al. reported no difference in cure rates between short courses (one to three days) and long courses (seven to 14 days) of sulfamethoxazole-trimethoprim for the treatment of uncomplicated cystitis in children <18 years of age.[35]

Stable Therapy
In a randomized, double-blind, crossover trial, El-Chaar et al. evaluated the differences in taste and adherence with brand and generic antibiotic suspensions in children.[56] While there was no difference in adherence, children verbally expressed a preference for Bactrim® compared to the generic sulfamethoxazole-trimethoprim product (P=0.0342).

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Sulfonamides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Sulfadiazine	tablet	N/A	N/A	$$$$$
Combination Products				
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*	$	$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The sulfonamides are approved to treat a variety of infections, including central nervous system, dermatological, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-5] All of the sulfonamides are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the sulfonamides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the sulfonamide. Sulfadiazine and sulfamethoxazole-trimethoprim are recommended as specific therapy for the treatment of susceptible pathogens causing encephalitis, diabetic foot infections, urinary tract infections, sinusitis, prophylaxis/treatment of *Pneumocystis (carinii) jiroveci* pneumonia, prophylaxis/treatment of *Toxoplasma* encephalitis, as well as for the secondary prevention of rheumatic fever.[5-6,10,15,16,19,24] They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections, granuloma inguinale, and pertussis.[7-8,14,23] There are very few clinical studies that directly compare the efficacy and safety of the sulfonamides.[28,39,50] However, the sulfonamides been shown to be comparable in efficacy to antibacterial agents in other classes.[31,32,33,36-38,42,43,46-48,50]

The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.[1]

There is insufficient evidence to support that one brand sulfonamide is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand sulfonamide products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand sulfonamide product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Tetracyclines
AHFS Class 081224
May 3, 2023

I. Overview

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-9] They bind reversibly to the 30S subunit of bacterial ribosomes and exert a bacteriostatic effect by blocking protein synthesis.[1-9]

The tetracyclines exhibit broad-spectrum antibacterial activity and are most active against aerobic gram-positive and gram-negative bacteria. They also have activity against many atypical pathogens. The widespread use of the tetracyclines has led to an increase in resistance. Cross-resistance has also been reported among the various agents. Tigecycline has been shown to have activity against tetracycline-resistant pathogens. It is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. There has been no cross-resistance observed between tigecycline and other antibacterials.[1-9]

Xerava® (eravacycline) is a fluorocycline tetracycline Food and Drug Administration (FDA)-approved for the treatment of complicated intra-abdominal infections in adults.[5] Nuzyra® (omadacycline) is an aminomethylcycline tetracycline FDA-approved for the treatment of adult patients with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections caused by designated susceptible microorganisms.[7]

The tetracyclines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation with the exception of eravacycline and omadacycline. This class was last reviewed in May 2021.

Table 1. Tetracyclines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Demeclocycline	tablet	N/A	demeclocycline
Doxycycline	capsule, delayed-release capsule, delayed-release tablet, injection, suspension (reconstituted), syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	doxycycline
Eravacycline	injection	Xerava®	none
Minocycline	capsule, injection, tablet	Minocin®	minocycline
Omadacycline	injection, tablet	Nuzyra®	none
Tetracycline	capsule	N/A	tetracycline
Tigecycline	injection	Tygacil®*	tigecycline

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

The tetracyclines have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the tetracyclines that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Tetracyclines[1-9]

Organism	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Gram-Positive Organisms							
Bacillus anthracis	✔	✔		✔		✔	
Enterococcus faecalis			✔		✔	✔	✔
Enterococcus faecium			✔			✔	
Listeria monocytogenes	✔	✔		✔		✔	
Staphylococcus aureus	✔	✔	✔	✔	✔		✔
Staphylococcus epidermidis							✔
Staphylococcus lugdunensis					✔		
Streptococci, viridans group						✔	
Streptococcus agalactiae							✔
Streptococcus anginosus			✔		✔		✔
Streptococcus pneumoniae	✔	✔		✔	✔	✔	✔
Streptococcus pyogenes					✔	✔	✔
Gram-Negative Organisms							
Acinetobacter species	✔	✔		✔		✔	
Bacteroides species			✔			✔	✔
Bartonella bacilliformis	✔	✔		✔		✔	
Brucella species	✔	✔		✔		✔	
Calymmatobacterium granulomatis	✔	✔		✔		✔	
Campylobacter fetus	✔			✔		✔	
Citrobacter freundii			✔				✔
Enterobacter aerogenes	✔	✔		✔		✔	
Enterobacter cloacae			✔		✔		✔
Escherichia coli	✔	✔	✔	✔		✔	✔
Francisella tularensis	✔	✔		✔		✔	
Haemophilus ducreyi	✔	✔		✔		✔	
Haemophilus influenzae	✔	✔		✔	✔	✔	✔
Haemophilus parainfluenzae					✔		
Klebsiella species	✔	✔		✔		✔	✔
Klebsiella oxytoca			✔				
Klebsiella pneumoniae			✔		✔		
Legionella pneumophila					✔		✔
Neisseria gonorrhoeae	✔	✔		✔		✔	
Neisseria meningitidis				✔			
Parabacteroides distasonis			✔				

Organism	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Shigella species	✔	✔		✔		✔	
Vibrio cholerae	✔	✔		✔		✔	
Yersinia pestis	✔	✔		✔		✔	
Miscellaneous Organisms							
Actinomyces species	✔	✔		✔		✔	
Balantidium coli		✔				✔	
Borrelia recurrentis	✔	✔		✔		✔	
Chlamydophila pneumoniae					✔		
Chlamydophila psittaci	✔	✔		✔		✔	
Chlamydia trachomatis	✔	✔		✔		✔	
Clostridium species	✔	✔		✔		✔	✔
Clostridium perfringens			✔				
Entamoeba species	✔	✔		✔		✔	
Fusobacterium nucleatum	✔	✔		✔		✔	
Mycobacterium marinum				✔			
Mycoplasma pneumoniae	✔	✔		✔	✔	✔	
Peptostreptococcus micros							✔
Plasmodium falciparum		✔					
Propionibacterium acnes	✔	✔		✔		✔	
Rickettsia species	✔	✔		✔		✔	
Treponema pallidum	✔	✔		✔		✔	
Treponema pertenue	✔	✔		✔		✔	
Ureaplasma urealyticum	✔	✔		✔		✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the tetracyclines are summarized in Table 3.

Table 3. Treatment Guidelines Using the Tetracyclines

Clinical Guideline	Recommendation(s)
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[10]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease. • Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE. • Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE. • Recommended prophylaxis for dental procedures at high-risk: o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure. o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure. Antimicrobial therapy: principles • The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues. • Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks). • In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate. • The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. Antimicrobial therapy: regimens • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in β-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	○ Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: ○ Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). ○ Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. ○ Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: ○ Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: ○ *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. ○ *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ○ *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. ○ *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. ○ *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. ○ *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): ○ Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). ○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin

Clinical Guideline	Recommendation(s)
	orally.
American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[11]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: o Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. o Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. o Previous infective endocarditis. o Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. o Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered. • Patients with known valvular heart disease should not receive antibiotics before

Clinical Guideline	Recommendation(s)
	blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[12]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy.

Clinical Guideline	Recommendation(s)
	○ For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. ○ Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: ○ Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. ○ Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: ○ Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). ○ Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: ○ Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. ○ Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. ○ Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. ○ Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: ○ Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: ○ For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. ○ For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK,

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	and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[13] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be

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	considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[14]	<u>Impetigo and ecthyma</u> • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. <u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u> • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/μL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. <u>Recurrent skin abscesses</u> • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection.

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	• After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. <u>Erysipelas and cellulitis</u> • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. <u>Necrotizing fasciitis</u> • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis.

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	Pyomyositis
	• Cultures of blood and abscess material should be obtained.
	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	Clostridial gas gangrene or myonecrosis
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	Animal bites
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  ○ are immunocompromised;
	  ○ are asplenic;
	  ○ have advanced liver disease;
	  ○ have preexisting or resultant edema of the affected area;
	  ○ have moderate to severe injuries, especially to the hand or face; or
	  ○ have injuries that may have penetrated the periosteum or joint capsule.
	• Oral treatment options
	  ○ Amoxicillin-clavulanate is recommended.
	  ○ Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  ○ First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided.
	• Intravenous
	  ○ β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems.
	• Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given.
	
	Cutaneous anthrax
	• Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax.
	• Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure.
	
	Bacillary angiomatosis and cat scratch disease
	• Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol:

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	○ Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. ○ Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. <u>Erysipeloid</u> • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. <u>Glanders</u> • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. <u>Bubonic plague</u> • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. <u>Tularemia</u> • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
World Gastroenterology Organization: **Acute Diarrhea (2012)**[15]	<u>General considerations</u> • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: ○ *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. ○ Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. ○ Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera ○ First-line: doxycycline. ○ Alternative: azithromycin or ciprofloxacin. • Shigellosis ○ First-line: ciprofloxacin. ○ Alternative: pivmecillinam or ceftriaxone. • Amebiasis ○ First-line: metronidazole. • Giardiasis ○ First-line: metronidazole. ○ Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* ○ First-line: azithromycin.

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	○ Alternative: fluoroquinolones (e.g., ciprofloxacin).
American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)**[16]	Epidemiology • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. Diagnosis • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. Treatment of acute disease • The usage of balanced electrolyte rehydration over other oral rehydration options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness. • In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. Evaluation of persisting symptoms • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. Prevention • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during

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	a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)**[17]	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more. • Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures. • Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified. • Recommended antimicrobial agents by pathogen: o *Campylobacter* ▪ First choice: Azithromycin ▪ Alternative: Ciprofloxacin o *Clostridium difficile* ▪ First choice: Oral vancomycin ▪ Alternative: Fidaxomicin ▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). o Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, TMP-SMX, or amoxicillin. o *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or TMP-SMX or azithromycin o *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: TMP-SMX or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. o *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone

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	○ Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside ○ *Yersinia enterocolitica* ▪ First choice: TMP-SMX ▪ Alternative: Cefotaxime or ciprofloxacin ○ *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response ○ *Cyclospora cayetanensis* ▪ First choice: TMP-SMX ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer durations of TMP-SMX treatment ○ *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. ○ *Cystoisospora belli* ▪ First choice: TMP-SMX ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide ○ *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole ▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
American College of Gastroenterology: **Clinical Guideline on the Treatment of *Helicobacter pylori* Infection (2017)**[18]	<u>Evidence-based first-line treatment strategies for providers in North America</u> • Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen. • Clarithromycin triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason. • Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin. • Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option.

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	• Sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days is a suggested first-line treatment option.
	• Hybrid therapy consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for seven days is a suggested first-line treatment option.
	• Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10 to 14 days is a suggested first-line treatment option.
	• Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, fluoroquinolone, and nitroimidazole for five to seven days is a suggested first-line treatment option.
	
	<u>When first-line therapy fails, options for salvage therapy</u>
	• In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline).
	• Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.
	• Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.
	• The following regimens can be considered for use as salvage treatment:
	  ○ Bismuth quadruple therapy for 14 days is a recommended salvage regimen.
	  ○ Levofloxacin triple regimen for 14 days is a recommended salvage regimen.
	  ○ Concomitant therapy for 10 to 14 days is a suggested salvage regimen.
	  ○ Clarithromycin triple therapy should be avoided as a salvage regimen.
	  ○ Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen.
	  ○ High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.

Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)**[19]	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori.* • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht VI/ Florence Consensus Report (2022)**[20]	<u>Treatment</u> • It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalized use of such a susceptibility-guided strategy in routine clinical practice remains to be established. • If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered. • The treatment duration of bismuth quadruple therapy should be 14 days, unless 10-

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	days effective therapies are available. • In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies. • The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days. • In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally. • The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days. • The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies. • Potassium-Competitive Acid Blockers (P-CAB; vonoprazan where available) – antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections. • Empiric second line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimize treatment success. • After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option. • After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment. • After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high- dose dual therapy might also be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered. • After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin- containing regimen or a combination of bismuth with different antibiotics should be used. • In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options.

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	Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth.

Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[21]	Genital herpes
	• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management.
	• Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy.
	• Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued.
	• Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes.
	• Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability.
	• Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged.
	• Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.
	• Recommended regimens for first episodes of genital herpes:
	  ○ acyclovir 400 mg orally three times daily for seven to 10 days
	  ○ famciclovir 250 mg orally three times daily for seven to 10 days
	  ○ valacyclovir 1,000 mg orally twice daily for seven to 10 days.
	• Treatment can be extended if healing is incomplete after 10 days of therapy.
	• Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing.
	• Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection.
	• Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners.
	• Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir.
	• Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.
	• Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons.
	• Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners.

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	• Recommended regimens for suppressive therapy of genital herpes:
	  ○ acyclovir 400 mg orally twice daily
	  ○ famciclovir 250 mg orally twice daily
	  ○ valacyclovir 500 mg orally once daily
	  ○ valacyclovir 1,000 mg orally once daily.
	• Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year).
	• Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment.
	• Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider.
	• Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
	• Recommended regimens for episodic treatment of recurrent HSV-2 genital herpes:
	  ○ acyclovir 800 mg orally twice daily for five days
	  ○ acyclovir 800 mg orally three times daily for two days
	  ○ famciclovir 1,000 mg orally twice daily for one day
	  ○ famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days
	  ○ famciclovir 125 mg orally twice daily for five days
	  ○ valacyclovir 500 mg orally twice daily for three days
	  ○ valacyclovir 1,000 mg orally once daily for five days.
	• Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing.
	• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.
	• HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose.
	• Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended.
	• Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation.
	• Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men.
	• Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2

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	acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: o acyclovir 400 to 800 mg orally two to three times daily o famciclovir 500 mg orally twice daily o valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: o acyclovir 400 mg orally three times daily for five to 10 days o famciclovir 500 mg orally twice daily for five to 10 days o valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: o acyclovir 400 mg orally three times daily o valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. Pediculosis pubis (pubic lice infestation) • Recommended regimens: o Permethrin 1% cream rinse applied to affected areas and washed off

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	after 10 minutes. ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off. ○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. ○ Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for eradication. • Alternative regimens: ○ Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. Bacterial vaginosis • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and

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	HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u>

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	• Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy.
	• Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy.
	• However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen.
	• Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.
	
	Severe vulvovaginal candidiasis
	• Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	Non-albicans vulvovaginal candidiasis
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended.
	• If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks.
	
	Genital warts
	• Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience.
	• There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal

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	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. • Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours. Cervical warts • For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated. • Management of exophytic cervical warts should include consultation with a specialist. • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Vaginal warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution Urethral meatus warts • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal Intra-anal warts • Management of intra-anal warts should include consultation with a colorectal specialist. • Recommended regimens: ○ Cryotherapy with liquid nitrogen. ○ Surgical removal. ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)**[22]	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole.

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	• For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023)**[23]	• Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should not normally be more than five days. • Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). • The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring mechanical ventilation cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas* species) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. • The route of administration (oral or intravenous) depends on the patient's ability to eat and the pharmacokinetics of the antibiotic, although it is preferable that antibiotics be given orally.

Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[24]
 	
Reviewed and deemed current as of 04/2013
	<u>Outpatient treatment</u>
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  ○ Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  ○ Levofloxacin (oral therapy).
	  ○ Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	<u>Inpatient treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.

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	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and Treatment of Adults with Community-Acquired Pneumonia (2019)**[25]	Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting: • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or o doxycycline 100 mg twice daily or o a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. o Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). o Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: o combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or o monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid.

Clinical Guideline	Recommendation(s)
	• Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines (2016)**[26]	Empiric Therapy • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known o Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant o It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem o In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available Pathogen-Specific Therapy • MRSA o Vancomycin or linezolid are recommended treatments • *P. aeruginosa* o It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy o In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli o Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species o Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens o If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin Duration of therapy • Seven day course of treatment
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults**	Community-acquired infection in adults: mild to moderate severity • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline

Clinical Guideline	Recommendation(s)
and Children (2010)[27]	as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. <u>Health care-associated infection:</u> • Therapy should be based on microbiologic results. To achieve empiric coverage,

Clinical Guideline	Recommendation(s)
	multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. <u>Cholecystitis and cholangitis:</u> • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology: **Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease (2020)**[28]	• Prophylactic antibiotic therapy is only recommended for adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal risk or low risk. If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high-risk only if it meets the following three criteria: the tick bite was from (a) an identified *Ixodes* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours. • For high-risk *Ixodes* spp. bites in all age groups, administer a single dose of oral doxycycline within 72 hours of tick removal over observation. • Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children. • For patients with erythema migrans, use oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil. For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin. • Patients with erythema migrans should be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses. If azithromycin is used, the indicated duration is five to 10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States.
Infectious Diseases Society of America: **Guideline on Diagnosis and Management of Babesiosis (2020)**[29]	• Treat babesiosis with the combination of atovaquone plus azithromycin or the combination of clindamycin plus quinine. Atovaquone plus azithromycin is the preferred antimicrobial combination for patients experiencing babesiosis, while clindamycin plus quinine is the alternative choice. The duration of treatment is seven to 10 days in immunocompetent patients but often is extended when the patient is immunocompromised.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[30]	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients

Clinical Guideline	Recommendation(s)
	who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.

Clinical Guideline	Recommendation(s)
	Management of methicillin-resistant *Staphylococcus aureus* pneumonia • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
Centers for Disease Control and Prevention: **Antimicrobial Treatment and**	• For adults with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides

Clinical Guideline	Recommendation(s)
Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (2021)[31]	(amikacin, tobramycin, plazomicin), or trimethoprim-sulfamethoxazole. . • For children with pneumonic or septicemic plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin) or aminoglycosides (gentamicin or streptomycin). Alternatives include tetracyclines (doxycycline), chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), or trimethoprim-sulfamethoxazole. • For adults with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin, streptomycin). Alternatives include chloramphenicol, fluoroquinolones (ofloxacin, gemifloxacin), aminoglycosides (amikacin, tobramycin, plazomicin), tetracyclines (tetracycline, omadacycline, minocycline, eravacycline), or trimethoprim-sulfamethoxazole. • For children with bubonic or pharyngeal plague, first-line options include fluoroquinolones (ciprofloxacin, levofloxacin), tetracyclines (doxycycline), or aminoglycosides (gentamicin or streptomycin). Alternatives include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), aminoglycosides (amikacin, tobramycin), tetracyclines (tetracycline, minocycline), or trimethoprim-sulfamethoxazole. • First-line treatments of patients of all ages and pregnant women with plague meningitis include chloramphenicol, levofloxacin, and moxifloxacin.
Centers for Disease Control and Prevention: **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis—United States (2016)[32]**	• The Centers for Disease Control and Prevention recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in patients of all ages, including children aged <8 years, and should be initiated immediately in persons with signs and symptoms suggestive of rickettsial disease. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain Spotted Fever; however, epidemiologic studies in which Centers for Disease Control and Prevention case report data have been used suggested that patients with Rocky Mountain Spotted Fever treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline. • Chloramphenicol is associated with adverse hematologic effects, which have resulted in its limited use in the United States, and monitoring of blood indices is required if this drug is used. • If chloramphenicol is substituted for doxycycline in the empiric treatment of tickborne rickettsial diseases, ehrlichiosis and anaplasmosis will not be covered and Rocky Mountain Spotted Fever treatment might be suboptimal. • Rifampin could be an alternative for the treatment of mild illness due to anaplasmosis in the case of pregnancy or documented allergy to tetracycline-class drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the tetracyclines are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Tetracyclines[1-9]

Indication	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Central Nervous System Infections							
Treatment of asymptomatic *Neisseria meningitidis* carriers				✔			
Dermatological Infections							
Acne	✔	✔		✔		✔	
Skin and skin-structure infections	✔	✔		✔	✔	✔	✔ §#
Staphylococcus aureus infections	✔					✔	
Treponema pertenue infections	✔ †	✔ †		✔ †		✔ †	
Yaws	✔ †	✔ †		✔ †		✔ †	
Gastrointestinal Infections							
Cholera	✔	✔		✔		✔	
Intestinal amebiasis	✔	✔				✔	
Genitourinary Infections							
Chancroid	✔	✔		✔		✔	
Chlamydial infection	✔	✔		✔		✔	
Endocervical infections		✔		✔		✔	
Granuloma inguinale	✔	✔		✔		✔	
Rectal infections		✔		✔		✔	
Syphilis	✔ †	✔ †		✔ †		✔ †	
Treponema pallidum infections	✔ †	✔ †		✔ †		✔ †	
Urethritis (gonococcal)	✔ †	✔ †					
Urethritis/cervicitis (gonococcal)				✔		✔ ‡	
Urethritis/cervicitis (non-gonococcal)	✔	✔		✔		✔	
Urinary tract infections	✔	✔		✔		✔	
Respiratory Infections							
Anthrax	✔ †	✔		✔ †		✔ †	
Community-acquired bacterial pneumonia					✔		✔ #
Haemophilus influenzae infections	✔	✔		✔		✔	
Mycoplasma pneumonia	✔	✔		✔		✔	
Respiratory tract infections	✔	✔		✔		✔	
Streptococcus pneumoniae infections	✔	✔		✔		✔	
Streptococcus pyogenes infections	✔					✔	
Miscellaneous Infections							

Indication	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Acinetobacter species infections	✔	✔		✔		✔	
Actinomycotic infections	✔ †	✔ †		✔ †		✔ †	
Bacteroides species infections	✔					✔	
Bartonellosis	✔	✔		✔		✔	
Brucellosis	✔ *	✔ *		✔ *		✔ *	
Campylobacter fetus infections	✔	✔		✔		✔	
Clostridial infections	✔ †	✔ †		✔ †		✔ †	
Disease caused by rickettsiae	✔	✔		✔		✔	
Escherichia coli infections	✔	✔		✔		✔	
Enterobacter aerogenes infections	✔	✔		✔		✔	
Fusobacterium fusiforme infections	✔ †	✔ †		✔ †		✔ †	
Inclusion conjunctivitis		✔		✔		✔	
Intra-abdominal infections			✔				✔ §#
Listeriosis	✔ †	✔ †		✔ †		✔ †	
Lymphogranuloma venereum	✔	✔		✔		✔	
Malaria prophylaxis		✔					
Periodontitis				✔			
Plague		✔		✔		✔	
Psittacosis	✔	✔		✔		✔	
Q fever	✔	✔		✔		✔	
Relapsing fever	✔	✔		✔		✔	
Rickettsialpox	✔	✔		✔		✔	
Rocky Mountain spotted fever	✔	✔		✔		✔	
Shigellosis	✔	✔		✔		✔	
Spotted fevers	✔	✔		✔		✔	
Tick fevers	✔	✔		✔		✔	
Trachoma	✔	✔		✔		✔	
Tularemia	✔	✔		✔		✔	
Typhus	✔	✔		✔		✔	
Vincent's infection	✔ †	✔ †		✔ †		✔ †	

*****In conjunction with streptomycin.
†Alternative therapy for the following infections when penicillin is contraindicated.
‡Tetracycline is not a recommended alternative for uncomplicated gonorrhea according to the Centers for Disease Control and Prevention sexually transmitted diseases guidelines.
§Complicated infections.
#Infections caused by susceptible isolettes of the designated microorganisms (see Table 2).

IV. Pharmacokinetics

The pharmacokinetic parameters of the tetracyclines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Tetracyclines[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Demeclocycline	Not reported	41 to 91	Liver	Renal (34 to 56) Feces (13 to 46)	10 to 15
Doxycycline	100	80 to 93	Liver	Renal (35 to 45)	18 to 22
Eravacycline	Not reported	79 to 90	Liver	Renal (34), Feces (47)	20
Minocycline	90	76	Not reported	Renal/Feces	11 to 22
Omadacycline	34.5	20	Not metabolized	Renal 27 (IV), 14.4 (oral), Feces (77.5 to 84.0)	16
Tetracycline	Readily absorbed	5	Liver	Renal (60)	8 to 10
Tigecycline	Not reported	71 to 89	Liver	Renal (33) Feces (59)	42

V. Drug Interactions

Major drug interactions with the tetracyclines are listed in Table 6.

Table 6. Major Drug Interactions with the Tetracyclines[2]

Generic Name(s)	Interaction	Mechanism
Tetracyclines	Acitretin	Concurrent use of acitretin and tetracyclines may result in an increased risk of pseudotumor cerebri (benign intracranial hypertension).
Tetracyclines	Digoxin	Co-administration may result in increased serum levels of digoxin in a small subset of patients (10%). Monitor digoxin levels and signs of toxicity.
Tetracyclines	Methoxyflurane	Co-administration may enhance the risk for renal toxicity; deaths have been reported. Do not co-administer. If possible seek alternative agents.
Tetracyclines	Penicillins	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins. Consider avoiding this combination if at all possible.
Tetracyclines	Retinoids	Acitretin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Doxycycline	Methotrexate	Concurrent use of doxycycline and methotrexate may result in an increased risk of methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations).
Eravacycline	Strong CYP3A inducers	Concurrent use of eravacycline and strong CYP3A inducers may result in reduced eravacycline concentrations and efficacy.
Minocycline	Atazanavir	Concurrent use of atazanavir and minocycline may result in decreased atazanavir exposure and plasma concentrations.
Omadacycline	Anticoagulants	Concurrent use of anticoagulants (e.g., warfarin, heparin) and omadacycline may result in increased risk of bleeding.
Omadacycline	Cation containing products	Concurrent use of omadacycline and cation containing products (e.g., iron, calcium, bismuth subsalicylate) may result in decreased effectiveness of omadacycline.

VI. Adverse Drug Events

The most common adverse drug events reported with the tetracyclines are noted in Table 7. The use of tetracyclines during the period of tooth development (from the last half of pregnancy through eight years of age) may cause permanent discoloration of teeth. Due to the risk of this discoloration, the tetracyclines should not be used in children under eight years of age (except for the treatment and postexposure prophylaxis of anthrax), unless other drugs are not likely to be effective or are contraindicated. This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses.

Table 7. Adverse Drug Events (%) Reported with the Tetracyclines[1-9]

Adverse Events	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Cardiovascular							
Atrial fibrillation	-	-	-	-	<2	-	-
Bradycardia	-	-	-	-	-	-	✔
Hypertension	-	-	-	-	3	-	-
Hypotension	-	-	1	-	-	-	-
Palpitations	-	-	✔	-	-	-	-
Pericarditis	✔	✔	-	✔	-	✔	-
Tachycardia	-	-	-	-	<2	-	-
Central Nervous System							
Anxiety	-	-	✔	-	-	-	-
Bulging fontanels	✔	✔	-	✔	-	✔	-
Depression	-	-	✔	-	-	-	-
Dizziness	✔	-	✔	-	-	-	3
Fatigue	-	-	-	-	<2	-	-
Fever	-	-	-	-	-	✔	-
Headache	✔	-	-	✔	2 to 3	-	6
Insomnia	-	-	✔	-	3	-	-
Intracranial hypertension	-	✔	-	✔	-	-	-
Pseudotumor cerebri	✔	-	-	✔	-	✔	✔
Vertigo	-	-	-	-	<2	-	-
Dermatological							
Erythema multiforme	✔	✔	-	✔	-	-	-
Erythematous rash	✔	✔	-	✔	<2	✔	-
Exfoliative dermatitis	-	✔	-	✔	-	✔	-
Maculopapular rash	✔	✔	-	✔	-	✔	-
Nail discoloration	-	-	-	-	-	✔	-
Oncolysis	-	-	-	-	-	✔	-
Photosensitivity	✔	✔	-	✔	-	✔	✔
Pruritus	-	-	-	-	<2	-	<2
Rash	-	-	✔	-	-	✔	3
Skin hyperpigmentation	✔	-	-	✔	-	-	-
Stevens-Johnson syndrome	✔	✔	-	✔	-	-	✔
Toxic epidermal necrolysis	-	✔	-	✔	-	-	-

Adverse Events	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Urticaria	✔	✔	-	✔	<2	✔	-
Endocrine and Metabolic							
Diabetes insipidus syndrome	✔	-	-	-	-	-	-
Gamma-glutamyl transferase increased	-	-	-	-	3	-	-
Nephrogenic diabetes insipidus	✔	-	-	-	-	-	-
Thyroid dysfunction	✔	-	-	✔	-	-	-
Gastrointestinal							
Abdominal pain	-	-	-	-	<2	-	6
Anorexia	✔	✔	-	✔	-	✔	<2
Black hairy tongue	-	-	-	-	-	✔	-
Constipation	-	-	-	-	2	-	-
Diarrhea	✔	✔	2	✔	3	✔	12
Dyspepsia	-	-	-	-	<2	✔	2
Dysphagia	✔	✔	-	✔	-	✔	-
Enamel hypoplasia	-	-	-	-	-	✔	-
Enterocolitis	✔	✔	-	✔	-	✔	-
Esophageal ulcerations	✔	✔	-	✔	-	✔	-
Esophagitis	-	✔	-	✔	-	✔	-
Glossitis	✔	✔	-	✔	-	✔	-
Nausea	✔	✔	7	✔	2 to 22	✔	24 to 35
Oral candidiasis	-	-	-	-	<2	-	-
Oral pigmentation	-	✔	-	-	-	-	-
Pancreatitis	✔	-	✔	-	-	✔	✔
Tooth discoloration	✔	✔	-	✔	-	✔	✔
Vomiting	✔	-	4	✔	3 to 11	✔	16 to 20
Genitourinary							
Acute renal failure	✔	-	-	✔	-	✔	-
Anogenital inflammatory lesions	-	✔	-	-	-	✔	-
Azotemia	-	-	-	-	-	✔	✔
Balanitis	✔	-	-	✔	-	-	-
Leukorrhea	-	-	-	-	-	-	<2
Monilial overgrowth	✔	-	-	✔	-	✔	<2
Renal damage	-	-	-	✔	-	✔	-
Vaginitis	-	-	-	-	-	-	<2
Vulvovaginal candidiasis	-	-	-	-	<2	-	-
Hepatic							
Hepatic cholestasis	-	-	-	-	-	-	✔
Hepatic dysfunction	-	-	-	-	-	-	✔
Hepatic failure	✔	-	-	-	-	✔	✔
Hepatitis	✔	-	-	-	-	-	-
Hepatotoxicity	✔	-	-	✔	-	✔	-

Adverse Events	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Jaundice	-	-	-	-	-	-	<2
Hematologic							
Anemia	-	-	-	-	<2	-	5
Eosinophilia	✔	✔	-	✔	-	✔	<2
Hemolytic anemia	✔	✔	-	✔	-	✔	-
Leukopenia	-	-	✔	-	-	-	-
Neutropenia	✔	✔	✔	✔	-	✔	-
Porphyria	-	-	-	✔	-	-	-
Prothrombin time increased	-	-	-	-	-	-	<2
Thrombocytopenia	✔	✔	-	✔	<2	✔	<2
Thrombocytopenic purpura	-	-	-	-	-	✔	-
Thrombophlebitis	-	-	-	-	-	✔	<2
Laboratory Test Abnormalities							
Acidosis	-	-	-	-	-	-	✔
Alkaline phosphatase increased	-	-	-	-	<2	-	3
Aminotransferase increased	-	-	-	-	2 to 4	-	-
Amylase increased	-	-	✔	-	-	-	3
Bilirubinemia	-	-	-	-	-	-	2
Blood urea nitrogen increased	✔	✔	-	✔	-	✔	3
Creatinine increased	-	-	-	-	-	-	<2
Creatinine clearance decreased	-	-	✔	-	-	-	-
Hyperphosphatemia	-	-	-	-	-	-	✔
Hypocalcemia	-	-	✔	-	-	-	<2
Hypoglycemia	-	-	-	-	-	-	<2
Hyponatremia	-	-	-	-	-	-	2
Hypoproteinemia	-	-	-	-	-	-	5
Partial thromboplastin time prolonged	-	-	✔	-	-	-	-
Total bilirubin increased	-	-	-	-	<2	-	✔
Transaminases increased	✔	-	✔	-	-	-	4 to 5
Musculoskeletal							
Arthralgia	-	-	-	-	-	✔	-
Polyarthralgia	✔	-	-	✔	-	-	-
Respiratory							
Cough	-	-	-	-	-	-	4
Dyspnea	-	-	✔	-	-	-	3
Pleural effusion	-	-	✔	-	-	-	-
Pneumonia	-	-	-	-	-	-	2
Pulmonary infiltrates	✔	-	-	✔	-	-	-
Other							
Abnormal healing	-	-	-	-	-	-	3
Abscess	-	-	-	-	-	-	2

Adverse Events	Demeclocycline	Doxycycline	Eravacycline	Minocycline	Omadacycline	Tetracycline	Tigecycline
Allergic reaction	-	-	-	-	-	-	<2
Anaphylactoid purpura	✔	-	-	✔	-	✔	-
Anaphylaxis	✔	✔	✔	✔	-	✔	✔
Angioneurotic edema	✔	✔	-	✔	-	✔	-
Chest pain	-	-	✔	-	-	-	-
Chills	-	-	-	-	-	-	<2
Hyperhidrosis	-	-	✔	-	<2	-	-
Hypersensitivity reaction	-	-	✔	✔	<2	✔	-
Infection	-	-	-	-	-	-	7
Injection/infusion site reaction	-	-	8	-	5	-	<2
Lupus erythematosus exacerbation	✔	✔	-	✔	-	✔	-
Lupus-like syndrome	✔	-	-	✔	-	-	-
Myasthenic syndrome	✔	-	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	<2	-	-
Phlebitis	-	-	-	-	-	-	3
Pruritus	-	-	-	-	-	-	<2
Septic shock	-	-	-	-	-	-	<2
Stools abnormal	-	-	-	-	-	-	<2
Superinfection	-	-	-	-	-	-	✔
Taste perversion	-	-	✔	-	<2	-	<2
Thyroid gland discoloration	✔	✔	-	✔	-	✔	-
Tinnitus	✔	✔	-	✔	-	-	-
Visual disturbances	✔	-	-	-	-	-	-
Wound dehiscence	-	-	1	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Boxed Warning for Tigecycline[1,8]

WARNING
An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in Tygacil®-treated patients vs comparator. The cause of this mortality risk difference of 0.6% (95% confidence interval, 0.1 to 1.2) has not been established. Tygacil® should be reserved for use in situations when alternative treatments are not suitable.

VII. Dosing and Administration

The usual dosing regimens for the tetracyclines are listed in Table 9.

Table 9. Usual Dosing Regimens for the Tetracyclines[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Demeclocycline	Unspecified infections: Tablet: 150 mg four times daily or 300 mg twice daily Gonorrhea (patients sensitive to penicillin): Tablet: 600 mg as an initial dose, followed by 300 mg every 12 hours for four days (total of 3 g)	Unspecified infections in children >8 years of age: Tablet: 7 to 13 mg/kg/day divided into two to four doses	Tablet: 150 mg 300 mg
Doxycycline	Unspecified infections: Oral formulations: 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every six hours), followed by a maintenance dose of 100 mg/day or 50 mg every 12 hours; for severe infections, 100 mg every 12 hours Acute epididymo-orchitis: Oral formulations: 100 mg daily for at least 10 days Inhalational anthrax (post-exposure): Oral formulations: 100 mg twice daily for 60 days Malaria prophylaxis: Oral formulations: 100 mg daily, beginning one to two days before travel to the malarious area; prophylaxis should be continued daily during travel in the malarious area and for four weeks after the traveler leaves the malarious area Nongonococcal urethritis: Oral formulations: 100 mg twice daily for at least seven days Syphilis: Oral delayed release formulations: 100 mg twice daily for 14 days (early, <1 year, primary or secondary infection); 100 mg twice daily for 28 days (latent, >1 year or duration unknown) Uncomplicated gonococcal infections (except anorectal infections in men): Oral formulations: 100 mg twice daily for at least seven days; alternative regimen, 300 mg immediately followed	Unspecified infections in children >8 years of age <45 kg (>45 kg see adult dose): All formulations: 4.4 mg/kg divided into two doses on the first day, followed by 2.2 mg/kg given as a single daily dose or divided into two doses, on subsequent day; for more severe infections up to 4.4 mg/kg may be used Inhalational anthrax (post-exposure) <45 kg (>45 kg see adult dose): Oral formulations: 2.2 mg/kg twice daily for 60 days Malaria prophylaxis in children >8 years of age: Oral formulations: 2.2 mg/kg daily, beginning one to two days before travel to the malarious area; prophylaxis should be continued daily during travel in the malarious area and for four weeks after the traveler leaves the malarious area; maximum dose, 100 mg daily	Capsule: 50 mg 75 mg 100 mg 150 mg Delayed release capsule: 75 mg Delayed release tablet: 75 mg 100 mg 150 mg 200 mg Injection: 100 mg Suspension (reconstituted): 25 mg/5 mL Syrup: 50 mg/5 mL Tablet: 50 mg 75 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	in one hour by a second 300 mg dose Uncomplicated urethral, endocervical, or rectal infection: Oral formulations: 100 mg twice daily for at least seven days		
Eravacycline	Complicated intra-abdominal infections: Injection: 1 mg/kg every 12 hours for four to 14 days	The safety and effectiveness in pediatric patients have not been established.	Injection: 50 mg 100 mg
Minocycline	Unspecified infections: Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours; alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily Injection: 200 mg initially, followed by 100 mg administered over 60 minutes every 12 hours Gonococcal infections (except urethritis and anorectal infections in men, uncomplicated): Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days Gonococcal urethritis (in men, uncomplicated), meningococcal carrier state: Capsule, tablet: 100 mg every 12 hours for five days *Mycobacterium marinum* infections: Capsule, tablet: 100 mg every 12 hours for six to eight weeks Syphilis: Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours for 10 to 15 days Urethral, endocervical, or rectal infections: Capsule, tablet: 100 mg every 12 hours for at least seven days	Unspecified infections in children >8 years of age: Capsule, injection, tablet: 4 mg/kg initially, followed by 2 mg/kg every 12 hours	Capsule: 50 mg 75 mg 100 mg Injection: 100 mg Tablet: 50 mg 75 mg 100 mg
Omadacycline	Community-acquired bacterial pneumonia: Injection: loading dose: 200 mg IV infusion over 60 minutes OR 100 mg IV infusion over 30 minutes twice on day one; maintenance, 100 mg IV infusion	Safety and effectiveness in pediatric patients below the age of 18 years has not been established.	Injection: 100 mg Tablet: 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	over 30 minutes once daily Tablet: maintenance, 300 mg orally once daily Acute bacterial skin and skin structure infections: Injection: loading dose, 200 mg IV infusion over 60 minutes OR 100 mg IV infusion over 30 minutes twice on day one; maintenance, 100 mg IV infusion over 30 minutes once daily Tablet: 450 mg once a day on day one and day two; maintenance, 300 mg once daily		
Tetracycline	Unspecified infections: Capsule: 500 mg twice daily or 250 mg four times daily; for sever infections dose may be increased to 500 mg four times daily Brucellosis: Capsule: 500 mg four times daily for three weeks plus streptomycin 1 g intramuscular twice daily the first week and once daily the second week Plague: Capsule: 500 mg every 6 hours for 10 to 14 days Anthrax: Capsule: 250 to 500 mg every six hours for five to nine days Gonorrhea: Capsule: 500 mg four times daily for seven days Syphilis: Capsule: 500 mg four times daily for 14 days (early, <1 year, primary or secondary infection); 500 mg four times daily for 28 days (latent, >1 year or duration unknown) Tularemia (mild to moderate): Capsule: 500 mg four times a day for at least 14 days Urethral, endocervical, or rectal infections: Capsule: 500 mg four times a day for at least seven days	Unspecified infections in children >8 years of age: Capsule: 25 to 50 mg/kg/day divided in four equal doses	Capsule: 250 mg 500 mg
Tigecycline	Intra-abdominal infections:	Safety and efficacy in	Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for five to 14 days Community-acquired bacterial pneumonia: Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for seven to 14 days Skin and skin-structure infections: Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for five to 14 days	children have not been established.	50 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the tetracyclines are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Tetracyclines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
O'Riordan et al.[33] (2019) OASIS-I Omadacycline 100 mg IV every 12 hours for 2 doses followed by 100 mg IV every 24 hours with the option to switch to 300 mg orally every 24 hours vs linezolid 600 mg IV every 12 hours with the option to switch to 600 mg orally every 12 hours	DB, MC, RCT Adults with qualifying ABSSI. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=655 Total treatment was for 7 to 14 days	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement of at least 20% reduction of ABSSSI primary lesion size compared to baseline 48 to 72 hours after the first dose of study drug [ECR window] and no use of rescue antibiotics) Secondary: Number of Participants with clinical response (CR: defined as symptom improvement, no use of rescue antibiotics, and patient survival), in the mITT	Primary: Omadacycline was noninferior to linezolid for percentage of patients with early clinical response (84.8% vs 85.5%; 95% CI, -6.3 to 4.9). Secondary: Omadacycline was noninferior to linezolid in the investigator-assessed clinical response at the PTE (86.1% vs 83.6%; 95% CI, -3.2 to 8.2). Number of adverse events was similar between omadacycline and linezolid (48.3% vs 45.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Population at the Post Therapy Evaluation (PTE) Visit, adverse events	
O'Riordan et al.[34] (2019) OASIS-II Omadacycline 450 mg orally once a day on days 1 and 2, followed by 300 mg orally once a day vs linezolid 600 mg orally every 12 hours	DB, MC, RCT Adults with qualifying ABSSI. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=735 Total treatment was for 7 to 14 days.	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement of at least 20% reduction of ABSSSI primary lesion size compared to baseline 48 to 72 hours after the first dose of study drug [ECR window] and no use of rescue antibiotics) Secondary: Number of Participants with clinical response (CR: defined as symptom improvement, no use of rescue antibiotics, and patient survival) in the mITT Population at the	Primary: Omadacycline was noninferior to linezolid for early clinical response (87.5% vs 82.5%; 95% CI, -0.2 to 10.3). Secondary: Omadacycline was noninferior to linezolid in the investigator-assessed clinical response at the PTE (84.2% vs 80.8%; 95% CI, -2.2 to 8.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Post Therapy Evaluation (PTE) Visit	
Montravers et al.[35] (2013) Tigecycline as monotherapy or in combination with other antibacterials	MA Patients with a mean age of 63.2±14.9 years of age who received tigecycline for complicated skin and soft tissue infection were included	N=254 Duration varied	Primary: Mean Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores Secondary: Not reported	Primary: Clinical response rates at the end of treatment were 79.6% for all patients who received the standard dosage (183/230), 86.7% for patients who received tigecycline as monotherapy (143/165), 75.0% for patients with a nosocomial infection (96/128), 75.3% for patients with an Acute Physiology and Chronic Health Evaluation II score >15 (61/81) and 58.3% for patients with a Sequential Organ Failure Assessment score >7 (7/12). Secondary: Not reported
Lauf et al.[36] (2014) Tigecycline 150 mg IV every 24 hours, with or without placebo for up to 28 days vs ertapenem 1 g IV every 24 hours, with or without adjunctive IV vancomycin for up to 28 days Patients with osteomyelitis were treated for up to 42 days	DB, RCT Hospitalized men and women ≥18 years of age with diabetes mellitus who had a foot infection that did not extend above the knee, with or without osteomyelitis. The infection had to be of acute onset or a worsening within 14 days prior to the screening visit.	N=955 (without osteomyelitis) N=118 (with osteomyelitis) 12 to 92 days after the last dose for patients without osteomyelitis and 25 to 27 weeks for patients with osteomyelitis	Primary: Clinical response within the clinically evaluable and the clinically modified intent-to-treat populations at the test-of-cure visit Secondary: Microbiologic efficacy of tigecycline, in vitro susceptibility data on tigecycline	Primary: At the test-of-cure assessment in the patients without osteomyelitis, 77.5% of tigecycline-treated subjects and 82.5% of ertapenem ± vancomycin-treated subjects in the clinically evaluable population were considered cured, and 71.4% of those treated with tigecycline subjects and 77.9% of those who received ertapenem ± vancomycin in the clinically modified intent-to-treat population were considered cured. The tigecycline regimen did not meet the primary study endpoint of noninferiority to the ertapenem ± vancomycin regimen for the clinically evaluable population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −5.5%; 95% CI, −11.0 to 0.1) or clinically modified intent-to-treat population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −6.7; 95% CI, −12.3 to −1.1). Secondary: In the population without osteomyelitis, the cure rates for most baseline isolates were either slightly higher or similar for ertapenem ± vancomycin as compared with tigecycline-treated subjects. However, participants in the tigecycline regimen with *Escherichia coli* (21/28; 75.0%), MRSA (29/44; 65.9%), and *S. agalactiae* infections (35/40; 87.5%) had higher cure rates compared to subjects receiving ertapenem ± vancomycin (28/38,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				73.7%; 17/26, 65.4%; and 40/48, 83.3%; respectively). The cure rates for tigecycline-treated participants with methicillin-susceptible *S. aureus* (MSSA) or *Klebsiella pneumoniae* infections were lower than expected compared with those treated with ertapenem ± vancomycin. For subjects with baseline bacteremia, excluding contaminants, in the primary study, the clinical cure rate at the test-of-cure visit was 6/7 (86%) for tigecycline-treated subjects and 14/14 (100%) for ertapenem-treated subjects.
Chuang et al.[37] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with complicated skin and soft tissue infections	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to complicated skin and skin structure infections. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Gastrointestinal Infections				
Kearney et al.[38] (2000)	OL Patients with peptic	N=224 6 weeks	Primary: Defining treatment success rates for *H*	Primary: The intent-to-treat cure rates for BMT-H_2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H_2) vs tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)	ulcer disease or prescribed H_2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection		*pylori* infection at end of study Secondary: Adverse events	The per-protocol cure rates for BMT-H_2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H_2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H_2 and MLC groups, and between BMT-PPI and BMT-H_2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H_2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H_2 and BMT-PPI treatment groups than the MLC group (P=0.049).
Magaret et al.[39] (2001) Tetracycline 250 mg QID, bismuth	MC, RCT Patients years of age failing prior treatment for *H*	N=48 6 weeks	Primary: Negative ^{14}C-UBT of <50 disintegrations per minute at time of	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	*pylori*		follow-up indicating cure of infection Secondary: Side effects and compliance	72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[40] (2003) Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	RCT, XO Patients 18 to 80 years of age with at least one previous failure *of H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated ^{13}C-urea breath test to confirm successful treatment Secondary: Not reported	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60). Secondary: Not reported
Perri et al.[41]	OL, PRO, RCT	N=135	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)	Patients with *H pylori* infection confirmed by ^{13}C-urea breath test after failure of one or more standard regimens	6 weeks	Eradication rates as defined by negative ^{13}C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.
Katelaris et al.[42] (2002) Tetracycline 500	MC, OL, PG, RCT Patients ≥18 years of age with *H pylori*	N=405 8 weeks	Primary: At week eight, ^{13}C-urea breath test to determine the	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days (BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)	infection confirmed by a positive urease test and confirmatory histology and ^{13}C-urea breath test		outcome of eradication therapy Secondary: Compliance and adverse event profile	By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analyses, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.
Uygun et al.[43] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002).

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mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)				Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[44] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and amoxicillin)	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary: Not reported	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95% CI, 74 to 92; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[45] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[46] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 7 days (standard therapy)				
Zheng et al.[47] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[48] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole

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citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days			Secondary: Safety	treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[49] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump inhibitor clarithromycin and amoxicillin for the treatment of *H pylori*	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).
Luther et al.[50] (2010)	MA Patients with *H*	N=1,679 (9 trials)	Primary: Eradication rate, compliance rate,	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to

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Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)	*pylori* infection	Variable duration	adverse events Secondary: Not reported	1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Genitourinary Infections				
Romanowski et al.[51] (1993) Minocycline 100 mg nightly for 7 days vs doxycycline 100 mg BID for 7 days	DB, RCT Patients with nongonococcal urethritis, mucopurulent cervicitis, or whose sexual partner had either condition or a positive culture for *Chlamydia* treatments	N=253 7 weeks	Primary: Clinical cure (symptoms subsiding or resolving by day 14) Secondary: Adverse effects	Primary: The proportion with urethritis or cervicitis did not differ by treatment group at any follow-up visit (men: doxycycline, 82%; minocycline, 88%; women: doxycycline, 90%; minocycline, 91%; combined: doxycycline, 85%; minocycline, 89%; P>0.08). Unprotected sexual contact did not affect clinical or microbiological cure rates. Secondary: Adverse effects occurred more frequently in the doxycycline group (men: 43 vs 26%; P=0.05; women: 62 vs 35%; P=0.009). Although the proportion with dizziness did not differ by drug administered (P=0.1), dizziness was reported more often by women (11 vs 3%).
Kovacs et al.[52] (1989) Minocycline 100 mg BID for day 1 followed by 100 mg/day for days 2 to 10	PRO, RCT, SB Patients with *Chlamydia trachomatis* infection of the cervix	N=103 12 weeks	Primary: Efficacy (resolution of signs and symptoms of infections, and eradication of organism)	Primary: Minocycline and doxycycline showed equal effectiveness in the eradication of mycoplasmas in over 80% of the treated patients. Minocycline appeared to have a slight advantage with respect to the resolution of the gynecological symptoms that were associated with the chlamydial infection (83.3 vs 81.2%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxycycline 100 mg BID for day 1 followed by 100 mg/day for days 2 to 10			Secondary: Adverse events	A 10-day course of either drug resulted in a negative result of a chlamydial culture for all patients at the follow-up assessment, which occurred between 11 days to 12 weeks after therapy. Secondary: A total of 19 patients reported adverse events and 11 of these patients received minocycline therapy while the remaining eight patients were treated with doxycycline. The adverse events were generally mild, the most frequent event being gastric upset, which was seen in both treatment groups, and giddiness/dizziness in the minocycline treatment group.
Mena et al.[53] (2009) Doxycycline 100 mg BID for 7 days vs azithromycin 1 g as a single dose	RCT, SC Men with nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *Mycoplasma genitalium* infection Secondary: Not reported	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *Mycoplasma genitalium*. Of those testing positive at initial follow-up (10 to 17 days post therapy), 13% (95% CI, 3 to 35) were from the azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *Mycoplasma genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent two to six weeks. Secondary: Not reported
Heystek et al.[54] (2009) Moxifloxacin 400 mg QD for 14 days vs doxycycline 100 mg BID for 14 days, metronidazole 400 mg TID for 14	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=434 14 days	Primary: Clinical success two to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate at two to 14 days posttreatment, clinical success	Primary: Clinical success rates two to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the per protocol population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the intent to treat population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At two to 14 days posttreatment, clinical cure rates were 81.5% with moxifloxacin and 83.2% with the comparator regimen in the per protocol population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the intent to treat

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days, ciprofloxacin 500 mg as a single dose			rate at 21 to 35 days posttreatment (clinical failures at day two to 14 posttreatment carried forward for follow-up), bacteriological response	population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the per protocol population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the intent to treat (95% CI, -5.8 to 9.1).
Respiratory Infections				
Daniels et al.[55] (2010) Doxycycline 200 mg/day for 7 days vs placebo All patients received systemic corticosteroids.	DB, PC, RCT Hospitalized patients ≥45 years of age with an acute exacerbation of COPD	N=223 (265 exacerbations) 30 days	Primary: Clinical response on day 30 Secondary: Clinical response on day 10, clinical cure on days 10 and 30, antibiotic treatment for lack of efficacy, lung function, time to treatment failure, symptoms, microbiological response	Primary: At 30 days, clinical success was observed in 61 (n=78) and 53% (n=72) of patients receiving doxycycline and placebo (OR, 1.3; 95% CI, 0.8 to 2.0; P=0.32). Secondary: At 10 days, doxycycline showed "superiority" over placebo in terms of clinical success (OR, 1.9; 95% CI, 1.1 to 3.2; P=0.03). At 10 days, clinical cure was observed in 67 (n=86) and 51% (n=69) of patients receiving doxycycline and placebo (OR, 1.9; 95% CI, 1.2 to 3.2; P=0.01). At 30 days, the corresponding proportions were 51 (n=65) and 41% (n=56) (OR, 1.4; 95% CI, 0.9 to 2.3; P=0.15). Time to treatment failure was not significantly longer with doxycycline compared to placebo (P=0.19). Thirty-seven (n=46) and 46% (n=62) of patients had treatment failure. OL antibiotic treatment for lack of efficacy was applied in 15 (n=19) and 28% (n=38) of patients receiving doxycycline and placebo by 10 days (OR, 0.5; 95% CI, 0.03 to 0.9; P=0.01). At 30 days, the corresponding proportions were 33 (n=42) and 45% (n=61) (OR, 0.7; 95% CI, 0.1 to 1.1; P=0.13). Paired lung function data were available for 85% (n=224) of patients on days one and 10 and in 71% (n=189) of patients on days one and 30. The mean increase in FEV_1 on day 10 was 0.16±0.26 L with doxycycline and

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				0.11±0.26 L with placebo (mean difference, 0.05 L; 95% CI, -0.02 to 0.12; P=0.016). On day 30, the mean increase was 0.15±0.33 and 0.08±0.25 L with doxycycline and placebo (mean difference, 0.07 L; 95% CI, -0.03 to 0.13; P=0.22). The mean change in total symptom scores on day 10 was -10.1±9.0 and -6.2±8.6 with doxycycline and placebo (mean difference, -2.3; 95% CI, -3.9 to -0.8; P=0.003). The corresponding changes at day 30 were -9.4±9.7 and -8.3±8.6 (mean difference, -1.0; 95% CI, -3.7 to 1.8; P=0.50). Separate mean symptom scores of cough and sputum purulence were significantly more reduced with doxycycline at 10 days, but not at 30 days (P value not reported). Two hundred and fourteen potential bacterial pathogens were isolated in 158 exacerbations. Bacteriological success was accomplished in 67 (52/78) and 34% (25/73) of patients receiving doxycycline and placebo (OR, 3.8; 95% CI, 1.9 to 7.5; P<0.001).
van Velzen et al.[56] (2017) Doxycycline 100 mg/day for 7 days (200 mg on the first day) vs placebo	DB, RCT Patients ≥45 years of age with a smoking history of ≥10 pack-years, mild-to-severe COPD, ≥1 exacerbation in the past three years were randomized if they experienced an exacerbation	N=305 2 years	Primary: Time to next exacerbation Secondary: Treatment non-response at day 21 (three weeks after the first exacerbation) and day 84 (late follow-up)	Primary: Median time to next exacerbation was 148 days (95% CI, 95 to 200) in the doxycycline group compared with 161 days (95% CI, 118 to 211) in the placebo group (HR, 1.01; 95% CI, 0.79 to 1.31; P=0.91). Secondary: The proportion of patients not responding to treatment at day 21 or day 84 was not significantly different between groups.
Maesen et al.[57] (1989) Doxycycline 100 mg BID for 7 days vs	DB, RCT Patients admitted to the hospital because of purulent exacerbations of chronic respiratory	N=41 15 days	Primary: Bacteriological and clinical assessment Secondary: Not reported	Primary: Bacteriological and clinical assessment before and immediately after treatment showed no significant differences between the doxycycline and the minocycline groups, nor did further evaluation after seven days follow-up. Secondary:

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minocycline 100 mg BID for 7 days	disease			Not reported
Mokabberi et al.[58] (2010) Levofloxacin 500 mg IV QD vs doxycycline 100 mg IV BID Patients were allowed to switch from IV to oral therapy at the discretion of the physician.	DB, PRO, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 two months	Primary: Response to treatment, failure to treatment and complications, length of stay Secondary: Not reported	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893). Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73 and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001). Secondary: Not reported
Tanaseanu et al.[59] (2008) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV BID Patients were allowed to switch to oral	DB, MC, RCT Patients >18 years of age hospitalized with community-acquired pneumonia	N=891 7 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent to treat populations at test of cure Secondary: Health care resource utilization, safety	Primary: At the test of cure assessment in the clinically evaluable and clinical modified intent to treat populations, there were no significant differences in the clinical cure rates for tigecycline as compared to levofloxacin. Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1; P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of patients who switched to oral therapy (tigecycline, 89.9%; levofloxacin, 87.8%) or in the median duration of oral therapy in either group (3.9 days for tigecycline vs 3.32 for levofloxacin). In the clinical modified intent to treat population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1,

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levofloxacin after 3 days if specific criteria were met.				P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the two treatment groups in hospital length of stay during the primary hospitalization (tigecycline: mean [SD], 9.8 [6.0] days; levofloxacin, 9.8 [6.0] days; P=0.883). There was no difference in mean duration of study antibiotic therapy (tigecycline, 9.8 [3.1] days; levofloxacin, 10.0 [3.2] days; P=0.453). There were no significant differences between the treatment groups in the rate of rehospitalization, admission for intensive care unit care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More tigecycline-treated patients than levofloxacin-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for tigecycline versus levofloxacin (P<0.001). Discontinuations for adverse events were low (tigecycline, 6.1% and levofloxacin, 8.1%).
Tanaseanu et al.[60] (2009) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Patients ≥18 years of age with a community-acquired pneumonia	N=428 7 to 14 days	Primary: Clinical response in the clinically evaluable population and clinical modified intent to treat populations at the test of cure visit (10 to 21days posttreatment) Secondary: Microbiologic eradication rates	Primary: In the clinically evaluable population, clinical cure rates at the test of cure visit were 88.9% for tigecycline and 85.3% for levofloxacin (P=0.4025). In the clinical modified intent to treat population, clinical cure rates were 83.7% for tigecycline and 81.5% for levofloxacin (P<0.6269). Tigecycline was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable population, eradication rates at the test of cure visit were similar among the treatment groups for common pathogens. The most common isolate was *Streptococcus pneumoniae*, with similar eradication for tigecycline (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *Mycoplasma pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of tigecycline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
Ramirez et al.[61] (2019) OPTIC Omadacycline 100 mg IV every 12 hours for two doses on Day 1, followed by 100 mg IV daily OR 300 mg orally daily vs moxifloxacin 400 mg IV or orally daily	DB, DD, MC, NI, RCT Adults with qualifying CABP. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=774 Total treatment duration was 7 to 14 days with follow-up of 72 to 120 hours after the first dose for the primary endpoint and follow-up of 5 to 10 days after last dose of study drug for the secondary endpoints	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement 72 to 120 hours after the first dose of study drug [ECR window], no use of rescue antibiotics, and patient survival) Secondary: Number of participants with investigator assessment of clinical success at the post therapy evaluation visit.	Primary: Omadacycline was noninferior to moxifloxacin for percentage of patients with early clinical response (81.1% vs 82.7%; 95% CI, -7.1 to 3.8). Secondary: Clinical success at post therapy evaluation was high and similar between omadacycline and moxifloxacin (87.6% vs 85.1%; 95% CI, -2.4 to 7.4).
Miscellaneous Infections				
Wormser et al.[62] (2006) Doxycycline for 10 days vs doxycycline for 10	DB, RCT Patients with early Lyme disease	N=180 30 months	Primary: Complete response rate (resolution of erythema migrans and symptoms, return to pre-Lyme-disease health)	Primary: No significant differences in clinical response were found at 20 days (P>0.2). No significant differences in clinical response were found at 30 months (P>0.2). Secondary: The doxycycline-ceftriaxone group had a significantly higher incidence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days with a single IV dose of ceftriaxone vs doxycycline for 20 days			Secondary: Adverse events	diarrhea than 10-day and 20-day doxycycline treatment groups (P<0.001). Patient in the doxycycline-ceftriaxone treatment group were more likely to experience an adverse drug event than patient in the 10-day doxycycline (P=0.055) and 20-day doxycycline (P=0.035) treatment groups.
Roushan et al.[63] (2010) Gentamicin 5 mg/kg QD for five days plus doxycycline 100 mg BID for eight weeks (gentamicin-doxycycline group) vs streptomycin 1 g IM for two weeks plus doxycycline 100 mg BID for 45 days (streptomycin-doxycycline group)	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin-doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).
Keramat et al.[64] (2009) Ciprofloxacin 15 mg/kg BID plus rifampin 15 mg/kg	PRO, RCT Patients ≥18 years of age with acute brucellosis	N=178 8 to 12 weeks	Primary: Response and relapse rates Secondary: Not reported	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all three groups (DR, 96.7%; CR, 95.2%; CD, 87.3%). There were no significant differences among the treatment groups (P=0.09). Therapeutic failure was seen in 12 cases, though no significant differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group) vs doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group)				were noted among the three groups (P=0.88). After six months, 12 patients relapsed (DR, 7.7%; CR, 8.3%; CD, 17.5%; P=0.35).
Solomkin et al.[65] (2017) IGNITE1 Eravacycline 1 mg/kg every 12 hours vs ertapenem 1 g every 24 hours	AC, DB, DD, MC, NI, RCT Patients ≥18 years of age with cIAIs that required percutaneous or surgical interventions within 48 hours	N=541 14 days TOC visit was on days 25 to 31	Primary: Clinical response defined as clinical cure, clinical failure, or indeterminate/missing at the TOC visit in the micro-ITT population Secondary: Clinical response defined as clinical cure, clinical failure, or indeterminate/missing at the TOC visit in the MITT and CE populations, safety	Primary: The clinical cure rates for the micro-ITT population (N=446) were 86.8% in the eravacycline group and 87.6% in the ertapenem group (difference, -0.8%; 95% CI, -7.1 to 5.5; P-value not reported). A margin of 10% of was used to determine noninferiority. The clinical failure rates were 8.6% for eravacycline and 4.9% for ertapenem and indeterminate/missing rates were 4.5% for eravacycline and 7.5% for ertapenem (P values not reported). Secondary: The clinical cure rates for the MITT population (N=538) were 87.0% in the eravacycline group and 88.8% in the ertapenem group (difference, -1.8%; 95% CI, -7.4 to 3.8; P value not reported). The clinical failure rates were 7.0% for patients in the eravacycline group and 5.6% for patients in the ertapenem group and indeterminate/missing rates were 5.9% for the eravacycline group and 5.6% for the ertapenem group (P values not reported). The clinical cure rates for the CE population (N=477) were 92.9% in the eravacycline group and 94.5% in the ertapenem group (difference, -1.7%; 95% CI, -6.3 to 2.8; P value not reported). The clinical failure rate was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				7.1% for the eravacycline group and 5.5% for the ertapenem group (P value not reported). There were more treatment-emergent adverse effects in the eravacycline group compared to the ertapenem group (41.9% vs 28.0%, respectively). Nausea was reported in 8.1% of patients in the eravacycline group and 0.7% on the ertapenem group and phlebitis was reported for 3.0% and 0.4%, respectively.
Solomkin et al.[66] (2019) IGNITE4 Eravacycline 1 mg/kg every 12 hours IV vs meropenem 1 g every 8 hours IV	DB, MC, NI, PRO, RCT Patients ≥18 years of age with cIAIs that required percutaneous or surgical interventions within 48 hours	N=500 (n=400 for microbiological intent-to-treat population) 4 to 14 days of treatment 6 to 8 weeks of patient participation	Primary: To demonstrate statistical NI in clinical cure rates at the test-of-cure visit (25 to 31 days from start of therapy) in the microbiological intent-to-treat population using a NI margin of 12.5% Secondary: Microbiological and safety outcomes	Primary: The cure rate was 90.8% for eravacycline and 91.2% for meropenem, a difference of −0.5% with a 95% CI of −6.3% to 5.3%, meeting the predetermined criterion for NI. Secondary: Clinical cure rates were high across all visits and populations, ranging from 90.8% to 96.9% in the eravacycline arm and from 91.2% to 96.4% in the meropenem arm. Treatment-emergent adverse events occurred in 37.2% (93/250) of patients in the eravacycline group compared to 30.9% (77/249) in the meropenem group. The majority of treatment-emergent adverse events seen in patients who received eravacycline were gastrointestinal disorders such as nausea (n = 12), vomiting (n = 9), and diarrhea (n = 6).
Mwengee et al.[67] (2006) Gentamicin 2.5 mg/kg IM every 12 hours for seven days vs doxycycline 100	OL, RCT Adults and children with symptoms of bubonic, septicemic, or pneumonic plague lasting less than or equal to three days	N=65 2 weeks	Primary: Efficacy Secondary: Not reported	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin (95% CI, 81.1 to 99.0) and 97% for doxycycline (95% CI, 83.4 to 99.8). *Yersinia pestis* isolates obtained from 30 patients belonged to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg (adults) or 2.2 mg/kg (children) orally every 12 hours for seven days				biotype *antiqua* and were susceptible to gentamicin and doxycycline, which had MICs of 0.13 mg/L and 0.25 to 0.5 mg/L, respectively. Serum concentrations of antibiotics were within therapeutic ranges, and adverse events were infrequent. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment (P<0.05). Both gentamicin and doxycycline were effective therapies for adult and pediatric plague, with high rates of favorable responses and low rates of adverse events. Secondary: Not reported
Boulanger et al.[68] (2004) Streptomycin vs gentamicin vs tetracycline vs gentamicin plus tetracycline	RETRO Patients with plague whose cases were reported in New Mexico during 1985 to 1999	N=75 Duration varied	Primary: Mean number of hospital days, fever days, complications, and deaths Secondary: Not reported	Primary: The mean number of fever days after the initiation of antimicrobial treatment was 3.5 days for the streptomycin group, 2.6 days for the gentamicin group, 1.9 days for the gentamicin-tetracycline group and 2.6 days for the tetracycline group (P=0.23). The mean duration of hospital days was 6.2 days in the streptomycin group, 7.2 days in the gentamicin group, and 6.0 days in the gentamicin-tetracycline group (P=0.57). There were no deaths among the 50 patients in the four treatment groups. The mean numbers of fever days, hospital days, and complications and the number of deaths did not differ between patients treated with streptomycin and those treated with gentamicin. Secondary: Not reported
Eckmann et al.[69] (2013) Tigecycline as monotherapy or in combination with	MA Patients with a mean of 63.1+14.0 years of age who received tigecycline	N=785 Duration varied	Primary: Mean Acute Physiology and Chronic Health Evaluation II and Sequential Organ	Primary: Clinical response rates at the end of treatment were 77.4% for all patients (567/733), 80.6% for patients who received tigecycline as monotherapy (329/408), 75.2% for patients with a nosocomial infection (354/471), 75.8% for patients with an Acute Physiology and Chronic Health Evaluation II score >15 (250/330) and 54.2% (32/59) for patients with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
other antibacterials	for complicated intra-abdominal infection were included		Failure Assessment scores Secondary: Not reported	Sequential Organ Failure Assessment score > 7. Secondary: Not reported
Guirao et al.[70] (2013) Tigecycline as monotherapy or in combination with other antibacterials	MA Patients with a mean of 63 years of age who received tigecycline for complicated skin and soft-tissue infection or complicated intra-abdominal infection were included	N=1,039 Duration varied	Primary: Adverse events, mortality, Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores Secondary: Not reported	Primary: Nausea and vomiting were reported in <2% of patients. The most common serious adverse events were multi-organ failure (4.0 and 10.0% in complicated skin and soft-tissue infection and complicated intra-abdominal infection patients, respectively) and sepsis (4.0 and 6.1%, respectively). Death was recorded for 24/254 (9.4%) complicated skin and soft-tissue infection and 147/785 (18.7%) complicated intra-abdominal infection patients. Mortality rates were higher in the group with a baseline Acute Physiology and Chronic Health Evaluation II score of >15 compared with those with a score of <15 (18.7 vs 3.5% for complicated skin and soft-tissue infection patients and 23.8 vs 16.0% for complicated intra-abdominal infection patients). A similar trend was seen when complicated intra-abdominal infection patients were stratified by Sequential Organ Failure Assessment score. Secondary: Not reported
Babinchak et al.[71] (2005) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg	MA Adults with complicated intra-abdominal infections	N=1,642 (2 trials) 47 to 56 days	Primary: Clinical response (infection and associated signs and symptoms resolved) Secondary: Safety	Primary: Clinical cure rates were 86.1% for patients in the tigecycline group, vs 86.2% for patients in the imipenem-cilastatin group (P<0.0001 for non-inferiority). Secondary: Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [P=0.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [P=0.008]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [P=0.719]) were the most frequently reported adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV every 6 hours				
Fomin et al.[72] (2008) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1,259 5 to 14 days	Primary: Clinical response at the test-of-cure visit in the microbiologically evaluable and microbiological modified intent-to-treat populations Secondary: Safety	Primary: Clinical cure rates at the test-of-cure visit were 92.4% for tigecycline vs 88.8% for imipenem-cilastatin in the microbiologically evaluable population (95% CI, 2.2 to 9.4). Clinical cure rates for the modified intent-to-treat populations were 87.3% for tigecycline vs 83.5% for imipenem-cilastatin (95% CI, -2.5, 10.0) at the test-of-cure visit. Secondary: The most commonly reported treatment emergent adverse events for tigecycline and imipenem-cilastatin were nausea (14.7 and 11.8%, respectively; P=0.267) and vomiting (10.7 and 7.3%, respectively; P=0.146). The imipenem-cilastatin group had significantly higher treatment emergent adverse events of fever, hyperglycemia, and dyspnea (P=0.017, P=0.031, and P=0.011, respectively) compared to tigecycline. The tigecycline treatment group had significantly higher treatment emergent adverse events of amylase and blood urea nitrogen increase (P=0.011 and P=0.003, respectively).
Mallick et al.[73] (2007) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1005 5 to 14 days	Primary: Clinical response, safety, and health care resource utilization Secondary: Not reported	Primary: Clinical cure rates were 88.1% for tigecycline and 87.0% for imipenem–cilastatin (P=0.59). Treatment-emergent adverse events, regardless of study drug causality or severity, occurred in 73.8% of tigecycline- and 71.6% of imipenem–cilastatin-treated patients (P=0.346). Of the three most frequently reported adverse events, tigecycline was associated with a significantly higher rate of nausea (24.4%) relative to imipenem–cilastatin (19.0%; P<0.010) and a significantly higher rate of vomiting (19.2% relative to imipenem–cilastatin (14.3%; P<0.008). There were no significant differences between the groups in terms of occurrence of diarrhea (13.8% with tigecycline; 13.2% with imipenem–cilastatin; P=0.719).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between the tigecycline and the imipenem– cilastatin groups for any health resource utilization, clinical outcome, or antibiotic discontinuation rates.
Chen et al.[74] (2010) Imipenem-cilastatin 500-500 mg every six hours vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	MC, OL, RCT Patients ≥18 years of age with complicated intra-abdominal infections	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure visit (12 to 37 days after therapy) for the microbiologically evaluable and microbiologic modified intent-to-treat populations Secondary: Not reported	Primary: In the microbiologically evaluable population, 86.5% of patients receiving tigecycline and 97.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.05 to 0.7). In the microbiologic modified intent-to-treat population, 81.7% of patients receiving tigecycline and 90.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.4 to 4.9). In the clinically evaluable population, 87.0% of patients receiving tigecycline and 95.4% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -18.3 to 1.5). In the clinical microbiologic modified intent-to-treat population (those with complicated appendicitis), 80.4% of patients receiving tigecycline and 89.8% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for tigecycline compared to 53.9% for imipenem-cilastatin (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6 vs 3.9%; P<0.001) and vomiting (12.4 vs 2.0%; P=0.005). Secondary: Not reported
Towfigh et al.[75] (2010) Ceftriaxone 2 g IV QD plus metronidazole 1 to 2 g IV daily in divided doses for	MC, OL, RCT Patients ≥18 years of age with community-origin complicated intra-abdominal infections	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable population at the test-of-cure visit Secondary:	Primary: In the clinically evaluable population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the microbiologically evaluable population were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)			Bacteriological efficacy and safety	66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the microbiologically evaluable population, clinical cure rates for the different pathogens were similar between the two treatment groups. At test-of-cure in the microbiologically evaluable population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more serious adverse events among the treatment groups (P=1.000). The most frequently reported serious adverse events overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%), and ileus (1.3%).

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SC=single center, XO=cross over
Miscellaneous abbreviations: ABSSSI=Acute bacterial skin and skin structure infection, CI=confidence interval, COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume in one second, *H pylori=Helicobacter pylori*, MRSA=Methicillin-resistant *Staphylococcus aureus*, OR=odds ratio, RR=relative risk, SD=standard deviation

Additional Evidence

Dose Simplification
Dunbar-Jacob et al. evaluated compliance with oral therapies for the treatment of pelvic inflammatory disease.[76] Patients were randomly assigned to receive either inpatient therapy (parenteral cefoxitin and doxycycline for two days, followed by doxycycline orally for 14 days) or outpatient therapy (parenteral cefoxitin as a single dose and doxycycline orally for 14 days). Patients took an average of 70% of the prescribed doses. The doses of doxycycline were taken for less than half of outpatient days of treatment, unscheduled drug holidays occurred on almost 25% of outpatient days, and only 16.9% of doses were taken within the optimal timing interval. Lee et al. evaluated compliance rates with bismuth subsalicylate, metronidazole, and tetracycline for the treatment of *Helicobacter pylori* infections.[77] The enhanced group received medication counseling from a pharmacist, along with a medication calendar and a medication box. There was no significant difference between the groups in the number of patients taking more than 60% of the medications. However, there was a significant difference in the number of patients taking more than 90% of the medications (67% of the control group vs 89% of the enhanced compliance group; P<0.01).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Tetracyclines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Demeclocycline	tablet	N/A	N/A	$$$$$
Doxycycline	capsule, delayed-release capsule, delayed-release tablet, injection, suspension (reconstituted), syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	$$$-$$$$$	$$
Eravacycline	injection	Xerava®	$$$$$	N/A
Minocycline	capsule, injection, tablet	Minocin®	$$$$$	$$
Omadacycline	injection, tablet	Nuzyra®	$$$$$	N/A
Tetracycline	capsule	N/A	N/A	$$$$
Tigecycline	injection	Tygacil®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as numerous miscellaneous infections.[1-9] All agents are available in a generic formulation with the exception of eravacycline and omadacycline.

Xerava® (eravacycline) is a fluorocycline tetracycline Food and Drug Administration (FDA)-approved in 2018 for the treatment of complicated intra-abdominal infections in adults.[5] Eravacycline was compared to ertapenem in the IGNITE1 trial and meropenem in the IGNITE4 trial. In both trials eravacycline was found to be non-inferior to the active comparator group.[65,66] Nuzyra® (omadacycline) is an aminomethylcycline tetracycline FDA-approved in 2018 for the treatment of adult patients with community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections caused by designated susceptible microorganisms.[7] In the OPTIC trial that analyzed community-acquired bacterial pneumonia patients, omadacycline was shown to have a similar clinical success rate as moxifloxacin.[61] In both the OASIS-I and OASIS-II trials that analyzed acute bacterial skin and skin structure infections patients, omadacycline was shown to have similar clinical success rate at early clinical response at 48 to 72 hours after the first dose as linezolid.[33,34]

There are many guidelines that define the appropriate place in therapy for the tetracyclines. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the tetracycline. The tetracyclines are recommended for the treatment of susceptible pathogens causing endocarditis, encephalitis, cholera, *Helicobacter pylori* infections, sexually transmitted diseases, anthrax, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, intra-abdominal infections, Lyme disease, plague, and tickborne rickettsial diseases.[10-11,13,15,18,19,21-23,25,27,28,31,32]

There are few published studies that directly compare the tetracyclines. Doxycycline and minocycline have demonstrated similar efficacy and safety when used for the treatment of genitourinary and respiratory infections.[51,52,57] The tetracyclines have also been shown to be comparable in efficacy to antibacterial agents in other classes.[35-75]

There is insufficient evidence to support that one brand tetracycline is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand tetracyclines within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand tetracycline is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antibacterials, Miscellaneous
AHFS Class 081228
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I. Overview

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-19] The Food and Drug Administration-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents.

Bacitracin inhibits bacterial cell well synthesis and prevents the incorporation of amino acids and nucleotides into the cell wall.[20] The lincosamides (clindamycin and lincomycin) bind to the 50S subunit of bacterial ribosomes to inhibit protein synthesis.[1,2,20] Colistimethate and polymyxin B are surface active agents that penetrate and disrupt the bacterial cell membrane.[1,2,20] Daptomycin is a cyclic lipopeptide that binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of the synthesis of protein, which results in bacterial cell death.[2,5] Linezolid acts early in translation by binding to a site on the bacterial 23S ribosomal ribonucleic acid (RNA) of the 50S subunit. It prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.[2] Rifaximin binds to bacterial deoxyribonucleic acid (DNA)-dependent RNA polymerase, thereby inhibiting bacterial RNA synthesis.[11] Rifamycin belongs to the ansamycin class of antibacterial drugs and acts by inhibiting the beta-subunit of the bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription. This results in inhibition of bacterial synthesis and consequently growth of bacteria.[10] Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan.[13] Vancomycin binds to the bacterial cell wall causing immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.[1,2,20]

Dalbavancin and oritavancin are semisynthetic lipoglycopeptides that interfere with cell wall synthesis and are bactericidal against *Staphylococcus aureus* and *Streptococcus pyogenes in vitro*. They are FDA-approved for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates.[4,8,9] Oritavancin is available as two branded products, Kimyrsa® and Orbactiv®. These products have differences in dose strength, duration of infusion and preparation instructions, including reconstitution and dilution instructions and compatible diluents. Orbactiv® is administered by intravenous infusion over three hours while Kimyrsa® is infused over one hour.[8,9] Tedizolid phosphate is an oxazolidinone-class antibacterial that is also approved for the treatment of ABSSSI.[12] It is the second agent in its class, the first being linezolid. Tedizolid is only approved for use against susceptible isolates of *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible [MSSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group and *Enterococcus faecalis*. According to the FDA, ABSSSIs are skin infections which have a minimum lesion surface area of at least 75 cm^2 and includes cellulitis, erysipelas, wound infection, and major cutaneous abscess.[12]

Pylera®, a combination product containing bismuth, metronidazole and tetracycline, is used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. It contains all three of the antibacterial components in a single capsule.[16,17] Bismuth, metronidazole and tetracycline are all active as antibacterial agents. The antibacterial action of bismuth salts is not well understood.[16,17,19] Metronidazole is metabolized through reductive pathways into reactive intermediates that have cytotoxic actions.[16,17,19] Tetracycline interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis.[16,17,19]

Lefamulin is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: *Streptococcus pneumoniae, Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydophila pneumoniae*.[6] It inhibits bacterial protein synthesis by binding to the 50S subunit at the peptidyl transferase center, thereby preventing peptide bond formation. This unique

mechanism of action has been associated with a low probability of cross-resistance to other antimicrobial classes based on *in vitro* studies.[6,21]

The miscellaneous antibacterials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Bacitracin, clindamycin, colistimethate, daptomycin, lincomycin, linezolid, polymyxin B sulfate, and vancomycin are available in a generic formulation. This class was last reviewed in May 2021.

Table 1. Antibacterials, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Bacitracin	injection	N/A	none†
Clindamycin	capsule, injection, solution	Cleocin®*	clindamycin
Colistimethate	injection	Coly-Mycin M Parenteral®*	colistimethate
Dalbavancin	injection	Dalvance®	none
Daptomycin	injection	Cubicin®*	daptomycin
Lefamulin	injection, tablet	Xenleta®	none
Lincomycin	injection	Lincocin®*	lincomycin
Linezolid	suspension, tablet, injection	Zyvox®*	linezolid
Oritavancin	injection	Kimyrsa®, Orbactiv®	none
Polymyxin B sulfate	injection	N/A	polymyxin B sulfate
Rifamycin	delayed-release tablet	Aemcolo DR®	none
Rifaximin	tablet	Xifaxan®	Xifaxan®
Tedizolid	injection, tablet	Sivextro®	none
Telavancin	injection	Vibativ®	none
Vancomycin	capsule, injection, solution	Firvanq®*, Vancocin®*	vancomycin
Combination Products			
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	none

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List.
N/A=Not available.

The miscellaneous antibacterials have been shown to be active against the strains of microorganisms indicated in Tables 2 and 3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the antibacterials, miscellaneous that are noted in Tables 5 to 7. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Single Entity Antibacterials, Miscellaneous[1-19]

Organism	Bacitr-acin	Clinda-mycin	Colisti-methate	Dalba-vancin	Dapto-mycin	Lefam-ulin	Linco-mycin	Linezolid	Orita-vancin	Polym-yxin B Sulfate	Rifax-imin	Tedizolid	Telava-ncin	Vanco-mycin
Gram-Positive Aerobes														
Enterococcus faecalis				✔	✔				✔			✔	✔	✔
Enterococcus faecium								✔					✔	
Staphylococcus aureus	✔	✔		✔	✔	✔	✔	✔	✔			✔	✔	✔
Staphylococcus epidermidis		✔											✔	✔
Streptococcus agalactiae		✔		✔	✔			✔	✔			✔	✔	
Streptococcus anginosus				✔					✔			✔	✔	
Streptococcus dysgalactia				✔	✔				✔				✔	
Streptococcus pneumoniae		✔				✔	✔	✔						
Streptococcus pyogenes		✔		✔	✔			✔	✔			✔	✔	
Gram-Negative Aerobes														
Enterobacter species			✔							✔				
Escherichia coli			✔							✔	✔			
Haemophilus influenzae						✔				✔				
Klebsiella species			✔							✔				
Pseudomonas aeruginosa			✔							✔				
Gram-Positive Anaerobes														
Clostridium difficile														✔
Clostridium perfringens		✔												
Peptostreptococcus species		✔												
Gram-Negative Anaerobes														
Bacteroides fragilis		✔												
Fusobacterium necrophorum		✔												
Fusobacterium nucleatum		✔												
Prevotella melaninogenica		✔												
Other Bacteria														
Chlamydophila pneumoniae						✔								
Legionella pneumophila						✔								
Mycoplasma pneumoniae						✔								

Table 3. Microorganisms Susceptible to the Combination Antibacterials, Miscellaneous[1-19]

Organism	Colloidal Bismuth Subcitrate, Metronidazole, and Tetracycline
Gram-Positive Aerobes	
Helicobacter pylori	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antibacterials are summarized in Table 4.

Table 4. Treatment Guidelines Using the Antibacterials, Miscellaneous

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)[22]**	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before

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	they can be recommended in all patients. <u>Antimicrobial therapy: regimens</u> • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in β-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in β-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months.

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	○ *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): ○ Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). ○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with Valvular Heart Disease (2020)**[23]	Secondary prevention of rheumatic fever • In patients with rheumatic heart disease, secondary prevention of rheumatic fever is indicated. • Penicillin G benzathine intramuscular every four weeks, penicillin V potassium orally twice daily, sulfadiazine orally once daily, or macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine). • In patients with documented valvular heart disease, the duration of rheumatic fever prophylaxis should be ≥10 years or until the patient is 40 years of age (whichever is longer). Lifelong prophylaxis may be recommended if the patient is at high risk of group A streptococcus exposure. Secondary rheumatic heart disease prophylaxis is required even after valve replacement. Endocarditis prophylaxis • Antibiotic prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa in patients with valvular heart disease who have any of the following: ○ Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts. ○ Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords, or clips. ○ Previous infective endocarditis. ○ Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. ○ Cardiac transplant with valve regurgitation attributable to a structurally abnormal valve. • In patients with valvular heart disease who are at high risk of infective endocarditis, antibiotic prophylaxis is not recommended for nondental procedures (e.g., transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy, or cystoscopy) in the absence of active infection. Recommendations for medical therapy for infective endocarditis • In patients with infective endocarditis, appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained, with guidance from antibiotic sensitivity data and the infectious disease experts on the multidisciplinary team. • Patients with suspected or confirmed infective endocarditis associated with drug use should be referred to addiction treatment for opioid substitution therapy. • In patients with infective endocarditis and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable

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	to temporarily discontinue anticoagulation. • In patients with left-sided infective endocarditis caused by streptococcus, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci deemed stable by the multidisciplinary team after initial intravenous antibiotics, a change to oral antibiotic therapy may be considered if transesophageal echocardiography (echocardiogram) before the switch to oral therapy shows no paravalvular infection, if frequent and appropriate follow-up can be assured by the care team, and if a follow-up transesophageal echocardiography (echocardiogram) can be performed one to three days before the completion of the antibiotic course. • In patients receiving vitamin K antagonist anticoagulation at the time of infective endocarditis diagnosis, temporary discontinuation of vitamin K antagonist anticoagulation may be considered. • Patients with known valvular heart disease should not receive antibiotics before blood cultures are obtained for unexplained fever.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[24]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate β-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy.

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	○ Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. ○ High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. ○ The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. ○ Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. ○ For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. ○ For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. ○ Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: ○ Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. ○ Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: ○ Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). ○ Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: ○ Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. ○ Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. ○ Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam: ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance:

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	• Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[25]** **(Was reviewed and deemed current as of July 2011)**	<u>Empirical therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and

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	corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

European Federation of Neurological Societies: **Guideline on the Management of Community-Acquired Bacterial Meningitis (2008)[26]**	Empirical therapy
	• Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours.
	• Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected.
	
	Pathogen specific therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  ○ Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours.
	  ○ Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily.
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  ○ Ceftriaxone or cefotaxime plus vancomycin±rifampicin.
	  ○ Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin.

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	• Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Disease Society of America: **Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis (2017)**[27]	<u>Empiric Therapy</u> • Empiric therapy should be used when infection is suspected but cultures are not yet available. • Vancomycin plus an anti-pseudomonal β-lactam (e.g. cefepime, ceftazidime, or meropenem) is recommended. • Choice of anti-pseudomonal β-lactam should be based on local resistance patterns. • In seriously ill adult patients vancomycin troughs should be maintained at 15 to 20 µg/mL • For patients who have experienced anaphylaxis with β-lactams and have a contraindication to meropenem, the recommended agent for gram-negative coverage is aztreonam or ciprofloxacin • Empiric therapy should be adjusted in patients who are colonized or infected elsewhere with highly drug resistant pathogens <u>Pathogen Specific Therapy</u> • Methicillin-susceptible *S. aureus* o Recommended treatment includes nafcillin or oxacillin o In patients who cannot receive β-lactams, vancomycin is recommended • Methicillin-resistant *S. aureus* o Recommended treatment includes vancomycin • *P. acnes* o Recommended treatment includes penicillin G • *Pseudomonas* species o Recommended treatment includes cefepime, ceftazidime, or meropenem; alternative therapy includes aztreonam or a fluoroquinolone • Gram-negative bacilli o Recommended treatment includes ceftriaxone or cefotaxime • Extended-spectrum β-lactamase–producing gram-negative bacilli o Recommended treatment includes meropenem • *Acinetobacter* species o Recommended treatment includes meropenem; alternative therapy includes colistimethate sodium or polymyxin B

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	• *Candida* species
	  o Recommended treatment includes liposomal amphotericin B, often combined with 5-flucytosine
	• *Aspergillus* or *Exserohilum*
	  o Recommended treatment includes voriconazole
	• In patient with intracranial or spinal hardware such as a cerebrospinal fluid shunt or drain
	  o Use of rifampin as part of combination therapy is recommended
	<u>Duration of Therapy</u>
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms
	  o Duration is recommended to be 10 days
	• Infections caused by a coagulase-negative *staphylococcus* or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features
	  o Duration is recommended to be 10 to 14 days
	• Infections caused by *S. aureus* or gram-negative bacilli
	  o Duration is recommended to be 10 to 14 days
	• Patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy
	• It is recommended that therapy be continued for 10 to 14 days after the last positive culture

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[28]	<u>Impetigo and ecthyma</u>
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	<u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u>
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as

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	temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline

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	where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended.
	• Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract.
	
	<u>Necrotizing fasciitis</u>
	• Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA).
	• Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis.
	
	<u>Pyomyositis</u>
	• Cultures of blood and abscess material should be obtained.
	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	<u>Clostridial gas gangrene or myonecrosis</u>
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	<u>Animal bites</u>
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  ○ are immunocompromised;
	  ○ are asplenic;
	  ○ have advanced liver disease;
	  ○ have preexisting or resultant edema of the affected area;
	  ○ have moderate to severe injuries, especially to the hand or face; or
	  ○ have injuries that may have penetrated the periosteum or joint capsule.
	• Oral treatment options
	  ○ Amoxicillin-clavulanate is recommended.
	  ○ Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  ○ First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided.
	• Intravenous

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	○ β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. <u>Cutaneous anthrax</u> • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. <u>Bacillary angiomatosis and cat scratch disease</u> • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: ○ Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. ○ Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. <u>Erysipeloid</u> • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. <u>Glanders</u> • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. <u>Bubonic plague</u> • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. <u>Tularemia</u> • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
International Diabetes Federation: **Clinical Practice Recommendation on the Diabetic Foot (2017)[29]**	• All clinically infected diabetic foot wounds require antimicrobial therapy. Nevertheless, antimicrobial therapy for clinically non-infected wounds is not recommended. • Select specific antibiotic agents for treatment, based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection, patient history (e.g., allergies or intolerance) and cost. • A course of antibiotic therapy of one to two weeks is usually adequate for most

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	mild and moderate infections. o For more serious skin and soft tissue infections, three weeks is usually sufficient. o Antibiotics can be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed. • Initially, parenteral antibiotics therapy is needed for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding. • For patients with a foot ulcer and severe peripheral arterial disease, antibiotics play an important role in treating and preventing further spread of infection. In some cases, a successful revascularization for these patients may transiently increase the bacterial activity. • For diabetic foot osteomyelitis, six weeks of antibiotic therapy is required for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment is needed after all infected bone is resected. The regimen should usually cover Staphylococcus aureus as it is the most common pathogen. However, without revascularization, some patients will not have adequate blood flow to allow for adequate antibiotic tissue concentrations in the area of the infection. • For patients with foot ulcers and necrotizing fasciitis, antibiotics to cover both aerobic and anaerobic microorganisms is recommended.
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults (2017)[30]**	Treatment of *Clostridium difficile* infections • Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of *Clostridium difficile* infections recurrence. • Antibiotic therapy for *Clostridium difficile* infections should be started empirically for situations where a substantial delay in laboratory confirmation is expected, or for fulminant *Clostridium difficile* infections. • Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of *Clostridium difficile* infections. The dosage is vancomycin 125 mg orally four times per day or fidaxomicin 200 mg twice daily for 10 days. • In settings where access to vancomycin or fidaxomicin is limited, use metronidazole for an initial episode of nonsevere *Clostridium difficile* infections only. The suggested dosage is metronidazole 500 mg orally three times per day for 10 days. Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity. • For fulminant *Clostridium difficile* infections, vancomycin administered orally is the regimen of choice. If ileus is present, vancomycin can also be administered per rectum. The vancomycin dosage is 500 mg orally four times per day and 500 mg in approximately 100 mL normal saline per rectum every six hours as a retention enema. Intravenously administered metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present. The metronidazole dosage is 500 mg intravenously every 8 hours. • Fulminant *Clostridium difficile* infections, previously referred to as severe, complicated *Clostridium difficile* infections, may be characterized by hypotension or shock, ileus, or megacolon. • If surgical management is necessary for severely ill patients, perform subtotal colectomy with preservation of the rectum. Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes. • Treat a first recurrence of *Clostridium difficile* infections with oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin, OR • Treat a first recurrence of *Clostridium difficile* infections with a 10-day course of fidaxomicin rather than a standard 10-day course of vancomycin, OR

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	• Treat a first recurrence of *Clostridium difficile* infections with a standard 10-day course of vancomycin rather than a second course of metronidazole if metronidazole was used for the primary episode. • Antibiotic treatment options for patients with >1 recurrence of *Clostridium difficile* infections include oral vancomycin therapy using a tapered and pulsed regimen, a standard course of oral vancomycin followed by rifaximin, or fidaxomicin. • Fecal microbiota transplantation is recommended for patients with multiple recurrences of *Clostridium difficile* infections who have failed appropriate antibiotic treatments. • There are insufficient data at this time to recommend extending the length of anti–*C. difficile* treatment beyond the recommended treatment course or restarting an anti–*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of *Clostridium difficile* infections treatment, respectively. • Either metronidazole or vancomycin is recommended for the treatment of children with an initial episode or first recurrence of nonsevere *Clostridium difficile* infections. • For children with an initial episode of severe *Clostridium difficile* infections, oral vancomycin is recommended over metronidazole. • For children with a second or greater episode of recurrent *Clostridium difficile* infections, oral vancomycin is recommended over metronidazole. • Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of *Clostridium difficile* infections following standard antibiotic treatments.
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **2021 Focused Update Guidelines on Management of *Clostridium difficile* Infection in Adults (2021)**[31]	• For patients with an initial *Clostridium difficile* infection episode, using fidaxomicin rather than a standard course of vancomycin is suggested. This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative. • In patients with recurrent *Clostridium difficile* infection episodes, fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin is suggested. Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first *Clostridium difficile* infection recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin. • For patients with a recurrent *Clostridium difficile* infection episode within the last six months, using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone is suggested. This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations. In settings where logistics is not an issue, patients with a primary *Clostridium difficile* infection episode and other risk factors for *Clostridium difficile* infection recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe *Clostridium difficile* infection on presentation) may particularly benefit from receiving bezlotoxumab. Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited. The FDA warns that "in patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefit outweighs the risk."
World Gastroenterology Organization:	General considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is

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Acute Diarrhea (2012)[32]	known. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
American College of Gastroenterology: **Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)[33]**	<u>Epidemiology</u> • Diagnostic evaluation using stool culture and culture-independent methods if available should be used in situations where the individual patient is at high risk of spreading disease to others, and during known or suspected outbreaks. <u>Diagnosis</u> • Stool diagnostic studies may be used if available in cases of dysentery, moderate-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy. • Traditional methods of diagnosis (bacterial culture, microscopy, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection. If available, the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. • Antibiotic sensitivity testing for management of the individual with acute diarrheal infection is currently not recommended. <u>Treatment of acute disease</u> • The usage of balanced electrolyte rehydration over other oral rehydration options in the elderly with severe diarrhea or any traveler with cholera-like watery diarrhea is recommended. Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. • The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness. • Bismuth subsalicylates can be administered to control rates of passage of

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	stool and may help travelers function better during bouts of mild-to-moderate illness. • In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. • The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of traveler's diarrhea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. • Use of antibiotics for community-acquired diarrhea should be discouraged as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. <u>Evaluation of persisting symptoms</u> • Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. • Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. <u>Prevention</u> • Patient level counseling on prevention of acute enteric infection is not routinely recommended but may be considered in the individual or close contacts of the individual who is at high risk for complications. • Individuals should undergo pretravel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. • Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but may be useful where low-dose pathogens are responsible for the illness as for example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. <u>Prophylaxis</u> • Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. • Probiotics, prebiotics, and synbiotics for prevention of traveler's diarrhea are not recommended. • Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2017)**[34]	• In most people with acute watery diarrhea and without recent international travel, empiric antimicrobial therapy is not recommended. An exception may be made in people who are immunocompromised or young infants who are ill-appearing. Empiric treatment should be avoided in people with persistent watery diarrhea lasting 14 days or more. • Asymptomatic contacts of people with acute or persistent watery diarrhea should not be offered empiric or preventive therapy, but should be advised to follow appropriate infection prevention and control measures. • Antimicrobial treatment should be modified or discontinued when a clinically plausible organism is identified. • Recommended antimicrobial agents by pathogen: o *Campylobacter* ▪ First choice: Azithromycin ▪ Alternative: Ciprofloxacin

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	○ *Clostridium difficile* ▪ First choice: Oral vancomycin ▪ Alternative: Fidaxomicin ▪ Fidaxomicin not currently recommended for people <18 years of age. Metronidazole is still acceptable treatment for nonsevere *C. difficile* infection in children and as a second-line agent for adults with nonsevere *C. difficile* infection (e.g., who cannot obtain vancomycin or fidaxomicin at a reasonable cost). ○ Nontyphoidal *Salmonella enterica* ▪ Antimicrobial therapy is usually not indicated for uncomplicated infection. ▪ Antimicrobial therapy should be considered for groups at increased risk for invasive infection: neonates (up to three months old), persons >50 years old with suspected atherosclerosis, persons with immunosuppression, cardiac disease (valvular or endovascular), or significant joint disease. If susceptible, treat with ceftriaxone, ciprofloxacin, TMP-SMX, or amoxicillin. ○ *Salmonella enterica* Typhi or Paratyphi ▪ First choice: Ceftriaxone or ciprofloxacin ▪ Alternative: Ampicillin or TMP-SMX or azithromycin ○ *Shigella* ▪ First choice: Azithromycin or ciprofloxacin, or ceftriaxone ▪ Alternative: TMP-SMX or ampicillin if susceptible ▪ Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. ○ *Vibrio cholerae* ▪ First choice: Doxycycline ▪ Alternative: Ciprofloxacin, azithromycin, or ceftriaxone ○ Non–*Vibrio cholerae* ▪ First choice: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: ceftriaxone plus doxycycline ▪ Alternative: Usually not indicated for noninvasive disease. Single-agent therapy for noninvasive disease if treated. Invasive disease: TMP-SMX plus an aminoglycoside ○ *Yersinia enterocolitica* ▪ First choice: TMP-SMX ▪ Alternative: Cefotaxime or ciprofloxacin ○ *Cryptosporidium* spp ▪ First choice: Nitazoxanide (HIV-uninfected, HIV-infected in combination with effective combination antiretroviral therapy) ▪ Alternative: Effective combination antiretroviral therapy: Immune reconstitution may lead to microbiologic and clinical response ○ *Cyclospora cayetanensis* ▪ First choice: TMP-SMX ▪ Alternative: Nitazoxanide (limited data) ▪ Patients with HIV infection may require higher doses or longer durations of TMP-SMX treatment ○ *Giardia lamblia* ▪ First choice: Tinidazole (note: based on data from HIV-uninfected children) or Nitazoxanide ▪ Alternative: Metronidazole (note: based on data from HIV-uninfected children) ▪ Tinidazole is approved in the United States for children aged ≥3

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	years. It is available in tablets that can be crushed. ▪ Metronidazole has high frequency of gastrointestinal side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA approved for the treatment of giardiasis. o *Cystoisospora belli* ▪ First choice: TMP-SMX ▪ Alternative: Pyrimethamine ▪ Potential second-line alternatives: Ciprofloxacin or Nitazoxanide o *Trichinella* spp ▪ First choice: Albendazole ▪ Alternative: Mebendazole ▪ Therapy less effective in late stage of infection, when larvae encapsulate in muscle
American College of Gastroenterology: **Clinical Guideline on the Treatment of *Helicobacter pylori* Infection (2017)**[35]	<u>Evidence-based first-line treatment strategies for providers in North America</u> • Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen. • Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason. • Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin. • Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10 to 14 days is a recommended first-line treatment option. • Sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, clarithromycin, and a nitroimidazole for five to seven days is a suggested first-line treatment option. • Hybrid therapy consisting of a PPI and amoxicillin for seven days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for seven days is a suggested first-line treatment option. • Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10 to 14 days is a suggested first-line treatment option. • Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for five to seven days followed by a PPI, fluoroquinolone, and nitroimidazole for five to seven days is a suggested first-line treatment option. <u>When first-line therapy fails, options for salvage therapy</u> • In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient (unchanged from previous ACG guideline). • Bismuth quadruple therapy or levofloxacin salvage regimens are the preferred treatment options if a patient received a first-line treatment containing clarithromycin. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics. • Clarithromycin or levofloxacin-containing salvage regimens are the preferred treatment options, if a patient received first-line bismuth quadruple therapy. Selection of best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics. • The following regimens can be considered for use as salvage treatment: o Bismuth quadruple therapy for 14 days is a recommended salvage

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	regimen. ○ Levofloxacin triple regimen for 14 days is a recommended salvage regimen. ○ Concomitant therapy for 10 to 14 days is a suggested salvage regimen. ○ Clarithromycin triple therapy should be avoided as a salvage regimen. ○ Rifabutin triple regimen consisting of a PPI, amoxicillin, and rifabutin for 10 days is a suggested salvage regimen. ○ High-dose dual therapy consisting of a PPI and amoxicillin for 14 days is a suggested salvage regimen.
Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)**[36]	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori.* • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht VI/ Florence Consensus Report (2022)**[37]	Treatment • It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalized use of such a susceptibility-guided strategy in routine clinical practice remains to be established. • If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered. • The treatment duration of bismuth quadruple therapy should be 14 days, unless 10- days effective therapies are available. • In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies. • The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days. • In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally. • The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days. • The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies. • Potassium-Competitive Acid Blockers (P-CAB; vonoprazan where available) – antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections. • Empiric second line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimize treatment success. • After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the

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	combination of bismuth with other antibiotics, or rifabutin, may be an option. • After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment. • After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high- dose dual therapy might also be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered. • After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered. • After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin- containing regimen or a combination of bismuth with different antibiotics should be used. • In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options. Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth.
Centers for Disease Control and Prevention: **Sexually Transmitted Infections Treatment Guidelines (2021)**[38]	Genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can

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	develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy. • Recommended regimens for first episodes of genital herpes: o acyclovir 400 mg orally three times daily for seven to 10 days o famciclovir 250 mg orally three times daily for seven to 10 days o valacyclovir 1,000 mg orally twice daily for seven to 10 days. • Treatment can be extended if healing is incomplete after 10 days of therapy. • Acyclovir 200 mg orally five times daily is also effective but is not recommended because of frequency of dosing. • Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. • Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners. • Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. • Discordant heterosexual couples in which a partner has a history of genital HSV-2 infection should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. • Recommended regimens for suppressive therapy of genital herpes: o acyclovir 400 mg orally twice daily o famciclovir 250 mg orally twice daily o valacyclovir 500 mg orally once daily o valacyclovir 1,000 mg orally once daily. • Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year). • Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment. • Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider. • Episodic treatment of recurrent herpes is most effective if initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. • Recommended regimens for episodic treatment of recurrent HSV-2 genital

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	herpes: ○ acyclovir 800 mg orally twice daily for five days ○ acyclovir 800 mg orally three times daily for two days ○ famciclovir 1,000 mg orally twice daily for one day ○ famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days ○ famciclovir 125 mg orally twice daily for five days ○ valacyclovir 500 mg orally twice daily for three days ○ valacyclovir 1,000 mg orally once daily for five days. • Acyclovir 400 mg orally three times daily is also effective but is not recommended because of frequency of dosing. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose. • Optimal therapies for HSV-2 meningitis have not been well studied; however, acyclovir 5 to 10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. • Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy. Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation. • Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women. Condoms are less effective for preventing transmission from women to men. • Randomized clinical trials have demonstrated that PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships. Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women. • The patients who have genital herpes and their sex partners can benefit from evaluation and counseling to help them cope with the infection and prevent sexual and perinatal transmission. • Lesions caused by HSV are common among persons with human immunodeficiency virus (HIV) infection and might be severe, painful, and atypical. HSV shedding is increased among persons with HIV infection. • Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV. • Recommended regimens for daily suppressive therapy of genital herpes in patients infected with HIV: ○ acyclovir 400 to 800 mg orally two to three times daily ○ famciclovir 500 mg orally twice daily ○ valacyclovir 500 mg orally twice daily • Recommended regimens for episodic treatment of genital herpes in patients infected with HIV: ○ acyclovir 400 mg orally three times daily for five to 10 days ○ famciclovir 500 mg orally twice daily for five to 10 days

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	○ valacyclovir 1,000 mg orally twice daily for five to 10 days • If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected, and a viral culture obtained for phenotypic sensitivity testing. • Foscarnet (40 to 80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. • Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective. • Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV. • Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. However, such treatment might not protect against transmission to neonates in all cases. • Recommended regimen for suppression of recurrent genital herpes among pregnant women: ○ acyclovir 400 mg orally three times daily ○ valacyclovir 500 mg orally twice daily • Treatment recommended starting at 36 weeks' gestation. • Infants exposed to HSV during birth should be followed in consultation with a pediatric infectious disease specialist. • All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS. Pediculosis pubis (pubic lice infestation) • Recommended regimens: ○ Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes. ○ Piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens: ○ Malathion 0.5% lotion applied for eight to 12 hours and washed off. ○ Ivermectin 250 µg/kg orally and repeated in seven to 14 days. • Pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Scabies • The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. • Scabies among adults frequently is sexually acquired, although scabies among children usually is not. • Recommended regimens: ○ Permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours. ○ Ivermectin 200 µg/kg orally and repeated in two weeks. • Oral ivermectin has limited ovicidal activity; a second dose is required for

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	eradication. • Alternative regimens: o Lindane 1% lotion (1 oz) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours. • Lindane is an alternative regimen because it can cause toxicity; it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed. • Infants and children aged <10 years should not be treated with lindane. • Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies. Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin, and cost. • Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. • Permethrin is the preferred treatment for pregnant women. • Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotropic virus-1 infection, and persons with hematologic malignancies. • Combination treatment for crusted scabies is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases. <u>Bacterial vaginosis</u> • Bacterial vaginosis (BV) is a highly prevalent condition and the most common cause of vaginal discharge worldwide. However, in a nationally representative survey, the majority of women with BV were asymptomatic. • Treatment for BV is recommended for women with symptoms. • Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection and reduce the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2. • Recommended regimens for bacterial vaginosis include: o Metronidazole 500 mg orally twice daily for seven days. o Metronidazole 0.75% gel 5 g intravaginally once daily for five days. o Clindamycin 2% cream 5 g intravaginally at bedtime for seven days. • Alternative regimens include: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin 100 mg ovules intravaginally once at bedtime for three days. o Secnidazole 2 g oral granules in a single dose • Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended. • Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or

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	pudding before ingestion. A glass of water can be taken after administration to aid in swallowing. • Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. • BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis. <u>Uncomplicated vulvovaginal candidiasis</u> • Uncomplicated vulvovaginal candidiasis is defined as sporadic or infrequent vulvovaginal candidiasis, mild to moderate vulvovaginal candidiasis, candidiasis likely to be *Candida albicans*, or candidiasis in non-immunocompromised women. • Short-course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated vulvovaginal candidiasis. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include: o Butoconazole 2% cream 5 g single intravaginal application. o Clotrimazole 1% cream 5 g intravaginally daily for seven to 14 days. o Clotrimazole 2% cream 5 g intravaginally daily for three days. o Miconazole 2% cream 5 g intravaginally daily for seven days. o Miconazole 4% cream 5 g intravaginally daily for three days. o Miconazole 100 mg vaginal suppository one suppository daily for seven days. o Miconazole 200 mg vaginal suppository one suppository for three days. o Miconazole 1,200 mg vaginal suppository one suppository for one day. o Tioconazole 6.5% ointment 5 g single intravaginal application. o Terconazole 0.4% cream 5 g intravaginally daily for seven days. o Terconazole 0.8% cream 5 g intravaginally daily for three days. o Terconazole 80 mg vaginal suppository one suppository daily for three days. o Fluconazole 150 mg oral tablet in single dose. <u>Complicated vulvovaginal candidiasis</u> • Complicated vulvovaginal candidiasis is defined as recurrent vulvovaginal candidiasis, severe vulvovaginal candidiasis, non-albicans candidiasis, or candidiasis in women with diabetes, immunocompromising conditions, underlying immunodeficiency, or immunosuppressive therapy. • Most episodes of recurrent vulvovaginal candidiasis caused by *Candida albicans* respond well to short duration oral or topical azole therapy. • However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150, or 200 mg oral dose of fluconazole every third day for a total of three doses (day one, four, and seven) to attempt mycologic remission before initiating a maintenance antifungal regimen. • Recommended maintenance regimen is oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for six months. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered.

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	Severe vulvovaginal candidiasis
	• Severe vulvovaginal candidiasis is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy.
	• Either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.
	
	Non-albicans vulvovaginal candidiasis
	• The optimal treatment of non-albicans vulvovaginal candidiasis remains unknown. However, a longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) is recommended.
	• If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for three weeks.
	
	Genital warts
	• Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience.
	• There is no definitive evidence to suggest that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts.
	• Because of uncertainty regarding the effect of treatment on future transmission of human papilloma virus and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution.
	• Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.
	• In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment.
	• The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe.
	• Most genital warts respond within three months of therapy.
	• Recommended regimens for external anogenital warts (patient-applied):
	  ○ Podofilox 0.5% solution or gel.
	  ○ Imiquimod 3.75% or 5% cream.
	  ○ Sinecatechins 15% ointment.
	• Recommended regimens (provider administered):
	  ○ Cryotherapy with liquid nitrogen or cryoprobe.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	  ○ Surgical removal
	• Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided.
	• Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours.
	
	Cervical warts
	• For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesion must be performed before treatment is initiated.

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	• Management of exophytic cervical warts should include consultation with a specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Vaginal warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution
	
	Urethral meatus warts
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal
	
	Intra-anal warts
	• Management of intra-anal warts should include consultation with a colorectal specialist.
	• Recommended regimens:
	  ○ Cryotherapy with liquid nitrogen.
	  ○ Surgical removal.
	  ○ Trichloroacetic acid or bichloracetic acid 80 to 90% solution.

American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[39]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis

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	• Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. <u>Choice of antibiotic for acute bacterial rhinosinusitis</u> • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. <u>Treatment failure for acute bacterial rhinosinusitis</u> • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)[40]**	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)[41]**	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided

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	doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[42] Reviewed and deemed current as of 04/2013	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
American Thoracic Society and Infectious Diseases Society of America: **Diagnosis and**	<u>Antibiotics recommended for empiric treatment of community-acquired pneumonia (CAP) in adults in outpatient setting:</u> • For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens: o amoxicillin one gram three times daily or

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Treatment of Adults with Community-Acquired Pneumonia (2019)[43]	○ doxycycline 100 mg twice daily or ○ a macrolide (e.g., azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin ER 1,000 mg daily) only in areas with pneumococcal resistance to macrolides is <25%. • For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia monotherapy or combination therapy is recommended. ○ Monotherapy includes a respiratory fluoroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily). ○ Combination therapy includes amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND a macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy) <u>Regimens recommended for empiric treatment of CAP in adults without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* in inpatient setting</u>: • In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa,* the following is recommended: ○ combination therapy with a β-lactam (e.g., ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) or ○ monotherapy with a respiratory fluroquinolone (e.g., levofloxacin 750 mg daily, moxifloxacin 400 mg daily). • In adults with contraindications to macrolides and fluroquinolones combination therapy with a B-lactam (e.g., ampicillin + sulbactam, cefotaxime, ceftaroline) and doxycycline 100 mg twice daily is recommended. • Corticosteroid use is not recommended. • It is recommended that anti-influenza treatment, such as oseltamivir, be prescribed for adults with CAP who test positive for influenza in the inpatient setting, independent of duration of illness before diagnosis. <u>Adults with CAP and risk factors for MRSA or *P. aeruginosa* in inpatient setting</u>: • It is recommended to empirically cover for MRSA or *P. aeruginosa* in adults with CAP if locally validated risk factors for either pathogen are present. • Empiric treatment options for MRSA include vancomycin or linezolid. • Empiric treatment options for *P. aeruginosa* include piperacillin-tazobactam, cefepime, ceftazidime, aztreonam, meropenem, or imipenem.
American Thoracic Society/ Infectious Diseases Society of America: **Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines**	<u>Empiric Therapy</u> • It is recommended that empiric therapy be informed by the local distribution of pathogens associated with ventilator-associated or hospital-acquired pneumonia and local sensitivities • In patients with suspected ventilator-associated pneumonia coverage for *S. aureus P. aeruginosa*, and other gram-negative bacilli is recommended • Methicillin-resistant staphylococcus aureus (MRSA) should be covered in patients with a risk factor for antimicrobial resistance, patients being treated in units where >10 to 20% of *S. aureus* isolates are methicillin resistant, or patients in units where the prevalence of MRSA is not known

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(2016)[44]	○ Standard therapy for MRSA coverage includes vancomycin or linezolid • Methicillin-susceptible staphylococcus aureus (MSSA) should be covered in patients without risk factors for antimicrobial resistance, who are being treated in intensive care units (ICU) where <10 to 20% of *S. aureus* isolates are methicillin resistant ○ It is recommended that MSSA coverage includes a regimen containing piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem ○ In regimens not containing one of the drugs mentioned above oxacillin, nafcillin, or cefazolin are preferred agents for MSSA coverage • One agent active against *P. aeruginosa* is recommended for ventilator-associated or hospital-acquired pneumonia or two agents from different classes in patients with a risk factor for antimicrobial resistance, patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available • Therapy should be de-escalated to a narrower regimen when culture and sensitivity results are available <u>Pathogen-Specific Therapy</u> • MRSA ○ Vancomycin or linezolid are recommended treatments • *P. aeruginosa* ○ It is recommended that therapy should be based on susceptibility testing and is not recommended to be aminoglycoside monotherapy ○ In patients with septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known therapy is recommended to include two antibiotics to which the isolate is susceptible • Extended-spectrum β-lactamase-producing gram-negative bacilli ○ Therapy should be based on the results of susceptibility testing • *Acinetobacter* Species ○ Treatment with either a carbapenem or ampicillin/sulbactam is suggested if the isolate is susceptible to these agents • Carbapenem-Resistant Pathogens ○ If pathogen is sensitive only to polymyxins standard therapy is intravenous polymyxins with adjunctive inhaled colistin <u>Duration of therapy</u> • Seven day course of treatment
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**	<u>Prophylaxis to Prevent First Episode of Opportunistic Disease</u> • Coccidioidomycosis ○ Preferred: Fluconazole 400 mg PO daily ○ Alternative: None listed • *Histoplasma capsulatum* infection ○ Preferred: Itraconazole 200 mg PO daily ○ Alternative: None listed • Malaria ○ Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region. Refer to the Centers for Disease Control and Prevention webpage for the most recent recommendations based on region and drug susceptibility • *Mycobacterium avium* Complex (MAC) Disease ○ Preferred: Azithromycin 1200 mg PO once weekly, or Clarithromycin 500 mg PO BID, or Azithromycin 600 mg PO twice weekly

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(2022)[45]	○ Alternative: Rifabutin (dose adjusted based on concomitant ART); rule out active TB before starting rifabutin • *Pneumocystis* Pneumonia (PCP) ○ Preferred: TMP-SMX (trimethoprim-sulfamethoxazole) 1 double strength (DS) tablet PO daily, or TMP-SMX 1 SS tablet daily ○ Alternative: TMP-SMX 1 DS PO three times weekly, or Dapsone 100 mg PO daily or 50 mg PO BID, or Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or Aerosolized pentamidine 300 mg via Respigard II nebulizer every month, or Atovaquone 1500 mg PO daily, or (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily • Syphilis ○ Preferred: Benzathine penicillin G 2.4 million units IM for 1 dose ○ Alternative: *For penicillin-allergic patients*: ▪ Doxycycline 100 mg PO BID for 14 days, or ▪ Ceftriaxone 1 g IM or IV daily for eight to 10 days, or ▪ Azithromycin 2 g PO for 1 dose – not recommended for men who have sex with men or pregnant women • Talaromycosis (Penicilliosis) ○ Preferred: For persons who reside in endemic areas, itraconazole 200 mg PO once daily; For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily three days before travel, and continue for one week after leaving the endemic area ○ Alternative: For persons who reside in endemic areas, fluconazole 400 mg PO once weekly; For those traveling to the highly endemic regions, take the first dose of fluconazole 400 mg three days before travel, continue 400 mg once weekly, and take the final dose after leaving the endemic area • *Toxoplasma gondii* Encephalitis ○ Preferred: TMP-SMX 1 DS PO daily ○ Alternative: TMP-SMX 1 DS PO three times weekly, or TMP-SMX 1 SS PO daily, or Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly; or Atovaquone 1500 mg PO daily; or (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily <u>Treatment of AIDS-Associated Opportunistic Infections (only preferred therapy is summarized here, please see full guideline for alternative therapies and additional information)</u> • Empiric therapy pending definitive diagnosis of bacterial enteric infections ○ Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. If a pathogen is identified, antibiotic susceptibilities should be performed to confirm and inform antibiotic choices given increased reports of antibiotic resistance. Reflex culture for antibiotic susceptibilities should also be done if diagnosis is made using PCR-based methods. ○ Empiric antibiotic therapy may be indicated for patients with CD4 count 200 to 500 cells/mm^3 where diarrhea is severe enough to compromise quality of life or the ability to work and is indicated in patients with CD4 count <200 cells/mm^3 or concomitant AIDS-defining illness and with clinically severe diarrhea (≥6 stools per day or bloody stool) and/or accompanying fever or chills. ○ Empiric Therapy: Ciprofloxacin 500 to 750 mg PO (or 400 mg IV)

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	q12h • Campylobacteriosis o For Mild Disease and If CD4 Count >200 cells/µL: ▪ No therapy unless symptoms persist for more than several days o For Mild-to-Moderate Disease (If Susceptible): ▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, or ▪ Azithromycin 500 mg PO daily (Note: Not for patients with bacteremia) o For Campylobacter Bacteremia: ▪ Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h + an aminoglycoside o Duration of Therapy: ▪ Gastroenteritis: seven to 10 days (five days with azithromycin) ▪ Bacteremia: ≥14 days ▪ Recurrent bacteremia: two to six weeks • Clostridium difficile Infection (CDI) o Fidaxomicin 200 mg PO two times daily for 10 days o Vancomycin 125 mg (PO) QID for 10 days • Salmonellosis o All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20 to 100 fold) and mortality (by up to 7-fold) compared to HIV negative individuals o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h, if susceptible • Shigellosis o Ciprofloxacin 500 to 750 mg PO (or 400 mg IV) q12h o Note: Increased resistance of Shigella to fluoroquinolones is occurring in the United States. Avoid fluoroquinolones if ciprofloxacin MIC is ≥0.12 µg/mL, even if the laboratory identifies the isolate as sensitive. Many Shigella strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of Shigella isolates from HIV-infected individuals should be performed routinely. • Bartonellosis o For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis: Doxycycline 100 mg PO or IV q12h, or Erythromycin 500 mg PO or IV q6h o CNS Infections: (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h o Confirmed Bartonella Endocarditis: (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) for two weeks, then continue with doxycycline 100 mg IV or PO q12h o Other Severe Infections: (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) q12h, or (Erythromycin 500 mg PO or IV q6h) +/- RIF 300 mg PO or IV q12h o Duration of therapy: at least three months • Candidiasis (Mucocutaneous) o For Oropharyngeal Candidiasis; Initial Episodes (for 7 to 14 Days): ▪ Fluconazole 100 mg PO daily o For Esophageal Candidiasis (for 14 to 21 Days): ▪ Fluconazole 100 100 mg (up to 400 mg) PO or IV daily ▪ Itraconazole oral solution 200 mg PO daily o For Uncomplicated Vulvo-Vaginal Candidiasis: ▪ Oral fluconazole 150 mg for one dose ▪ Topical azoles (clotrimazole, butoconazole, miconazole,

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	tioconazole, or terconazole) for three to seven days ○ For Severe or Recurrent VulvoVaginal Candidiasis: ▪ Fluconazole 100 to 200 mg PO daily for ≥7 days ▪ Topical antifungal ≥7 days • Chagas Disease (American Trypanosomiasis) ○ For Acute, Early Chronic, and Reactivated Disease: ▪ Benznidazole 5 to 8 mg/kg/day PO in 2 divided doses for 30 to 60 days (not commercially available in the United States; contact the CDC) • Coccidioidomycosis ○ Clinically Mild Infections (e.g., Focal Pneumonia): ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day ○ Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): ▪ Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily ▪ Lipid formulation amphotericin B 4 to 6 mg/kg IV daily ▪ Duration of therapy: continue until clinical improvement, then switch to an azole ○ Meningeal Infections: ▪ Fluconazole 400 to 800 mg IV or PO daily ○ Chronic Suppressive Therapy: ▪ Fluconazole 400 mg PO daily ▪ Itraconazole 200 mg PO twice a day • Community-Acquired Pneumonia (CAP) ○ Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia ○ Empiric Outpatient Therapy: ▪ A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: High-dose amoxicillin or amoxicillin/clavulanate ▪ Alternative Beta-Lactams: Cefpodoxime or cefuroxime, or Levofloxacin 750 mg PO once daily, or moxifloxacin 400 mg PO once daily, especially for patients with penicillin allergies. ○ Empiric Therapy for Hospitalized Patients with Non-Severe CAP: ▪ An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam; Levofloxacin 750 mg IV once daily, or moxifloxacin, 400 mg IV once daily, especially for patients with penicillin allergies. ○ Empiric Therapy for Hospitalized Patients with Severe CAP: ▪ An IV beta-lactam plus IV azithromycin, or ▪ An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) ▪ Preferred Beta-Lactams: Ceftriaxone, cefotaxime, or ampicillin-sulbactam ○ Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia: ▪ An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every eight to 12 hours or levofloxacin 750 mg IV once daily) ▪ Preferred Beta-Lactams: Piperacillin-tazobactam, cefepime, imipenem, or meropenem ○ Empiric Therapy for Patients at Risk for Methicillin-Resistant

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	Staphylococcus aureus Pneumonia: ▪ Add vancomycin IV or linezolid (IV or PO) to the baseline regimen ▪ Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production • Cystoisosporiasis (Formerly Isosporiasis) o For Acute Infection: ▪ TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or ▪ TMP-SMX (160 mg/800 mg) PO (or IV) BID for seven to 10 days ▪ Can start with BID dosing first and increase daily dose and/ or duration (up to three to four weeks) if symptoms worsen or persist ▪ IV therapy may be used for patients with potential or documented malabsorption o Chronic Maintenance Therapy (Secondary Prophylaxis): ▪ In patients with CD4 count <200/µL, TMP-SMX (160 mg/ 800 mg) PO three times weekly • Mycobacterium avium Complex (MAC) Disease o At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance: ▪ Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO daily, or ▪ If drug interaction or intolerance precludes the use of clarithromycin, (azithromycin 500 to 600 mg + ethambutol 15 mg/kg) PO daily o Duration: At least 12 months of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART • Pneumocystis Pneumonia (PCP) o Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX o Duration of PCP treatment: 21 days • Syphilis o Early Stage (Primary, Secondary, and Early-Latent Syphilis): ▪ Benzathine penicillin G 2.4 million units IM for one dose o Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses o Late-Stage (Tertiary–Cardiovascular or Gummatous Disease): ▪ Benzathine penicillin G 2.4 million units IM weekly for three doses (Note: rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management) o Neurosyphilis (Including Otic or Ocular Disease): ▪ Aqueous crystalline penicillin G 18 to 24 million units per day (administered as 3 to 4 million units IV q4h or by continuous IV infusion) for 10 to 14 days +/- benzathine penicillin G 2.4 million units IM weekly for three doses after completion of IV therapy
Infectious Diseases Society of America: **Diagnosis and Management of**	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small

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Complicated Intra-Abdominal Infection in Adults and Children (2010)[46]	bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or

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	ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health care-associated infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[47]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to β-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to β-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A β-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response.

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	• For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve) • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. Management of methicillin-resistant *Staphylococcus aureus* pneumonia • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin.

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	• Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. <u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u> • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
American Society of Clinical Oncology/ Infectious Diseases Society of America: **Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression (2018)**[48]	• Risk of febrile neutropenia (FN) should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors. • Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia (e.g., most patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or hematopoietic stem-cell transplantation (HSCT) treated with myeloablative conditioning regimens). Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. • Antifungal prophylaxis with an oral triazole or parenteral echinocandin is recommended for patients who are at risk for profound, protracted neutropenia, such as most patients with AML/MDS or HSCT. Antifungal prophylaxis is not routinely recommended for patients with solid tumors. Additional distinctions between recommendations for invasive candidiasis and invasive mold infection are provided within the full text of the guideline. • Prophylaxis is recommended, e.g., trimethoprim-sulfamethoxazole (TMP-SMX), for patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* (e.g., those with ≥20 mg prednisone equivalents daily for ≥1 month or those on the basis of purine analogs). • Herpes simplex virus–seropositive patients undergoing allogeneic HSCT or

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	leukemia induction therapy should receive prophylaxis with a nucleoside analog (e.g., acyclovir). • Treatment with a nucleoside reverse transcription inhibitor (e.g., entecavir or tenofovir) is recommended for patients who are at high risk of hepatitis B virus reactivation. • Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy for malignancy and all family and household contacts and health care providers.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2022)**[49]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis during neutropenia. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate. o Moxifloxacin. o Levofloxacin o Oral antibiotic regimen recommended should not be used if quinolone

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	prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): o Intravenous antibiotic monotherapy is preferred. o Intravenous combination therapy could be considered especially in cases of resistance. <u>Antibacterial agents: empiric gram-positive activity</u> • Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. o Requires dose adjustment in patients with renal insufficiency. Infectious disease consult strongly recommended. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. o Mental status changes may occur, especially in the setting of renal dysfunction. • Ceftazidime o Poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum β-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS

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	infection. ○ Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency. ○ Empiric therapy for neutropenic fever. ○ Data are limited, but it is expected that doripenem, like meropenem, would be efficacious. • Piperacillin-tazobactam ○ Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. ○ Use for suspected intra-abdominal source. ○ Not recommended for meningitis. ○ Empiric therapy for neutropenic fever. <u>Antibacterial agents: other</u> • Aminoglycosides ○ Activity primarily against gram-negative organisms. ○ Sometimes used as part of combination therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate ○ Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. ○ Ciprofloxacin alone has no activity against anaerobes. ○ Addition of amoxicillin-clavulanate is effective with aerobic Gram-positive organisms with anaerobes. ○ Oral combination therapy in low-risk patients. ○ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. ○ Increasing Gram-negative resistance in many centers. ○ Data support fluoroquinolones for prophylaxis; however, in other clinical scenarios the risk:benefit analysis should be evaluated. Fluoroquinolone side effects should be considered. • Levofloxacin/ moxifloxacin ○ Good activity against gram-negative and atypical organisms. ○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. ○ Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole ○ Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. ○ Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia. ○ Interactions with methotrexate.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for**	<u>Common principles</u> • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it

Clinical Guideline	Recommendation(s)
antimicrobial prophylaxis in surgery (2013)[50]	is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. <u>Cardiac procedures</u> • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. <u>Thoracic procedures</u> • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. <u>Gastroduodenal procedures</u> • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. <u>Biliary tract procedures</u> • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone.

Clinical Guideline	Recommendation(s)
	Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. Colorectal procedures • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation. • Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity. Head and neck procedures • Clean procedures: o Antimicrobial prophylaxis is not required. • Clean-contaminated procedures: o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures. o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam. o Clindamycin is a reasonable alternative in patients with a documented β-

Clinical Guideline	Recommendation(s)
	lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. Neurosurgery procedures • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). Cesarean delivery procedures • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. Hysterectomy procedures • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended.

Clinical Guideline	Recommendation(s)
	Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.
American Association for the Study of Liver Diseases/ European Association for the Study of the Liver: **Practice Guideline: Hepatic Encephalopathy in Chronic Liver Disease (2014)**[51]	• Identify and treat precipitating factors for hepatic encephalopathy. • Lactulose is the first choice for treatment of episodic overt hepatic encephalopathy. • Rifaximin is an effective add-on therapy to lactulose for prevention of overt hepatic encephalopathy recurrence. • Oral branched-chain amino acids can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy. • Intravenous L-ornithine L-aspartate can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy. • Neomycin is an alternative choice for treatment of overt hepatic encephalopathy. • Metronidazole is an alternative choice for treatment of overt hepatic encephalopathy. • Lactulose is recommended for prevention of recurrent episodes of hepatic encephalopathy after the initial episode. • Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of hepatic encephalopathy after the second episode. • Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-transjugular intrahepatic portosystemic shunt (TIPS) hepatic encephalopathy. • Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding) or liver function or nutritional status

Clinical Guideline	Recommendation(s)
	improved, prophylactic therapy may be discontinued. • Treatment of minimal hepatic encephalopathy and covert hepatic encephalopathy is not routinely recommended apart from a case-by-case basis. • Daily energy intakes should be 35 to 40 kcal/kg ideal body weight. • Daily protein intake should be 1.2 to 1.5 g/kg/day. • Small meals or liquid nutritional supplements evenly distributed throughout the day and a late-night snack should be offered. • Oral branched-chain amino acid supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antibacterials are noted in Tables 5 to 7. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the Single Entity Antibacterials, Miscellaneous (Drugs B-L)[1-19]

Indication	Bacitracin	Clindamycin	Colistimethate	Dalbavancin	Daptomycin	Lefamulin	Lincomycin
Dermatological Infections							
Skin and skin-structure infections		✔ *§		✔	✔		
Genitourinary Infections							
Endometritis		✔ *§					
Gynecologic infections		✔ *§					
Nongonococcal tubo-ovarian abscess		✔ *§					
Pelvic cellulitis		✔ *§					
Postsurgical vaginal cuff infection		✔ *§					
Respiratory Infections							
Empyema	✔	✔ *§					
Lung abscess		✔ *§					
Pneumonia	✔	✔ §				✔	
Pneumonitis		✔ *					
Respiratory tract infection		✔ *§					
Miscellaneous Infections							
Bacteremia					✔		
Bone and/or joint infections		✔ §					
Endocarditis					✔		
Intra-abdominal infections		✔ *§					
Septicemia		✔ *					
Serious infections due to susceptible organisms			✔				✔

§Injection formulation.
*Oral formulation.

Table 6. FDA-Approved Indications for the Single Entity Antibacterials, Miscellaneous (Drugs L-V)[1-19]

Indication	Linezolid	Oritavancin	Polymyxin B Sulfate	Rifamycin	Rifaximin	Tedizolid	Telavancin	Vancomycin
Central Nervous System Infections								
Meningeal infections			✔					
Dermatological Infections								
Diabetic foot infections	✔							

Indication	Linezolid	Oritavancin	Polymyxin B Sulfate	Rifamycin	Rifaximin	Tedizolid	Telavancin	Vancomycin
Skin and skin-structure infections	✔	✔				✔	✔	
Gastrointestinal Infections								
Enterocolitis								✔ *
Irritable bowel syndrome with diarrhea					✔			
Pseudomembranous colitis due to *Clostridium difficile*								✔ *
Travelers' diarrhea				✔	✔			
Urinary tract infections			✔					
Respiratory Infections								
Hospital-acquired and ventilator-associated bacterial pneumonia							✔	
Pneumonia (community-acquired)	✔							
Pneumonia (nosocomial)	✔							
Respiratory tract infections (lower)								✔ §
Miscellaneous Infections								
Endocarditis								✔ §
Hepatic encephalopathy					✔			
Septicemia			✔					
Serious infections due to susceptible organisms			✔					✔ §
Vancomycin-resistant *Enterococcus faecium* infections	✔							

§Injection formulation
*Oral formulation

Table 7. FDA-Approved Indications for the Combination Antibacterials, Miscellaneous[1-19]

Indication	Bismuth, Metronidazole and Tetracycline
Gastrointestinal Infections	
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history within the past five years) to eradicate *Helicobacter pylori* (in combination with omeprazole)	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the single entity agents miscellaneous antibacterials and the components of the combination products are listed in Table 8.

Table 8. Pharmacokinetic Parameters of the Antibacterials, Miscellaneous[1-19]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bacitracin	Minimal	Not reported	Not reported	Renal (10 to 40)	1.5
Bismuth	Not reported	>90	Not reported	Renal	>120
Clindamycin	Oral: 90	60 to 95	Liver	Renal (10) Feces (4)	2 to 4
Colistimethate	Not reported	Not reported	Not reported	Not reported	2 to 3
Dalbavancin	Not reported	93 to 99	Not reported	Renal (33) Feces (20)	204
Daptomycin	Not reported	83 to 93	Not reported	Renal (78.0) Feces (5.7)	7.7 to 8.3
Lefamulin	Not reported	94.8 to 97.1	Liver	Renal (5.3 to 15.5) Feces (77.3 to 88.5)	3 to 20
Lincomycin	Not reported	28 to 86	Liver	Renal (13.8 to 24.8) Feces (30 to 40)	5.4
Linezolid	100	31	Liver	Renal (30) Feces (9)	Oral: 4.26 to 5.40 Intravenous: 4.4 to 4.8
Metronidazole	Well absorbed	<20	Liver	Renal (60 to 80) Feces (6 to 15)	8
Oritavancin	Not reported	85	Not metabolized	Renal/Feces	245
Polymyxin B sulfate	Not reported	79 to 92	Not reported	Renal (0 to 4)	6
Rifamycin	<0.1	80	Not reported	Feces (86)	Not reported
Rifaximin	Not reported	62 to 67.5	Not reported	Renal (<1.00) Feces (96.62)	6
Tedizolid	91	70 to 90	Not reported	Renal (18) Feces (82)	12
Telavancin	Not reported	90	Not reported	Renal (64 to 76)	6 to 8
Tetracycline	Readily absorbed	65	Liver	Renal/Feces	8 to 11
Vancomycin	Oral: negligible	55	Not reported	Intravenous: Renal (40 to 100)	4 to 6

V. Drug Interactions

Major drug interactions with the miscellaneous antibacterials are listed in Table 9.

Table 9. Major Drug Interactions with the Antibacterials, Miscellaneous[2]

Generic Name(s)	Interaction	Mechanism
Bacitracin	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.

Generic Name(s)	Interaction	Mechanism
Colistimethate	Aminoglycosides	Concurrent use of colistimethate and aminoglycosides may result in respiratory depression.
Daptomycin	Statins	Coadministration of daptomycin and statins may increase the risk of rhabdomyolysis. The mechanism for this interaction is currently unknown.
Lefamulin	Strong and Moderate CYP3A Inducers or P-gp Inducers	Concomitant use of oral or intravenous lefamulin with strong CYP3A4 inducers or P-gp inducers decreases lefamulin levels, which may reduce the efficacy of lefamulin.
Lefamulin	Strong and Moderate CYP3A Inhibitors or P-gp Inhibitors	Concomitant use of lefamulin tablets with strong CYP3A inhibitors or P-gp inhibitors increases lefamulin AUC, which may increase the risk of adverse reactions with lefamulin tablets.
Lefamulin	CYP3A4 Substrates	Concomitant use of lefamulin tablets with sensitive CYP3A4 substrates increases the level of CYP3A4 substrates, which may increase the risk of toxicities associated with cardiac conduction. Concomitant use with CYP3A substrates known to prolong the QT interval is contraindicated. Concomitant use of sensitive CYP3A substrates with lefamulin tablets requires close monitoring for adverse effects of these drugs (for example, alprazolam, diltiazem, verapamil, simvastatin, vardenafil). Concomitant use of lefamulin injection with CYP3A4 substrates does not affect the exposure of CYP3A4 substrates.
Lincomycin	Aluminum salts	Gastrointestinal absorption is decreased for lincomycin and delayed for clindamycin when they are administered with kaolin-pectin antidiarrheals.
Lincomycin	Nondepolarizing muscle relaxants	The lincosamides may enhance the actions of the nondepolarizing muscle relaxants, possibly contributing to profound and severe respiratory depression.
Linezolid	Anorexiants	Toxicity of anorexiants may be increased by coadministration of linezolid. Headache, hyperpyrexia, elevated blood pressure, and bradycardia may occur. Anorexiants can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with linezolid.
Linezolid	Norepinephrine reuptake inhibitors	Toxic effects may be increased with concurrent administration of norepinephrine reuptake inhibitors and linezolid. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of norepinephrine reuptake inhibitors and linezolid may be additive.
Linezolid	Serotonin–norepinephrine reuptake inhibitors	Linezolid and serotonin–norepinephrine reuptake inhibitors may exert additive pharmacologic activity potentially leading to severe central nervous system toxicity.
Linezolid	Serotonin reuptake blockers	Serotonin reuptake blockers and linezolid increase central nervous system serotonin activity, perhaps synergistically. This may cause central nervous system toxicity.
Linezolid	Sympathomimetics	Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur. The mechanism differs depending on the type of sympathomimetics involved.
Linezolid	Tetracyclic antidepressants	The mechanism is unknown. Tetracyclic antidepressants are thought to act by blocking reuptake of neurotransmitters, including norepinephrine. The concomitant use of monoamine oxidase inhibitors could potentiate sympathomimetic activity.
Linezolid	Tricyclic antidepressants	Severe, sometimes lethal, toxicity may occur. The mechanism for this interaction in currently unknown.
Linezolid	Triptans	Inhibition of monoamine oxidase by linezolid may decrease the metabolic elimination of triptans. Other mechanisms may exist.

Generic Name(s)	Interaction	Mechanism
		The potential for development of serotonin syndrome is a possibility.
Linezolid	Bupropion	Use of bupropion with linezolid is contraindicated due to the potential for hypertensive crisis. The inhibitory effects of bupropion on norepinephrine and dopamine reuptake may be enhanced by concomitant use of linezolid.
Linezolid	Buspirone	The risk of linezolid-induced hypertension may be increased by coadministration of buspirone. The mechanism for this interaction is currently unknown.
Linezolid	Cyclobenzaprine	Cyclobenzaprine is a tricyclic amine structurally related to tricyclic antidepressants. Though the mechanism of action is unknown, it is likely that adrenergic activity is enhanced with concurrent administration.
Linezolid	Dextromethorphan	A severe and potentially fatal toxic reaction may occur when dextromethorphan is administered to patients receiving linezolid. The mechanism for this interaction is currently unknown.
Linezolid	Levodopa	Linezolid may decrease the enzymatic degradation of dopamine and norepinephrine formed from levodopa.
Linezolid	Meperidine	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving linezolid. The excitatory interaction may be due to additive increases of central nervous system serotonin activity. The depressive form may result from inhibition of hepatic metabolism of meperidine.
Linezolid	Methylphenidate	Pharmacologic effects of methylphenidate may be increased by linezolid. Headache, gastrointestinal symptoms and hypertension may occur.
Linezolid	Nefazodone	Unexpected toxicity may occur in some patients. The mechanism for this interaction is currently unknown.
Linezolid	Tramadol	A severe reaction potentially involving the respiratory, cardiovascular, and central nervous systems may occur shortly after administering tramadol to patients receiving linezolid. The seizure threshold may also be reduced.
Linezolid	Catechol O-methyltransferase inhibitors	The combination of linezolid with Catechol O-methyltransferase inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism.
Linezolid	Monoamine oxidase inhibitors	Adverse effects may be increased with concurrent administration of linezolid and monoamine oxidase inhibitors.
Linezolid	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving linezolid.
Linezolid	Apraclonidine	Hypertension may be potentiated. The mechanism is unknown.
Linezolid	Sibutramine	Use of high-dose sibutramine with linezolid has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome.
Linezolid	Tryptophan	The combination of linezolid and tryptophan may produce severe unexpected toxicity in some patients.
Linezolid	Trazodone	Linezolid and trazodone may increase central nervous system serotonin activity, perhaps synergistically.
Metronidazole	Anticoagulants	The anticoagulant effect of warfarin may be enhanced and hemorrhage could occur due to decreased metabolism of warfarin by metronidazole.
Metronidazole	Busulfan	Busulfan trough concentrations may be elevated, increasing risk of serious toxicity. Avoid coadministration of busulfan and metronidazole.
Metronidazole	Disulfiram	Acute toxic psychosis may occur during the coadministration of

Generic Name(s)	Interaction	Mechanism
		metronidazole and disulfiram.
Metronidazole	Human immunodeficiency virus protease inhibitors	Coadministration of metronidazole and human immunodeficiency virus protease inhibitors may cause an alcohol intolerance reaction. The alcohol and aldehyde dehydrogenase-mediated metabolic pathway of propylene glycol or alcohol, an excipient in human immunodeficiency virus protease inhibitors, may be blocked by metronidazole.
Oritavancin	Heparin	Concurrent use of heparin and oritavancin may result in falsely elevated aPTT test results.
Oritavancin	Warfarin	Concurrent use of oritavancin and warfarin may result in increased warfarin exposure.
Polymyxin B Sulfate	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Telavancin	5-HT_3 receptor antagonists	Concurrent use of 5-HT_3 receptor antagonists and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Azole antifungals	Concurrent use of telavancin and azole antifungals may result in increased risk of QT interval prolongation.
Telavancin	Class I and III antiarrhythmics	Concurrent use of antiarrhythmics and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Gonadotropin releasing hormone agonists	Concurrent use may result in increased risk of QT-interval prolongation.
Telavancin	Tyrosine kinase inhibitors	Concurrent use of tyrosine kinase inhibitors and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Quinolones	Concurrent use of quinolones and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Phenothiazines	Concurrent use of telavancin and phenothiazines may result in an increased risk of QT interval prolongation.
Telavancin	Tricyclic antidepressants	Concurrent use of tricyclic antidepressants and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Alfuzosin	Concurrent use of alfuzosin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Apomorphine	Concurrent use of apomorphine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Asenapine	Concurrent use of asenapine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Astemizole	Concurrent use of astemizole and telavancin may result in increased risk of QT interval prolongation.
Telavancin	Clozapine	Concurrent use of clozapine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Erythromycin	Concurrent use of erythromycin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Fingolimod	Concurrent use of fingolimod and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Heparin	Concurrent use of heparin and telavancin may result in artificial prolongation of aPTT test results.
Telavancin	Lopinavir	Concurrent use of lopinavir/ritonavir and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Lumefantrine	Concurrent use of artemether/lumefantrine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Mefloquine	Concurrent use of mefloquine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Methadone	Concurrent use of methadone and telavancin may result in

Generic Name(s)	Interaction	Mechanism
		increased risk of QT interval prolongation.
Telavancin	Mifepristone	Concurrent use of mifepristone and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Octreotide	Concurrent use of octreotide and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Quinine	Concurrent use of quinine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Salmeterol	Concurrent use of salmeterol and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Solifenacin	Concurrent use of solifenacin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Telithromycin	Concurrent use of telavancin and telithromycin may result in increased risk of QT interval prolongation.
Telavancin	Tetrabenazine	Concurrent use of telavancin and tetrabenazine may result in an increased risk of QT interval prolongation.
Telavancin	Toremifene	Concurrent use of telavancin and toremifene may result in an increased risk of QT interval prolongation.
Tetracyclines	Acitretin	Concurrent use of acitretin and tetracyclines may result in an increased risk of pseudotumor cerebri (benign intracranial hypertension).
Tetracyclines	Digoxin	Co-administration may result in increased serum levels of digoxin in a small subset of patients (10%). Monitor digoxin levels and signs of toxicity.
Tetracyclines	Methoxyflurane	Co-administration may enhance the risk for renal toxicity; deaths have been reported. Do not co-administer. If possible seek alternative agents.
Tetracyclines	Penicillins	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins. Consider avoiding this combination if at all possible.
Tetracyclines	Retinoids	Acitretin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Vancomycin	Piperacillin-Tazobactam	Concurrent use of piperacillin-tazobactam and vancomycin may result in increased risk of acute kidney injury.
Vancomycin	Amikacin	Concurrent use of amikacin and vancomycin may result in additive ototoxicity and/or nephrotoxicity.
Vancomycin	Gentamicin	Concurrent use of gentamicin and vancomycin may result in nephrotoxicity.
Vancomycin	Tobramycin	Concurrent use of tobramycin and vancomycin may result in additive ototoxicity and/or nephrotoxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antibacterials are listed in Tables 10 to 11. The boxed warnings for bacitracin, clindamycin, lincomycin, metronidazole, polymyxin B sulfate, and telavancin are listed in Tables 12 to 17.

Table 10. Adverse Drug Events (%) Reported with the Single Entity Antibacterials, Miscellaneous[1-19]

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Cardiovascular															
Atrial fibrillation	-	-	-	-	<1	<2	-	-	-	-	-	-	-	-	-
Atrial flutter	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Cardiac arrest	-	✔	-	-	<1	-	-	-	-	-	-	-	-	-	-
Cardiopulmonary arrest	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	7	-	-	-	-	-	-	>2 to 5	-	-	-
Edema	-	-	-	-	7	-	-	✔	<2	-	-	15	-	-	-
Flattening T-wave	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	1 to 6	-	-	<1	-	-	-	-	<2	-	-
Hypotension	-	✔	-	-	2 to 5	-	✔	-	-	-	-	>2 to 5	-	-	✔
Myocardial infarction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Palpitation	-	-	-	-	-	<2	-	-	-	-	-	-	<2	-	-
Prolonged QT interval	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	-	<1	-	-	-	<2	-	-
Central Nervous System															
Anxiety	-	-	-	-	5	<2	-	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-
Depression	-	-	-	-	-	-	-	-	-	-	-	7	-	-	-
Dizziness	-	-	✔	<2	2 to 6	-	✔	<2	<1	✔	-	13	2	6	✔
Drowsiness	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	<1	-	-	-	-	-	-	12	-	-	-
Fever	-	-	✔	-	2 to 7	-	-	2	-	-	✔	6	-	-	✔
Hallucinations	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Headache	-	-	✔	5	5 to 7	2	-	1 to 11	<1	-	3	10	6	11	-
Incoordination	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insomnia	-	-	-	-	5 to 9	3	-	3	-	-	-	13	<2	13	-
Irritability	-	-	-	-	-	-	-	-	-	✔	-	-	-	-	-
Mental status change	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Neurotoxicity	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Paresthesia	-	-	✔	-	<1	-	-	-	-	✔	-	-	<2	-	-
Peripheral neuropathy	-	-	-	-	-	-	-	<1	-	-	-	-	<2	-	-
Pseudotumor cerebri	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Seizure	-	-	✔	-	-	-	-	<1	-	-	-	-	-	5	-
Somnolence	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Syncope	-	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Tingling of extremities	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	<1	-	✔	-	-	-	-	<2	-	-	✔
Vertigo	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Visual disturbances	-	-	-	-	-	-	-	-	-	-	-	-	<2	-	-
Weakness	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Dermatologic															
Dermatitis	-	-	-	-	-	-	-	-	-	-	-	-	<2	-	-
Eczema	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Erythema	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-
Erythema multiforme	-	✔	-	-	-	-	✔	-	<2	-	-	-	-	-	-
Exfoliative dermatitis	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-	-
Flushing	-	-	-	<2	<1	-	-	-	-	-	-	-	<2	-	-
Heat rash	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Petechia	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Photosensitivity	-	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Pruritus	-	✔	✔	2	3 to 6	-	✔	<1	<2	-	-	9	<2	36	-
Rash	✔	✔	✔	3	4 to 7	-	✔	2	<2	✔	-	5	-	4	✔
Stevens-Johnson syndrome	-	✔	-	-	-	-	✔	<1	-	-	-	-	-	-	✔
Urticaria	-	✔	✔	<2	-	-	✔	-	<2	-	-	-	<2	-	✔
Gastrointestinal															
Abdominal distention	-	-	-	-	<1	-	-	-	-	-	-	<2	-	-	-
Abdominal pain	-	✔	-	<2	6	<2	✔	✔	-	-	✔	2 to 9	-	2	-
Anal discomfort	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Appetite decreased	-	-	-	-	<1	-	-	-	-	-	-	-	-	3	-
Black stool	-	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Clostridioides difficile associated diarrhea	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Colitis	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	6 to 11	<2	-	2	-	-	4	3	-	-	-
Diarrhea	-	✔	-	4	5 to 12	12	✔	3 to 11	<1	-	-	2 to 6	4	7	-
Dry mouth	-	-	-	-	<1	-	-	-	-	-	-	2 to 5	-	-	-
Duodenal ulcer	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Dyspepsia	-	-	-	-	1 to 4	<2	-	<1	-	-	<2	-	-	-	-
Dysphagia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Enamel hypoplasia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enterocolitis	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Epigastric distress	-	-	-	-	<1	<2	-	-	-	-	-	-	-	-	-
Esophagitis	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	-	<1	-	-	-	-	-	-	11	-	-	-
Gastritis	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	-	<2	2	-	-	-	-	-	-	-	-	-	-
Gastrointestinal upset	-	-	✔	-	✔	-	-	-	-	-	-	<2	-	-	-
Gingival pain	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Glossitis	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Hematochezia	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Loose stools	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Melena	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Nausea	✔	✔	-	6	6 to 10	3 to 5	✔	3 to 10	<1	-	-	14	8	5 to 27	✔
Oral candidiasis	-	-	-	<2	-	<2	-	-	-	-	-	-	<2	-	-
Oral moniliasis	-	-	-	-	-	-	-	<1	-	-	-	-	-	-	-
Pseudomembranous colitis	-	✔	-	<2	-	-	✔	-	-	-	-	-	<2	-	✔
Rectal hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rectal itching/burning	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	<1	-	✔	-	-	-	-	-	-	-	-
Stool abnormality	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste alteration	-	✔	-	-	<1	-	-	1	-	-	-	<2	-	33	-
Tooth disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tongue discoloration	-	-	-	-	-	-	-	✔	-	-	-	-	-	-	✔
Vomiting	✔	✔	-	3	3 to 12	3	✔	1 to 4	<1	-	-	2	3	5 to 14	-
Genitourinary															
Abnormal kidney function	✔	✔	✔	-	<1	-	✔	-	-	✔	-	<2	-	-	✔
Acute kidney failure	-	-	✔	-	2 to 3	-	-	-	-	✔	-	-	-	-	✔
Azotemia	✔	✔	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinary retention	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Urinary tract infections	-	-	-	-	2 to 7	-	-	-	-	-	-	-	-	-	-
Vaginitis	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-	-
Vulvovaginal infection	-	-	-	<2	-	<2	-	-	-	-	-	-	<2	-	-
Hematologic															

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Agranulocytosis	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-	✔
Anemia	-	-	-	<2	2 to 13	<2	✔	✔	<2	-	-	8	<2	-	-
Bone marrow toxicity	✔	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Eosinophilia	-	✔	-	<2	2	-	-	✔	<2	✔	-	-	-	-	✔
Hematoma	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Leukocytosis	-	-	-	-	<1	-	-	-	-	✔	-	-	-	-	-
Leukopenia	-	✔	-	<2	-	-	✔	1 to 2	-	-	-	-	<2	-	-
Neutropenia	-	✔	-	<2	-	-	✔	<1	-	-	-	<2	-	-	✔
Pancytopenia	-	-	-	-	-	-	✔	<1	-	-	-	-	-	-	-
Thrombocythemia	-	-	-	<2	<1	-	-	-	-	-	-	-	-	-	-
Thrombocytopenia	-	✔	-	<2	<1	<2	✔	1 to 10	-	-	-	-	-	7	✔
Thrombocytosis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Hepatic															
Hepatotoxicity	-	-	-	<2	-	-	-	-	-	-	-	-	-	-	-
Jaundice	-	✔	-	-	<1	-	✔	-	-	-	-	-	-	-	-
Liver enzymes increased	-	-	-	-	-	<3	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities															
Abnormal liver function tests	-	✔	-	<2	1 to 3	-	✔	1	-	-	-	-	<2	-	-
Alanine aminotransferase increased	-	-	-	✔	2 to 3	<3	2 to 10	-	<1	-	-	-	-	-	-
Alkaline phosphatase increased	-	-	-	<2	2	<2	1 to 4	-	-	-	-	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	2 to 3	<3	2 to 5	-	<1	-	-	<2	-	-	-
Blood urea nitrogen increased	-	-	✔	-	-	-	-	<2	-	-	-	-	-	-	✔
Electrolyte disturbance	-	-	-	-	<6	-	-	-	-	-	-	-	-	-	-
Gamma-glutamyl transferase increased	-	-	-	-	-	<2	-	-	-	-	-	-	-	-	-
Hemoglobin decreased	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-
Hyperbilirubinemia	-	-	-	-	-	-	<1	-	<2	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Hypoglycemia	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-
International normalized ratio	-	-	-	<2	2	-	-	-	-	-	-	-	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
increased															
Phosphorus increased	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-
Platelet count decreased	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
Prothrombin time prolonged	-	-	-	-	<1	-	-	-	✔	-	-	-	-	-	-
Serum creatinine increased	-	-	✔	-	3 to 7	-	-	<1	-	-	-	-	-	8	✔
Serum lactate dehydrogenase increased	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Musculoskeletal															
Arthralgia	-	-	-	-	1 to 3	-	-	-	-	-	-	6	-	-	-
Back pain	-	-	-	-	7	-	-	-	-	-	-	-	-	-	-
Muscle cramps/weakness	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	<1	-	-	-	<2	-	-	2 to 5	-	-	-
Tendonitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tenosynovitis	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Weakness	-	-	-	-	5	-	-	-	-	-	-	<2	-	-	-
Respiratory															
Apnea	-	-	✔	-	-	-	-	✔	-	-	-	-	-	-	-
Bronchospasm	-	-	-	<2	-	-	-	-	<2	-	-	-	-	-	-
Cough	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	2 to 3	-	-	✔	-	✔	-	6	-	8	-
Pharyngitis	-	-	-	-	-	-	-	-	-	-	-	<2	-	-	-
Pharyngolaryngeal pain	-	-	-	-	8	-	-	-	-	-	-	<2	-	-	-
Pleural effusion	-	-	-	-	6	-	-	-	-	-	-	-	-	-	-
Pneumonia	-	-	-	-	3	-	-	-	-	-	-	2 to 5	-	-	-
Polyarthritis	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory arrest	-	-	✔	-	-	-	-	-	-	✔	-	-	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Upper respiratory tract infection	-	-	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Wheezing	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Other															
Anaphylaxis	✔	✔	-	<2	<1	-	✔	<1	-	✔	-	<2	-	-	-
Angioedema	-	-	-	-	-	-	✔	-	<2	-	-	-	-	-	-
Angioneurotic edema	-	-	-	-	-	-	-	-	-	-	-	<2	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Lefa-mulin	Linco-mycin	Linez-olid	Orita-vancin	Polym-yxin B Sulfate	Rifa-mycin	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Asthenia	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-
Ataxia	-	-	✔	-	-	-	-	-	-	✔	-	-	-	-	-
Bacteremia	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	<1	-	-	-	-	✔	-	-	<2	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyskinesia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Extravasation	-	-	-	-	-	-	-	-	<2	-	-	-	-	-	-
Flu syndrome	-	-	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Fungal infections	-	-	-	-	2 to 3	-	-	1 to 2	-	-	-	-	-	-	-
Hypoesthesia oral	-	-	-	-	<1	-	-	-	-	-	-	2 to 5	-	-	-
Injection site reactions	-	✔	-	<2	3 to 6	≤7	-	-	<1	-	-	-	-	3	-
Jitteriness	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Limb abscess	-	-	-	-	-	-	-	-	≤4	-	-	-	-	-	-
Limb pain	-	-	-	-	2 to 9	-	-	-	-	-	-	-	-	-	-
Lymphadenopathy	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Neoplasm	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Neuromuscular blockade	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osteomyelitis	-	-	-	-	6	-	-	-	<2	-	-	-	-	-	-
Pain	✔	-	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Pain at injection site	✔	✔	-	-	-	≤7	✔	-	-	-	-	-	-	4	✔
Phlebitis	-	-	-	<2	-	-	-	-	<1	-	-	-	-	-	-
Redman syndrome	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✔
Rigors	-	-	-	-	<1	-	-	-	-	-	-	-	-	4	-
Sepsis	-	-	-	-	5	-	-	✔	-	-	-	-	-	-	-
Serum sickness-like reaction	-	-	-	-	-	-	✔	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Slurred speech	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Sweating increased	-	-	-	-	5	-	-	-	-	-	-	-	-	-	-
Thrombophlebitis	-	✔	-	-	-	-	-	-	-	-	-	-	-	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Adverse Drug Events (%) Reported with the Combination Antibacterials, Miscellaneous[1-19]

Adverse Events	Bismuth, Metronidazole and Tetracycline
Cardiovascular	
Chest pain	1
Hypertension	<1
Palpitations	<1
Pericarditis	1
Central Nervous System	
Anxiety	1
Ataxia	✔
Depression	✔
Dizziness	✔
Fatigue	✔
Fever	✔
Headache	✔
Insomnia	✔
Irritability	✔
Nervousness	✔
Peripheral neuropathy	✔
Seizure	✔
Syncope	✔
Tinnitus	✔
Vertigo	✔
Visual disturbance	✔
Weakness	✔
Dermatologic	
Photosensitivity	✔
Pruritus	✔
Rash	✔
Stevens-Johnson syndrome	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain/discomfort	✔
Anorexia	2
Blood in stool	✔
Constipation	✔
Diarrhea	✔
Discoloration of teeth	✔
Dry mouth	1
Duodenal ulcer	1
Dyspepsia	✔
Dysphagia	✔
Enamel hypoplasia	✔
Enterocolitis	✔
Epigastric distress	✔
Eructation	<1
Esophageal ulceration	✔
Esophagitis	✔
Extraintestinal cancer	✔
Flatulence	<1
Gastrointestinal hemorrhage	1
Glossitis	<1
Intestinal obstruction	<1
Melena	3
Nausea	12

Adverse Events	Bismuth, Metronidazole and Tetracycline
Oral moniliasis	✔
Rectal hemorrhage	<1
Stool abnormality	1
Taste alteration	1
Tongue discoloration	2
Tooth disorder	<1
Vomiting	✔
Genitourinary	
Dysuria	✔
Incontinence	✔
Urinary tract infections	<1
Vaginitis	4
Laboratory Test Abnormalities	
Alanine aminotransferase increased	✔
Aspartate aminotransferase increased	✔
Musculoskeletal	
Arthritis	✔
Back pain	2
Rheumatoid arthritis	<1
Tendonitis	<1
Weakness	4
Respiratory	
Cough	<1
Pharyngitis	2
Rhinitis	1
Upper respiratory tract infection	2
Other	
Anaphylaxis	✔
Angioneurotic edema	✔
Conjunctivitis	✔
Neoplasm	✔
Pain	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 12. Boxed Warning for Bacitracin[1]

WARNING
Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible. Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded, and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

Table 13. Boxed Warning for Clindamycin[1]

WARNING
Clostridium difficile–associated diarrhea has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents

alters the normal flora of the colon, leading to overgrowth of *Clostridium difficile*–associated diarrhea.

Because clindamycin therapy has been associated with severe colitis, which may end fatally, reserve it for serious infections for which less toxic antimicrobial agents are inappropriate. Do not use clindamycin in patients with nonbacterial infections, such as most upper respiratory tract infections.

Clostridium difficile produces toxins A and B, which contribute to the development of *Clostridium difficile*–associated diarrhea. Hypertoxin-producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *Clostridium difficile*–associated diarrhea must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because *Clostridium difficile*–associated diarrhea has been reported to occur more than two months after the administration of antibacterial agents.

If *Clostridium difficile*–associated diarrhea is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Institute appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation as clinically indicated.

Table 14. Boxed Warning for Lincomycin[1]

WARNING
Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including Lincomycin and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. Because lincomycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhea. Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *Clostridium difficile* associated diarrhea must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since *Clostridium difficile* associated diarrhea has been reported to occur over two months after the administration of antibacterial agents. If *Clostridium difficile* associated diarrhea is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated

Table 15. Boxed Warning for the Polymyxin B Sulfate[1]

WARNING
When this drug is given intramuscularly or intrathecally, it should be given only to hospitalized patients, so as to provide constant supervision by a physician. Nephrotoxicity: Renal function should be carefully determined, and patients with renal damage and nitrogen retention should have reduced dosage. Patients with nephrotoxicity due to polymyxin B sulfate usually show albuminuria, cellular casts, and azotemia. Diminishing urine output and a rising blood urea nitrogen are indications for discontinuing therapy with this drug. Neurotoxicity: Neurotoxic reactions may be manifested by irritability, weakness, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision. These are usually associated with high serum levels found in patients with impaired renal function or nephrotoxicity.

Concurrent therapy: The concurrent or sequential use of other neurotoxic or nephrotoxic drugs with polymyxin B sulfate, particularly bacitracin, streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, cephaloridine, paromomycin, viomycin, and colistin should be avoided.

Neuromuscular blockade: The neurotoxicity of polymyxin B sulfate can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia or muscle relaxants.

Use in pregnancy: The safety of this drug in human pregnancy has not been established.

Table 16. Boxed Warning for Telavancin[1]

WARNING
Patients with pre-existing moderate/severe renal impairment (creatinine clearance ≤ 50 mL/minute) who were treated with telavancin for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed vs vancomycin. Use of telavancin in patients with pre-existing moderate/severe renal impairment (creatinine clearance ≤ 50 mL/minute) should be considered only when the anticipated benefit to the patient outweighs the potential risk. Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. Women of childbearing potential should have a serum pregnancy test prior to administration of telavancin. Avoid use of telavancin during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes 21 in humans.

Table 17. Boxed Warning for Metronidazole[1]

WARNING
Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. Its use should be reserved.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antibacterials are listed in Table 18.

Table 18. Usual Dosing Regimens for the Antibacterials, Miscellaneous[1-19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Bacitracin	Dosing information for adults is not included in the prescribing information.	Unspecified infections: Injection: Infants <2,500 g, 900 units/kg/day IM in two to three divided doses; infants >2,500 g, 1,000 units/kg/day IM in two to three divided doses	Injection: 50,000 units
Clindamycin	Serious infections: Capsule: 150 to 300 mg every six hours Injection: 600 to 1,200 mg/day IM/IV in two to four	Serious infections: Capsule: 8 to 16 mg/kg/day divided into three or four equal doses Solution: 8 to 12 mg/kg/day divided into three or four equal doses	Capsule: 75 mg 150 mg 300 mg Injection:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	equal doses More severe infections: Capsule: 300 to 450 mg every six hours Injection: 1,200 to 2,700 mg/day IM/IV in two to four equal doses	 Severe infections: Solution: 13 to 16 mg/kg/day divided into three or four equal doses More severe infections: Capsule: 16 to 20 mg/kg/day divided into three or four equal doses Solution: 17 to 25 mg/kg/day divided into three or four equal doses Unspecified infections in neonates <1 month of age: Injection: 15 to 20 mg/kg/day in three to four equal doses Unspecified infections in patients one month to 16 years of age: Injection: 20 to 40 mg/kg/day in three to four equal doses	150 mg/mL Solution: 75 mg/5 mL
Colistimethate	Serious infections due to susceptible organisms: Injection: 2.5 to 5 mg/kg per day in two to four divided doses	Serious infections due to susceptible organisms: Injection: 2.5 to 5 mg/kg per day in two to four divided doses	Injection: 150 mg
Dalbavancin	Skin and skin-structure infections: Injection: 1500 mg as a single dose, or 1000 mg dose followed by 500 mg dose one week later	Skin and skin-structure infections: Injection: Birth to <6 years of age, 22.5 mg/kg (maximum 1500 mg) as a single dose; 6 to <18 years of age, 18 mg/kg (maximum 1500 mg) as a single dose	Injection: 500 mg
Daptomycin	Bacteremia, endocarditis: Injection: 6 mg/kg IV once daily for two to six weeks Skin and skin-structure infections: Injection: 4 mg/kg IV once daily for seven to 14 days	Bacteremia in patients one to 17 years of age: Injection: In patients 12 to 17 years, 7 mg/kg; in patients seven to 11 years, 9 mg/kg; in patients one to six years, 12 mg/kg once every 24 hours for up to 42 days Skin and skin-structure infections in patients one to 17 years of age: Injection: In patients 12 to 17 years, 5 mg/kg; in patients seven to 11 years, 7 mg/kg; in patients two to six years, 9 mg/kg; in patients one to less than two years, 10 mg/kg once every 24 hours for up to 14 days	Injection: 350 mg 500 mg
Lefamulin	Community-acquired bacterial pneumonia: Injection: 150 mg every 12 hours by IV infusion over 60 minutes for five to seven	The safety and effectiveness in patients less than 18 years of age has not yet been established.	Injection: 150 mg/15 mL Tablet: 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days Tablet: 600 mg every 12 hours for five days		
Lincomycin	Serious infections: Injection: 600 IM every 24 hours; 600 mg to 1 g IV every eight to 12 hours More severe infections: Injection: 600 mg IM every 12 hours or more often; 600 mg to 1 g IV every eight to 12 hours	Serious infections in patients >1 month of age: Injection: 10 mg/kg IM every 24 hours; 10 to 20 mg/kg IV in divided doses More severe infections in patients ≥1 month of age: Injection: 10 mg/kg IM every 12 hours; 10 to 20 mg/kg IV in divided doses	Injection: 300 mg/mL
Linezolid	Pneumonia (community-acquired): Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Pneumonia (nosocomial): Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (complicated): Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated): Suspension, tablet: 400 mg orally every 12 hours for 10 to 14 days (adults) or 600 mg orally every 12 hours (adolescents) Vancomycin-resistant *Enterococcus faecium* infections: Suspension, tablet: 600 mg every 12 hours for 14 to 28 days	Pneumonia (community-acquired) in patients from birth to 11 years of age: Suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Pneumonia (community-acquired) in patients ≥12 years of age: Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Pneumonia (nosocomial) in patients from birth to 11 years of age: Suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Pneumonia (nosocomial) in patients ≥12 years of age: Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (complicated) in patients from birth to 11 years of age: Suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Skin and skin-structure infections (complicated) in patients ≥12 years of age: Suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients <5 years of age: Suspension, tablet: 10 mg/kg orally every eight hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients five to	Suspension: 100 mg/5 mL Tablet: 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		11 years of age: Suspension, tablet: 10 mg/kg orally every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients >12 years of age: Suspension, tablet: 600 mg orally every 12 hours Vancomycin-resistant *Enterococcus faecium* infections in patients from birth to 11 years of age: Suspension, tablet: 10 mg/kg every eight hours for 14 to 28 days Vancomycin-resistant *Enterococcus faecium* infections in patients≥12 years of age: Suspension, tablet: 600 mg every 12 hours for 14 to 28 days	
Oritavancin	Skin and skin-structure infections: Injection: one 1200 mg dose IV infused over three hours (Orbactiv®) or one hour (Kimyrsa®)	Safety and efficacy in children have not been established.	Injection: 400 mg (Orbactiv®) 1,200 mg (Kimyrsa®)
Polymyxin B sulfate	Meningitis: Injection: Intrathecal, 50,000 units/day for three to four days, then every other day for ≥2 weeks after cerebral spinal fluid cultures are negative Unspecified infections: Injection: IM, 25,000 to 30,000 units/kg/day divided every four to six hours; IV, 15,000 to 25,000 units/kg/day divided every 12 hours	Meningitis in patients <2 years of age: Injection: Intrathecal, 20,000 units/day for three to four days, then 25,000 units/day every other day for ≥2 weeks after cerebral spinal fluid cultures are negative Meningitis in patients >2 years of age: Injection: Intrathecal, 50,000 units/day for three to four days, then every other day for ≥2 weeks after cerebral spinal fluid cultures are negative Unspecified infections in infants: Injection: IM, up to 40,000 units/kg/day divided every four to six hours; IV, up to 40,000 units/kg/day divided every 12 hours Unspecified infections in children: Injection: IM, 25,000 to 30,000 units/kg/day divided every four to six hours; IV, 15,000 to 25,000 units/kg/day divided every 12 hours	Injection: 500,000 units
Rifamycin	Travelers' diarrhea caused by noninvasive strains of	Safety and efficacy in children have not been established.	Delayed-release tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Escherichia coli: Delayed-release tablet: 388 mg (two tablets) orally twice daily (in the morning and evening) for three days		194 mg
Rifaximin	Hepatic encephalopathy: Tablet: 550 mg twice daily Irritable bowel syndrome with diarrhea: Tablet: 550 mg three times daily for 14 days Traveler's diarrhea: Tablet: 200 mg three times daily for three days	Traveler's diarrhea in patients ≥12 years of age: Tablet: 200 mg three times daily for three days	Tablet: 200 mg 550 mg
Tedizolid	Skin and skin-structure infections: Injection: 200 mg administered once daily as an IV infusion over one hour for six days Tablet: 200 mg administered once daily orally for six days	Skin and skin-structure infections in patients ≥12 years of age: Injection: 200 mg administered once daily as an IV infusion over one hour for six days Tablet: 200 mg administered once daily orally for six days	Injection: 200 mg Tablet: 200 mg
Telavancin	Skin and skin-structure infections: Injection: 10 mg/kg IV every 24 hours for seven to 14 days Hospital-acquired and ventilator-associated bacterial pneumonia: Injection: 10 mg/kg IV every 24 hours for seven to 21 days	Safety and efficacy in children have not been established.	Injection: 750 mg
Vancomycin	*Clostridium difficile*-associated diarrhea: Capsule, solution: 125 mg four times daily for 10 days Enterocolitis: Capsule, solution: 500 mg to 2 g per day divided in three or four doses for seven to 10 days Unspecified infections: Injection: 500 mg IV every six hours or 1 g IV every 12 hours	*Clostridium difficile*-associated diarrhea and enterocolitis in children: Capsule, solution: 40 mg/kg/day in three to four divided doses for seven to 10 days Unspecified infections in patients <1 month of age: Injection: 15 mg/kg IV as an initial dose, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every eight hours thereafter up to the age of one month Unspecified infections in patients ≥1 month of age: Injection: 10 mg/kg IV per dose every six hours	Capsule: 125 mg 250 mg Injection: 250 mg 500 mg 750 mg 1 g 1.25 g 1.5 g 5 g 10 g Solution: 25 mg/mL 50 mg/mL 250 mg/5 mL
Combination Products			

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Colloidal bismuth subcitrate, metronidazole, and tetracycline	Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history within the past five years) to eradicate *Helicobacter pylori* (in combination with omeprazole): Capsule: Three capsules four times daily for 10 days; administer with 20 mg twice daily of omeprazole	Safety and efficacy in children have not been established.	Capsule: 140-125-125 mg

IM= intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antibacterials are summarized in Table 19.

Table 19. Comparative Clinical Trials with the Antibacterials, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Boucher et al.[52] (2014) DISCOVER 1 Dalbavancin 1 g IV on day one, followed by 500 mg IV on day eight vs vancomycin 1 g (or 15 mg/kg) IV every 12 hours for ≥3 days with option to switch to oral linezolid 600 mg every 12 hours to complete 10 to 14 days of therapy	DB, DD, MC, RCT Adult patients with an acute bacterial SSSI who were thought to require ≥3 days of IV therapy who had ≥1 systemic sign of infection within 24 hours before randomization	N=573 10 to 14 days	Primary: Early clinical response (cessation of spread of infection-related erythema, absence of fever at 48 to 72 hours) Secondary: Clinical status at end of therapy	Primary: Early clinical response indicating treatment success was noted in 240 of 288 patients (83.3%) treated with dalbavancin compared to 233 of 285 patients (81.8%) in the vancomycin-linezolid group (difference, 1.5%; 95% CI, -4.6 to 7.9). Secondary: Clinical status indicating treatment success at the end of treatment was documented in a similar proportion of patients in the dalbavancin and vancomycin-linezolid groups in a pooled analysis of data from DISCOVER1 and DISCOVER2 (90.7 vs 92.1%, respectively; difference, -1.5; 95% CI, -4.8 to 1.9).
Boucher et al.[52] (2014) DISCOVER 2 Dalbavancin 1 g IV on day one, followed by 500 mg IV on day eight vs	DB, DD, MC, RCT Adult patients with an acute bacterial SSSI who were thought to require ≥3 days of IV therapy who had ≥1 systemic sign of infection within 24 hours before	N=739 10 to 14 days	Primary: Early clinical response (cessation of spread of infection-related erythema, absence of fever at 48 to 72 hours) Secondary: Clinical status at	Primary: Early clinical response indicating treatment success was noted in 285 of 371 patients (76.8%) treated with dalbavancin and 288 of 368 patients (78.3%) in the vancomycin-linezolid group (difference, -1.5; 95% CI, -7.4 to 4.6). Secondary: Clinical status indicating treatment success at the end of treatment was documented in a similar proportion of patients in the dalbavancin and vancomycin-linezolid groups in a pooled analysis of data from DISCOVER1 and DISCOVER2 (90.7 vs 92.1%, respectively; difference, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 1 g (or 15 mg/kg) IV every 12 hours for ≥3 days with option to switch to oral linezolid 600 mg every 12 hours to complete 10 to 14 days of therapy	randomization		end of therapy	1.5; 95% CI, -4.8 to 1.9).
Loeffler et al.[53] (2002) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 to 12 hours	RETRO Patients <18 years of age with signs and symptoms of serious invasive infection	N=127 2 to 73 days	Primary: Clinical responses (cure, improved, failure, or indeterminate), microbiologic response (eradication, presumed eradication, presumed persistence, persistence, or indeterminate), adverse events Secondary: Not reported	Primary: Overall favorable clinical response rate (either cure or improved) was 69% and similar across all age groups. The overall favorable microbiologic response rate (either eradicated or presumed eradicated) was 78%. A total of 8% of patients experienced treatment-related non-venous adverse events. Pain (2%) and maculopapular rash (2%) were the most frequently reported drug-related adverse events. Five patients discontinued treatment due to adverse laboratory events (three of the five were related to treatment: gamma-glutamyl transferase, total bilirubin, and eosinophils). Forty-six patients died due to reasons unrelated to quinupristin-dalfopristin toxicities. Secondary: Not reported
Davis et al.[54] (2007) Daptomycin 4 mg/kg IV once daily for 3 to 14 days	OL, PRO Adult patients with complicated SSSIs at risk for MRSA infection	N=53 14 days	Primary: Clinical resolution and duration of therapy Secondary: Not reported	Primary: The most common diagnoses were cellulitis (31%), abscess (22%), and both cellulitis with abscess (37%). Microbiology differed significantly between groups, with *Staphylococcus aureus* found in 27 patients (51%) in the daptomycin group and 167 patients (79%) in the vancomycin group and MRSA in 22 (42%) and 159 (75%), respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin historical controls				The proportions of patients with clinical improvement or resolution of their infections on days three and five were 90 vs 70% and 98 vs 81% in the daptomycin vs vancomycin groups, respectively (P<0.01 for both comparisons), and 100% at the EOT in both groups. Among patients with complete resolution of their infections (41 patients [77%] with daptomycin vs 89 patients [42%] with vancomycin, P<0.05), median duration of IV therapy was four and seven days, respectively, (P<0.001). Secondary: Not reported
Pertel et al.[55] (2009) Daptomycin 4 mg/kg IV once daily for 7 to 14 days vs vancomycin according to standard of care for 7 to 14 days	MC, RCT, SB Adults diagnosed with cellulitis or erysipelas requiring hospitalization and IV antibiotic therapy	N=103 7 to 14 days	Primary: Clinical success rate Secondary: Not reported	Primary: The clinical success rates were 94.0% for daptomycin and 90.2% for vancomycin (95% CI, -6.7 to 14.3). Of the 50 patients in the daptomycin group, 36 (72.0%) were assessed as cured, 11 (22.0%) were improved and three (6.0%) had no follow-up data. Of the 51 patients in the vancomycin group, 28 (54.9%) were assessed as cured, 18 (35.3%) were improved, one (2.0%) had worsened and four (7.8%) had no follow-up data. Among the patients with cellulitis clinical success rates were also similar for daptomycin-treated (78.6%) and comparator-treated patients (72.7%). The mean durations of study drug administration were 6.1 days for daptomycin- and 6.2 days for vancomycin-treated patients (P=0.847). There were no significant differences between treatments in the time to achievement of any of the predefined endpoints. The median time to stabilization of infection was similar for daptomycin and vancomycin (P=0.875; 86.5 vs 85.5 hours). No differences were observed between daptomycin- and vancomycin-treated patients in the median time to defervescence (P=0.690; 12.4 vs 16.3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hours), cessation of erythema advancement (P=0.833; 21.0 vs 22.0 hours), or readiness for hospital discharge (P=0.993; 84.0 vs 85.5 hours). No differences were seen between the groups in the median time to 50% improvement for investigator-assessed composite scores (P=0.755; 39.9 vs 41.2 hours) as well as patient-reported pain (P=0.632; 37.3 vs 40.0 hours) or tightness/swelling scores (P=0.307; 31.0 vs 31.5 hours). Secondary: Not reported
Kauf et al.[56] (2015) Daptomycin 4 mg/kg IV QD vs vancomycin dosed at the investigator's discretion according to institutional protocol	MC, OL, PRO, RCT Patients ≥18 years of age hospitalized for complicated SSSI caused by suspected or documented MRSA infection that necessitated IV antibiotics	N=250 30 days after discharge	Primary: Infection-related length of stay Secondary: Clinical response, and patient-reported outcomes	Primary: For the primary end point, there was no significant difference between the daptomycin and vancomycin arms. Secondary: Although the unadjusted differences in clinical success were not significant, logistic regression analysis showed that vancomycin treatment, relative to daptomycin treatment, was associated with a decreased chance of achieving clinical success within two days (OR, 0.498; 95% CI, 0.249 to 0.997; P=0.049). Significant variables in the two-day response included count of Systemic Inflammatory Response Syndrome (P=0.041), Gram-negative infection (P=0.006), and baseline vancomycin use (P=0.031). Similarly, clinical success rates were not significantly different within two and three days of treatment when analyzed by infection type or pathogen. No notable differences in patient-reported outcomes (pain, health-related quality of life, or infection status) by group were observed.
Bradley et al.[57] (2017) Daptomycin administered once daily with dosing by patient age: 12 to 17 years, 5 mg/kg; 7 to 11 years, 7 mg/kg; 2 to 6 years, 9	Evaluator-blinded, MC, RCT Patients one to 17 years of age with complicated SSSI caused by Gram-positive pathogens	N=389 ≤14 days of treatment	Primary: Safety Secondary: Efficacy (clinical and microbiological response)	Primary: The most common adverse events were diarrhea (7% daptomycin, 5% standard-of-care) and increased creatine phosphokinase (6% daptomycin, 5% standard-of-care). The proportions of safety population patients with treatment-related adverse events were similar between the daptomycin (14%) and standard-of-care (17%) groups. Secondary: The study was neither designed nor powered to confirm noninferiority of efficacy outcomes. Clinical success rates (blinded evaluator-assessed complete/partial resolution of complicated SSSI signs and symptoms seven

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg; 12 to 23 months, 10 mg/kg vs standard-of-care treatment (primarily clindamycin or vancomycin)				to 14 days after end-of-treatment) in the intent-to-treat population were similar for the daptomycin (91%) and standard-of-care (87%) groups.
Yogev et al.[58] (2003) Linezolid 10 mg/kg IV/oral every 8 hours vs vancomycin 10 to 15 mg/kg IV every 6 to 24 hours (based on age) After 3 days of treatment, linezolid group was permitted to switch to oral linezolid, and vancomycin group was permitted to switch to an oral appropriate agent based on susceptibility tests.	RCT Hospitalized children <12 years of age with complicated SSSIs caused by resistant gram-positive bacteria	N=120 10 to 28 days	Primary: Patient clinical outcome and pathogen eradication rates Secondary: Not reported	Primary: Clinical cure rate was 93.2% with linezolid vs 90% with vancomycin (P=0.594). Patients with a diagnosis of skin abscess had a significantly higher cure rate in the linezolid group compared to vancomycin (100 vs 60%, respectively; P=0.005). Patients with cellulitis or other types of infection had similar cure rates (P=NS for all). There was no statistically significant difference in eradication rates between treatment groups for all types of infections (P=NS for all). Fewer patients experienced adverse events with linezolid therapy compared to vancomycin (23 vs 48%, respectively; P=0.006). Vancomycin-treated patients experienced a greater incidence (statistically significant) of red man syndrome, pruritus, and rash. All other adverse events were not significantly different between treatment groups. The authors did not indicate the rate at which vancomycin was being infused. Secondary: Not reported
Li et al.[59]	MC, OL, RCT	N=144	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Linezolid 600 mg IV/oral BID vs vancomycin 1 g IV BID	Patients with complicated skin and soft tissue infections as the primary site of MRSA infection	Treatment: ≤4 weeks Observation: ≤4 weeks	Length of hospital stay Secondary: Not reported	In the clinically evaluable population, the unadjusted mean length of hospital stay was 5.3 days shorter with linezolid vs vancomycin (15.7 vs 21 days, respectively; P=0.0025). After adjusting for baseline variables, the between-treatment difference in mean length of hospital stay increased to 6.5 days with linezolid vs vancomycin (14.3 vs 20.8 days, respectively; P<0.001). Mean duration of IV therapy was shorter in the linezolid group (5.8 vs 12.6 days; P<0.0001). Clinically evaluable patients had to be treated for ≥7 days, which may have extended the length of hospital stay for patients receiving vancomycin IV as compared to the linezolid group that had the option to switch to oral therapy. Secondary: Not reported
Itani et al.[60] (2005) Linezolid 600 mg IV/oral every 12 hours vs vancomycin 1 g IV every 12 hours	MC, OL, RCT Hospitalized patients with complicated skin and soft tissue infections due to MRSA	N=1,200 7 days	Primary: Length of stay, duration of IV treatment, and hospital discharge rates Secondary: Not reported	Primary: Linezolid was associated with a shorter length of stay (P<0.01), decreased duration of IV antibiotic therapy (P<0.0001), and higher rates of hospital discharge (P<0.05) as compared to vancomycin therapy. Secondary: Not reported
Itani et al.[61] (2010) Linezolid 600 mg IV/oral every 12 hours for 7 to 14 days vs	OL, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections due to MRSA	N=1,077 7 to 10 days posttreatment	Primary: Clinical response, microbiologic outcome, length of stay, duration of IV therapy, safety Secondary: Not reported	Primary: In the per protocol population, clinical success was reported in 92% of patients receiving linezolid compared to 88% of patients receiving vancomycin at the end of treatment (P=0.168). At the end of the study, clinical success rates were similar among the treatment groups (84% with linezolid and 80% with vancomycin; P=0.249). In the modified intent to treat population, clinical success was reported in 89% of patients receiving linezolid compared to 85% of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 15 mg/kg mg IV every 12 hours for 7 to 14 days				vancomycin at the end of treatment (P=0.090). At the end of the study, clinical success rates were similar among the treatment groups (81% with linezolid and 74% with vancomycin; P=0.048). In the per protocol population at the end of treatment, linezolid achieved a significantly higher rate of microbiologic success than vancomycin (85.4 vs 68.8%, respectively; P<0.001). At the end of the study, linezolid was comparable with vancomycin (75.0 vs 68.4%, respectively; P=0.127). In the modified intent-to-treat population, linezolid had a numerically higher success rate than vancomycin (74 vs 66%; 95% CI, -0.1 to 15.2; P=0.055). In the per protocol population, the median and mean lengths of stay were 6.0 and 7.6 days, respectively, in the linezolid group, compared to 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.022). The mean duration of IV therapy was significantly shorter in the linezolid group than in the vancomycin group (5.6 vs 10.4 days; P<0.001). In the modified intent-to-treat population, the median and mean lengths of stay were 5.0 and 7.7 days, respectively, in the linezolid group, as compared to 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.016). The mean duration of IV therapy was significantly shorter in the linezolid group than in the vancomycin group (5.3 vs 9.8 days; P<0.001). The percentage of patients who experienced ≥1 adverse event was similar in both treatment groups (linezolid, 48%; vancomycin, 51%). Treatment-related adverse events occurred in 23% of patients in the linezolid arm and 22% of patients in the vancomycin arm. Treatment- related nephrotoxic adverse events occurred more often in the vancomycin group. There were 11 deaths in the linezolid group and seven deaths in the vancomycin group. Secondary: Not reported
Sharpe et al.[62]	OL, RCT	N=60	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Linezolid 600 mg oral every 12 hours vs vancomycin 1 g IV every 12 hours All patients received perioperative cefazolin.	Patients ≥18 years of age with MRSA-related complicated skin and soft-tissue infections of the lower extremities	Treatment: 7 to 21 days Tests of cure: 10 days posttreatment	Clinical cure, improvement, or failure; microbiological eradication, persistence, or recurrence; duration of hospitalization and drug treatment Secondary: Not reported	Linezolid was associated with a greater incidence of cure (50 vs 20% for vancomycin) and improvement (47 vs 23% for vancomycin; P=0.015 for both comparisons). Microbiological outcomes were similar overall between treatment groups (P=0.052). Median length of therapy was 10 days for both treatment arms; of these, seven days of treatment were administered on an outpatient basis for the linezolid group compared to four outpatient days of treatment with vancomycin. Secondary: Not reported
Wilcox et al.[63] (2009) Linezolid 600 mg IV every 12 hours for 7 to 28 days vs vancomycin 1 g IV every 12 hours for 7 to 28 days	MC, OL Adults >13 years of age who had a central venous, pulmonary artery, or arterial catheter in place for 13 days and suspected catheter-related infection	N=739 6 to 8 weeks	Primary: Microbiologic outcome at test of cure Secondary: Clinical outcomes and safety	Primary: Microbiologic outcomes at test of cure met non-inferiority criteria in the two primary analysis populations. In the subset with complicated SSSIs, success occurred in 146 (89.6%) of 163 linezolid patients and in 134 (89.9%) of 149 control patients (95% CI, -7.1 to 6.4). In the subset with suspected catheter-related infection, microbiologic success occurred in 82 (86.3%) of 95 linezolid recipients and in 67 (90.5%) of 74 control patients (95% CI, -13.8 to 5.4). Secondary: In the subset of patients with complicated SSSIs, clinical success occurred in 123 (77.8%) of 158 linezolid recipients and in 113 (77.9%) of 145 control patients at test-of-cure. In the subset with suspected catheter-related infection, success occurred in 70 (75.3%) of 93 linezolid recipients and in 59 (80.8%) of 73 control patients. Sensitivity analysis did not alter clinical outcomes in the subsets with complicated SSSIs (linezolid group, 75.0%; control group, 74.8%) or suspected catheter-related infection (linezolid group, 73.7%; control group, 79.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events, including those unrelated to treatment, occurred in 244 linezolid recipients (67.2%) and were similar between groups. Mortality rates were 10.4% for linezolid recipients (28 of 269 patients) and 10.1% for control subjects (26 of 257) in the modified intent-to-treat population through test of cure, and they were 21.5% for linezolid recipients (78 of 363) and 16.0% for the control group (58 of 363; 95% CI, -0.2 to 11.2) for all treated patients through post-study treatment day 84.
Itani et al.[64] (2012) Vancomycin IV 15 mg/kg every 12 hours vs linezolid oral 600 mg every 12 hours	RETRO Adults with complicated skin and soft tissue infections caused by MRSA	N=305 7 to 14 days	Primary: Efficacy and tolerability Secondary: Not reported	Primary: At end of study, the OR for clinical success of oral linezolid therapy vs IV vancomycin therapy was 4.0 (95% CI, 1.3 to 12.0; P=0.01), and the OR for microbiologic success at end of study was 2.7 (95% CI, 1.2 to 5.7; P=0.01). Overall rates of adverse events in each group were consistent with reported safety profiles for each drug. Secondary: Not reported
Yue et al.[65] (2013) Vancomycin vs linezolid	MA 9 RCTs comparing linezolid with vancomycin in the treatment of skin and soft tissue infections	N=3,144 Duration varied	Primary: clinical cure, microbiological cure, and skin and soft tissue infections -related and treatment-related mortality Secondary: Not reported	Primary: Linezolid was associated with a significantly better clinical (RR, 1.09; 95% CI, 1.03 to 1.16) and microbiological cure rate in adults (RR, 1.08; 95% CI, 1.01 to 1.16). For those infections due to MRSA, linezolid was significantly more effective than vancomycin in clinical (RR, 1.09; 95% CI, 1.03 to 1.17) and microbiological cure rates (RR, 1.17; 95% CI, 1.04 to 1.32). No RCT reported skin and soft tissue infections-related and treatment-related mortality. There was no significant difference in all-cause mortality between linezolid and vancomycin (RR, 1.44; 95% CI, 0.75 to 2.80). There were fewer incidents of red man syndrome (RR, 0.04; 95% CI, 0.01 to 0.29), pruritus (RR, 0.36; 95% CI, 0.17 to 0.75) and rash (RR, 0.27; 95% CI, 0.12 to 0.58) in the linezolid group compared to vancomycin, however, more people reported thrombocytopenia (RR, 13.06; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.72 to 99.22), and nausea (RR, 2.45; 95% CI, 1.52 to 3.94) when treated with linezolid.
O'Riordan et al.[66] (2019) OASIS-I Linezolid 600 mg IV every 12 hours with the option to switch to 600 mg orally every 12 hours vs omadacycline 100 mg IV every 12 hours for 2 doses followed by 100 mg IV every 24 hours with the option to switch to 300 mg orally every 24 hours	DB, MC, RCT Adults with qualifying ABSSI. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=655 Total treatment was for 7 to 14 days	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement of at least 20% reduction of ABSSSI primary lesion size compared to baseline 48 to 72 hours after the first dose of study drug [ECR window] and no use of rescue antibiotics) Secondary: Number of Participants with clinical response (CR: defined as symptom improvement, no use of rescue antibiotics, and patient survival), in the mITT Population at the Post Therapy Evaluation (PTE) Visit, adverse	Primary: Omadacycline was noninferior to linezolid for percentage of patients with early clinical response (84.8% vs 85.5%; 95% CI, -6.3 to 4.9). Secondary: Omadacycline was noninferior to linezolid in the investigator-assessed clinical response at the PTE (86.1% vs 83.6%; 95% CI, -3.2 to 8.2). Number of adverse events was similar between omadacycline and linezolid (48.3% vs 45.7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			events	
O'Riordan et al.[67] (2019) OASIS-II Linezolid 600 mg orally every 12 hours vs omadacycline 450 mg orally once a day on days 1 and 2, followed by 300 mg orally once a day	DB, MC, RCT Adults with qualifying ABSSI. Female patients must not have been pregnant at the time of enrollment and must have agreed to reliable method of birth control during the study and for 30 days following the last dose of the study.	N=735 Total treatment was for 7 to 14 days.	Primary: Number of participants with early clinical response (ECR: defined as symptom improvement of at least 20% reduction of ABSSSI primary lesion size compared to baseline 48 to 72 hours after the first dose of study drug [ECR window] and no use of rescue antibiotics) Secondary: Number of Participants with clinical response (CR: defined as symptom improvement, no use of rescue antibiotics, and patient survival) in the mITT Population at the Post Therapy Evaluation (PTE) Visit	Primary: Omadacycline was noninferior to linezolid for early clinical response (87.5% vs 82.5%; 95% CI, -0.2 to 10.3). Secondary: Omadacycline was noninferior to linezolid in the investigator-assessed clinical response at the PTE (84.2% vs 80.8%; 95% CI, -2.2 to 8.9).
Corey et al.[68]	AC, DB, MC, RCT	N=1,019	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2015) SOLO II Oritavancin 1,200 mg IV once, followed by placebo every 12 hours vs vancomycin 1 g or 15 mg/kg IV every 12 hours	Patients ≥18 years of age with acute bacterial SSSI suspected or proven to be due to a gram-positive pathogen, with erythema, edema and/or induration surrounding each lesion of ≥75 cm^2, presenting with signs and symptoms of systemic inflammation and would require ≥7 days of therapy	7 to 10 days	Composite outcome at ECE Secondary: Investigator-assessed clinical cure at PTE, lesion area decrease of ≥20% from baseline at ECE	A total of 403 (80.1%) patients in the oritavancin group and 416 (82.9%) patients in the vancomycin group achieved a primary efficacy outcome at ECE (difference, -2.7; 95% CI, -7.5 to 2.0; P value not reported). Secondary: Oritavancin was noninferior to vancomycin for the investigator assessed clinical cure endpoint at PTE (82.7 vs 80.5%, respectively; difference, 2.2; 95% CI, -2.6 to 7.0; P value not reported) and ≥20% reduction in lesion size endpoint at ECE (85.9 vs 85.3%, respectively; difference, 0.6; 95% CI, -3.7 to 5.0; P value not reported).
Corey et al.[69] (2014) SOLO I Oritavancin 1,200 mg IV once, followed by placebo every 12 hours vs vancomycin 1 g or 15 mg/kg IV every 12 hours	AC, DB, MC, RCT Patients ≥18 years of age with acute bacterial SSSI suspected or proven to be due to a gram-positive pathogen, with erythema, edema and/or induration surrounding each lesion of ≥75 cm^2, presenting with signs and symptoms of systemic inflammation and would require ≥7 days of therapy	N=968 7 to 10 days	Primary: Composite outcome at ECE Secondary: Investigator-assessed clinical cure at PTE, lesion area decrease of ≥20% from baseline at ECE	Primary: A total of 391 (82.3%) patients in the oritavancin group and 378 (78.9%) patients in the vancomycin group achieved a primary efficacy outcome at ECE (difference, 3.4; 95% CI, -1.6 to 8.4; P value not reported). Secondary: Oritavancin was noninferior to vancomycin for the investigator assessed clinical cure endpoint at PTE (79.6 vs 80.0%, respectively; difference, -0.4; 95% CI, -5.5 to 4.7; P value not reported) and ≥20% reduction in lesion size endpoint at ECE (86.9 vs 82.9%, respectively; difference, 4.1; 95% CI, -0.5 to 8.6; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Moran et al.[70] (2014) ESTABLISH-2 Tedizolid phosphate 200 mg IV QD vs linezolid 600 mg IV BID	AC, DB, DD, MC, RCT Patients ≥12 years of age with acute bacterial SSSIs that had a minimum lesion area of 75 cm^2, were suspected or documented to be associated with a gram-positive pathogen and had at least one systemic or regional sign of infection	N=666 Patients randomized to tedizolid phosphate received treatment for six days and patients randomized to linezolid received treatment for 10 days, with the option to step down to oral therapy after receiving ≥2 IV doses of active treatment or placebo	Primary: Early clinical response 48 to 72 hours after start of treatment Secondary: Response at day 7, programmatic and investigator-assessed EOT response, investigator assessed post therapy response seven to 14 days after EOT, changes in patient-reported pain, investigator-assessed response at late follow-up, favorable microbiologic response	Primary: Early clinical response was achieved in 283 (85%) patients in the tedizolid phosphate group and 276 (83%) patients in the linezolid group, demonstrating non-inferiority of tedizolid phosphate to linezolid (2.6% difference; 95% CI, -3.0 to 8.2; P value not reported). There were no meaningful differences between groups in rates of early clinical response, irrespective of type of acute bacterial SSSI, geographic region, baseline pathogen and timing of oral step-down. Secondary: There was no significant difference between the linezolid group and the tedizolid group with regards to response at day seven (0.9% difference; 95% CI, -3.2 to 4.9; P value not reported), programmatic assessed EOT response (-4.1% difference; 95% CI,-8.8 to 0.3; P value not reported), investigator assessed EOT response (-2.0% difference; 95% CI, -5.7 to 1.2; P value not reported), and post therapy assessment (0.3%; 95% CI, -4.8 to 5.3; P value not reported). Improvements in patient reported pain were similar between treatment groups (P value not reported). There was no significant difference between treatment groups with regards to investigator assessed response at late follow-up (-1.1% difference; 95% CI, -3.8 to 1.3; P value not reported) and favorable microbiological response to gram-positive pathogens (-1.4 % difference; 95% CI, -8.0 to 5.1; P value not reported).
Prokocimer et al.[71] (2013) ESTABLISH-1 Tedizolid phosphate 200mg PO QD vs linezolid 600 mg	AC, DB, DD, MC, RCT Adults ≥18 years with cellulitis/erysipelas, major cutaneous abscess, or wound infection surrounded by erythema with a minimum total	N=667 Patients randomized to tedizolid phosphate received treatment for six days and patients randomized to	Primary: Early clinical response assessed at 48 to 72 hours in the intent-to-treat analysis set Secondary: Objective sustained clinical response at EOT in the intent-	Primary: Response rates at the 48 to 72 hour assessment were 79.5% (95% CI, 74.8 to 83.7; P value not reported) of 332 patients in the tedizolid phosphate group and 79.4% (95% CI, 74.7 to 83.6; P value not reported) of 335 patients in the linezolid group; a treatment difference of 0.1% (95% CI, -6.1 to 6.2; P value not reported). Response rates in patients with cellulitis/erysipelas treated with tedizolid phosphate (74.8%, N=135) were lower than for all infections combined (79.5%, N=332) as well as in patients treated with linezolid (71.9%, N=139 vs 79.4%, N=335). P values were not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PO BID	lesion area of 75 cm^3, accompanied by at least one local and one regional or one systemic sign of infection, and a gram-positive pathogen was suspected or documented	linezolid received treatment for 10 days	to-treat and clinically evaluable EOT analysis set, investigators assessment of clinical success at the PTE in the intent-to-treat and clinically evaluable PTE analysis set	Secondary: Absolute treatment difference with regards to sustained clinical response at EOT in the ITT analysis set was -2.6% (95% CI, -9.6 to 4.2; P value not reported) and -0.9% (95% CI, -7.7 to 5.4; P value not reported) in the clinically evaluable EOT analysis set. Absolute treatment difference with regards to investigators assessment of clinical success at the PTE in the ITT analysis set was -0.5% (95% CI, -5.8 to 4.9) and -0.8% (95% CI, -4.6 to 3.0) in the clinically evaluable PTE analysis set. In patients treated with tedizolid phosphate, response rates for cellulitis/erysipelas (63.9%, N=133) were lower than for all infections combined (69.3%, N=332) in the ITT analysis set as well as the clinically evaluable EOT analysis set (68.8%, N=112; cellulitis/erysipelas group vs 80.2%, N=273; all infections combined). In patients treated with linezolid, similar results were observed in the intent-to-treat analysis set (62.2%, N=135 vs 71.9%, N=335) and the clinically evaluable EOT analysis set (68.4%, N=117 vs 81.1%, N=286).
De Anda et al.[72] (2017) ESTABLISH-1 & ESTABLISH-2 Tedizolid phosphate 200 mg once daily for six days vs linezolid 600 mg twice daily for 10 days	Post-hoc analysis of 2 DB, MC, RCTs Subgroup analysis was performed on US outpatients (defined as patients who were not in hospital at the time of treatment initiation) with ABSSSI caused by presumed or proven gram-positive pathogens	N=813 14 days post-therapy	Primary: Early clinical response (48 to 72 hours after the start of treatment) Secondary: Investigator-assessed clinical response at end of therapy and post-therapy evaluation (7 to 14 days after therapy)	Primary: Early clinical response (≥20% reduction in lesion size at 48 to 72 hours) was similar between treatment groups (tedizolid, 82.4%; linezolid, 79.0%; 95% CI, -2.1 to 8.8). Secondary: Clinical success rates at end of therapy were slightly higher than early response rates but remained similar between the tedizolid (87.1%) and linezolid (86.1%) treatment groups. Rates of clinical success at post-therapy evaluation were also similar between the tedizolid (83.1%) and linezolid (83.7%) treatment groups.
Stryjewski et al.[73]	PostHoc	N=1,794	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) Vancomycin vs telavancin	Patients with various complicated SSSIs	Duration varied	Efficacy Secondary: Not reported	Among clinically evaluable patients with major abscesses (n = 619), cure rates were 91% for telavancin and 90% for vancomycin (95% CI for the difference, -3.6 to 5.7). In patients with infective cellulitis (n = 519), cure was achieved in 87% and 88% of telavancin- and vancomycin-treated patients, respectively (95% CI for the difference, -6.2 to 5.2). Cure rates in patients with wound infections were 85% in the telavancin group and 86% in the vancomycin group (95% CI for the difference, -10.5 to 9.0). Cure rates for each type of complicated SSSIs in patients infected with MRSA were also similar between the two treatment arms. Among clinically evaluable patients infected with Panton-Valentine leucocidin-positive MRSA (n = 447), cure rates were 93% for telavancin and 90% for vancomycin (95% CI for the difference, -2.2 to 8.2). Secondary: Not reported
Stryjewski et al.[74] (2008) Telavancin 10 mg/kg IV once daily for 7 to 14 days vs vancomycin 1 g IV BID for 7 to 14 days	AC, DB, RCT (2 trials) Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=1,867 7 to 14 days posttreatment	Primary: Clinical response at the test-of-cure visit (seven to 14 days after the last dose of study medication), microbiological response, safety Secondary: Not reported	Primary: In all treated patients at the test-of-cure visit (study 0017), cure rates were 75.8% with telavancin and 74.8% with vancomycin (95% CI, -4.8 to 6.8). In study 0018, cure rates were 77.1% with telavancin and 73.7% with vancomycin (95% CI, -1.9 to 8.7). In the clinically evaluable population at the test-of-cure visit (study 0017), cure rates were 87.9% with telavancin and 86.5% with vancomycin (95% CI, -3.6 to 6.3). In study 0018, cure rates were 88.7% with telavancin and 87.6% with vancomycin (95% CI, -3.4 to 5.6). In the pooled analysis of all treated patients (study 0017 and 0018), cure rates were 76.5% with telavancin and 74.2% with vancomycin (95% CI, -1.6 to 6.2). In the clinically evaluable population (pooled analysis), cure rates were 88.3% with telavancin and 87.1% with vancomycin (95% CI, -2.1 to 4.6).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Among the microbiologically evaluable patients, baseline pathogens were eradicated at the test-of-cure visit in 89.8 and 87.3% of patients who received telavancin and vancomycin, respectively (95% CI, -1.4 to 6.2). Among patients with MRSA infection at baseline, cure rates were 91% with telavancin and 86% with vancomycin (95% CI, -1.1 to 9.3). Microbiologic eradication in patients with MRSA was 90% in the telavancin group and 85% in the vancomycin group (95% CI, -0.9 to 9.8). Overall therapeutic response was also evaluated. Patients were cured and pathogens were eradicated at the test-of-cure visit in 88.6 and 86.2% of patients in the telavancin and vancomycin treatment groups, respectively (95% CI, -1.6 to 6.4). Adverse events were reported in 79 and 72% of patients who received telavancin and vancomycin, respectively. The incidence of serious adverse events was higher in the telavancin treatment group than in the vancomycin treatment group (7 vs 4%). More patients discontinued telavancin therapy than discontinued vancomycin therapy because of an adverse event (8 vs 6%). Except for taste disturbance, mild nausea, vomiting, and foamy urine in the telavancin group, adverse events were of similar type and severity between the treatment groups. Secondary: Not reported
Chen et al.[75] (2011) Cephalexin 40 mg/kg/day orally in divided doses TID for seven days vs clindamycin 20 mg/kg/day orally	RCT Patients six months to 18 years of age with uncomplicated skin and soft tissue infections not requiring hospitalization	N=200 3 months	Primary: Clinical improvement at 48 to 72 hours from the initiation of treatment Secondary: Resolution of disease at seven days	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary: A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by seven days (P=0.33). Only one patient developed a new skin and soft tissue infection while on therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in divided doses TID for seven days				Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the three-month follow-up, 18% of patients had a recurrent skin and soft tissue infection. The risk of new skin and soft tissue infection did not differ according to isolation of MRSA vs MSSA from initial wound culture (21% MRSA vs 16% MSSA; P=0.51) or by cephalexin or clindamycin assignment (20 vs 16%; P=0.46). There were no serious adverse events related to study treatment.
Khawcharoenporn et al.[76] (2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs clindamycin 300 mg QID	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety Secondary: Not reported	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91 vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Stevens et al.[77] (2000) Oxacillin 2 g IV every six hours followed by dicloxacillin 500 mg orally every six hours vs linezolid 600 mg IV every 12 hours	DB, DD, MC, RCT Hospitalized patients ≥18 years of age with a suspected gram-positive complicated skin and soft tissue infection	N=819 10 to 21 days	Primary: Clinical outcome and microbiological outcome based on resolution or improvement of clinical signs/ symptoms of skin and soft tissue infections at the end of treatment compared to baseline Secondary: Not reported	Primary: Of clinically evaluable patients (N=600), clinical cure rate was 88.6% in the linezolid group compared to 85.8% in the oxacillin and dicloxacillin group (P=0.300). Of microbiologically evaluable patients (N=294), the cure rate was 88.1% in the linezolid group compared to 86.1% in the oxacillin and dicloxacillin group (P=0.606). No statistically significant differences were noted in the frequency of adverse events between treatment groups. Secondary: Not reported
Stryjewski et al.[78] (2005) Telavancin 7.5 mg/kg IV once daily vs standard therapy (nafcillin or oxacillin 2 g IV every 6 hours, cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV BID)	AC, DB, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=167 7 to 14 days posttreatment	Primary: Clinical response, microbiological response, safety Secondary: Not reported	Primary: The median duration of treatment was seven days in both groups. At the test-of-cure visit (seven to 14 days after the last dose of study medication), cure rates were 79% with telavancin and 80% with standard therapy (P=0.53). At the test-of-cure visit, 7% of patients receiving telavancin failed treatment compared to 4% of patients in the standard therapy group (no P value reported). For patients with S. *aureus* infection at baseline, 80% of patients in the telavancin group were cured and 77% of patients in the standard therapy group were cured (P=0.80). For patients with MRSA infection at baseline, cure rates were 82% for the telavancin group and 69% for the standard therapy group (P=1.00).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A similar percentage of patients in each group (5%) discontinued therapy due to adverse events. Fewer serious adverse events were reported in the telavancin group than were for the standard therapy group. Secondary: Not reported
Stryjewski et al.[79] (2006) Telavancin 10 mg/kg IV once daily vs standard therapy (nafcillin or oxacillin 2 g IV every 6 hours, cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV BID)	AC, DB, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=195 7 to 14 days posttreatment	Primary: Clinical cure in the clinically evaluable population, microbiological response, safety Secondary: Not reported	Primary: Overall, at the test-of-cure visit (seven to 14 days after the last dose of study medication), cure rates were 82% with telavancin and 85% with standard therapy (P=0.37). Overall, at the test-of-cure visit, 3% of patients receiving telavancin failed treatment compared to 6% of patients in the standard therapy group (no P value reported). In the clinically evaluable population at the test-of-cure visit, 96% of patients in the telavancin group and 94% of patients in the standard therapy group were cured (P=0.53). In the microbiologically evaluable population at the test-of-cure visit, 97% of patients in the telavancin group and 93% of patients in the standard therapy group were cured (P=0.37). In the microbiologically evaluable patients with *Staphylococcus aureus* at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.36). In the microbiologically evaluable patients with MRSA at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.42). Among the microbiologically evaluable population, baseline pathogens were considered eradicated at the EOT in 89% of patients in the telavancin group and in 77% of patients in the standard-therapy group (P=0.09). At test-of-cure, pathogen eradication was higher, although not significantly, in those patients receiving telavancin (94 vs 83%; P=0.06). In patients with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Staphylococcus aureus at baseline, eradication at test-of-cure was obtained in 92% of the patients receiving telavancin and 78% of the patients receiving standard therapy (P=0.07). In patients infected with MRSA, eradication rates were significantly higher in the telavancin group (92 vs 68%; P=0.04). Adverse events were reported in 56 and 57% of the patients receiving telavancin and standard therapy, respectively. Similar percentages of patients in both groups experienced severe adverse events (6 and 4% for the telavancin and standard therapy groups, respectively). Secondary: Not reported
Chuang et al.[80] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with complicated SSSIs	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to complicated SSSIs. No MRSA isolates were noted among Indian patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Corey et al.[81] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin and complicated skin and soft tissue infections who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA complicated skin and soft tissue infections was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[82] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin and soft tissue infections who required ≥5 days of parenteral	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftaroline 600 mg every 12 hours for 5 to 14 days	antibacterial therapy		evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	In patients with MRSA isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[83] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin and soft tissue infections who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			success rate, safety	Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Dryden et al.[84] COVERS (2016) Aztreonam 1 g every eight hours plus vancomycin 15 mg/kg every 12 hours vs ceftaroline 600 mg every eight hours	DB, MC, NI, RCT Patients ≥ 18 years of age with complicated SSSI and signs of systemic inflammatory response and/or underlying comorbidities associated with impair immune response	N=772 35 days after last dose of antibiotic therapy	Primary: Proportion of patients clinically cured at the test-of-cure visit (eight to 15 days after the last dose) in the co-primary clinically evaluable and modified intent-to-treat populations Secondary: Clinical response at test-of-cure in the microbiological modified intent-to-treat and microbiologically evaluable populations, clinical and per-pathogen microbiological response at test-of-cure in the	Primary: The proportion of patient clinically cured at the test-of-cure visit for the modified intent-to-treat population was 78.3% in the ceftaroline group compared with 79.2% in the vancomycin plus aztreonam group. In the clinically evaluable group, the proportion of patients clinically cured was 86.6 and 85.3%. Non-inferiority was demonstrated for the modified intent-to-treat (difference, -0.95%; 95% CI, -6.90 to 5.41) and clinically evaluable (difference, 1.27%; 95% CI, -4.32 to 7.48) populations. Secondary: Clinical response at the test-of-cure visit in the microbiological modified intent-to-treat population was 80.2 and 79.4% for the ceftaroline and vancomycin plus aztreonam groups, respectively and 90.1 and 86.6% in the microbiologically evaluable population. Microbiological responses were predominately derived from clinical responses; therefore, clinical and microbiological response rates were similar at test-of-cure by baseline pathogen and for patients with monomicrobial and polymicrobial infections. Among patients who were clinically cured at the test-of-cure visits, relapse at the late follow-up visits occurred in 0.9% of patients in the ceftaroline group and 1.7% of patients in the vancomycin plus aztreonam group. There were no new infections, reinfections or recurrences reported. The study treatments were generally well tolerated and the incidence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			microbiologically evaluable population, clinical relapse and reinfection or recurrence at the late follow-up visit, safety	adverse events was similar for the ceftaroline and vancomycin plus aztreonam groups (45.8 vs 45.5%).
Korczowski et al.[85] (2016) Ceftaroline fosamil IV vs IV comparator (vancomycin or cefazolin, plus optional aztreonam) optional switch to oral antibacterials from day four	MC, RCT, SB Hospitalized pediatric patients aged between two months and 17 years with acute bacterial SSSI	N=159 21 to 35 days	Primary: Safety Secondary: Clinical efficacy (at study day three [early clinical response], end of IV treatment, end of therapy, and test-of-cure [8 to 15 days after last dose])	Primary: A similar proportion of patients in each study group experienced at least one treatment-emergent adverse event (48% of patients in the ceftaroline fosamil group and 43% of patients in the comparator group). Rates of study drug-related treatment-emergent adverse events were similar for ceftaroline fosamil (22%) and comparator (23%). One serious adverse event, considered to be related to IV study drug, occurred in the ceftaroline fosamil group (hypersensitivity). A total of six patients discontinued study drug (IV or oral) because of an adverse event. There were four patients (4%) who discontinued ceftaroline fosamil because of adverse events: hypersensitivity, osteomyelitis, a gastrointestinal viral infection, and a rash. In the comparator group, two patients (4%) discontinued treatment because of adverse events of vomiting and drug hypersensitivity. Secondary: At Study Day three, the clinical response of a ≥20% reduction in infection area from baseline was seen in 85% of patients in both the ceftaroline fosamil and the comparator group. Clinical cure rates were numerically higher in the ceftaroline fosamil group compared with the comparator group at both the end of treatment (96 and 88%, respectively) and the test-of-cure visits (94 and 87%, respectively). Clinical cure rates were numerically higher in the ceftaroline fosamil group in all age groups. Of the patients clinically cured at test-of-cure, 98% reached sustained cure in the ceftaroline fosamil group, compared with 100% in the comparator group.
Pullman et al.[86] (2017)	AC, DB, MC, RCT Patients ≥18 years	N=660 28 days	Primary: Objective response at 48 to 72 hours (±	Primary: The percentage of responders at the 48 to 72 hours objective response assessment in the intent-to-treat population was 78.2% for delafloxacin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aztreonam 2 g IV every 12 hours plus vancomycin 15 mg/kg IV vs delafloxacin 300 mg IV every 12 hours	of age with acute bacterial SSSI		2 hours) following treatment initiation Secondary: Microbiological response in the microbiological intent-to-treat and microbiologically evaluable populations, safety	and 80.9% for vancomycin plus aztreonam (difference, -2.6%; 95% CI, -8.78 to 3.57), which met non-inferiority criteria. Secondary: In the microbiologically evaluable population at follow-up, microbiological responses were documented in 97.8 and 98.4% of patients treated with delafloxacin and vancomycin plus aztreonam, respectively. Treatment-emergent adverse events were observed in 47.5% in the delafloxacin group and 59.2% in the vancomycin plus aztreonam group. Treatment-emergent adverse events leading to drug discontinuation were higher in the vancomycin plus aztreonam group compared with the delafloxacin group, 4.3 and 0.9%, respectively.
Gastrointestinal Infections				
Kearney et al.[87] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H2) vs tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg	OL Patients with peptic ulcer disease or prescribed H2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05). The per-protocol cure rates for BMT-H2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H2 and MLC groups, and between BMT-PPI and BMT-H2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H2 and BMT-PPI treatment groups than the MLC group (P=0.049).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)				
Magaret et al.[88] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	MC, RCT Patients years of age failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[89] (2003) Tetracycline 500	RCT, XO Patients 18 to 80 years of age with at	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	least one previous failure of *H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin		urease test, or a validated 13C-urea breath test to confirm successful treatment Secondary: Not reported	Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60). Secondary: Not reported
Perri et al.[90] (2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group)	OL, PRO, RCT Patients with *H pylori* infection confirmed by 13C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative 13C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)				
Katelaris et al.[91] (2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days (BTM14)	MC, OL, PG, RCT Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and 13C-urea breath test	N=405 8 weeks	Primary: At week eight, 13C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analyses, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)				
Uygun et al.[92] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was NS (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[93] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line therapy (proton-pump inhibitor,	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary: Not reported	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95% CI, 74 to 92; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)	clarithromycin and amoxicillin)			A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[94] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				Secondary: Not reported
Malfertheiner et al.[95] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported
Zheng et al.[96] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(PAC)				
de Boer et al.[97] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[98] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump inhibitor clarithromycin and	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	amoxicillin for the treatment of *H pylori*		symptoms of endoscopic gastritis	
Luther et al.[99] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Steffen et al.[100] (2018) ERASE Rifamycin SV-MMX® 400 mg twice daily (RIF-	DB, MC, NI, RCT International adult visitors to India, Guatemala, or Ecuador with acute travelers' diarrhea	N=835 3 days	Primary: Time to last unformed stool Secondary: Clinical cure rate, treatment failure	Primary: Median time to last unformed stool in the RIF-MMX group was 42.8 h versus 36.8 h in the ciprofloxacin group indicating non-inferiority of RIF-MMX to ciprofloxacin (P=0.0035). Secondary: Secondary efficacy endpoint results confirmed those of the primary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MMX) vs ciprofloxacin 500 mg twice daily			rate, requirement of rescue therapy, microbiological eradication rate	analysis indicating equal efficacy for both compounds. While patients receiving ciprofloxacin showed a significant increase of Extended Spectrum Beta Lactamase Producing—*Escherichia coli* (ESBL-*E. Coli*) colonization rates after 3-days treatment (6.9%), rates did not increase in patients receiving RIF-MMX (−0.3%).
Hu et al.[101] (2012) Rifaximin	MA RCTs of rifaximin for the prevention of travelers' diarrhoea published in PubMed, the Cochrane Central Register of Controlled Trials, Embase, and the Science Citation Index were searched	N=502 Duration varied	Primary: Occurrence of travelers' diarrhoea over a two-week treatment period. Secondary: Requirement for antibiotic treatment, occurrence of mild diarrhea, occurrence of travelers' diarrhoea in the third week after drug withdrawal, incidence of travelers' diarrhoea associated with isolation of diarrheagenic *Escherichia coli* and adverse events	Primary: Rifaximin treatment showed a significant protection against travelers' diarrhoea (RR, 0.41; 95% CI, 0.30 to 0.56; P<0.00001). Secondary: Rifaximin treatment resulted in less antibiotic-treated travelers' diarrhoea (RR, 0.30; 95% CI, 0.18 to 0.49; P<0.00001). There was no significant difference between rifaximin and placebo in the occurrence of mild diarrhoea (RR, 1.11; 95% CI, 0.78 to 1.59; P=0.55) and the occurrence of travelers' diarrhoea in the third week after drug withdrawal (RR, 0.73; 95% CI, 0.30 to 1.73; P=0.47). Enterotoxigenic *Escherichia coli* was the major cause of travelers' diarrhoea, and all trials reported no differences in adverse events between rifaximin and placebo.
Pimentel et al.[102] (2011) TARGET 1 TARGET 2 Rifaximin 550 mg	DB, PC, RCT (2 trials) Patients ≥18 years of age with irritable bowel syndrome without constipation	N=1,260 12 weeks	Primary: Proportion of patients who had adequate relief of global irritable bowel syndrome symptoms (weeks	Primary: Significantly more patients in the rifaximin group than in the placebo group experienced adequate relief of global irritable bowel syndrome symptoms during at least 2 of the first 4 weeks after treatment (40.8 vs 31.2%; P=0.01, in TARGET 1; 40.6 vs 32.2%; P=0.03, in TARGET 2; 40.7 vs 31.7%; P<0.001, in the two studies combined).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID daily for 14 days vs placebo			three through six) Secondary: Proportion of patients who had adequate relief of irritable bowel syndrome related bloating, percentage of patients who had a response to treatment as assessed by daily self-ratings of global irritable bowel syndrome symptoms and individual symptoms of bloating, abdominal pain, and stool consistency	The proportion of patients with a response to treatment was significantly greater in the rifaximin group than in the placebo group (42.7 vs 30.6%; P<0.001, in TARGET 1; 37.8 vs 28.4%; P=0.007, in TARGET 2; 40.2 vs 29.5%; P<0.001, in the two studies combined). Secondary: More patients in the rifaximin group than in the placebo group had adequate relief of bloating during at least two of the first four weeks after treatment (39.5 vs 28.7%; P=0.005, in TARGET 1; 41.0 vs 31.9%; P=0.02, in TARGET 2; 40.2 vs 30.3%; P<0.001, in the two studies combined). A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of irritable bowel syndrome-related bloating (39.2 vs 32.5%; P=0.05, in TARGET 1; 43.5 vs 30.9%; P<0.001, in TARGET 2; 41.3 vs 31.7%; P<0.001, in the two studies combined). A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of irritable bowel syndrome-related abdominal pain and discomfort during the primary evaluation period (44.3 vs 36.3%; P=0.03, in TARGET 1; 42.9 vs 34.4%; P=0.02, in TARGET 2). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period (46.6 vs 38.5%; P=0.04, in TARGET 1; 46.7 vs 36.3%; P=0.008, in TARGET 2), and a significantly greater proportion of patients in the rifaximin group had relief with respect to the individual components of this end point. More patients in the rifaximin group than in the placebo group in both studies had adequate relief of global irritable bowel syndrome symptoms within the first month, with continued relief during the first two months and during all three months in both studies (P=0.05 in TARGET 1, P=0.005 in TARGET 2, and P<0.001 in the two studies combined, for relief during all three months). Patients treated with rifaximin had adequate relief of global irritable bowel

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				syndrome symptoms during the entire three months of the study compared to placebo (P=0.003 in TARGET 1, P=0.01 in TARGET 2, and P<0.001 in the two studies combined) and of IBS-related bloating compared to placebo (P=0.01 in TARGET 1, P<0.001 in TARGET 2, and P<0.001 in the two studies combined). The incidence of adverse events was similar in the two groups.
Martinez-Sandoval et al.[103] (2010) Rifaximin 600 mg once daily for 2 weeks vs placebo	DB, MC, RCT Healthy students ≥18 years of age attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico	N=210 2 weeks	Primary: Occurrence of travelers' diarrhea Secondary: Incidence of travelers' diarrhea resulting from all causes; incidence of travelers' diarrhea associated with diarrheagenic *Escherichia coli*; incidence of travelers' diarrhea associated with invasive bacterial pathogens; incidence of travelers' diarrhea occurring in the seven-day follow-up period; protection rates against travelers' diarrhea, travelers' diarrhea associated with diarrheagenic *Escherichia coli*,	Primary: Prophylactic treatment with rifaximin significantly reduced the risk of developing travelers' diarrhea compared to placebo (15 vs 47%, respectively; P<0.0001). Secondary: A smaller percentage of patients who received rifaximin developed travelers' diarrhea (20%) compared to those who received placebo (48%; P<0.0001). A smaller percentage of patients who developed travelers' diarrhea in the rifaximin group received rescue therapy compared to placebo (14 vs 32%, respectively; P=0.003). There was no significant difference in the percentage of patients who developed travelers' diarrhea associated with diarrheagenic *Escherichia coli* with rifaximin compared to placebo (9 vs 18%, respectively; P=0.098). Travelers' diarrhea was not associated with invasive bacterial pathogens in any patient. The percentage of individuals who developed travelers' diarrhea associated with unidentified pathogens was significantly lower in the rifaximin vs placebo group (11 vs 30%, respectively; P=0.01). A greater percentage of patients who received rifaximin completed the 14-day treatment course without developing travelers' diarrhea (76%) compared to those who received placebo (51%; P=0.0004). The percentage of patients who experienced mild diarrhea, but did not develop travelers' diarrhea, was similar between the rifaximin and placebo groups (29 vs 21%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and travelers' diarrhea associated with invasive bacterial pathogens; number of participants with symptoms of enteric infection and mild diarrhea without travelers' diarrhea	During the seven-day post-treatment period, the percentage of patients who developed travelers' diarrhea was similar for rifaximin (16%) vs placebo (15%). The protection rates achieved with rifaximin prophylaxis were similar for travelers' diarrhea (58%; 95% CI, 35 to 73) and travelers' diarrhea requiring rescue antibiotic therapy (56%; 95% CI, 23 to 75).
Zanger et al.[104] (2013) Rifaximin 200 mg tablets BID vs placebo	DB, PC, PG, SC Individuals 18 to 64 years of age who were planning a 6 to 28 day journey to south and southeast Asia	N=239 Duration varied	Primary: Time to the first episode of classic travelers' diarrhoea, defined as three or more loose stools in 24 hours, accompanied by one or more enteric symptoms. Secondary: Not reported	Primary: Forty-eight (41%) of 117 participants in the placebo group and 30 (25%) of 122 in the rifaximin group reported classic episodes of travelers' diarrhoea. From departure to seven days after return, rifaximin provided 48% protection (95% CI, 16 to 68) by lowering the incidence of travelers' diarrhoea from 199 (150 to 264) per 100 person-days in the placebo group to 104 (072 to 148) in the intervention group (incidence rate ratio, 052; 95% CI, 032 to 084; P=0005). The number needed to treat was 570 (95% CI, 344 to 1,669) to prevent one case of classic travelers' diarrhoea during the first three weeks of follow-up. Secondary: Not reported
Steffen et al.[105] (2003) Rifaximin 600 mg TID vs rifaximin 1,200 mg TID	DB, MC, PG, RCT Adult travelers affected by acute diarrhea with at least one sign of enteric infection	N=380 Treatment: 3 days Follow-up: 5 days	Primary: Time elapsed from ingestion of first dose to passage of the last unformed stool; wellness (clinical cure) Secondary: Number of subjects with	Primary: Median time to last unformed stool was 32.5 and 32.9 hours for rifaximin 600 and 1,200 mg, respectively, compared to 60 hours for placebo (P=0.0001 for each treatment group vs placebo). Clinical cure within 120 hours was noted at a greater rate with rifaximin 600 and 1,200 mg (79.2 and 81.0%, respectively) compared to placebo (60.5%; P=0.001 for each treatment group vs placebo). Secondary: Improvement of diarrhea was greater in the rifaximin 600 mg group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			improvement of diarrhea during 24 hour intervals, number of unformed stools passed per time interval, number of subjects declared "well," treatment failures, and microbiological cure	compared to placebo. In the 24 to 48 hour interval, improvement was seen in 87% of patients given rifaximin 600 mg and 72% in placebo-treated patients (P=0.007); in the 48 to 72 hour interval, improvement was seen in 91% of patients given rifaximin 600 mg and 78% in placebo-treated patients (P=0.008). Although the rate of improvement was greater than placebo overall, the differences did not reach statistical significance. Mean number of unformed stools passed was 3.1 for rifaximin groups vs 3.8 for placebo (day one), 1.6 for rifaximin groups vs 2.6 for placebo (day 2), 0.5 for rifaximin groups vs 0.9 for placebo (final day; P=0.001, repeated measures analysis of variance). Treatment failures were noted 16.0 to 16.7% of the time with both rifaximin groups vs 34.8% with placebo-treated patients (P=0.001). Rate of microbiological cure was not significantly different across treatment groups. The most common adverse events were gastrointestinal related. Headache was also frequently reported, though with no difference between groups. Fatigue was reported more often with rifaximin 1,200 mg (1.1%; P=0.023).
Dupont et al.[106] (2005) Rifaximin 200 mg once daily vs rifaximin 200 mg BID vs rifaximin 200 mg TID	DB, PC, RCT Healthy students ≥18 years of age attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico	N=210 2 weeks	Primary: Occurrence of diarrhea Secondary: Occurrence of mild diarrhea (defined as passage of one to two unformed stools plus a symptom) and number of days of occurrences of moderate to severe enteric	Primary: Over the two week treatment period, diarrhea developed in 53.7% of patients in the placebo group, 12% of patients in the once-daily rifaximin group (RR, 0.22; 95% CI, 0.10 to 0.49), 19.23% of patients in the rifaximin BID group (RR, 0.36; 95% CI, 0.19 to 0.66), 12.96% of patients in the rifaximin TID group (RR, 0.24; 95% CI, 0.12 to 0.50), and 14.74% of the combined rifaximin groups (RR, 0.27; 95% CI, 0.17 to 0.43). Diarrhea was prevented in all of the rifaximin groups (P<0.001 for each rifaximin group vs placebo). The protection rates were 72 and 77% against travelers' diarrhea and antibiotic-treated diarrhea, respectively (P<0.001 for both). Secondary: Rifaximin reduced the occurrence of mild diarrhea compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			symptoms per 100 person-days of observation	(P=0.02). In those who did not develop diarrhea, rifaximin significantly reduced the occurrence of moderate and severe intestinal problems (P=0.009 for pain or cramps; P=0.02 for excessive gas) compared to placebo. The incidence of adverse events was comparable between the rifaximin groups and the placebo group.
DuPont et al.[107] (2007) Rifaximin 200 mg TID for 3 days vs loperamide 4 mg initially, followed by 2 mg after each unformed stool vs rifaximin 200 mg TID for 3 days plus loperamide 4 mg initially, followed by 2 mg after each unformed stool	RCT Adults with acute diarrhea (≥3 unformed stools in 24 hours) with ≥ 1 symptom of enteric infection	N=310 5 days	Primary: Median time from beginning therapy until passing the last unformed stool Secondary: Not reported	Primary: Rifaximin and rifaximin-loperamide significantly reduced the median time until passage of the last unformed stool (32.5 and 27.3 hours, respectively) compared to loperamide (69 hours; P=0.0019). The mean number of unformed stools passed during illness was lower with rifaximin-loperamide (3.99) compared to rifaximin (6.23; P=0.004) or loperamide alone (6.72; P=0.002). All treatments were well tolerated with a low incidence of adverse events. Secondary: Not reported
Louie et al.[108] (2011) Fidaxomicin 200 mg BID for 10 days	DB, MC, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *Clostridium difficile* infection, as well as	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium*	Primary: Clinical cure rates in the modified intent to treat analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the per protocol analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin 125 mg orally QID for 10 days	the presence of *Clostridium difficile* toxin A, B, or both in the stool		*difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within four weeks after treatment)	Secondary: Recurrence in the modified intent to treat analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the per protocol analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.
Cornely, Crook et al.[109] (2012) Fidaxomicin 200 mg every 12 hours for 10 days vs vancomycin 125 mg orally every 6 hours daily for 10 days	DB, MC, PRO, RCT Patients ≥16 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=535 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30days of treatment	Primary: In the per protocol population, clinical cure rates in the fidaxomicin group (91.7%) were non-inferior to the rates in the vancomycin group (90.6%; one-sided 97.5% CI, -4.3). In the modified intent to treat population, clinical cure rates in the fidaxomicin group (87.7%) were non-inferior to the rates in the vancomycin group (86.8%; treatment difference, 0.9; 95% CI, -4.9 to 6.7; P=0.754). Secondary: In the modified intent to treat population, significantly more patients in the vancomycin group had a recurrence compared to the fidaxomicin group (26.9 vs 12.7%; treatment difference, -14.2; 95% CI, -21.4 to -6.8; P=0.0002). In this population, there was a significantly higher rate of sustained clinical response in the fidaxomicin group compared to the vancomycin group (76.6 vs 63.4%; treatment difference, 13.2; 95% CI, 5.3 to 21.0; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			completion)	
Cornely, Miller et al.[110] (2012) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, PRO, RCT Patients >15 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=178 28 days posttreatment	Primary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30 days of treatment completion) Secondary: Not reported	Primary: In patients with no prior episode of *Clostridium difficile* infection, there was a significantly greater proportion of patients in the vancomycin group (24.8%) that had a recurrence compared to the fidaxomicin group (12.9%; treatment difference, -11.8; 95% CI, 17.1 to 6.5; P<0.001). In patients with one prior episode of *Clostridium difficile* infection, there was no significant difference in recurrence between the vancomycin and fidaxomicin groups (32.3 vs 20.3%; treatment difference -12.3; 95% CI, -25.4 to 1.5; P=0.08). Secondary: Not reported
McFarland et al.[111] (2002) Vancomycin ≤1 g to ≥2 g orally per day; taper, pulse, or combination with another antimicrobial vs metronidazole ≤1 g to 2 g PO per day; taper or pulse	DB, PC, RCT (2 trials) Patients 18 to 91 years of age with recurrent episodes of *Clostridium difficile* disease; ≥1 prior episode within 1 year	N=163 2-4 months	Primary: Incidence of another *Clostridium difficile* recurrence during study subsequent to the enrollment episode, or incidence of cure (i.e., absence of recurrence) two months after antibiotic treatment Secondary: Not reported	Primary: *Clostridium difficile* was cleared in 89% of the vancomycin group vs 59% of the metronidazole group (P<0.001). Tapered and pulsed dose courses of vancomycin resulted in fewer recurrences than metronidazole (P=0.01 and P=0.02, respectively). Overall failure rates did not differ significantly (P=0.77). Secondary: Not reported
Bricker et al.[112] (2005) Vancomycin oral	MA of RCTs Patients with diarrhea who recently received	N=582 Variable duration	Primary: Initial resolution of diarrhea, initial conversion of stool to *Clostridium*	Primary: For initial symptomatic resolution, metronidazole, bacitracin, teicoplanin, fusidic acid, and rifaximin were as effective as vancomycin. Vancomycin was more effective than placebo (P=0.03) in a small study (N=21).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metronidazole or bacitracin or fusidic acid* or teicoplanin* or rifaximin vs placebo	antibiotics for an infection other than *Clostridium difficile*		*difficile* cytotoxin and/or stool culture negative, recurrence of diarrhea, recurrence of fecal *Clostridium difficile* cytotoxin and/or positive stool culture, patient response to cessation of prior antibiotic therapy Secondary: Rates of sepsis, emergent surgery, fecal diversion or colectomy, and death	With regards to symptomatic cure, metronidazole, bacitracin and fusidic acid were found similar to vancomycin. Teicoplanin was slightly more effective than vancomycin (P=0.06). For initial bacteriologic resolution, vancomycin was more effective than placebo (P=0.03); teicoplanin was more effective than vancomycin (P=0.002); and metronidazole, fusidic acid, and rifaximin were as effective as vancomycin (P=0.008). In terms of bacteriologic cure, in comparison with vancomycin, teicoplanin was more effective (P=0.006), metronidazole was as effective (P=0.07), and fusidic acid was less effective (P=0.01). Patients were retreated in various ways, which made it difficult to compare the antibacterials for efficacy. There were a total of 9 deaths, 5 of which were specified to be due to underlying illness and not related to treatment. Secondary: These end points occurred infrequently in all of the studies.
Zar et al.[113] (2007) Vancomycin 125 mg orally QID for 10 days vs metronidazole 250 mg orally QID for 10 days	DB, PC, RCT Patients with *Clostridium difficile*-associated diarrhea	N=172 21 days	Primary: Clinical cure Secondary: Not reported	Primary: Among the patients with mild *Clostridium difficile*-associated diarrhea, treatment with metronidazole or vancomycin resulted in clinical cure in 90 and 98% of the patients, respectively (P=0.36). Among the patients with severe *Clostridium difficile*-associated diarrhea, treatment with metronidazole or vancomycin resulted in clinical cure in 76 and 97% of the patients, respectively (P=0.02). Clinical symptoms recurred in 15% of the patients treated with metronidazole and 14% of those treated with vancomycin. Secondary: Not reported
Nelson[114] (2007)	MA	N=1157 (12 RCT)	Primary: Clinical cure	Primary: No single antibiotic was clearly superior to others. Teicoplanin showed in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vancomycin vs metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin	Patients with *Clostridium difficile*-associated diarrhea	Variable duration	Secondary: Not reported	some outcomes significant benefit over vancomycin and fusidic acid, and a trend towards benefit compared to metronidazole. Only one placebo controlled trial was done and no conclusions can be drawn from it due to small size and classification error. Only one study investigated synergistic antibiotic combination, metronidazole and rifampin, and there was no advantage to the drug combination. Secondary: Not reported
Song et al.[115] (1998) Gentamicin plus metronidazole vs cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic	MA Patients scheduled to undergo elective surgery of the colon	147 trials 12 years	Primary: Rate of surgical wound infections Secondary: Not reported	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR, 1.17; 95% CI, 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR, 1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
agents as monotherapy or combination therapy				
Genitourinary Infections				
Ugwumadu et al.[116] (2003) Clindamycin 300 mg orally BID vs placebo	DB, PC, RCT Pregnant women ≥12 to 22 weeks gestation with abnormal vaginal flora or bacterial vaginosis	N=485 5 days	Primary: Spontaneous preterm delivery (birth ≥24 but <37 weeks) and late miscarriage (pregnancy loss ≥13 but <24 weeks) Secondary: Not reported	Primary: Incidence of spontaneous preterm delivery was 11/244 (5%) in the clindamycin group vs 28/241(12%) in the placebo group; incidence of miscarriage was 2/244 (1%) in the clindamycin group vs 10/241(4%) in the placebo group (P=0.001 for both). Overall, women receiving clindamycin had significantly fewer miscarriages or spontaneous preterm deliveries than did those in the placebo group. Adverse events included gastrointestinal upset (five patients receiving clindamycin vs 10 receiving placebo), rash (one patient receiving clindamycin vs two receiving placebo), vulvovaginal candidiasis (one patient receiving clindamycin vs one receiving placebo), throat irritation (one patient receiving placebo), and headache (four patients receiving clindamycin vs one receiving placebo). Overall, there was no statistically significant difference in reported adverse events (P=0.10). Secondary: Not reported
Hepatic Encephalopathy				
Sidhu et al.[117] (2011) Rifaximin 400 mg TID for 8 weeks vs placebo	DB, PC, RCT Patients 18 to 65 years of age with cirrhosis and minimal hepatic encephalopathy	N=284 8 weeks	Primary: Reversal of minimal hepatic encephalopathy at eight weeks Secondary: Not reported	Primary: In the intent-to-treat analysis, the percentage of patients showing reversal of minimal hepatic encephalopathy was significantly higher in rifaximin group than in the placebo group (75.5 vs 20.0%, respectively; P<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bass et al.[118] (2010) Rifaximin 550 mg BID vs placebo Concomitant use of lactulose was allowed throughout the study.	DB, PC, RCT Patients ≥18 years of age who had ≥2 episodes of overt hepatic encephalopathy (Conn score, ≥2) associated with hepatic cirrhosis during the previous 6 months, remission (Conn score, 0 or 1) at enrollment, and a score of ≤25 on the Model for End-Stage Liver Disease scale	N=299 6 months	Primary: Time to the first breakthrough episode of hepatic encephalopathy Secondary: Time to the first hospitalization involving hepatic encephalopathy and safety	Primary: Breakthrough episodes of hepatic encephalopathy were reported in 22.1% of patients receiving rifaximin and 45.9% of patients in the placebo group (HR, 0.42; 95% CI, 0.28 to 0.64; P<0.001). Four patients would need to be treated with rifaximin for 6 months to prevent one episode of overt hepatic encephalopathy. Secondary: Hospitalization involving hepatic encephalopathy occurred in 13.6% of patients receiving rifaximin and 22.6% of patients receiving placebo (HR, 0.50; 95% CI, 0.29 to 0.87; P=0.01). Nine patients would need to be treated with rifaximin for six months to prevent one hospitalization involving hepatic encephalopathy. The incidence of adverse events reported during the study was similar in the rifaximin group (80.0%) and the placebo group (79.9%). A total of 20 patients died during the study (9 in the rifaximin group and 11 in the placebo group). Most of the deaths were attributed to conditions associated with disease progression.
Williams et al.[119] (2000) Rifaximin 200 mg TID vs rifaximin 400 mg TID vs rifaximin 800 mg TID	DB, MC, PG, RCT Patients with cirrhosis and mild to moderate hepatic encephalopathy who had experienced recent deterioration in their neuropsychiatric status	N=54 7 days	Primary: Change in the portal-systemic encephalopathy index (calculated on the basis of asterixis, number connection test time Secondary: Not reported	Primary: There was a significant reduction in the mean portal-systemic encephalopathy index in the rifaximin 1,200 and 2,400 mg/day groups (95% CI, -17.4 to -3.1 and -17.8 to -3.6, respectively). Mean values for blood ammonia levels on days one and seven, respectively, were 132.8 and 107.1 in the rifaximin 600 mg/day group, 143.5 and 143.0 in the 1,200 mg/day group, and 183.3 and 188.6 in the 2,400 mg/day group. Rifaximin was well tolerated. Nausea and gastrointestinal system disorders were the most frequent adverse events. Secondary: Not reported
Bucci et al.[120] (1993)	DB, RCT Patients 42 to 60	N=58 15 days	Primary: Mental status using Parsons-Smith	Primary: There was an improvement in cognitive function in both groups. Patients receiving rifaximin had a significant improvement starting on day six

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifaximin 400 mg TID vs lactulose 10 g TID	years of age with cirrhosis and signs/symptoms of portosystemic encephalopathy		point scale, presence of asterixis, 'A' cancellation test, Reitan test, electro-encephalographic irregularities, adverse events Secondary: Not reported	(P<0.05), and those receiving lactulose had a significant improvement starting on day 12 (P<0.01). Starting on day nine, the comparison between the two groups was significantly in favor of rifaximin (P<0.01). The presence of asterixis decreased in both groups. There was a significant difference for both treatments starting on day nine compared to baseline (P<0.01). There was no significant difference between the groups. The 'A' cancellation test showed a progressive improvement in the two groups. The difference became significant starting on day six with rifaximin and day nine with lactulose compared to baseline. The Reitan test showed good recovery of manipulation. There was no significant difference between the treatment groups. Improvement was noted starting on day nine in both groups. There was a significant improvement in electroencephalographic irregularities at day six with rifaximin and day nine with lactulose. The difference between the two treatment groups was significant on day six (P<0.05), as well as days 12 and 15 (P<0.01). There was a significant reduction in fasting ammonia levels beginning on day five. Levels were normal after seven days with both treatments. The comparison between the two treatments was significantly in favor of rifaximin on days three, five and 12 (P<0.05). Diarrhea, flatulence and dyspepsia appeared in 50% of patients treated with lactulose. In those treated with rifaximin, the frequency and severity of the adverse events was minimal. Body weight decreased in 28.6% of those treated with lactulose and in 6.7% of those treated with rifaximin.
Paik et al.[121] (2005) Rifaximin 400 mg TID vs	OL, RCT In-patients with episodic hepatic encephalopathy who had decompensated liver cirrhosis and	N=54 7 days	Primary: Grade of mental state, severity of flapping tremor, number connection test, blood ammonia levels,	Primary: Mean blood levels and grades of blood NH_3 significantly decreased with rifaximin (P<0.01) and lactulose (P<0.01). Mean blood NH_3 concentrations were similar after both treatments. Mental state was significantly improved by rifaximin and by lactulose (P<0.01 and P<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lactulose 90 mL/day	stage 1 to 3 hepatic encephalopathy (according to Conn's modification of Parsons-Smith classification) and serum ammonia levels >75 µmol/L		hepatic encephalopathy index, and efficacy of treatment Secondary: Not reported	Grades of flapping tremor and number connection test were improved to a similar degree by rifaximin and lactulose. Mean hepatic encephalopathy indexes improved in the rifaximin group (P=0.000) and in the lactulose group (P=0.000). There was no significant difference between the treatment groups. Blood NH_3 and hepatic encephalopathy grades improved in 78.1% and 81.3%, respectively, of the patients in the rifaximin group. In the lactulose group, 59.1% of the patients showed reduced blood ammonia grades and 72.7% showed improved hepatic encephalopathy grades. There was no significant difference between the treatment groups. Rifaximin was considered effective in 84.4% of patients and lactulose was considered effective in 95.4% of patients (P=0.315). One patient treated with rifaximin complained of abdominal pain, and one patient treated with lactulose experienced severe diarrhea. Secondary: Not reported
Neff et al.[122] (2006) Rifaximin 1,200 mg/day vs lactulose 60 g/day, titrated as necessary	RETRO Patients with end-stage liver disease and stage 1 or 2 hepatic encephalopathy	N=39 Variable duration	Primary: Hospitalizations and length of stay Secondary: Not reported	Primary: There were 19 total hospitalizations in the lactulose group (nine patients) and three hospitalizations in the rifaximin group. The average length of stay was shorter in the rifaximin group at 3.5 days compared to 5.0 days in the lactulose group (P<0.0001). Secondary: Not reported
Leevy et al.[123] (2007) Lactulose 30 mL	RETRO Patients with hepatic	N=146 ≥6 months	Primary: Mean number of hospitalizations during each	Primary: There were fewer hospitalizations during the rifaximin period compared to the lactulose period (0.5 vs 1.6; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for ≥6 months, then rifaximin 400 mg TID for ≥6 months	encephalopathy		treatment period Secondary: Average length of hospitalization, mean total time hospitalized, clinical status	Secondary: There were fewer days of hospitalization (2.5 vs 7.3; P<0.001) and fewer total weeks hospitalized (0.4 vs 1.8; P<0.001) during the rifaximin period compared to the lactulose period. Hepatic encephalopathy grade at the end of each treatment period reflected less severe illness with rifaximin than with lactulose (P<0.001). The percentage of patients with stage 3 or 4 hepatic encephalopathy was 6% with rifaximin and 25%with lactulose. Significantly fewer patients had asterixis at the end of the rifaximin period (63%) than the lactulose period (93%; P<0.001). The percentages of patients with diarrhea, flatulence, and abdominal pain were significantly higher during the lactulose period than the rifaximin period (all, P<0.001). The percentage of patients with headache did not differ between treatment periods (P=0.718).
Mas et al.[124] (2003) Rifaximin 400 mg TID vs lactitol 20 g TID	DB, RCT Patients with grade I to III acute hepatic encephalopathy for <2 days duration and a portal-systemic encephalopathy index higher than zero	N=103 5 to 10 days	Primary: Efficacy and safety Secondary: Not reported	Primary: There were significant improvements in hepatic encephalopathy endpoints and ammonemia levels following treatment with rifaximin and lactitol. There was no significant difference between the treatment groups at the EOT (hepatic encephalopathy grade, P=0.9211; mental state, P=0.8480; asterixis, P=0.3177). The overall portal-systemic encephalopathy index decreased more progressively in the rifaximin group than in the lactitol group (P<0.01). With regards to the global assessment of efficacy at the end of treatment; both groups showed a similar clinical efficacy without significant differences. After grouping the responses into two classes (resolution/improvement vs unchanged/failure), the results were similar in both groups: 81.6 vs 18.4%, respectively, in the rifaximin group and 80.4 vs 19.6%, respectively, in the lactitol group. The percentage of patients with complete hepatic encephalopathy resolution was higher in the rifaximin group (53.1%) than in the lactitol group (37.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatments were well tolerated. In the rifaximin group, two patients reported mild diarrhea and one patient reported abdominal pain. In the lactitol group, one patient reported mild diarrhea and one described vomiting.
Jiang et al.[125] (2008) Rifaximin vs nonabsorbable disaccharides	MA Patients ≥18 years of age with serum ammonia levels ≥75 µmol/L, signs and symptoms of acute, chronic, or minimal hepatic encephalopathy	N=264 (5 trials) Variable duration	Primary: Clinical efficacy Secondary: Adverse events	Primary: There was no significant difference in clinical efficacy for hepatic encephalopathy between rifaximin and nonabsorbable disaccharides (RR, 1.08; 95% CI, 0.85 to 1.38; P=0.53). Secondary: Diarrhea and abdominal pain were the most frequently reported adverse events. There was no difference in diarrhea between the treatment groups (RR, 0.90; 95% CI, 0.17 to 4.70; P=0.90). A significant difference on abdominal pain was noted (RR, 0.28; 95% CI, 0.08 to 0.95; P=0.04).
Festi et al.[126] (1993) <u>Study 1</u> Rifaximin 1,200 mg/day for 21 days <u>Study 2</u> Rifaximin 1,200 mg/day for 21 days vs neomycin 3,000 mg/day for 21 days <u>Study 3</u> Rifaximin 1,200 mg/day for 21 days vs	OL (Study 1), RCT (Study 2 and 3) Patients 40 to 75 years of age with clinical and biochemical signs of mild hepatic encephalopathy and liver cirrhosis	N=136 21 days	Primary: Neurological signs, electro-encephalographic abnormalities, ammonia levels Secondary: Not reported	Primary: <u>Study 1</u> Rifaximin significantly reduced the frequency of neurologic signs. After five days of treatment, the percentage of patients who exhibited asterixis was significantly lower than at baseline; after 15 days of treatment, no patients showed this neurologic sign. After seven days, a significantly lower percentage of patients exhibited electroencephalography abnormalities. Blood ammonia levels were significantly improved with rifaximin after five days. Blood ammonia concentrations reached normal values and remained within the normal range throughout the study. <u>Study 2</u> Both rifaximin and neomycin reduced the neurologic signs of hepatic encephalopathy, but at different rates. Treatment with rifaximin led to a significant reduction in the frequency of asterixis after three days compared to five days with neomycin. A significantly lower percentage of patients exhibited electro-encephalographic abnormalities with rifaximin and neomycin compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lactulose 40 g/day for 21 days				baseline (P<0.001). Ammonia levels were significantly reduced by rifaximin and neomycin. Normal values were achieved after seven days of treatment. <u>Study 3</u> Both rifaximin and lactulose reduced the neurologic signs of hepatic encephalopathy compared to baseline (P<0.05). Electro-encephalographic abnormalities significantly decreased in frequency with rifaximin and lactulose compared to baseline. Ammonia levels were significantly decreased with both treatments (P<0.01). Secondary: Not reported
Miglio et al.[127] (1997) Rifaximin 400 mg TID for 14 days each month vs neomycin 1 g TID for 14 days each month	DB, RCT Patients with cirrhosis and chronic hepatic encephalopathy of grade 1 or 2	N=60 6 months	Primary: Improvement of at least one grade of hepatic encephalopathy, neurological signs, Reitan test, ammonia levels, liver function tests Secondary: Not reported	Primary: There was a progressive reduction in hepatic encephalopathy grade with rifaximin and neomycin. There was no significant difference between the two treatment groups. The improvement in hepatic encephalopathy was significant after 30 days (P<0.001 for each group). In both groups, the disturbances in speech, memory, behavior and mood, gait, asterixis, writing, serial subtraction of 7s and five-pointed star tests showed the highest improvement (P<0.001). The Reitan test only showed a significant improvement in the rifaximin group (P<0.02). Blood ammonia levels were decreased from 210.2 to 88.9 µg/100 mL in the rifaximin group (P<0.001) and from 202.1 to 86.2 µg/100 mL in the neomycin group (P<0.001). There was no significant difference between the treatment groups. There were significant decreases in aspartate aminotransferase (P<0.02) and alanine transaminase (P<0.01 in the rifaximin group and P<0.03 in the neomycin group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Respiratory Infections				
File et al.[128] (2019) LEAP 1 Lefamulin 150 mg IV every 12 hours vs moxifloxacin 400 mg IV every 24 hours Patients could be switched from IV to PO study drug (lefamulin 600 mg PO q12h or moxifloxacin 400 mg PO every 24h) at the investigator's discretion after six doses (≥3 days) of IV treatment if predefined criteria were met If MRSA was suspected, either linezolid or placebo was added to moxifloxacin or lefamulin,	AC, DB, DD, MC, PG Patients ≥18 years fulfilled the FDA entry criteria for CABP; having radiographic findings suggestive of pneumonia, PORT risk classes ≥III[†], acute illness ≤7 days, and ≥3 CABP symptoms (dyspnea, new or increased cough, purulent sputum production, chest pain)	N=551 10 days	Primary: ECR responder rate in the ITT population at 96 ± 24 hours after the first study drug dose Secondary: IACR at TOC (test of cure, 5 to 10 days after the last dose of the study drug) in mITT and CE populations, ECR in the microITT analysis set, IACR at TOC in the microITT and ME-TOC analysis sets, by-pathogen microbiological response at TOC in the microITT set and safety and tolerability	Primary: Lefamulin was non-inferior to moxifloxacin with or without adjunctive linezolid for ECR responder rate (87.3% vs 90.2%; 95% CI, −8.5 to 2.8). Secondary: Lefamulin was non-inferior to moxifloxacin with or without adjunctive linezolid for IACR success rate. For IACR at TOC in the mITT population, IACR success rate was 81.7% in the lefamulin group and 84.2% in the moxifloxacin ± linezolid group (treatment difference, −2.6%; 95% CI, −8.9 to 3.9). For IACR at TOC in CE population, the IACR success rate was 86.9% in the lefamulin group and 89.4% in the moxifloxacin ± linezolid group (treatment difference, −2.5%; 95% CI, −8.4 to 3.4). The ECR rate in the microITT analysis set was 87.4% in the lefamulin group and 93.1% in the moxifloxacin ± linezolid group (treatment difference, −5.7%; 95% CI, −12.8 to 1.5). The IACR success rate at TOC in the microITT analysis set was 79.9% in the lefamulin group and 85.5% in the moxifloxacin ± linezolid group (treatment difference, −5.7%; 95% CI, −14.1 to 2.8). The IACR success rate in the ME-TOC analysis set (which included all patients who met the criteria for inclusion in both the microITT and CE sets), was 83.9% in the lefamulin group and 90.1% in the moxifloxacin ± linezolid group (treatment difference, −6.2%; 95% CI, −14.3 to 1.9). ECR responder rates by baseline pathogen were generally high and similar between groups. ECR responder rates for the most frequently identified baseline pathogens in the microITT analysis set were *S. pneumoniae* (88.2% for lefamulin vs 93.8% for moxifloxacin ± linezolid), *H. influenzae* (92.2% for lefamulin vs 94.7% for moxifloxacin ± linezolid), *M. pneumoniae* (84.2% for lefamulin vs 90.0% for moxifloxacin ±

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
respectively				linezolid), *M. catarrhalis* (92.0% for lefamulin vs 100.0% for moxifloxacin ± linezolid), *L. pneumophila* (88.9% for lefamulin vs 85.7% for moxifloxacin ± linezolid), and *C. pneumoniae* (90.9% for lefamulin vs 94.7% for moxifloxacin ± linezolid). Responder rates for *S. aureus* were 100.0% in both groups. Overall, the rate of TEAEs was similar for the 2 treatment groups (38.1% and 37.7% for lefamulin and moxifloxacin ± linezolid, respectively), as was the rate of study drug-related TEAEs (15.0% and 14.3%, respectively). The most common study drug-related TEAEs in the lefamulin group were general disorders and administration site conditions (6.6%), while the most common study drug-related TEAEs in the moxifloxacin ± linezolid group were GI disorders (8.1%).
Alexander et al.[129] (2019) LEAP 2 Lefamulin 600 mg PO every 12 hours for five days vs moxifloxacin 400 mg PO every 24 hours for seven days	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age, acute illness of ≤7 days' duration with ≥3 symptoms of lower respiratory tract infection (dyspnea, new or increased cough, purulent sputum production, and chest pain due to pneumonia), ≥2 vital sign abnormalities (fever or hypothermia, hypotension, tachycardia, tachypnea), ≥1 other clinical sign or laboratory finding of CABP	N=738 7 days	Primary: Clinical response at 96 hours (within a 24-hour window) after the first dose of either study drug in the ITT population Secondary: IACR at TOC in the mITT population and in the CE population, ECR in the microITT analysis set, IACR at TOC in the microITT and ME-TOC analysis sets, by-pathogen microbiological response at TOC in the microITT and	Primary: ECR rates were 90.8% with lefamulin and 90.8% with moxifloxacin (difference, 0.1%; 1-sided 97.5%CI, –4.4% to ∞). Secondary: Rates of IACR success were 87.5% with lefamulin and 89.1% with moxifloxacin in the mITT population (difference, –1.6% [1-sided 97.5%CI, –6.3% to ∞and 89.7% and 93.6%, respectively]), and in the CE population (difference, –3.9%; 1-sided 97.5% CI, –8.2% to ∞) at TOC. The ECR responder rate in the microITT analysis set was 90.7% in the lefamulin group and 93.0% in the moxifloxacin group (treatment difference, −2.3%; 95% CI, −8.2 to 3.6). the IACR success rate at TOC in the microITT analysis set was 85.9% in the lefamulin group and 87.6% in the moxifloxacin group (treatment difference −1.8%; 95% CI: −8.7 to 5.1) The IACR success rate at TOC in the ME-TOC analysis set was 88.5% in the lefamulin group and 91.5% in the moxifloxacin group (treatment difference −3.0%; 95% CI: −9.4, 3.7). ECR responder rates by baseline pathogen were generally high and similar between groups. ECR responder rates for the most frequently identified baseline pathogens in the microITT analysis set were *S. pneumoniae* (89.4% for lefamulin vs 91.3% for moxifloxacin), *H. influenzae* (89.3%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(hypoxemia, auscultatory and/or percussion findings consistent with pneumonia, WBC count >10,000 cells/mm3 or <4,500 cells/mm3 or >15% immature neutrophils regardless of total WBC count), radiographically document pneumonia within 48 hours before enrollment, PORT Risk Class of II to IV†, and an appropriate candidate for oral antibiotic therapy.		ME-TOC analysis sets and safety and tolerability	for lefamulin vs 91.7% for moxifloxacin), *M. pneumoniae* (100% in both groups), *M. catarrhalis* (85.7% for lefamulin vs 100% for moxifloxacin), *L. pneumophila* (81.3% for lefamulin vs 94.1% for moxifloxacin), and *C. pneumoniae* (93.8% for lefamulin vs 100% for moxifloxacin). Responder rates for *S. aureus* were 100% in both groups. Overall, the rate of TEAEs was higher in the lefamulin group than in the moxifloxacin group (32.6% vs 25.0%, respectively), as was the rate of study drug-related TEAEs (15.8% vs 7.9%, respectively). At least one serious TEAE occurred in 17 (4.6%) and 18 (4.9%) patients in the lefamulin and moxifloxacin groups.
Rubinstein et al.[130] (2001) Linezolid 600 mg IV every 12 hours vs vancomycin 1 g IV every 12 hours Both regimens included aztreonam 1 to 2 g IV every 8 hours.	DB, MC, RCT Patients ≥18 years of age with nosocomial pneumonia	N=396 Treatment: 7 to 21 days Follow-up: 12 to 28 days posttreatment	Primary: Cure, failure, microbiological success or failure Secondary: Not reported	Primary: Rates of clinical cure for the intent-to-treat population were 53.4% (86/161) vs 52.1% (74/142) with linezolid and vancomycin, respectively (P=0.79). In the clinically evaluable population, clinical cure rate was 66.4% (71/107) with linezolid and 68.1% (62/91) with vancomycin (P=0.79). Microbiological success rate was 67.9% (36/53) with linezolid and 71.8% (28/39) with vancomycin (P=0.69). Safety assessments were done for the intent-to-treat population. Diarrhea was more frequent in linezolid recipients (4.4 vs 2.6%); however, abnormal liver function tests were more common with vancomycin (1.6 vs 1.0%) as was incidence of rash (1.6 vs 0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were 36 deaths in the linezolid group and 49 with vancomycin (17.7 vs 25.4%, respectively; P=0.06). Secondary: Not reported
Wunderink et al.[131] (2003) Linezolid 600 mg IV every 12 hours vs vancomycin 1 g IV every 12 hours Patients could have also received aztreonam 1 to 2 g IV every 8 hours.	DB, MC, RCT Patients >18 years of age with pneumonia acquired 48 hours after admission to an inpatient facility	N=345 Treatment: 7 to 21 days Follow-up: 15 to 21 days posttreatment	Primary: Clinical outcomes (cure or failure) and microbiologic outcomes (success and failure) at follow-up visit Secondary: Not reported	Primary: 55.4% of total enrolled patients (345/623) were clinically evaluable. Clinical cure rates were equivalent between linezolid- and vancomycin-treated patients (67.9 and 64.9%, respectively; P=NS). 25.5% of total patients (159/623) were microbiologically evaluable. Microbiological success rates were similar between linezolid- and vancomycin-treated patients (61.8 and 53.2%, respectively; P=NS). More patients had multiple-lobe involvement in the linezolid group vs the vancomycin group (56.1 vs 44.3%; P=0.004).
Wunderink et al.[132] (2008) Linezolid 600 mg every 12 hours vs vancomycin 1 g every 12 hours	MC, OL, RCT Patients with MRSA ventilator-associated pneumonia	N=149 30 days	Primary: Microbiological response and clinical cure Secondary: Clinical outcome, mortality, ventilator use at the EOT and follow-up visits, health resource outcomes (duration of mechanical ventilation, hospitalization,	Primary: Due to the limited number of patients per treatment group, the study did not have sufficient power to establish non-inferiority between linezolid and vancomycin for the primary end point. Overall, 56.5% of linezolid-treated patients achieved a microbiological cure compared to 47.4% of vancomycin-treated patients (P=0.757; 95% CI, -21.1 to 39.4). Clinical cure was demonstrated in 66.7% of linezolid-treated patients compared to 52.9% of vancomycin-treated patients (P=0.375). Secondary: The survival rate (86.7 vs 70.0%, respectively) mean duration of ventilation (10.4 vs 14.3 days, respectively), hospitalization (18.8 vs 20.1 days, respectively), intensive care unit stay (12.2 vs 16.2 days,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and intensive care unit stay)	respectively), and time spent alive and not receiving mechanical ventilation (15.5 vs 11.1 days, respectively) were not significantly different between linezolid-treated patients and vancomycin-treated patients.
Kaplan et al.[133] (2003) Linezolid IV then orally vs vancomycin IV then appropriate orally agent	RCT Hospitalized children (birth to 12 years of age) with antibiotic-resistant gram-positive infections (nosocomial pneumonia, complicated SSSIs, catheter-related bacteremia, and other infections)	N=321 10 to 28 days	Primary: Clinical cure rate and pathogen eradication rate Secondary: Not reported	Primary: Clinical cure rate was 74% with vancomycin and 79% with linezolid in the intent-to-treat population (P=0.36). The cure rate in the clinically evaluable population was 85 and 89% with vancomycin and linezolid, respectively (P=0.31). Eradication rates for MRSA were similar for both groups (P=0.89). Patients receiving linezolid required fewer days of IV therapy (P<0.001) and experienced fewer adverse drug events (P=0.003). Secondary: Not reported
Wunderink et al.[134] (2012) Vancomycin IV 15 mg/kg every 12 hours vs linezolid IV 600 mg every 12 hours	DB, MC, PRO Hospitalized adult patients with hospital-acquired or healthcare-associated MRSA pneumonia	N=1,184 7 to 14 days	Primary: Clinical outcome at end of study in evaluable per-protocol patients Secondary: Response in the modified intent-to-treat population at end of treatment and end of study and microbiologic response in the per protocol and modified intent-to-treat population at end of treatment and end of study,	Primary: In the Per protocol population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at end of study (95% CI, 0.5 to 21.6; P=0.042). Secondary: All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			survival and safety	
Fagon et al.[135] (2000) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 hours vs vancomycin 1 g IV every 12 hours Aztreonam, imipenem, or tobramycin were added if determined clinically necessary.	MC, OL, RCT Patients ≥18 years developing sufficiently severe nosocomial pneumonia that required ≥5 days of parenteral antibiotics	N=171 5 to 14 days	Primary: Clinical response at test-of-cure assessment (seven to 13 days after end of treatment if cure/improvement; 13 days after end of treatment if failure) in the bacteriologically evaluable population (by-pathogen bacteriologic response, by-patient bacteriologic response) Secondary: Clinical response for the all-treated population	Primary: Therapy was clinically successful in 58.3% of patients receiving vancomycin and 56.3% of patients receiving quinupristin-dalfopristin (-2% difference [95% CI, -16.8 to 12.8]). The by-pathogen bacteriologic response was similar between treatment groups (for *Streptococcus pneumoniae, Staphylococcus aureus*, MRSA). The by-patient bacteriologic success rate was 64.3 and 58.6% in the vancomycin and quinupristin-dalfopristin groups, respectively (-5.7% difference [-20.2 to 8.9%]). 32 patients died in the vancomycin group compared to 38 patients in the quinupristin-dalfopristin group (P=0.45). Secondary: The clinical success rate was similar between groups in the all-treated population (45.3% for vancomycin and 43.3% for quinupristin-dalfopristin (-1.9% difference [-13.2 to 9.3%]). There was no statistically significant difference between groups in reported adverse events (P=NS).
Rubinstein et al.[136] (2011) Telavancin 10 mg/kg IV once daily for 7 to 21 days vs vancomycin 1 g IV BID for 7 to 21	AC, DB, RCT (2 trials) Patients ≥18 years of age with hospital-acquired pneumonia due to gram-positive pathogens, including MRSA	N=1,503 7 to 14 days posttreatment	Primary: Clinical response at the follow-up/test-of-cure visit (seven to 14 days after treatment) Secondary: Not reported	Primary: In all treated patients at the follow-up/test-of-cure visit (study 0015), cure rates were 57.5% with telavancin and 59.1% with vancomycin (95% CI, -8.6 to 5.5). In study 0019, cure rates were 60.2% with telavancin and 60.0% with vancomycin (95% CI, -6.8 to 7.2). In the clinically evaluable population at the follow-up/test-of-cure visit (study 0015), cure rates were 83.7% with telavancin and 80.2% with vancomycin (95% CI, -5.1 to 12.0). In study 0019, cure rates were 81.3% with telavancin and 81.2% with vancomycin (95% CI, -8.2 to 8.4). In the pooled all treated population, cure rates with telavancin were 58.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days				compared to 59.5% with vancomycin (95% CI, –5.6 to 4.3). In the pooled clinically evaluable population, cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI, –4.3 to 7.7). In patients with pneumonia due to *Staphylococcus aureus*, the clinical response at the follow-up/test-of-cure visit was 78.1% with telavancin compared to 75.2% with vancomycin; 95% CI, -9.5 to 10.4). In patients with pneumonia due to MRSA, with or without other pathogens, the clinical response at the follow-up/test-of-cure visit was 74.8% with telavancin compared to 74.7% with vancomycin; 95% CI, -9.5 to 10.4). The incidence and types of adverse events were comparable between the treatment groups. Mortality rates with telavancin were 21.5% compared to 16.6% with vancomycin (95% CI, –0.7 to 10.6) for study 0015. Mortality rates were 18.5% with telavancin compared to 20.6% with vancomycin (95% CI, –7.8 to 3.5) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16 vs 10%).
Toma et al.[137] (1998) SMX-TMP 1,600-320 mg (≥60 kg) or 1,200-240 mg (<60 mg) QID for 21 days vs clindamycin 450 mg QID and primaquine 15 mg once daily for 21 days	DB, MC, RCT Patients ≥16 years of age with HIV-related PCP	N=116 21 days	Primary: Treatment success (>2-point improvement in the PCP score, calculated on the basis of body temperature, respiratory rate, cough, chest tightness, dyspnea, supplemental oxygen requirements, and chest radiograph), steroid use, duration of therapy, adverse	Primary: There was no statistically significant difference in the duration of therapy between the treatment groups (P=0.68). The treatment success rates for SMX-TMP and clindamycin-primaquine were 76% and 74%, respectively. There were no statistically significant differences between the treatment regimens with respect to dyspnea scores, PCP scores and lactate dehydrogenase values at any time. There was no statistically significant difference between treatment groups with respect to the use of steroids (12 patients per group; P=0.74). There was no significant difference in the rate of PCP recurrence between the two treatment arms (P=0.99). There was no significant difference in the rate of adverse effects experienced by the two treatment groups (P=0.57). Rash was the most frequent side effect in both groups. The incidence of rash was similar in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			events Secondary: Not reported	both groups (P=0.78). Secondary: Not reported
Allewelt et al.[138] (2004) Ampicillin-sulbactam vs clindamycin with or without cephalosporin Dosing varied per patient	MC, OL, PRO, RCT Patients with aspiration pneumonia and lung abscess	N=70 Mean 23.4 days	Primary: Clinical response Secondary: Not reported	Primary: Clinical response at EOT in the ampicillin-sulbactam group was 73.0 vs 66.7% in the clindamycin group (P=0.06 and P=0.02, respectively). Clinical response at seven to 14 days after therapy was 65.7% in the ampicillin-sulbactam group vs 63.5% in the clindamycin group (P=0.10 and P=0.04). Duration of therapy was 22.7 days in the ampicillin-sulbactam group vs 24.1 days in the clindamycin group. Secondary: Not reported
Miscellaneous Infections				
Smith et al.[139] (2021) SCAMP Ampicillin, gentamicin, and metronidazole (group 1) vs ampicillin, gentamicin, and clindamycin (group 2) vs	MC, OL, RCT Infants ≤33 weeks gestational age at birth with a postnatal age <121 days, who demonstrated physical, radiologic, and/or bacteriologic findings consistent with complicated intra-abdominal infection (cIAI) Due to slow enrollment, a protocol amendment	N=180 (128 randomized [R], 52 non-randomized [NR]) 30 days	Primary: Mortality within 30 days of study drug completion Secondary: Adverse events, outcomes of special interest, and therapeutic success (absence of death, negative cultures, and clinical cure score >4) 30 days after study drug completion	Primary: Twenty-nine (16%) infants were transferred or discharged before the 30-day safety and overall therapeutic success evaluations. Thirty-day mortality was 8%, 7%, and 9% in groups 1, 2, and 3, respectively. Secondary: There were no differences in safety outcomes between antibiotic regimens. After adjusting for treatment group and gestational age, mortality rates through end of follow-up were 4.22 (95% CI, 1.39 to 12.13), 4.53 (95% CI, 1.21 to 15.50), and 4.07 (95% CI, 1.22 to 12.70) for groups 1, 2, and 3, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
piperacillin-tazobactam and gentamicin (group 3) Doses stratified by postmenstrual age; Additional gram-positive therapy (e.g., vancomycin, nafcillin, oxacillin, linezolid) was permitted at the discretion of the treating physician	allowed eligible infants already receiving study regimens to enroll without randomization			
Linden et al.[140] (2003) Colistin (colistimethate) dose based on weight	PRO Critically ill patients (organ recipients as well as other non-transplant general surgery patients) with multi-drug resistant *Pseudomonas aeruginosa* infection	N=23 7 to 36 days	Primary: Favorable response, defined as complete or partial resolution of signs and symptoms at end of treatment; unfavorable response, defined as persistence or worsening of signs and symptoms or death Secondary: Not reported	Primary: Favorable clinical response was observed in 14 patients (61%). Seven patients died during therapy (30.4%). Majority of patients enrolled had pneumonia (n=18) or intra-abdominal infection (n=5). *Pseudomonas aeruginosa* bacteremia was associated with clinical failure (P=0.02).
Kasakou et al.[141] (2005) Colistin (colistimethate) 1.5	RETRO Hospitalized patients with multi-drug resistant gram-	N=50 4 to 72 days	Primary: Mortality Secondary: Clinical outcome	Primary: In-hospital mortality was 24% (12/50); age and temperature upon hospital admission were independent predictors of mortality. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 9 million IU IV per day Colistin was used as monotherapy or in combination with other antimicrobials.	negative bacilli managed with colistin for ≥72 hours		of infection, occurrence of renal dysfunction	Four patients developed two episodes of infection and were treated as two different cases. A total of 53.7% (29/54) had a cure and 13% (7/54) showed improvement and 33.3% (18/54) were unresponsive. Deterioration of renal function was noted in 8% (4/50) of patients receiving colistin. A total of 6/50 patients received colistin by an alternate route in addition to IV (intraventricular, nebulized, or irrigation solution). A total of 31/50 patients had concurrent administration with one or two additional agents such as, meropenem (60%), ampicillin-sulbactam (34%), ciprofloxacin (20%), piperacillin-clavulanic acid (20%), imipenem (16%), or amikacin plus gentamicin (14%).
El-Khoury et al.[142] (2003) Linezolid 600 mg IV/oral BID (<40 kg received 10 mg/kg BID)	MC, OL Solid organ transplant patients with vancomycin-resistant *Enterococcus faecium*	N=85 Variable duration	Primary: Clinical resolution of infection Secondary: Not reported	Primary: A total of 53 patients (62.4%) survived with linezolid treatment (clinical resolution), whereas death occurred in 32 patients (32.9%). Documented negative cultures post-therapy were obtained in 47 of patients that survived. Mean duration of therapy for cured patients was 23.5 days. Adverse reactions included thrombocytopenia (four patients), leukocytopenia (three patients), and increase in blood pressure (one patient). Secondary: Not reported
Linden et al.[143] (2001) Quinupristin-dalfopristin 7.5 mg/kg IV every 8	MC, PRO Patients with signs and symptoms of active infection caused by	N=396 20 days (mean)	Primary: Clinical response rate, bacteriological response rate, overall response	Primary: Clinical response rate was 68.8% in evaluable population; 51% in all-treated population (including indeterminate). Bacteriologic response rate was 68% in evaluable population; 59.8% in all-treated population. Overall response rate was 65.6% in evaluable population; 48.2% in all-treated population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours	vancomycin-resistant *Enterococcus faecium*		rate combined clinical and bacteriological responses Secondary: Not reported	Overall mortality rate in the all-treated group was 28.8% while receiving treatment and 56.6% at 30 days after therapy discontinuation. Arthralgia and myalgia were common adverse events and reasons for therapy discontinuation; however, reversible after treatment discontinuation. A total of 11 patients in the all-treated population experienced superinfection caused by gram-positive pathogens. Secondary: Not reported
Winston et al.[144] (2000) Quinupristin-dalfopristin, either 7.5 mg/kg IV every 8 hours or 5 mg/kg IV every 8 hours; infused over 60 minutes	PRO Hospitalized patients with signs and symptoms of infection confirmed by cultures that are positive for vancomycin-resistant *Enterococcus faecium*	N=24 3 to 36 days	Primary: Clinical responses and bacteriological response Secondary: Not reported	Primary: Eighty-three percent of patients experienced a clinical response (80% of patients given the 7.5 mg/kg dose and 88% of patients given the 5 mg/kg dose. Bacterial eradication occurred in 74% (17/23) of patients. Four patients failed to response to therapy and four patients experienced clinical and bacteriologic relapse of vancomycin-resistant *Enterococcus faecium* 22 to 67 days after treatment was discontinued. Two patients had persistent vancomycin-resistant *Enterococcus faecium*. Sixty-nine percent of patients died during hospitalization; four due to vancomycin-resistant *Enterococcus faecium* infection and 12 due to other causes, including liver failure, invasive fungal infection, cardiac failure, *Citrobacter freundii* bacteremia, acute leukemia and fungal infection, pancreatic carcinoma, and graft-vs-host disease. Thirty-three percent of patients experienced arthralgias and myalgias (a higher incidence with the use of high dose [eight patients experienced arthralgias and myalgias with 7.5 mg/kg and none in 5 mg/kg dose]). Six patients experienced superinfection due to *Candida* fungemia, *Enterobacter cloacae* pneumonia, and *Enterococcus faecalis*. Secondary: Not reported
Rehm et al.[145] (2001)	MC, PRO	N=37	Primary: Clinical responses,	Primary: Overall clinical success rate was 89.2% and bacteriological success rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Quinupristin-dalfopristin 7.5 mg/kg every 8 or 12 hours diluted in 100 mL (if using central venous catheter) or 240 mL (if using peripheral venous catheter) of D5W; as 1 hour infusion	Patients who participated in clinical trials with quinupristin/ dalfopristin for either emergency use or for assessment of safety and efficacy in Phase III studies and continued to receive quinupristin/ dalfopristin after hospital discharge	9 days inpatient & 22 days as outpatient (mean)	bacteriological response, adverse events Secondary: Not reported	was also 89.2%. 86.5% completed study without hospital readmission. Five patients required hospital readmission due to recurrent MRSA, central catheter-related bacteremia, chest pain, elevated liver enzymes, and neutropenic fever. Nineteen patients (51.4%) experienced non-venous clinical adverse events (most common: myalgia (18.9%), nausea (18.9%), arthralgia (13.5%), diarrhea, headache, and vomiting). Sixteen patients (43.2%) experienced venous access adverse events (most common: drug infusion pain, local edema, phlebitis). Five (13.5%) patients experienced abnormal lab results (anemia, azotemia, and elevated transaminase). Secondary: Not reported
Raad et al.[146] (2004) Linezolid 600 mg every 12 hours vs quinupristin-dalfopristin 7.5 mg/kg every 8 hours	OL, PRO, RCT Patients ≥18 years of age with infections caused by vancomycin-resistant *Enterococcus faecium*	N=40 39 months	Primary: Safety Secondary: Efficacy	Primary: The rate of myalgias/arthralgias in patients receiving quinupristin-dalfopristin was 33% as compared to 0% in patients receiving linezolid (P<0.01). All other reports of adverse effects were found to be NS (P>0.05). Secondary: Clinical response at the EOT were not significantly different between patients receiving quinupristin-dalfopristin and patients receiving linezolid (P=0.6). There was no statistically significant difference between the number of deaths caused by infection, relapse, or microbiological response between the two treatment arms (all P>0.05).
Kohno et al.[147] (2007) Linezolid 600 mg every 12 hours vs vancomycin 1 g every 12 hours	RCT Patients with nosocomial pneumonia, complicated skin and soft-tissue infections or sepsis caused by MRSA	N=151 7 to 14 days	Primary: Clinical success rates Secondary: Not reported	Primary: Clinical success rates in the MRSA microbiologically evaluable population were 62.9% and 50.0% for the linezolid and vancomycin groups, respectively (P=NS). Microbiological eradication rates were 79.0 and 30.0% for the linezolid and vancomycin groups, respectively (P<0.0001). At follow-up, the clinical success rates were 36.7% for both groups and the microbiological eradication rates were 46.8 and 36.7%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Reversible anemia (13%) and thrombocytopenia (19%) were reported more frequently in linezolid patients. Significantly low platelet counts were observed more frequently in patients receiving vancomycin than in linezolid patients (6 vs 3%). Mean changes in hemoglobin levels between the two groups were not different. Secondary: Not reported
Stevens et al.[148] (2002) Vancomycin 1 g IV once daily vs linezolid 600 mg IV BID Upon clinical improvement, linezolid-treated patients could be changed to linezolid 600 mg orally BID.	MC, OL, RCT Hospitalized/ institutionalized patients with MRSA infections	N=460 7 to 28 days	Primary: Clinical outcomes and microbiological outcomes Secondary: Not reported	Primary: Clinical cure rate was 73.2% with linezolid vs 73.1% with vancomycin (P=0.99) in evaluable patients with MRSA (N=116) at the test-of-cure visit. There were no differences in clinical response between vancomycin and linezolid for other population subgroups (P=NS). Microbiological success rate was 58.9% with linezolid vs 63.2% with vancomycin (P=0.65) in evaluable patients with MRSA at the test-of-cure visit. Adverse event rates were similar between groups (P=0.143). A total of 61% of the linezolid group received oral administration. Secondary: Not reported
Shorr et al.[149] (2005) Vancomycin 1 g IV every 12 hours vs	MA (PRO, RCT) Patients with *Staphylococcus aureus* bacteremia (pneumonia 48 hours after hospital admission,	N=144 7 to 35 days	Primary: Clinical cure of primary infection at EOT, microbiological eradication of *Staphylococcus aureus* bacteremia,	Primary: In clinically evaluable patients, incidence of cure was 55% (28/51) in patients given linezolid and 52% (25/48) in patients given vancomycin (1.12; 95% CI, 0.51 to 2.47). In the intent-to-treat population, clinical cure occurred in 28/74 (38%) patients given linezolid and 25/70 (36%) patients given vancomycin. In patients with MRSA bacteremia, 56% (14/25) of linezolid-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
linezolid 600 mg IV every 12 hours	complicated skin and soft tissue infections, or MRSA infections)		and overall survival Secondary: Not reported	patients and 46% (13/28) of vancomycin treated patients had a cure (1.47; 95% CI, 0.50 to 4.34). Microbiological success occurred in 69% of linezolid-treated patients and 73% of vancomycin-treated patients (OR, 0.83; 95% CI, 0.37 to 1.87). The survival rate was similar for both treatment groups in patients with MRSA bacteremia as well as overall *Staphylococcus aureus* bacteremia. Mean duration of therapy was shorter with IV linezolid than with vancomycin (8.6 vs 11.7; P=0.004). Linezolid was given IV for >7 days after which it could be switched to oral.
An et al.[150] (2013) Vancomycin vs linezolid	MA 9 RCTs comparing linezolid with vancomycin for MRSA infection	N=5,249 Duration varied	Primary: Efficacy, safety Secondary: Not reported	Primary: Linezolid was associated with greater efficacy compared to vancomycin for MRSA-related infection in terms of clinical treatment success (OR, 1.77; 95% CI, 1.22 to 2.56) and microbiological treatment success (OR, 1.78; 95% CI, 1.22 to 2.58). Although no difference was found regarding the overall incidence of drug-related adverse events and serious adverse events between the linezolid and vancomycin therapy groups (drug-related adverse events: OR, 1.20; 95% CI, 0.98 to 1.48; serious adverse events: OR, 1.00; 95% CI, 0.74 to 1.36), the linezolid therapy group was associated with significantly fewer patients experiencing abnormal renal function (OR, 0.39; 95% CI, 0.28 to 0.55). Secondary: Not reported
Fu et al.[151] (2013) Vancomycin or teicoplanin (glycopeptides)	MA 13 RCTs that assess the effectiveness and safety of linezolid in comparison with	N=3,863 Duration varied	Primary: Efficacy and safety Secondary: Not reported	Primary: Linezolid was slightly more effective than glycopeptides in the intent-to-treat population (OR, 1.05; 95% CI, 1.01 to 1.10), was more effective in clinically assessed patients (OR, 1.38; 95% CI, 1.17 to 1.64) and in all microbiologically assessed patients (OR, 1.38; 95% CI, 1.15 to 1.65). Linezolid was associated with better treatment in skin and soft-tissue

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs linezolid	glycopeptides (vancomycin and teicoplanin) for the treatment of Staphylococcus aureus infections			infections patients (OR, 1.61; 95% CI, 1.22 to 2.12), but not in bacteriemia (OR, 1.24; 95% CI, 0.78 to 1.97) or pneumonia (OR, 1.25; 95% CI, 0.97 to 1.60) patients. No difference of mortality between linezolid and glycopeptides was seen in the pooled trials (OR, 0.98; 95% CI, 0.83 to 1.15). While linezolid was associated with more hematological (OR, 2.23; 95% CI, 1.07 to 4.65) and gastrointestinal events (OR, 2.34; 95% CI, 1.53 to 3.59), a significantly fewer events of skin adverse effects (OR, 0.27; 95% CI, 0.16 to 0.46) and nephrotoxicity (OR, 0.45; 95% CI, 0.28 to 0.72) were recorded in linezolid. Secondary: Not reported
Chong et al.[152] (2010) Quinupristin - dalfopristin 7.5 mg/kg IV every 8 hours for ≥48 hours vs linezolid 600 mg IV every 12 hours for ≥48 hours	RETRO Patients ≥16 years of age with vancomycin-resistant *Enterococcus faecium*	N=113 Variable duration	Primary: Rates of 30-day mortality, microbiological response, and development of resistance Secondary: Not reported	Primary: The 30-day mortality rate was 48% in patients who received quinupristin-dalfopristin compared to 41% of patients who received linezolid (P=0.45). Microbiological response was observed in 60% of patients receiving quinupristin-dalfopristin compared to 66% of patients receiving linezolid (P=0.51). The development of resistance to quinupristin-dalfopristin in vancomycin-resistant *Enterococcus faecium* blood isolates was observed in 11% of patients for whom follow-up culture data were available. None of the patients developed resistance to linezolid (P=0.02). There were no significant differences in these relapse rates between the treatment groups (P=0.8). Antibiotic-induced thrombocytopenia was observed in 5% of patients in the linezolid group. Platelet counts of all patients recovered after discontinuation of linezolid therapy.
Polyzos et al.[153] (2012) Vancomycin	MA 6 RCTs evaluating telavancin in the	N=2,220 Duration varied	Primary: Efficacy and safety Secondary:	Primary: Regarding complicated skin and soft tissue infections, telavancin and vancomycin showed comparable efficacy in clinically evaluable patients (OR, 1.10; 95% CI, 0.82 to 1.48).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs telavancin	treatment of patients with infections due to Gram-positive organisms		Not reported	Among patients with MRSA infection, telavancin showed higher eradication rates (OR, 1.71; 95% CI, 1.08 to 2.70) and a trend towards better clinical response (OR, 1.55; 95% CI, 0.93 to 2.58). Regarding hospital-acquired pneumonia, telavancin was non-inferior to vancomycin in terms of clinical response; mortality rates for the pooled trials were comparable with telavancin (20.0%) and vancomycin (18.6%). Pooled data from complicated skin and soft tissue infections and hospital-acquired pneumonia studies on telavancin 10 mg/kg indicated higher rates of serum creatinine increases (OR, 2.22; 95% CI, 1.38 to 3.57), serious adverse events (OR, 1.53; 95% CI, 1.05 to 2.24), and adverse event-related withdrawals (OR, 1.49; 95% CI, 1.14 to 1.95) among telavancin recipients. Secondary: Not reported
Solomkin et al.[154] (2009) Ceftriaxone 2 g IV once daily plus metronidazole 500 mg IV BID for three to 14 days vs moxifloxacin 400 mg IV once daily for three to 14 days	DB, MC, RCT Patients ≥18 years of age with community-origin complicated intra-abdominal infections with an expected duration of treatment with IV antimicrobials of 3 to 14 days	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure visit (10 to 14 days after the EOT) Secondary: Clinical and bacteriological success rates on days three and five during treatment and at the EOT; bacteriological success rate at the test-of-cure visit; and clinical success rate at the test-of-cure visit in	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-to-treat populations. Secondary: During treatment, clinical improvement occurred in similar proportions of per protocol patients in the moxifloxacin group (31.0%) and the ceftriaxone plus metronidazole group (28.1%). In the intention-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole. In the per protocol population, clinical resolution at EOT occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at E occurred in 91.1% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients with bacteriologically proven complicated intra-abdominal infections	patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Towfigh et al.[155] (2010) Ceftriaxone 2 g IV once daily plus metronidazole 1 to 2 g IV daily in divided doses for four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)	MC, OL, RCT, Patients ≥18 years of age with community-origin complicated intra-abdominal infections	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable population at the test-of-cure visit Secondary: Bacteriological efficacy and safety	Primary: In the clinically evaluable population, clinical cure was reported in 70% of patients receiving TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the microbiologically evaluable population, clinical cure rates for the different pathogens were similar between the two treatment groups. At test-of-cure in the microbiologically evaluable population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no significant differences in the incidence of patients reporting one or more serious adverse events among the treatment groups (P=1.000). The most frequently reported serious adverse events overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%), and ileus (1.3%).
Gentry et al.[156]	RETRO	N=56	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Nafcillin vs vancomycin	Patients with staphylococcal endocarditis	Duration not specified	Clinical response Secondary: Not reported	In patients with methicillin-sensitive *Staphylococcus aureus* infection, complete response rate was 74% in the nafcillin group compared to 50% in the vancomycin group (P=0.12); however, these differences were not statistically significant. Mortality rate was 22% in the nafcillin group and 28% in the vancomycin group (P=0.73). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IV=intravenous, TID=three times daily, QID=four times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single center, SB=single-blind
Miscellaneous abbreviations: ECE=early clinical evaluation, EOT=end of therapy, HIV=human immunodeficiency virus, *H pylori=Helicobacter pylori*, HRQOL=health related quality of life, IV=intravenous, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*, PCP=*Pneumocystis carinii* pneumonia, PTE=post-therapy evaluation, SMX-TMP=sulfamethoxazole-trimethoprim, SSSI= skin and skin structure infection

Additional Evidence

Dose Simplification
Carroll et al. evaluated the efficacy of clindamycin administered for three doses (short-course) vs 15 doses (long-course) for the prophylaxis of wound infections in patients with head and neck cancer undergoing reconstructive surgery.[157] The incidence of wound infections and other complications was not significantly different among the treatment groups. Livingston et al. compared the efficacy of gentamicin and clindamycin given once daily vs every eight hours for the treatment of postpartum endometritis.[158] There was no significant different in the treatment success rates among the treatment groups (82 vs 69%, respectively; P=0.12). Cohen et al. evaluated the efficacy of vancomycin administered once-daily vs twice-daily in hospitalized patients.[159] There was no significant difference in clinical response rates among the treatment groups (92.1 vs 94.2%, respectively; P=0.72).

Stable Therapy
McCollum et al. evaluated converting patients from intravenous vancomycin to oral linezolid for the treatment of methicillin-resistant *Staphylococcus* species.[160] Of 177 patients treated with vancomycin, 58% were eligible for conversion to oral therapy with linezolid and 31% were eligible for early hospital discharge with continuation of oral therapy. Early discharge was associated with a decrease in the length of stay by 3.3 days. Li et al. assessed the use of linezolid or vancomycin for the treatment of complicated skin and soft-tissue infections on hospital length of stay.[59] Patients received intravenous linezolid followed by oral linezolid, or monotherapy with intravenous vancomycin for up to four weeks. Length of hospital stay was eight days in the linezolid group compared to 16 days in the vancomycin group (P=0.0025).

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 20. Relative Cost of the Antibacterials, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Bacitracin	injection	N/A	N/A	$$$$$
Clindamycin	capsule, injection, solution	Cleocin®*	$$-$$$$$	$
Colistimethate	injection	Coly-Mycin M Parenteral®*	$$$$$	$$$$$
Dalbavancin	injection	Dalvance®	$$$$$	N/A
Daptomycin	injection	Cubicin®*	$$$$$	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lefamulin	injection, tablet	Xenleta®	$$$$$	N/A
Lincomycin	injection	Lincocin®*	$$$$$	$$$$$
Linezolid	injection, suspension, tablet, injection	Zyvox®*	$$$$	$$$$
Oritavancin	injection	Kimyrsa®, Orbactiv®	$$$$$	N/A
Polymyxin B sulfate	injection	N/A	N/A	$$$$-$$$$$
Rifamycin	delayed-release tablet	Aemcolo DR®	$$$$$	N/A
Rifaximin	tablet	Xifaxan®	$$$$$	N/A
Tedizolid	injection, tablet	Sivextro®	$$$$$	N/A
Telavancin	injection	Vibativ®	$$$$$	N/A
Vancomycin	capsule, injection, solution	Firvanq®*, Vancocin®*	$$$$$	$$$$
Combination Products				
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-19] The Food and Drug administration (FDA)-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents.

The use of bacitracin is limited to the treatment of infants with pneumonia and empyema caused by susceptible strains of staphylococci. Treatment may cause renal failure due to tubular and glomerular necrosis; therefore, renal function should be carefully determined prior to and daily during therapy. The concurrent use of other nephrotoxic drugs should be avoided.[1,2,19] On January 31, 2020 the FDA requested that all current manufacturers of bacitracin for injection voluntarily withdraw their product from the market. Based on the FDA's review of currently available data, the FDA believes that the potential problems associated with bacitracin for injection are sufficiently serious to remove the drug from the market.[161] Polymyxin B sulfate and colistimethate are approved for the treatment of serious infections caused by susceptible gram-negative bacteria when less toxic drugs are ineffective or contraindicated.[1,2,19] The use of these agents has resulted in nephrotoxicity and neurotoxicity. Healthcare-Associated Ventriculitis and Meningitis Guidelines (2017) recommend colistimethate sodium or polymyxin B sulfate as alternative therapies for the treatment of *Acinetobacter* species.[27] Additionally, the 2016 Guidelines for the Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia recommend therapy with intravenous polymyxins with adjunctive inhaled colistin when pathogens are carbapenem-resistant and only sensitive to polymyxins.[44] Guidelines do not otherwise discuss the use of bacitracin, polymyxin B sulfate, or colistimethate and published clinical trials are limited.

The lincosamide antibacterials include clindamycin and lincomycin. Guidelines recommended the use of clindamycin for the treatment of skin and soft-tissue infections, bacterial vaginosis, and pelvic inflammatory disease.[28,29,38] Lincomycin is not discussed in the available guidelines and has no therapeutic advantage over clindamycin. Although there are many FDA-approved indications for clindamycin, the increased risk of *Clostridium difficile*-associated diarrhea (which may end fatally) limits the use of this agent. The lincosamides should be reserved for the treatment of serious infections for which less toxic antimicrobial agents are inappropriate.[1,2,19]

Daptomycin is approved for the treatment of complicated skin and skin-structure infections, *Staphylococcus aureus* bacteremia, and right-sided infective endocarditis.[5] The spectrum of activity with daptomycin is similar to that of vancomycin. Guidelines recommend daptomycin as one of several options for the initial treatment of soft-

tissue infections caused by methicillin-resistant *Staphylococcus aureus*.[47] Published studies have demonstrated similar clinical response rates when daptomycin was compared to vancomycin or penicillinase-resistant penicillins.[55,56]

Lefamulin is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by designated susceptible microorganisms.[6] It inhibits bacterial protein synthesis by binding to the 50S subunit at the peptidyl transferase center, thereby preventing peptide bond formation. This unique mechanism of action has been associated with a low probability of cross-resistance to other antimicrobial classes based on *in vitro* studies.[6,21] The safety and efficacy of lefamulin was assessed in the LEAP1 and LEAP2 trials. The results of LEAP1 showed lefamulin was noninferior to moxifloxacin for early clinical response and investigator assessment of clinical response success.[128] The LEAP2 trial showed noninferiority of 5 to 10 days of lefamulin compared to 7 to 10 days of moxifloxacin given in intravenous-to-oral or oral administration.[129]

Linezolid is approved for the treatment of skin and skin-structure infections, pneumonia, and vancomycin-resistant *Enterococcus faecium* infections. Guidelines recommend the use of linezolid as an initial treatment option for endocarditis (due to vancomycin-resistant *Enterococcus faecium*), meningitis (due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*), skin and soft-tissue infections (due to methicillin-resistant *Staphylococcus aureus*), diabetic foot infections, as well as community-acquired and nosocomial pneumonia (due to methicillin-resistant *Staphylococcus aureus*).[7] Several trials have demonstrated similar clinical response rates when linezolid was compared to vancomycin.[58,61,130-133,147-149] Linezolid can be administered either orally or parenterally when treating serious infections. Vancomycin is also available in an oral and injectable formulation; however, oral vancomycin has only been shown to be effective for the treatment of enterocolitis and *Clostridium difficile*-associated diarrhea. The intravenous formulation must be used for the treatment of serious infections caused by staphylococci, including methicillin-resistant strains. Studies have demonstrated a shorter length of hospital stay and duration of intravenous therapy with the use of linezolid compared to vancomycin.[59-62] Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy.[7]

Tedizolid phosphate is the second agent in the oxazolidinone class, the first being linezolid. It is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria in adults and pediatric patients 12 years of age and older.[12] FDA approval of tedizolid phosphate was based on two clinical trials, ESTABLISH-1 and ESTABLISH-2, that evaluated the safety and efficacy of the drug for treatment of ABSSSIs.[70,71] Both trials were randomized, double-blind, double-dummy, multinational, phase III, parallel group, non-inferiority studies comparing tedizolid to linezolid. In ESTABLISH-2, the primary endpoint of early clinical response (48 to 72 hours after treatment initiation) was achieved in 283 (85%) patients in the tedizolid phosphate group and 276 (83%) patients in the linezolid group, demonstrating non-inferiority of tedizolid phosphate to linezolid.[70] In ESTABLISH-1, the primary endpoint of early clinical response (48 to 72 hours after treatment initiation) was achieved in 79.5% of patients in the tedizolid phosphate group and 79.4% of patients in the linezolid group; a treatment difference of 0.1% (95% CI, -6.1 to 6.2; P value not reported).[71]

Telavancin is approved for the treatment of complicated skin and skin-structure infections caused by susceptible gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*).[13] For hospitalized patients with complicated skin and skin-structure infections, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered. Treatment options include telavancin, vancomycin, linezolid, daptomycin, and clindamycin. Two studies compared telavancin to standard therapy (penicillinase-resistant penicillin or vancomycin) in patients with complicated skin and skin-structure infections caused by gram-positive organisms.[78,79] Cure rates were similar among the treatment groups, including in patients with methicillin-resistant *Staphylococcus aureus* at baseline. Telavancin was also compared to vancomycin in patients with hospital-acquired pneumonia due to gram-positive organisms.[136] Cure rates were similar among the treatment groups, including in patients with methicillin-resistant *Staphylococcus aureus* at baseline. Increases in serum creatinine (up to 1.5 times baseline) have occurred more frequently in patients receiving telavancin (15%) compared to patients receiving vancomycin (7%).[13] Renal function should be monitored in patients receiving telavancin prior to the start of therapy, during treatment, and at the end of therapy.

Dalbavancin and oritavancin are semisynthetic lipoglycopeptides that interfere with cell wall synthesis and are bactericidal against *Staphylococcus aureus* and *Streptococcus pyogenes in vitro*. They are FDA-approved for the treatment of adult patients with ABSSSI caused by susceptible isolates.[4,8,9] FDA approval of oritavancin was based on two clinical trials, SOLO I and SOLO II, that evaluated the safety and efficacy of the drug for treatment of ABSSSIs. Both trials compared oritavancin to vancomycin and found that similar proportions of patients in each treatment group achieved the primary efficacy outcome at early clinical evaluation of cessation of spreading or reduction in size of baseline lesion, absence of fever, or absence of a need rescue for antibiotic medication at 48 to 72 hours.[68,69] Dalbavancin approval was based on the DISCOVER1 and DISCOVER2 trials, which compared treatment with dalbavancin to treatment with vancomycin with the option to switch to oral linezolid in adult patients with ABSSSI. In the DISCOVER1 trial, an early clinical response indicating treatment success was documented in 83.3% and 81.8% of patients in the dalbavancin and vancomycin-linezolid groups, respectively (difference, 1.5%; 95% CI, -4.6 to 7.9).[52] Similarly, in the DISCOVER2 trial, an early clinical response was documented in 76.8% and 78.3% of patients in the dalbavancin and vancomycin-linezolid groups, respectively (difference, -1.5; 95% CI, -7.4 to 4.6).[52]

Intravenous vancomycin is approved for the treatment of serious infections caused by susceptible strains of methicillin-resistant staphylococci, for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.[15,19] Vancomycin is also effective for the treatment of staphylococcal endocarditis, septicemia, bone infections, lower respiratory tract infections, as well as skin and skin-structure infections. As discussed previously, several studies have demonstrated similar clinical response rates when vancomycin was compared to daptomycin, linezolid, and quinupristin-dalfopristin.[55-56,130,131,134,144,147-149] Ototoxicity and nephrotoxicity have been reported with the use of intravenous vancomycin.[15] Ototoxicity may be transient or permanent and has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Rifaximin is approved for the treatment of travelers' diarrhea, irritable bowel syndrome with diarrhea (IBS-D), and to reduce the risk of overt hepatic encephalopathy recurrence.[11] For travelers' diarrhea, guidelines recommend empirical treatment with one of several antibiotics, including quinolones, azithromycin, sulfamethoxazole-trimethoprim, and rifaximin.[33] For the treatment of hepatic encephalopathy, guidelines recommend lactulose as initial therapy. Antibiotics are considered an alternative treatment option for acute and chronic encephalopathy.[51] Clinical trials have evaluated the short-term use of rifaximin for the treatment of acute hepatic encephalopathy.[119-127] Rifaximin was found to be as effective, or more effective, than lactulose and neomycin.[123,124,127] Bass et al. evaluated the long-term efficacy and safety of rifaximin in patients who were in remission from hepatic encephalopathy.[118] Over a six-month period, breakthrough episodes of hepatic encephalopathy were reported in 22% of patients receiving rifaximin compared to 46% of patients receiving placebo (P<0.001). Hospitalizations occurred in 14% of patients receiving rifaximin and in 23% of patients receiving placebo (P=0.01). This study did not directly compare rifaximin to other standard treatments for hepatic encephalopathy. Lactulose was used concomitantly by 91% of the patients in both treatment arms.

Aemcolo® (rifamycin) is indicated for the treatment of travelers' diarrhea caused by non-invasive strains of *Escherichia coli (E. coli)* in adults.[10] Results of the ERASE trial demonstrated the non-inferiority of rifamycin to ciprofloxacin based on the primary outcome of time to last unformed stool.[100]

Pylera® is used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. It contains all three of the antibacterial components (bismuth, metronidazole and tetracycline) in a single capsule. It should be used in combination with omeprazole for the treatment of *Helicobacter pylori* infections.[17] Guidelines recommend either proton-pump inhibitor-based triple therapy or quadruple therapy (proton-pump inhibitor or H_2-receptor antagonist, bismuth, tetracycline, and metronidazole) for the eradication of *Helicobacter pylori*.[35-37] Several clinical trials comparing quadruple therapy to triple therapy have demonstrated comparable efficacy, although this has not been consistently demonstrated.[88,90-92,94,99]

There is insufficient evidence to support that one brand miscellaneous antibacterial is safer or more efficacious than another within its given indication. Since the majority of these agents are not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use and due to concerns for the

development of resistance, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antibacterials within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Bacitracin possesses an extensive adverse effect profile compared to the other brands and generics in the class.

XI. Recommendations

No brand miscellaneous antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Bacitracin should not be placed in preferred status regardless of cost.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Central Alpha-Agonists, AHFS Class 240816
Amphetamine Derivatives AHFS Class 282004
Respiratory and CNS Stimulants, AHFS Class 282032
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 3, 2023

I. Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1-2] The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.[1] There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype in which both symptoms are displayed.[1] Untreated (or undertreated) ADHD is associated with adverse sequelae, including conduct disorder, antisocial personality traits, substance abuse, and other comorbidities.[1]

There are several central nervous system agents that are approved for the treatment of ADHD. This includes cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine, extended-release clonidine, extended-release guanfacine, and extended-release viloxazine.[3-29] The stimulants are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[4-25] Due to their potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, extended-release clonidine, extended-release guanfacine, and extended-release viloxazine are not considered controlled substances and have no known potential for abuse or dependence. Their mechanism of action in the treatment of ADHD is unknown. Atomoxetine and viloxazine are selective norepinephrine reuptake inhibitors, while clonidine and guanfacine are alpha$_2$-adrenergic agonists.[3,26-28]

The cerebral stimulants/agents used for ADHD that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Table 2 classifies the agents based on their duration of action. Many of the products are available in a generic formulation. This class was last reviewed in May 2021.

Table 1. Cerebral Stimulants/Agents Used for ADHD Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Central Alpha-Agonists			
Clonidine	extended-release tablet	Kapvay®*	clonidine
Amphetamine Derivatives			
Amphetamine	extended-release orally disintegrating tablet, extended-release suspension, extended-release tablet, tablet	Adzenys XR-ODT®, Dyanavel XR®, Evekeo®*	amphetamine
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*, Mydayis ER®	amphetamine-dextroamphetamine IR, Adderall XR®*†
Dextroamphetamine	sustained-release capsule, solution, tablet, transdermal patch	Dexedrine®*, ProCentra®*, Zenzedi®*, Xelstrym®	dextroamphetamine
Lisdexamfetamine	capsule, chewable tablet	Vyvanse®	Vyvanse®
Methamphetamine	tablet	Desoxyn®*	methamphetamine
Respiratory and CNS Stimulants			
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®*†	dexmethylphenidate

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Methylphenidate	chewable tablet, extended-release capsule, extended-release chewable tablet, extended-release orally disintegrating tablet, extended-release solution, extended-release tablet, solution, tablet, transdermal patch	Adhansia XR®, Aptensio XR®*, Concerta®*†, Cotempla XR-ODT®, Daytrana®*, Jornay PM®, Methylin®*, Quillichew ER®, Quillivant XR®, Relexxii ER®*, Ritalin®*, Ritalin LA®*	methylphenidate, Concerta®*†, Ritalin®*
Serdexmethylphenidate and dexmethylphenidate	capsule	Azstarys®	none
Central Nervous System Agents, Miscellaneous			
Atomoxetine	capsule	Strattera®*	atomoxetine
Guanfacine	extended-release tablet	Intuniv®*	guanfacine
Viloxazine	extended-release capsule	Qelbree ER®	none

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List.

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[3-24]

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Central Alpha-Agonists			
Clonidine			Kapvay®*
Amphetamine Derivatives			
Amphetamine sulfate	amphetamine sulfate, Evekeo®*		Adzenys XR-ODT®, Dyanavel XR®
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall®*		amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall XR®*, Mydayis ER®
Dextroamphetamine	dextroamphetamine, ProCentra®*, Zenzedi®*	dextroamphetamine, Dexedrine®*	Xelstrym®
Lisdexamfetamine			Vyvanse®
Methamphetamine		methamphetamine, Desoxyn®*	
Respiratory and CNS Stimulants			
Dexmethylphenidate	dexmethylphenidate, Focalin®*		dexmethylphenidate, Focalin XR®*
Methylphenidate	methylphenidate, Methylin®*, Ritalin®*	methylphenidate SR	Methylphenidate, Adhansia XR®, Aptensio XR®*, Concerta®*, Cotempla XR-ODT®, Daytrana®*, Jornay PM®, Ritalin LA®*, Quillichew ER®, Quillivant XR®, Relexxii ER®*
Serdexmethylphenidate and dexmethylphenidate			Azstarys®
Central Nervous System Agents, Miscellaneous			
Atomoxetine			Strattera®*
Guanfacine			Intuniv®*
Viloxazine			Qelbree ER®

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cerebral stimulants/agents used for attention-deficit/hyperactivity disorder (ADHD) are summarized in Table 3.

Table 3. Treatment Guidelines Using the Cerebral Stimulants/Agents Used for ADHD

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents (2019)**[32]	Preschool-aged children (four to five years of age) • The primary care clinician should prescribe evidence-based behavioral parent training in behavior management and/or behavioral classroom interventions as the first-line of treatment. • Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. Elementary and middle school-aged children (six to 11 years of age) • The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder (ADHD) along with parent training in behavior management and/or behavioral classroom intervention, preferably both. • The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order). Adolescents (12 to 18 years of age) • The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe evidence-based training interventions and/or behavioral interventions as treatment for ADHD. General considerations • Stimulant medications are highly effective for most adolescents in reduction of core symptoms of ADHD. • Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants. • Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications. • Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse. • Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine or extended-release clonidine. • Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
National Institute for Health and Clinical Excellence: **Attention Deficit Hyperactivity Disorder: Diagnosis and Management (2018)**[33]	Planning treatment for ADHD in children under five years of age • Offer an ADHD-focused group parent-training program to parents or carers of children under five years with ADHD as first-line treatment. • If after an ADHD-focused group parent-training program, ADHD symptoms across settings are still causing a significant impairment in a child under five years after environmental modifications have been implemented and reviewed, obtain advice from a specialist ADHD service with expertise in managing ADHD in young children. • Do not offer medication for ADHD for any child under five years without a

Clinical Guideline	Recommendation(s)
Last updated September 2019	second specialist opinion from an ADHD service with expertise in managing ADHD in young children. <u>Planning treatment for ADHD in children aged five years and over and young people</u> • Give ADHD-focused information and offer additional support as the first approach to parents and carers of all children aged five years and over and young people with ADHD. The support should be group based and ADHD focused. • Consider individual parent-training/education programs for parents and carers of children and young people with ADHD when there are particular difficulties for families in attending group sessions (for example, because of disability, needs related to diversity such as language differences, learning disability [intellectual disability], parental ill-health, problems with transport, or where other factors suggest poor prospects for therapeutic engagement) and when a family's needs are too complex to be met by group-based parent-training/education programs. • Offer medication for children aged five years and over and young people if their ADHD symptoms are still causing a persistent significant impairment in at least one domain after their parents have received ADHD-focused information, group-based support has been offered, and environmental modifications have been implemented and reviewed. • Consider a course of cognitive behavioral therapy (CBT) for young people with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain, addressing the following areas: o social skills with peers o problem-solving o self-control o active listening skills o dealing with and expressing feelings <u>Planning treatment for ADHD in adults</u> • Offer medication to adults with ADHD if their ADHD symptoms are still causing a significant impairment in at least one domain after environmental modifications have been implemented and reviewed. • Consider non-pharmacological treatment for adults with ADHD who have made an informed choice not to have medication, have difficulty adhering to medication, or have found medication to be ineffective or cannot tolerate it. • Consider non-pharmacological treatment in combination with medication for adults with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain. • When non-pharmacological treatment is indicated for adults with ADHD, offer the following as a minimum: a structured supportive psychological intervention focused on ADHD and regular follow‑up either in person or by phone. • Treatment may involve elements of or a full course of CBT. <u>Medication choice – children aged five years and over and young people</u> • Offer methylphenidate (either short or long acting) for children aged five years and over and young people if their ADHD symptoms are still causing a persistent significant impairment in at least one domain after their parents have received ADHD-focused information, group-based support has been offered and environmental modifications have been implemented and reviewed. • Consider switching to lisdexamfetamine for children aged five years and over and young people who have had a six-week trial of methylphenidate at an adequate dose and not derived enough benefit in terms of reduced ADHD symptoms and associated impairment. • Consider dexamphetamine for children aged five years and over and young

Clinical Guideline	Recommendation(s)

	people whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile.
	• Offer atomoxetine or guanfacine to children aged five years and over and young people if:
	  o they cannot tolerate methylphenidate or lisdexamfetamine or
	  o their symptoms have not responded to separate six-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.
	
	<u>Medication choice – adults</u>
	• Offer lisdexamfetamine or methylphenidate as first-line pharmacological treatment for adults with ADHD.
	• Consider switching to lisdexamfetamine for adults who have had a six-week trial of methylphenidate at an adequate dose but have not derived enough benefit in terms of reduced ADHD symptoms and associated impairment.
	• Consider switching to methylphenidate for adults who have had a six-week trial of lisdexamfetamine at an adequate dose but have not derived enough benefit in terms of reduced ADHD symptoms and associated impairment.
	• Consider dexamphetamine for adults whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile.
	• Offer atomoxetine to adults if:
	  o they cannot tolerate lisdexamfetamine or methylphenidate or
	  o their symptoms have not responded to separate six-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.
	
	<u>Further medication choices</u>
	• Obtain a second opinion or refer to a tertiary service if ADHD symptoms in a child aged five years or over, a young person or adult are unresponsive to one or more stimulants and one non-stimulant.
	• Do not offer any of the following medication for ADHD without advice from a tertiary ADHD service:
	  o guanfacine for adults
	  o clonidine for children with ADHD and sleep disturbance, rages or tics
	  o atypical antipsychotics in addition to stimulants for people with ADHD and coexisting pervasive aggression, rages or irritability
	
	<u>Medication choice – people with coexisting conditions</u>
	• Offer the same medication choices to people with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other people with ADHD.
	• For children aged five years and over, young people and adults with ADHD experiencing an acute psychotic or manic episode:
	  o stop any medication for ADHD
	  o consider restarting or starting new ADHD medication after the episode has resolved, taking into account the individual circumstances, risks and benefits of the ADHD medication.
	
	<u>Considerations when prescribing ADHD medication</u>
	• When prescribing stimulants for ADHD, think about modified-release once-daily preparations for the following reasons:
	  o convenience
	  o improving adherence
	  o reducing stigma (because there is no need to take medication at school or in the workplace)
	  o reducing problems of storing and administering controlled drugs at school
	  o the risk of stimulant misuse and diversion with immediate-release

Clinical Guideline	Recommendation(s)
	preparations o their pharmacokinetic profiles. • Immediate-release preparations may be suitable if more flexible dosing regimens are needed, or during initial titration to determine correct dosing levels. • When prescribing stimulants for ADHD, be aware that effect size, duration of effect and adverse effects vary from person to person. • Think about using immediate- and modified-release preparations of stimulants to optimize effect (for example, a modified-release preparation of methylphenidate in the morning and an immediate-release preparation of methylphenidate at another time of the day to extend the duration of effect). • Be cautious about prescribing stimulants for ADHD if there is a risk of diversion for cognitive enhancement or appetite suppression. • Do not offer immediate-release stimulants or modified-release stimulants that can be easily injected or insufflated if there is a risk of stimulant misuse or diversion. • Prescribers should be familiar with the requirements of controlled drug legislation governing the prescription and supply of stimulants. <u>Adherence to treatment</u> • Be aware that the symptoms of ADHD may lead to people having difficulty adhering to treatment plans (for example, remembering to order and collect medication). • Ensure that people are fully informed of the balance of risks and benefits of any treatment for ADHD and check that problems with adherence are not due to misconceptions (for example, tell people that medication does not change personality). • Encourage the person with ADHD to use the following strategies to support adherence to treatment: o being responsible for their own health, including taking their medication as needed o following clear instructions about how to take the medication in picture or written format, which may include information on dose, duration, adverse effects, dosage schedule (the instructions should stay with the medication, for example, a sticker on the side of the packet) o using visual reminders to take medication regularly (for example, apps, alarms, clocks, pill dispensers, or notes on calendars or fridges) o taking medication as part of their daily routine (for example, before meals or after brushing teeth) o attending peer support groups (for both the person with ADHD and for the families and carers). • Encourage parents and carers to oversee ADHD medication for children and young people. <u>Review of medication and discontinuation</u> • A healthcare professional with training and expertise in managing ADHD should review ADHD medication at least once a year and discuss with the person with ADHD (and their families and carers as appropriate) whether medication should be continued. The review should include a comprehensive assessment of the: o preference of the child, young person or adult with ADHD (and their family or carers as appropriate) o benefits, including how well the current treatment is working throughout the day o adverse effects o clinical need and whether medication has been optimized o impact on education and employment o effects of missed doses, planned dose reductions and periods of no treatment o effect of medication on existing or new mental health, physical health or

Clinical Guideline	Recommendation(s)
	neurodevelopmental conditions o need for support and type of support (for example, psychological, educational, social) if medication has been optimized but ADHD symptoms continue to cause a significant impairment. • Encourage people with ADHD to discuss any preferences to stop or change medication and to be involved in any decisions about stopping treatments. • Consider trial periods of stopping medication or reducing the dose when assessment of the overall balance of benefits and harms suggests this may be appropriate. If the decision is made to continue medication, the reasons for this should be documented.
British Association of Psychopharmacology: **Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology (2014)[34]**	<u>Treatment recommendations for children and adolescents</u> • All children with severe ADHD (conceptualized as hyperkinetic disorder) should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions. • The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is psychostimulant medication. • Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child. • Appropriate child and family-based psychological interventions should be available to all children with ADHD. These interventions should be tailored to the child's needs and not depend on the local availability of services. • Teachers should be given evidence-based information about ADHD. • Patient and parental preferences should be taken into account when designing a psychological intervention for ADHD. • Every effort should be made to facilitate the transition from adolescence to adulthood. This should include education of parents, children, and professionals involved in the care of these children and the development of appropriate services and shared care protocols to enable this transition. • Systems and protocols need to be implemented to allow early re-acces to services for young people who may have dropped out of treatment at an early age, but still have significant symptoms and impairment. <u>Treatment recommendations for adults</u> • Stimulant medications are the first-line drugs in adults with ADHD. • Although amphetamines, methylphenidate and atomoxetine are all effective in adults with ADHD, they cannot be considered equivalent because they have different mechanisms of actions and hazards. • Once methylphenidate, atomoxetine, and amphetamines have all been given a fair trial, third-line medications can be considered. These include bupropion, modafinil, tricyclic antidepressants, guanfacine and clonidine. • Co-administration of psychostimulant and other drugs (mainly atomoxetine) is an option for patients showing a limited or lack of clinical response. There is, however, limited evidence supporting either the efficacy or safety of combination therapy. • Psychological treatments are a complement to pharmacological treatment. • Different approaches have been used but the majority the evidence is for structured treatments employing a cognitive behavioral paradigm. • The use of different methods of delivery (group and individual therapy), different criteria for control groups and different outcome measures limit the generalization of results. <u>Abuse potential</u> • Abuse potential is related to drug action and formulation. Abuse is generally low

Clinical Guideline	Recommendation(s)
	among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.
American Academy of Sleep Medicine: **Practice Guideline for the Treatment of Central Disorders of Hypersomnolence (2021)**[35]	Adult patients with narcolepsy • Modafinil, pitolisant, sodium oxybate, and solriamfetol are recommended for the treatment of narcolepsy in adults. • Armodafinil, dextroamphetamine, and methylphenidate are suggested for the treatment of narcolepsy in adults. Adult patients with idiopathic hypersomnia • Modafinil is recommended for the treatment of idiopathic hypersomnia in adults. • Clarithromycin, methylphenidate, pitolisant, and sodium oxybate are suggested for the treatment of idiopathic hypersomnia in adults. Adult patients with Kleine-Levin syndrome • Lithium is suggested for the treatment of Kleine-Levin syndrome in adults. Adult patients with hypersomnia due to medical conditions • Hypersomnia secondary to alpha-synucleinopathies o Armodafinil is suggested for the treatment of hypersomnia secondary to dementia with Lewy bodies in adults. o Modafinil and sodium oxybate are suggested for the treatment of hypersomnia secondary to Parkinson's disease in adults. • Posttraumatic hypersomnia o Armodafinil and modafinil are suggested for the treatment of hypersomnia secondary to traumatic brain injury in adults. • Adult patients with genetic disorders associated with primary central nervous system somnolence o Modafinil is suggested for the treatment of hypersomnia secondary to myotonic dystrophy in adults. • Adult patients with hypersomnia secondary to brain tumors, infections, or other central nervous system lesions o Modafinil is suggested for the treatment of hypersomnia secondary to multiple sclerosis in adults. • Pediatric patients with narcolepsy o Modafinil and sodium oxybate are suggested for the treatment of narcolepsy in pediatric patients. A "strong" recommendation (i.e., "is recommended…") is one that clinicians should follow under most circumstances. A "conditional" recommendation (i.e., "is suggested…") is one that requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action. Under each disorder, strong recommendations are listed in alphabetical order followed by the conditional recommendations in alphabetical order. The interventions in all the recommendation statements were compared to no treatment.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults and Children (2021)**[36]	Pathway for the management of narcolepsy – Pharmacological management in adults • Excessive daytime sleepiness unique/main symptom o First-line monotherapy: modafinil, pitolisant, or solriamfetol o Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to another monotherapy, if not successful, change to second-line options o Second-line combination therapy: Pitolisant AND modafinil or solriamfetol; or sodium oxybate AND any wake-promoting agent (modafinil, solriamfetol, pitolisant, methylphenidate, amphetamines) o Second-line monotherapy: Sodium oxybate, methylphenidate, or

Clinical Guideline	Recommendation(s)
	amphetamines • Excessive daytime sleepiness and cataplexy o First-line monotherapy: Sodium oxybate or pitolisant o First-line combination therapies: venlafaxine/clomipramine AND a first-line wake-promoting agent; or sodium oxybate AND a first-line wake-promoting agent o Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to second-line options o Second-line combination therapy: Exchange sodium oxybate to venlafaxine/clomipramine (and vice-versa); or sodium oxybate, venlafaxine/clomipramine, and a first-line wake-promoting agent; or exchange venlafaxine/clomipramine to another antidepressant • Excessive daytime sleepiness, cataplexy, and disturbed nocturnal sleep o First-line monotherapy: sodium oxybate o First-line combination therapies: sodium oxybate and/or venlafaxine/clomipramine, and a first-line wake-promoting agent; or any wake-promoting agent, venlafaxine/clomipramine, and (only exceptionally and only short-term) z-drugs <u>Pathway for the management of narcolepsy – Pharmacological management in children</u> • Excessive daytime sleepiness unique/main symptom o First-line monotherapy: modafinil, methylphenidate, sodium oxybate, amphetamine derivatives, or pitolisant o Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to another monotherapy • Excessive daytime sleepiness and cataplexy o First-line monotherapy: Sodium oxybate o First-line combination therapy: modafinil or methylphenidate and sodium oxybate o Other combination therapies: modafinil, methylphenidate, and venlafaxine; or modafinil, methylphenidate, or pitolisant, and venlafaxine (or clomipramine or another antidepressant) and sodium oxybate o Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to second-line options • Excessive daytime sleepiness, cataplexy, and disturbed nocturnal sleep o First-line monotherapy: sodium oxybate o First-line combination therapies: sodium oxybate and/or venlafaxine/clomipramine, and a first-line wake-promoting agent
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[37]	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for

Clinical Guideline	Recommendation(s)
	treatment of obstructive sleep apnea. Supplemental oxygen • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea. Medical therapies intended to improve nasal patency • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. Positional therapies • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position.
American Academy of Sleep Medicine: **Practice Parameters for the Evaluation and Treatment of Extrinsic Circadian Rhythm Sleep Disorders (2015)**[38]	Shift work disorder • Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. • Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Cerebral Stimulants/Agents Used for ADHD[30]

Generic Name(s)	Attention Deficit-Hyperactivity Disorder	Narcolepsy	Exogenous Obesity	Binge Eating Disorder
Central Alpha-Agonists				
Clonidine	✔ *			
Amphetamine Derivatives				
Amphetamine sulfate	✔	✔ †	✔ †§	
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	✔	✔ †		
Dextroamphetamine	✔	✔		
Lisdexamfetamine	✔			✔ ‖
Methamphetamine	✔		✔ §	

Generic Name(s)	Attention Deficit-Hyperactivity Disorder	Narcolepsy	Exogenous Obesity	Binge Eating Disorder
Serdexmethylphenidate and dexmethylphenidate	✔			
Respiratory and CNS Stimulants				
Dexmethylphenidate	✔			
Methylphenidate	✔	✔ †‡		
Central Nervous System Agents, Miscellaneous				
Atomoxetine	✔			
Guanfacine	✔ *			
Viloxazine	✔			

*As monotherapy and as adjunctive therapy to stimulant medications.
†Immediate-release formulations.
‡Sustained-release formulations.
§As a short-term adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).
‖For use in moderate to severe Binge Eating Disorder. Not indicated for weight loss or treatment of obesity.

IV. Pharmacokinetics

The pharmacokinetic parameters of the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Cerebral Stimulants/Agents Used for ADHD[3-31]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Central Alpha-Agonists							
Clonidine	0.5 to 1.0	6 to 10	89	20 to 40	Liver (50)	Renal (40 to 60)	12 to 16
Amphetamine Derivatives							
Amphetamine	1 to 3	Up to 10	Well absorbed	20	Liver (not reported)	Renal (67 to 73)	7 to 34
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	Not reported	IR: 4 to 6 XR: 10 to 12	Well absorbed	Not reported	Liver (not reported)	Renal (1 to 75)	9 to 14
Dextroamphetamine	2 to 3	IR: 4 to 6 SR: 6 to 8	Well absorbed	Not reported	Liver (not reported)	Renal (17 to 73)	10 to 12
Lisdexamfetamine	Not reported	10	Rapid	Not reported	Blood (not reported)	Renal (96.0) Feces (0.3)	<1
Methamphetamine	Not reported	Not reported	Rapid	Not reported	Liver (not reported)	Renal (62)	4 to 5
Respiratory and CNS Stimulants							
Dexmethylphenidate	1	IR: 5 to 6 XR: 12	22 to 25	12 to 15	Liver (not reported)	Renal (90)	2.0 to 4.5
Methylphenidate	IR: 2 SR: 4 to 7 ER: 1 to 2 XR: 0.5 to 1.0 TD: 2	IR: 3 to 6 SR: 8 ER: 10 to 12 XR: 8 to 12 TD: 10 to 12	10 to 52	10 to 33	Liver (not reported)	Renal (90) Fecal (1 to 3)	3 to 4
Serdexmethylphenidate and dexmethylphenidate	<1	13	Not reported	Not reported	Liver (not reported)	Not reported	5.7 and 11.7
Central Nervous System Agents, Miscellaneous							
Atomoxetine	1 week	Not reported	63 to 94	98	Liver (not reported)	Renal (>80) Feces (<17)	5 to 22
Guanfacine	Not reported	Not reported	80	70	Liver (50)	Renal (50)	16
Viloxazine	Not reported	Not reported	Not reported	76 to 82	Liver (extensive)	Renal (90)	7

ER=extended-release (osmotic), IR=immediate-release, SR=sustained-release, TD=transdermal, XR=extended-release (non-osmotic)

V. Drug Interactions

Major drug interactions with the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 6.

Table 6. Major Drug Interactions with the Cerebral Stimulants/Agents Used for ADHD[31]

Generic Name(s)	Interaction	Mechanism
Central Alpha-Agonists		
Clonidine	Beta-adrenergic blockers	Withdrawal hypertension may be more severe in patients receiving clonidine and beta-adrenergic blockers. This combination may, on occasion, cause paradoxical hypertension.
Clonidine	Tricyclic antidepressants	The antihypertensive effects of clonidine may be decreased by tricyclic antidepressants. Tricyclic antidepressants may worsen rebound reactions from abrupt clonidine withdrawal.
Clonidine	Non-dihydropyridine calcium channel blockers	Concurrent use of clonidine and non-dihydropyridine calcium channel blockers may result in increased incidence of sinus bradycardia.
Clonidine	Mirtazapine	Concurrent use of mirtazapine and clonidine may result in hypertension, decreased antihypertensive effectiveness.
Clonidine	Tizanidine	The potential for symptomatic additive hypotension exists when tizanidine is coadministered with clonidine.
Amphetamine Derivatives		
Amphetamine derivatives	MAOIs	Toxicity of amphetamines may be increased by MAOIs. Headache, hyperpyrexia, elevated blood pressure and bradycardia may occur. Amphetamines can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with MAOIs.
Amphetamine derivatives	Urinary alkalinizers	Interaction may lead to pH-dependent diminished urinary elimination of amphetamines and increases risk of amphetamine toxicity.
Amphetamine derivatives	Thiazide diuretics	Concurrent use of amphetamines and thiazide diuretics may result in increased exposure to amphetamine.
Respiratory and CNS Stimulants		
Methylphenidates	MAOIs	Pharmacologic effects of methylphenidates may be increased. Headache, gastrointestinal symptoms and hypertension may occur. The mechanism of this interaction is not clear. Liberation of intraneuronal catecholamine stores may play a role.
Methylphenidates	Bupropion	Caution is advised with concomitant use of bupropion and methylphenidates, as this may result in an increased risk of seizures, especially in patients with a seizure history. Both agents may lower the seizure threshold.
Central Nervous System Agents, Miscellaneous		
Atomoxetine, viloxazine	MAOIs	Toxic effects may be increased with concurrent administration of atomoxetine/viloxazine and MAOIs. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of atomoxetine/viloxazine and MAOIs may be

Generic Name(s)	Interaction	Mechanism
		additive.
Atomoxetine	Albuterol	Concurrent use of albuterol and atomoxetine may result in an increase in heart rate and blood pressure.
Guanfacine	Conivaptan	Concurrent use of conivaptan and guanfacine may result in increased guanfacine exposure.
Viloxazine	Theophylline	Concurrent use of theophylline and viloxazine may result in increased theophylline exposure and risk of theophylline toxicity (nausea, vomiting, palpitations, seizures).
Viloxazine	Ozanimod	Concurrent use of ozanimod and viloxazine may result in increased risk of potentially life-threatening hypertensive crisis.
Viloxazine	CYP1A2 Substrates	Concurrent use of viloxazine and CYP1A2 substrates may result in increased exposure of the CYP1A2 substrate and risk of adverse events.

MAOIs=monoamine oxidase inhibitors

VI. Adverse Drug Events

The most common adverse drug events reported with the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Tables 7 to 10. The boxed warnings for the cerebral stimulants/agents used for ADHD are listed in Tables 11 to 16. Methylphenidate and amphetamines increase dopamine levels in the brain similar to cocaine and methamphetamine. They are classified as Schedule II controlled substances by federal regulation. Long-term abusive use can lead to tolerance and psychological dependence. There is no evidence to suggest that drug abuse results from prescribed stimulants if they are properly monitored.[1,39-41] Methylphenidate is a less potent sympathomimetic amine than mixed amphetamine salts, which may be associated with a lower potential for abuse.[40] The osmotic-release formulation of methylphenidate cannot be crushed and may decrease the potential for abuse. It has also been proposed that transdermal methylphenidate may possess less potential for abuse compared to orally-administered cerebral stimulants. Atomoxetine, clonidine, guanfacine, and viloxazine are not controlled substances.

Table 7. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[3]

Adverse Events	Clonidine
Cardiovascular	
Atrioventricular block	✔
Bradycardia	≤4
Cardiac arrhythmia	✔
Chest pain	✔
Congestive heart failure	✔
Electrocardiogram abnormalities	✔
Orthostatic hypotension	✔
Pallor	✔
Palpitations	1
Reynaud's phenomenon	✔
Syncope	✔
Tachycardia	1
Central Nervous System	
Abnormal sleep-related event	1 to 3
Aggressive behavior	✔
Agitation	✔
Anxiety	✔
Behavioral change	✔
Crying	1 to 3

Adverse Events	Clonidine
Delirium	✔
Dizziness	2 to 5
Emotional disorder	3 to 4
Fatigue/lethargy	12 to 15
Fever	✔
Hallucinations	✔
Headache	1 to 11
Insomnia	≤5
Irritability	3 to 6
Malaise	✔
Mental depression	1
Nervousness	1 to 3
Nightmares	✔
Paresthesia	✔
Restlessness	✔
Sleep terror	3
Somnolence	26 to 33
Tremor	✔
Vivid dreams	✔
Dermatological	
Flushing	✔
Rash	1
Urticaria	✔
Gastrointestinal	
Abdominal pain	≤3
Anorexia	1
Constipation	1 to 6
Diarrhea	≤1
Dry mouth	✔
Nausea	1 to 4
Thirst	1 to 3
Vomiting	✔
Weight gain	<1
Genitourinary	
Dysuria	✔
Enuresis	4
Erectile dysfunction	2 to 3
Gynecomastia	1
Libido decreased	✔
Nocturia	1
Pollakiuria	3
Sexual disturbances	3
Hepatic	
Hepatitis	✔
Liver function test abnormalities	≤1
Musculoskeletal	
Arthralgia	1
Leg cramps	≤1
Myalgia	1
Pain in extremities	✔
Weakness	10
Respiratory	
Asthma	4
Epistaxis	3

Adverse Events	Clonidine
Lower respiratory tract infection	2
Nasal congestion	2 to 4
Nasal dryness	✔
Nasopharyngitis	2
Upper respiratory tract infection	2 to 7
Special Senses	
Accommodation difficulties	✔
Blurred vision	✔
Dry eyes	✔
Eye pain	✔
Other	
Body temperature increase	≤2
Ear infection	✔
Ear pain	4
Flu-like syndrome	≤3
Throat pain	3 to 5
Thrombocytopenic purpura	✔
Viral infection	≤3

✔ Percent not specified.

Table 8. Adverse Drug Events (%) Reported with the Amphetamines[6-12,30]

Adverse Events	Amphetamine	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextroam-phetamine	Lisdexam-fetamine	Metham-phetamine
Cardiovascular					
Blood pressure increased	-	-	-	3	-
Cardiomyopathy	✔	✔ †	✔	✔	-
Heart rate increased	-	-	✔	2	✔
Hypertension	✔	✔ †	✔	✔	✔
Myocardial infarction	-	✔ *	✔	✔	✔
Palpitations	✔	✔ †, 2 to 4*	✔	✔	✔
Peripheral vascular disease	-	-	✔	-	-
Raynaud's disease	-	-	✔	-	✔
Sudden death	-	✔ *	✔	✔	✔
Tachycardia	✔	✔ †, 6*	✔	✔	✔
Central Nervous System					
Aggressive behavior	-	✔ †*	✔	-	-
Agitation	-	8*	-	3	-
Anxiety	-	8*	-	6	-
Depression	-	✔ †*	-	✔	-
Dizziness	✔	2 to 7*	✔	5	✔
Dyskinesia	✔	✔ †*	✔	✔	-
Dysphoria	✔	✔ †*	✔	✔	✔
Euphoria	✔	✔ †*	✔	✔	✔
Fever	-	5*	-	2	-
Headache	✔	✔ †, 26*	✔	12	✔
Insomnia	✔	12 to 27*	✔	13 to 27	✔
Irritability	-	✔ †*	-	10	-
Labile affect	-	-	-	3	-
Mania	-	-	✔	✔	✔
Nervousness	-	6 to 13*	-	-	-
Overstimulation	✔	✔ †	✔	✔	✔
Psychotic episodes	✔	✔ †	✔	✔	✔
Restlessness	✔	✔ †*	✔	3	✔
Seizures	-	✔ *	-	✔	✔
Somnolence	-	2 to 4*	-	2	-

Adverse Events	Amphetamine	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextroam-phetamine	Lisdexam-fetamine	Metham-phetamine
Speech disorder	-	2 to 4*	-	-	-
Stroke	-	✔ *	✔	✔	✔
Tic exacerbation	✔	✔ †*	✔	2	✔
Tourette's exacerbation	✔	✔ †*	✔	✔	✔
Tremor	✔	✔ †*	✔	2	✔
Twitching	-	2 to 4*	-	-	-
Dermatological					
Diaphoresis	-	2 to 4*	-	-	-
Hyperhidrosis	-	-	-	3	-
Photosensitivity	-	2 to 4*	-	-	-
Rash	-	✔ †*	✔	3	✔
Stevens-Johnson syndrome	-	✔ †*	-	✔	-
Toxic epidermal necrolysis	-	✔ †*	-	✔	-
Urticaria	✔	✔ †*	✔	✔	✔
Gastrointestinal					
Abdominal pain	-	11 to 14*	-	12	-
Anorexia	✔	-	✔	5	✔
Appetite decreased	-	22 to 36*	-	27 to 39	-
Constipation	✔	✔ †, 2 to 4*	✔	✔	✔
Diarrhea	✔	2 to 6*	✔	7	✔
Dry mouth	✔	2 to 35*	✔	4 to 26	✔
Dyspepsia	-	2 to 4*	-	-	-
Nausea	-	2 to 8*	-	6 to 7	✔
Other gastrointestinal disturbances	✔	-	✔	-	✔
Unpleasant taste	✔	✔ †*	✔	✔	✔
Vomiting	✔	2 to 7*	-	9	✔
Weight loss	✔	4 to 11*	✔	9	✔
Genitourinary					
Changes in libido	✔	2 to 4*	✔	≤2	✔
Impotence	✔	2 to 4*	✔	✔	✔
Prolonged erections	✔	-	-	-	-
Urinary tract infection	-	5*	-	-	-
Other					
Anaphylaxis	-	✔ *	-	✔	-
Angioedema	-	-	-	✔	-
Application site discomfort	-	-	69^	-	-
Blurred vision	-	✔ †*	✔	✔	-
Dysmenorrhea	-	2 to 4*	-	-	-
Dyspnea	-	2 to 4*	-	2	-
Growth suppression	-	-	✔	✔	✔
Hypersensitivity reactions	-	-	-	✔	-
Infection	-	2 to 4*	-	-	-
Rhabdomyolysis	✔	-	-	-	-
Tolerance	-	-	-	-	✔
Weakness	-	2 to 6*	-	-	-

†Immediate-release formulation.
*Extended-release formulation.
^Transdermal formulation.
✔ Percent not specified.
-Event not reported or incidence <1%.

Table 9. Adverse Drug Events (%) Reported with the Respiratory and CNS Stimulants[30]

Adverse Events	Dexmethylphenidate	Methylphenidate	Serdexmethylphenidate and dexmethylphenidate
Cardiovascular			

Adverse Events	Dexmethylphenidate	Methylphenidate	Serdexmethylphenidate and dexmethylphenidate
Angina	✔	✔	✔
Cardiac arrhythmia	✔	✔	✔
Chest pain	-	✔	-
Hypertension	✔	✔	✔
Hypotension	✔	✔	✔
Myocardial infarction	-	✔	-
Palpitations	✔	✔	✔
Pulse increase/decrease	✔	✔	✔
Raynaud's phenomenon	-	✔	✔
Sudden death	✔	-	✔
Systolic blood pressure increased	-	-	-
Tachycardia	3	✔	✔
Vasodilation	-	-	-
Central Nervous System			
Aggressive behavior	✔	✔	✔
Agitation	-	-	-
Anxiety	5 to 11	-	✔
Attention disturbance	-	-	-
Cerebral arteritis	✔	✔	✔
Cerebral occlusion	✔	✔	✔
Depression	✔	✔	✔
Dizziness	6	✔	✔
Drowsiness	✔	✔	✔
Dyskinesia	✔	✔	✔
Emotional instability	-	6†	-
Fatigue/lethargy	-	-	-
Fever	5	✔	5
Hallucinations	-	✔ †	-
Headache	25 to 39	✔, 28†	✔
Hyperkinesia	-	-	-
Hypertonia	-	-	-
Insomnia	✔	✔, 13 to 30†	✔
Jittery feeling	12	-	✔
Labile affect	-	✔	-
Mania	-	✔	-
Migraine	-	-	-
Nervousness	✔	✔	✔
Neuroleptic malignant syndrome	✔	✔	✔
Overstimulation	-	-	-
Paresthesia	-	✔	-
Psychotic episodes	-	-	-
Restlessness	12	-	✔
Seizures	-	✔ †	-
Somnolence	-	-	-
Tic	-	✔, 7†	-
Tourette's exacerbation	✔	✔	✔
Toxic psychosis	✔	✔	✔
Tremor	-	-	-
Vertigo	-	-	-
Dermatological			
Alopecia	-	✔	-
Application site reaction	-	✔ †	-
Dermatitis	-	-	-

Adverse Events	Dexmethylphenidate	Methylphenidate	Serdexmethylphenidate and dexmethylphenidate
Diaphoresis	-	-	-
Erythema	-	✔	-
Erythema multiforme	✔	✔	✔
Exfoliative dermatitis	✔	✔	✔
Hair loss	✔	✔	✔
Herpes simplex	-	-	-
Hyperhidrosis	-	✔	-
Rash	✔	✔	✔
Stevens-Johnson syndrome	-	-	-
Toxic epidermal necrolysis	-	✔	-
Urticaria	✔	✔	✔
Gastrointestinal			
Abdominal pain	15	✔	✔
Anorexia	5 to 7	✔, 5 to 46†	✔
Appetite decreased	30	✔, 26†	✔
Bruxism	-	✔	-
Constipation	-	✔	-
Diarrhea	-	✔	-
Dry mouth	7 to 20	✔	✔
Dyspepsia	5 to 9	✔	✔
Flatulence	-	-	-
Mouth ulceration	-	-	-
Nausea	9	✔, 12†	✔
Stomach cramps	✔	-	✔
Thirst	-	-	-
Unpleasant taste	-	-	-
Vomiting	-	✔, 10†	-
Weight loss	✔	✔, 9†	✔
Genitourinary			
Abnormal urine	-	-	-
Erectile disturbance	-	✔	-
Hematuria	-	-	-
Libido decreased	-	✔	-
Polyuria	-	-	-
Pyuria	-	-	-
Hematologic			
Agranulocytosis	-	-	-
Anemia	✔	✔	✔
Eosinophilia	-	-	-
Leukopenia	✔	✔	✔
Pancytopenia	-	✔	-
Thrombocytopenic purpura	✔	✔	✔
Hepatic			
Hepatic coma	✔	✔	✔
Liver function test abnormalities	✔	✔	✔
Musculoskeletal			
Arthralgia	✔	✔	✔
Back pain	-	-	-
Respiratory			
Cough	-	✔	-
Dyspnea	-	✔	-
Epistaxis	-	-	-
Lung disorder	-	-	-

Adverse Events	Dexmethylphenidate	Methylphenidate	Serdexmethylphenidate and dexmethylphenidate
Nasal congestion	-	✔, 6†	-
Nasopharyngitis	-	✔, 5†	-
Pharyngitis	-	✔	-
Pharyngolaryngeal pain	4 to 7	✔	✔
Respiratory tract infection	-	✔	-
Rhinitis	-	✔	-
Sinusitis	-	✔	-
Special Senses			
Abnormal vision	-	-	-
Accommodation difficulties	✔	✔	✔
Amblyopia	-	-	-
Blurred vision	✔	✔	✔
Dry eyes	-	✔	-
Eye pain	-	-	-
Mydriasis	-	✔	-
Other			
Accidental injury	-	✔	-
Allergic contact sensitization	-	✔ †	-
Anaphylaxis	-	✔ †	-
Drug abuse/dependence			✔
Dysmenorrhea	-	✔	-
Edema	-	-	-
Flu-like syndrome	-	-	-
Growth suppression	-	✔	✔
Hypersensitivity reactions	✔	✔	✔
Necrotizing vasculitis	✔	✔	✔
Pain	-	-	-
Thirst	-	-	-
Viral infection	-	28†	-

†Transdermal formulation.
✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Central Nervous System Agents, Miscellaneous[26-30]

Adverse Events	Atomoxetine	Guanfacine	Viloxazine
Cardiovascular			
Atrioventricular block	-	✔	-
Diastolic blood pressure increased	4 to 22	-	13 to 25
Flushing	≥2	-	-
Heart rate increased	-	-	22 to 34
Hypertension	1 to 9	✔	-
Hypotension	<2	4	-
Palpitations	3	-	-
QT prolongation	<1	-	-
Reynaud's phenomenon	✔	-	-
Sinus arrhythmia	-	✔	-
Stroke	✔	-	-
Systolic blood pressure increased	4 to 13	-	-
Tachycardia	2 to 24	-	4
Central Nervous System			
Abnormal dreams	4	-	-
Aggressive behavior	✔	-	-
Agitation	✔	✔	-

Adverse Events	Atomoxetine	Guanfacine	Viloxazine
Akathisia	✔	-	-
Anxiety	✔	✔	-
Attention disturbance	-	-	-
Chills	3	-	-
Confusion	-	-	-
Crying	2	-	-
Depression	-	✔	-
Disorientation	-	-	-
Dizziness	5 to 6	6 to 8	4
Drowsiness	-	-	6 to 19
Early morning awakening	<2	-	-
Fatigue/lethargy	6 to 9	14	4 to 12
Fever	3	-	1 to 3
Hallucinations	-	✔	-
Headache	2 to 19	21 to 24	10 to 17
Hostility	✔	-	-
Insomnia	2 to 15	12	2 to 23
Irritability	≤ 6	2	2 to 5
Jittery feeling	2	-	-
Mania	✔	-	-
Mood swings	1 to 2	-	-
Nervousness	-	-	-
Nightmare	-	✔	-
Panic disorder	✔	-	-
Paresthesia	4	-	-
Rigors	3	-	-
Seizure	-	✔	-
Sleep disorder	-	-	-
Sleep disturbance	3	-	-
Somnolence	4 to 11	18 to 38	-
Suicidal ideation	✔	-	≤2
Syncope	✔	✔	-
Tremor	2	-	-
Dermatological			
Dermatitis	2 to 4	-	-
Diaphoresis	2	-	-
Flushing	2	-	-
Hyperhidrosis	4	-	-
Rash	2	-	-
Urticaria	✔	-	-
Endocrine and Metabolic			
Dysmenorrhea	6	-	-
Hot flushes	8	-	-
Menstrual disturbances	2 to 3	-	-
Gastrointestinal			
Abdominal pain	7 to 18	10 to 11	6 to 7
Anorexia	<3	-	-
Appetite decreased	11 to 16	2	5 to 10
Constipation	1 to 9	3	6
Diarrhea	4	-	-
Dry mouth	4 to 21	3	-
Dyspepsia	4 to 6	✔	-
Fecal incontinence	-	-	-
Flatulence	2	-	-

Adverse Events	Atomoxetine	Guanfacine	Viloxazine
Gastroesophageal reflux disease	-	-	2
Nausea	7 to 26	4	4 to 12
Stomach discomfort	-	✔	-
Vomiting	3 to 11	✔	3 to 6
Weight increase	-	✔	-
Weight loss	2 to 30	-	-
Xerostomia	-	-	10
Genitourinary			
Dysuria	3	-	-
Ejaculatory disturbance	3	-	-
Enuresis	-	✔	-
Erectile disturbance	9	-	-
Impotence	3	-	-
Libido decreased	4	-	-
Orgasm abnormal	2	-	-
Prostatitis	2	-	-
Urinary retention	7	-	-
Hepatic			
Hepatotoxicity	✔	-	-
Jaundice	✔	-	-
Respiratory			
Asthma	-	✔	-
Cough	11	-	-
Dyspnea	-	-	-
Nasopharyngitis	-	-	-
Rhinitis	-	-	-
Rhinorrhea	4	-	-
Sinus headache	3	-	-
Sinusitis	6	-	-
Upper respiratory infection	-	-	7 to 8
Special Senses			
Amblyopia	-	-	-
Blurred vision	-	-	-
Mydriasis	<2	-	-
Tinnitus	-	-	-
Other			
Allergic contact sensitization	✔	-	-
Ear infection	3	-	-
Ear pain	-	-	-
Flu-like syndrome	✔	-	-
Hypersensitivity reactions	<1	✔	-
Influenza	3	-	-
Pallor	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Boxed Warning for the Amphetamines[30]

WARNING
Amphetamines have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly.

Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

Table 12. Boxed Warning for Atomoxetine[30]

WARNING
Suicidal ideation in children and adolescents: Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with attention deficit hyperactivity disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Closely monitor patients who are started on therapy for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescribing health care provider. Atomoxetine is approved for ADHD in children and adults. Atomoxetine is not approved for major depressive disorder (MDD). Pooled analysis of short-term (six- to 18-week), placebo-controlled trials of atomoxetine in children and adolescents (12 trials involving more than 2,200 patients, including 11 trials in ADHD and 1 trial in enuresis) has revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1,357 patients), compared to none in placebo-treated patients (0/851 patients). No suicides occurred in these trials

Table 13. Boxed Warning for Dexmethylphenidate[30]

WARNING
CNS stimulants, including dexmethylphenidate, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

Table 14. Boxed Warning for Methamphetamine[30]

WARNING
Methamphetamine has a high potential for abuse. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for nontherapeutic use or distribution to others, and the drug should be prescribed or dispensed sparingly. Misuse of methamphetamine may cause sudden death and serious cardiovascular adverse events.

Table 15. Boxed Warning for Methylphenidate and Serdexmethylphenidate-dexmethylphenidate[30]

WARNING
CNS stimulants, including methylphenidate, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Methylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Table 16. Boxed Warning for Viloxazine[30]

WARNING
In clinical studies, higher rates of suicidal thoughts and behavior were reported in patients with ADHD treated with viloxazine than in patients treated with placebo. Closely monitor all viloxazine-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.

VII. Dosing and Administration

The usual dosing regimens for the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 17.

Table 17. Usual Dosing Regimens for the Cerebral Stimulants/Agents Used for ADHD[3-30]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Central Alpha-Agonists			
Clonidine	Safety and efficacy have not been established in adults.	ADHD in patients ≥6 years of age: Tablet (ER): initial, 0.1 mg at bedtime; increase by 0.1 mg/day every seven days until desired response; doses should be administered twice daily; maximum, 0.4 mg/day	Tablet (ER): 0.1 mg
Amphetamines			
Amphetamine	ADHD: ODT (ER): 12.5 mg daily Tablet (ER), suspension (ER): Initial, 2.5 mg or 5 mg once daily in the morning, dose may be increased in increments of 2.5 to 10 mg daily every four to seven days; maximum, 20 mg daily Exogenous obesity: Tablet: usual dosage is up to 30 mg daily, taken in divided doses of 5 to 10 mg, 30 to 60 minutes before meals Narcolepsy: Tablet: 5 to 60 mg/day in divided doses	ADHD in children three to five years of age: Tablet: initial, 2.5 mg once daily, daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response ADHD in children six years of age or older: ODT (ER): initial, 6.3 mg once daily in the morning, daily dosage may be raised in increments of 3.1 or 6.3 mg at weekly intervals; maximum, 18.8 mg daily for patients six to 12 years, and 12.5 mg daily for patients 13 to 17 years Tablet (ER), suspension (ER): Initial, 2.5 mg or 5 mg once daily in the morning, dose may be increased in increments of 2.5 to 10 mg daily every four to seven days; maximum, 20 mg daily ODT (IR), tablet: initial, 5 mg once or twice daily, daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response Exogenous obesity in children ≥12 years of age: Tablet: usual dosage is up to 30 mg daily, taken in divided doses of 5 to 10 mg, 30 to 60 minutes before meals Narcolepsy in children six to 12 years of age: Tablet: initial, 5 mg daily,	ODT (ER): 3.1 mg 6.3 mg 9.4 mg 12.5 mg 15.7 mg 18.8 mg ODT (IR): 5 mg 10 mg 15 mg 20 mg Suspension (ER): 2.5 mg/mL Tablet: 5 mg 10 mg Tablet (ER): 5 mg 10 mg 15 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		daily dose may be raised in increments of 5 mg at weekly intervals until optimal response Narcolepsy in children 12 years of age and older: Tablet: initial, 10 mg once daily, daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response	
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	ADHD: Capsule (ER): 20 mg once daily in the morning Capsule (Mydayis ER®): initial, 12.5 mg daily in the morning, adjust in increments of 12.5 mg no sooner than weekly; maximum, 50 mg daily Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Tablet: 5 to 60 mg daily in divided doses	ADHD: Capsule (ER), ≥six years of age: 10 mg once daily in the morning; maximum, 30 mg/day Capsule (Mydayis ER®), ≥13 years of age: initial, 12.5 mg daily in the morning, adjust in increments of 12.5 mg no sooner than weekly; maximum, 25 mg daily Tablet, ≥three years of age: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in children six to 12 years of age: Tablet: 5 mg once daily; may increase by 5 mg weekly until optimal response Narcolepsy in children 12 years of age and older: Tablet: 10 mg once daily; may increase by 10 mg weekly until optimal response	Capsule (ER): (Adderall XR®) 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Capsule (ER): (Mydayis ER®) 12.5 mg 25 mg 37.5 mg 50 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextroamphetamine	ADHD: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Transdermal patch: initial, 9 mg/9 hours; Maximum recommended dose is 18 mg/9 hours; Apply one transdermal system 2 hours before an effect is needed and remove	ADHD in children six years of age and older: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Transdermal patch: initial, 4.5 mg/9 hours. Titrate dosage in weekly increments of 4.5 mg up to a maximum recommended dose of 18 mg/9	Capsule (SR): (Dexedrine® Spansule) 5 mg 10 mg 15 mg Solution: (Procentra®) 5 mg/5 mL Tablet: (Dexedrine®, Zenzedi®) 2.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	within 9 hours Narcolepsy: Capsule (SR), solution, tablet: 5 to 60 mg/day administered in divided doses	hours; Apply one transdermal system 2 hours before an effect is needed and remove within 9 hours ADHD in children three to five years of age: Solution, tablet: initial, 2.5 mg once daily; maintenance, up to 40 mg daily Narcolepsy in adolescents 12 years of age and older: Capsule (SR), solution, tablet: initial, 10 mg once daily; maintenance, 5 to 60 mg/day administered in divided doses Narcolepsy in children six to 12 years of age: Capsule (SR), solution, tablet: initial, 5 mg once daily; maintenance, 5 to 60 mg/day administered in divided doses	5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg Transdermal patch: (Xelstrym®) 4.5 mg/9 hours 9 mg/9 hours 13.5 mg/9 hours 18 mg/9 hours
Lisdexamfetamine	ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day Chewable tablet: initial, 30 mg daily in the morning, adjust dose in increments of 10 or 20 mg at weekly intervals; maximum, 70 mg daily Binge eating disorder: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	ADHD in children six years of age and older: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day Chewable tablet: initial, 30 mg daily in the morning, adjust dose in increments of 10 or 20 mg at weekly intervals; maximum, 70 mg daily	Capsule: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg Chewable tablet: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg
Methamphetamine	Exogenous obesity: Tablet: 5 mg taken 30 minutes before each meal ADHD: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Exogenous obesity in children 12 years of age and older: Tablet: 5 mg taken 30 minutes before each meal ADHD in children six years of age and older: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Tablet: 5 mg
Respiratory and CNS Stimulants			
Dexmethylphenidate	ADHD: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 40 mg/day	ADHD in children six years of age and older: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30	Capsule (ER): 5 mg 10 mg 15 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	mg/day Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg
Methylphenidate	Treatment of ADHD: Chewable tablet, solution, tablet: 20 to 30 mg/day administered in two or three divided doses Chewable tablet (Quillichew ER®): initial, 20 mg daily in the morning, adjust in increments of 10, 15, or 20 mg; maximum, 60 mg daily Capsule (ER) (new starts): initial, 10 or 20 mg once daily in the morning; maximum, 60 mg/day Capsule (ER) (patients currently receiving methylphenidate): administer equivalent total daily doses Suspension (ER): initial, 20 mg once daily in the morning; maximum, 60 mg/day Tablet (ER) (new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER)	ADHD in children six years of age and older: Capsule (ER): initial, 10 mg once daily in the morning; dosage may be increased weekly in increments of 10 mg; maximum, 60 mg daily Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Chewable tablet (Quillichew ER®): initial, 20 mg daily in the morning, adjust in increments of 10, 15, or 20 mg; maximum, 60 mg daily ODT: initial, 17.3 mg daily in the morning, may titrate weekly in increments of 8.6 to 17.3 mg; maximum, 51.8 mg Tablet (ER) (new starts): initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents) Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER)	Capsule (ER): (Adhansia XR®, Aptensio XR®, Jornay PM®, Ritalin LA®) 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg 45 mg 50 mg 55 mg 60 mg 70 mg 80 mg 85 mg 100 mg Suspension (ER): (Quillivant XR®) 25 mg/5 mL Chewable tablet: 2.5 mg 5 mg 10 mg Chewable tablet (ER): (Quillichew ER ®) 20 mg 30 mg 40 mg ODT (ER): (Cotempla XR-

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect Narcolepsy: Chewable tablet, solution, tablet (adults): 20 to 30 mg/day administered in two or three divided doses Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets	corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect Narcolepsy in children six years of age and older: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets	ODT®) 8.6 mg 17.3 mg 25.9 mg Solution: (Methylin®) 5 mg/5 mL 10 mg/5 mL Tablet (ER): (Concerta®, Relexxii ER®) 10 mg 18 mg 20 mg 27 mg 36 mg 54 mg 72 mg Tablet: (Ritalin®) 5 mg 10 mg 20 mg Transdermal patch: 10 mg/9 hours 15 mg/9 hours 20 mg/9 hours 30 mg/9 hours
Serdexmethylphenidate and dexmethylphenidate	ADHD: Capsule: initial, 39.2 mg-7.8 mg orally once daily in the morning. Increase the dosage after one week to 52.3 mg-10.4 mg once daily	ADHD in patients six to 12 years of age: Capsule: initial, 39.2 mg-7.8 mg orally once daily in the morning. Dosage may be increased to 52.3 mg-10.4 mg daily or decreased to 26.1 mg-5.2 mg daily after one week. Maximum recommended dosage is 52.3 mg-10.4 mg once daily ADHD in patients ≥13 years of age: Capsule: initial, 39.2 mg-7.8 mg orally once daily in the morning. Increase the dosage after one week to 52.3 mg-10.4 mg once daily	Capsule: 26.1 mg-5.2 mg 39.2 mg-7.8 mg 52.3 mg-10.4 mg
Central Nervous System Agents, Miscellaneous			
Atomoxetine	ADHD: Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day;	ADHD in children six years of age and older: Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance, 1.2	Capsule: 10 mg 18 mg 25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum, 100 mg/day	mg/kg/day; maximum, 1.4 mg/kg/day Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day.	40 mg 60 mg 80 mg 100 mg
Guanfacine	ADHD as monotherapy and as adjunctive therapy to stimulant medications: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	ADHD as monotherapy and as adjunctive therapy to stimulant medications in children six years of age and older: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Tablet (ER): 1 mg 2 mg 3 mg 4 mg
Viloxazine	ADHD: Capsule: initial, 200 mg once daily; dosage may be titrated in increments of 200 mg weekly to the maximum recommended dosage of 600 mg once daily, depending on response and tolerability	ADHD in patients six to 11 years of age: Capsule: initial, 100 mg once daily; titrate in increments of 100 mg at weekly intervals to the maximum recommended dosage of 400 mg once daily, depending on response and tolerability ADHD in patients ≥12 years of age: Capsule: initial, 200 mg once daily; after one week dosage may be titrated by an increment of 200 mg to the maximum recommended dosage of 400 mg once daily, depending on response and tolerability	Capsule (ER): 100 mg 150 mg 200 mg

ADHD=attention deficit hyperactivity disorder, ER=extended-release, ODT=orally disintegrating tablet, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cerebral stimulants/agents used for attention deficit hyperactivity disorder (ADHD) are summarized in Table 18.

Table 18. Comparative Clinical Trials with the Cerebral Stimulants/Agents Used for ADHD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder				
McCracken et al.[42] (2003) AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype)	N=51 5 weeks	Primary: SKAMP scales Secondary: Examination of the time course of AMP-XR	Primary: AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (P<0.0001). Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (i.e., 12 hours post dose).
Pliszka et al.[43] (2000) AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs	DB, PC, PG, RCT Children in grades one through five diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) Secondary: Not reported	Primary: More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (P<0.05). Behavioral effects of AMP-IR appeared to persist longer than with MPH-IR. Fourteen (70%) patients in the AMP-IR group required only a single morning dose, and 17 (85%) patients in the MPH-IR group received two or more doses per day (P=0.003). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Pelham et al.[44] (1999) AMP-IR (Adderall®) 7.5 or 12.5 mg twice daily vs MPH-IR (Ritalin®) 10 or 17.5 mg twice daily vs placebo	DB, PC, RCT, XO Children five to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information Secondary: Not reported	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (P<0.025). Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent behavioral changes throughout the entire day. The doses of AMP-IR that were assessed produced greater improvement than did the assessed doses of MPH-IR, particularly the lower dose of MPH-IR (P<0.01). Both drugs produced low and comparable levels of clinically significant side effects. Secondary: Not reported
Faraone et al.[45] (2002) AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (P<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (P≥0.26). Secondary: Not reported
Biederman et al.[46] (2002) AMP-XR (Adderall XR®) 10 to 30 mg daily vs	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (hyperactive-impulsive or	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on morning and	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (P<0.001). Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than placebo (P<0.001) at each assessment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	combined subtypes)		afternoon assessments	The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al.[47] (2005) AMP-XR (Adderall XR®) 10 to 60 mg daily	MC, OL, PRO Adults ≥18 years of age diagnosed with ADHD (any subtype)	N=725 10 weeks	Primary: ADHD-RS, CGI-I Secondary: SF-36	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (P<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed. At the end of the study, most patients obtained CGI-I ratings of much/very much improved (522/702; 74.4%). Secondary: At the end of the study, the AMP-XR groups reported significant improvements in all quality of life measurements (P<0.0001 for all) measured by the SF-36, including physical functioning and mental health parameters.
Cutler et al.[48] (2022) Amphetamine-ER tablet (Dyanavel XR®) 5 mg initial dose titrated weekly to a final dose of 20 mg vs placebo	DB, MC, RCT Patients 18 to 60 years of age with a diagnosis of ADHD	N=127 5 weeks	Primary: Permanent Product Measure of Performance Total (PERMP-T) scores (a validated and FDA-accepted, skill-adjusted, timed math test that is used to assess attention in people with ADHD) Secondary: Adverse events	Primary: The mean PERMP-T across all postdose time points at visit five was statistically significantly higher in the amphetamine-ER group than in the placebo group (302.8 vs 279.6; P=0.0043). Numerical differences favoring amphetamine-ER were seen at all time points, with statistically significant improvements in the amphetamine-ER group at 30 minutes and 1, 2, 4, 8, and 13 hours postdose, although the 10-, 12-, and 14-hour time points were not significant. Secondary: No deaths or serious adverse events (as defined by the US Food and Drug Administration) were reported in either treatment group in the study. Common adverse events included decreased appetite, insomnia, and dry mouth.
Childress et al.[49] (2018)	DB, MC, PC, PG, RCT	N=99 6 weeks	Primary: Change from pre-dose in the model-	Primary: The change from pre-dose in the model-adjusted average of SKAMP-combined score observed at four hours post-dose was met, with the LS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AMP-ER oral suspension 10 to 20 mg/day vs placebo	Children six to 12 years of age diagnosed with ADHD	(5 week, open-label, dose-optimization phase and 1 week randomized, placebo controlled phase)	adjusted average of SKAMP-combined score at four hours post-dose Secondary: Onset and duration of efficacy	mean treatment difference between AMP-ER oral suspension compared to placebo being -14.8 (95% CI, -17.9 to -11.6; P<0.0001). Secondary: The onset of treatment effect occurred at the earliest time point assessed, one hour post-dose (treatment difference LS mean [SE], -10.2 [1.61], P<0.0001). The duration of efficacy persisted until the final time point at 13 hours post-dose (treatment difference LS mean [SE], -9.2 [1.61], P<0.0001). At each post-dose time point measured throughout the laboratory classroom day, the change from pre-dose SKAMP-combined score was statistically significantly improved following treatment with AMP-ER oral suspension versus placebo.
Biederman et al.[50] (2002) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	2 DB, MC, PC, RCT Females seven to 13 years of age diagnosed with ADHD	N=51 9 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S (parents)	Primary: Atomoxetine significantly decreased ADHD-RS scores compared to placebo (P<0.05) for the entire duration of the study. Secondary: Atomoxetine statistically significantly decreased the parent-rated CPRS-R index scores compared to placebo (10.3 vs 1.0; P<0.001). Atomoxetine also statistically significantly decreased the parent-rated CGI-S scores compared to placebo (1.5 vs 0.6; P<0.001).
Durell et al.[51] (2013) Atomoxetine vs placebo	DB, PC, RCT Young adults 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: CAARS-Inv: SV total ADHD symptoms score with adult prompts Secondary: AAQoL-29, CGI-S, Patient Global Impression-Improvement, CAARS self-report, BRIEF-Adult Version Self Report and	Primary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CAARS: Inv: SV (-13.6±0.8 vs -9.3±0.8; 95% CI, -6.35 to -2.37; P<0.001). Secondary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CGI-S (-1.1±0.1 vs -0.7±0.1; 95% CI, -0.63 to -0.24; P<0.001) and CAARS Self-Report (-11.9±0.8 vs -7.8±0.7; 95% CI, -5.94 to -2.15; P<0.001) but not on the Patient Global Impression-Improvement score. Treatment with atomoxetine was superior to placebo on the AAQoL-29 and BRIEF-Adult Version Self-Report.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			assessments of depression, anxiety, sleepiness, driving behaviors, social adaptation and substance abuse	
Michelson et al.[52] (2001) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children eight to 18 years of age diagnosed with ADHD	N=297 8 weeks	Primary: ADHD-RS Secondary: CPRS-R, CHQ	Primary: Significant reduction in ADHD-RS was seen in both active groups (P<0.001). No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms. Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (P<0.05). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (P<0.05).
Kratochvil et al.[53] (2011) Atomoxetine 0.5 to 1.8 mg/kg/day vs placebo	DB, MC, PC, RCT Children five to six years of age diagnosed with ADHD	N=101 8 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Atomoxetine significantly reduced mean parent (P<0.009) and teacher (P=0.02) ADHD-RS total score compared to placebo. Secondary: A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much too very much improved (P=0.1) with no significant differences between groups. A total of 62% of children treated with atomoxetine had CGI-S scores of moderately or severely ill at the end of the study compared to 77% of children who received placebo. Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator.
Spencer et al.[54]	DB, MC, PC, RCT	N=291	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Atomoxetine up to 90 mg daily vs placebo	(pooled data) Children seven to 13 years of age diagnosed with ADHD	9 weeks	ADHD-RS Secondary: CPRS-R:S, CGI-S	Significant mean reductions in both active groups in all scales were reported (both studies) for ADHD-RS (P<0.001) and CPRS-R:S (P=0.023 for study one and P<0.001 for study two). Secondary: Atomoxetine displayed a significant mean reduction in CPRS-R:S index over placebo in both studies (study 1: -5.7 vs -2.6; P=0.023 and study 2: -8.8 vs -2.1; P<0.001). Atomoxetine displayed a statistically significant mean change in CGI-S scores over placebo in both studies (study 1: -1.2 vs -0.5; P=0.023 and study 2: -1.5 vs -0.7; P=0.001).
Adler et al.[55] (2014) Atomoxetine 20 to 50 mg twice daily vs placebo	DB, MC, PC, RCT Patients 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: BRIEF-A Secondary: Not reported	Primary: Significantly greater mean reductions were seen in the atomoxetine vs placebo group for the BRIEF-A GEC, Behavioral Regulation Index, and Metacognitive Index scores, as well as the Inhibit, Self-Monitor, Working Memory, Plan/Organize and Task Monitor subscale scores (P<0.05), with decreases in scores signifying improvements in executive functioning. Changes in the BRIEF-A Initiate (P=0.051), Organization of Materials (P=0.051), Shift (P=0.090), and Emotional Control (P=0.219) subscale scores were not statistically significant. The validity scales: Inconsistency (P=0.644), Infrequency (P=0.097), and Negativity (P=0.456) were not statistically significant, showing scale validity. Secondary: Not reported
Dittmann et al.[56] (2011) Atomoxetine 0.5 mg/kg/day for seven days, then 1.2 mg/kg/day (fast titration) vs	DB, PC, RCT Patients six to 17 years of age ADHD with comorbid ODD or conduct disorder	N=181 9 weeks	Primary: SNAP-ODD, SNAP-ADHD Secondary: CGI-S	Primary: Treatment with atomoxetine once daily at week nine, using either fast or slow titration to a target dose of 1.2 mg/kg/day, was significantly better compared to placebo in reducing ODD symptoms measured by SNAP-ODD scores (P<0.001). Comparing fast and slow titration separately, the decrease in ODD symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6; 95% CI, 7.2 to 9.9; atomoxetine-slow: 9.0; 95% CI, 7.7 to 10.3; and placebo: 12.0; 95% CI, 10.6 to 13.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atomoxetine 0.5 mg/kg/day for seven days, then 0.8 mg/kg/day for seven days, then 1.2 mg/kg/day (slow titration) vs placebo				Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores. Scores reflecting severity of conduct disorder symptoms, attention-deficit and disruptive behavior, were significantly reduced after nine weeks of atomoxetine treatment. Secondary: CGI-S and individual treatment behaviors showed were significantly reduced after treatment with atomoxetine. The most common adverse events included fatigue, sleep disorders, nausea, and gastrointestinal complaints and were reported the first three weeks of treatment in 60.0% of atomoxetine-fast, 44.3% of atomoxetine-slow, and 18.6% of placebo group study patients.
Hammerness et al.[57] (2009) Atomoxetine 0.5 to 1.4 mg/kg/day	OL, PRO Children six to 17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment	N=34 6 weeks	Primary: ADHD-RS, CGI Secondary: Not reported	Primary: There was a significant reduction in ADHD RS symptoms compared to baseline. There was a significant reduction in ADHD-RS symptoms score from baseline to the second week of atomoxetine treatment. There was a significant reduction in ADHD symptoms of inattention (-8.1; P<0.001) and hyperactivity (-5.7; P<0.001) at the end of atomoxetine treatment. A total of 56% of patients met criteria for the a priori definition of response; much or very much improved on the CGI plus >30% reduction in ADHD-RS symptoms. Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation. Secondary: Not reported
Adler et al.[58] (2008)	MC, OL	N=384	Primary: CAARS-Inv:SV	Primary: The mean CAARS-Inv:SV total ADHD symptom scores decreased 30.2%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atomoxetine 60 to 120 mg/day	Adults diagnosed with ADHD	4 years	total ADHD symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, HAM-D-17, HAMA, WRAADDS, SDS	from baseline to endpoint (-8.8; P<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (P<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; P<0.001 for both). SDS total and subscale scores improved 25.3% (-3.8; P<0.001). A slight increase was noted in HAM-D-17 scores (0.8; P=0.004), but this small change is not likely clinically relevant. There was no significant change in HAMA scores (0.4; P=0.216). HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; P<0.001).
Wietecha et al.[59] (2012) Atomoxetine 40 mg daily titrated to 100 mg daily after two weeks vs placebo	DB, PC, RCT Adults with ADHD having both a spouse/partner and child	N=502 24 weeks	Primary: CAARS-Inv: SV and CGI-S Secondary: Not reported	Primary: Treatment with atomoxetine resulted in a greater improvement in CAARS-Inv: SV (-16.43 vs -8.65; P<0.001) and CGI-S compared to placebo at week 24 (P<0.001). Secondary: Not reported
Biederman et al.[60] (2006) Atomoxetine 0.5 mg to 1.2 mg/kg daily vs	DB, FD, MC, RCT Females six to 12 years of age diagnosed with ADHD	N=57 18 days	Primary: SKAMP-A SKAMP-D Academic testing Secondary: Adverse events	Primary: The AMP-XR group experienced significantly greater mean changes in SKAMP-D scores from baseline compared to the atomoxetine group (-0.48 vs -0.04; P<0.001). The AMP-XR group experienced significantly greater mean changes in SKAMP-A scores from baseline compared to the atomoxetine group (-0.45 vs -0.05; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AMP-XR (Adderall XR®) 10 to 30 mg daily				Both AMP-XR and atomoxetine groups experienced a significant increase in the mean number of math problems attempted and answered correctly from baseline (P<0.001), but patients in the AMP-XR group attempted a significantly greater number of math problems than those in the atomoxetine group (P=0.04). Secondary: Both AMP-XR and atomoxetine were well tolerated. The number of adverse events was similar in both groups. Most adverse events reported were of mild or moderate severity.
Kemner et al.[61] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	MC, OL, PRO, RCT Children six to 12 years of age diagnosed with ADHD	N=1,323 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: The ADHD-RS change from baseline measured at each time point showed that both treatments were effective. MPH ER produced significantly greater improvements in ADHD-RS scores at weeks, one, two, and three (P<0.001). At week three, rates of treatment response (i.e., ≥25% reduction in ADHD-RS score) were significantly greater with MPH ER than were seen with atomoxetine (P<0.001). Significantly more children treated with MPH ER than with atomoxetine achieved a CGI-I score ≤2 after week three (P<0.001). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported
Newcorn al.[62] (2008) <u>Acute Comparison Trial</u> Atomoxetine 0.8 mg to 1.8 mg/kg/day	DB, PC, RCT, XO Children six to 16 years of age diagnosed with ADHD (any subtype)	Acute Comparison Trial: N=516 6 weeks XO Trial:	Primary: ADHD-RS Secondary: CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and	Acute Comparison Trial Primary: The proportion of patients responding to atomoxetine (45%) was significantly higher than the rate for placebo (24%; P=0.003). MPH-ER (56%) was also more effective than placebo (24%; P≤0.001). MPH-ER was found to be more effective than atomoxetine (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered twice daily vs MPH-ER (Concerta®) 18 mg to 54 mg once daily vs placebo <u>XO Trial</u> Atomoxetine 0.8 mg to 1.8 mg/kg/day administered twice daily Patients on MPH-ER were switched to atomoxetine during the XO trial.		N=178 6 weeks	Morning Behavior-Revised	Atomoxetine and MPH-ER produced greater improvements in CGI-S, CPRS and CHQ compared to placebo. MPH-ER also produced greater improvements compared to atomoxetine on CGI-S, CPRS and CHQ (P=0.004, P=0.003, P=0.02, respectively). XO Trial The responses to the two treatments in these patients were as follows: 34% responded to either atomoxetine or MPH-ER, but not both; 44% responded to both treatments; 22% did not respond to either treatment. Of the 70 patients who did not respond to MPH-ER in the initial trial, 43% subsequently responded to atomoxetine in the XO trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER. Of the patients classified as MPH-ER, 36% showed significantly worse response on atomoxetine, 18% showed significantly better response on atomoxetine, and 46% showed roughly the same response to treatment with atomoxetine. Of the 70 patients classified as MPH-ER nonresponders, 10% showed significantly worse response, 51% showed significantly better response, and 39% showed roughly the same response to treatment with atomoxetine.
Starr et al.[63] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®)	OL, RCT African American children six to 12 years of age diagnosed with ADHD	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (P<0.001). Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the MPH ER group starting at week three (P<0.03 for ≥30% reduction, P<0.006 for ≥50% reduction). Significantly more children treated with MPH ER than atomoxetine achieved a CGI-I score ≤2 after week three (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
18 mg once daily				Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported
Wang et al.[64] (2007) Atomoxetine 0.8 mg to 1.8 mg/kg/day vs MPH-IR 0.2 mg to 0.6 mg/kg/day in two divided doses	DB, MC, RCT Children six to 16 years of age diagnosed with ADHD	N=330 8 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S, treatment-emergent adverse events, weight	Primary: Atomoxetine was not significantly different than MPH in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; MPH, 81.5%; P=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-R:S and CGI-S scores from baseline (P<0.001 for all), the groups were not statistically significant from each other in both measures (P>0.05). Treatment-emergent adverse events that occurred significantly more frequently in the atomoxetine group, compared to the MPH group, included anorexia (37.2 vs 25.3%; P=0.024), nausea (20.1 vs 10.2%; P=0.014), somnolence (26.2 vs 3.6%; P<0.001), dizziness (15.2 vs 7.2%; P=0.024) and vomiting (11.6 vs 3.6%; P=0.007), most of which were of mild or moderate severity. Patients in the atomoxetine group experienced a small but significantly greater mean weight loss at the end of eight weeks compared to those in the MPH group (-1.2 vs -0.4 kg; P<0.001).
Kratochvil et al.[65] (2002) Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg daily	MC, OL Males seven to 15 years of age and females seven to nine year of age diagnosed with ADHD	N=228 10 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, safety	Primary: Both atomoxetine and MPH-IR were associated with marked improvement in inattentive and hyperactive-impulsive symptom clusters but were not statistically different (P=0.66). Secondary: There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (P<0.001). Tolerability was also similar between the two drugs with no statistical differences in discontinuations (P=0.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Statistically significant increases in pulse and BFI were seen with both atomoxetine and MPH-IR (P<0.05).
Sutherland et al.[66] (2012) Atomoxetine 40 mg to 100 mg/day vs atomoxetine 40 mg to 100 mg/day and buspirone 15 mg to 45 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference of -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine and 14.9% for placebo. Secondary: Not reported.
Ni et al.[67] (2013) Atomoxetine titrated up to 1.2 mg/kg/day vs MPH-IR titrated up to 60 mg/day	OL, RCT Patients 18 to 50 years of age diagnosed with ADHD	N=63 8 to 10 weeks	Primary: ASRS, CGI-ADHD-S, AAQoL, WFIS-S and safety Secondary: Not reported	Primary: At visit one (weeks four and five), both the MPH-IR and atomoxetine treatment groups experienced statistically significant reductions from baseline in ASRS scores for inattention (-5.77 and -8.93, respectively; P<0.001 for both) and hyperactivity-impulsivity (-3.69 and -8.11, respectively; P<0.001). The differences between the treatment groups was significant, favoring treatment with atomoxetine (P<0.05). Significant reductions from baseline in ASRS scores were apparent at visit two (eight to 10 weeks) for both the inattention (-9.25 and -10.20, respectively; P<0.001) and hyperactivity-impulsivity subtypes (-6.21 and -7.80, respectively; P<0.001); however, differences between treatment groups were not statistically significant. Both treatment groups experienced improved CGI-ADHD-S scores at all time points compared to baseline values (P<0.001 for all); however,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				differences between groups were not statistically significant. The mean AAQoL scores significantly increased from baseline to visit one (weeks four and five) and visit two (weeks eight to 10) for both treatment groups. The effect sizes as assessed by Cohen's d ranged from 0.59 to 1.63 (P<0.01). Both treatment groups experienced significant improvements in the severity of functional impairment (WFIS-S) from baseline to visit one (weeks four to five) or (weeks eight to 10). Cohen's d ranged from 0.49 to 1.70 for the MPH-IR group and 0.42 to 1.11 for the atomoxetine group. Differences between the treatment groups were not statistically significant. Decreased appetite, vomiting and palpitation were frequently reported in both treatment groups. There was no significant difference in the occurrence of adverse events between treatment groups. Moreover, there was no significant change in body weight, BP, or HR during the study period (P>0.05 for all). Secondary: Not reported
Sutherland et al.[68] (2012) Atomoxetine 40 to 100 mg daily vs atomoxetine 40 to 100 mg daily plus buspirone 15 to 45 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. Secondary: Not reported
Prasad et al.[69] (2007) Atomoxetine 0.5 mg to 1.8 mg/kg/day vs standard current therapy	MC, OL, RCT Children seven to 15 years of age diagnosed with ADHD	N=201 10 weeks	Primary: CHIP-CE Secondary: ADHD-RS, CGI-S, CGI-I, HSPP, FBIM	Primary: Quality of life greatly improved over the 10 weeks in the atomoxetine group vs the standard current therapy group as demonstrated by the significant increase in CHIP-CE (P<0.001). Secondary: ADHD-RS, CGI-S, and CGI-I scores were significantly improved in the atomoxetine group over the standard current therapy group (P<0.001 for all). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the standard current therapy group (P=0.03), but the groups were not significantly different in the other five HSPP domains (P>0.05). There was not a statistically significant difference between groups in reduction in FBIM scores (P>0.05).
Cheng et al.[70] (2007) Atomoxetine vs placebo	MA (9 trials) Patients diagnosed with ADHD	N=1,828 Variable duration	Primary: ADHD-RS Secondary: CTRS-RS, CPRS-R:S, CGI-S, CHQ	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (P<0.01 for all). Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (P<0.01 for all). Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (P<0.01).
Hazell et al.[71] (2003) Clonidine 0.1 to 0.2 mg/day	PC, RCT, TB Children six to 14 years of age with ADHD and co-morbid ODD or	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index) Secondary:	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 vs 6 of 29; P<0.01) but not the Hyperactive Index (13 of 37 vs 5 of 29; P=0.16). Compared to placebo, clonidine was associated with a greater reduction in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	conduct disorder		Not reported	standing SBP measured and with transient sedation and dizziness. Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo. Secondary: Not reported
Jain et al.[72] (2011) Clonidine XR 0.2 mg/day vs Clonidine 0.4 mg/day vs placebo	DB, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=236 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (inattention and hyperactivity), CPRS-R:S, CGI-S, CGI-I, PGA, treatment-emergent adverse events	Primary: Improvement from baseline to week five in ADHD-RS total score was significantly greater in both clonidine ER groups vs placebo (P<0.001). A significant improvement in ADHD-RS total score occurred beginning week one for the clonidine ER 0.2 mg/day group (P=0.02) and week two for the clonidine ER 0.4 mg/day group (P<0.0001) as compared to the placebo group and continued throughout the treatment period. Secondary: A significant improvement in mean change in ADHD-RS inattention score at week five vs baseline was -7.7 for both clonidine ER groups vs -3.4 for the placebo group (P<0.001 for clonidine ER 0.2 mg/day; P<0.006 for clonidine ER 0.4 mg/day). Improvements from baseline to week five in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (P<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both clonidine ER groups (P<0.01) at weeks three and five. Improvement in CGI-S and CGI-I from baseline to week five was significantly greater in both treatment groups vs placebo (P<0.0001 for CGI-S and P<0.003 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups vs placebo was observed at week two (P<0.001) and was maintained through week seven (P<0.02) in the clonidine ER 0.2 mg/day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group and through week five in the clonidine ER 0.4 mg/day group (P<0.009). The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on ECG were minor and due to the pharmacology of clonidine.
Kollins et al.[73] (2011) Clonidine-XR 0.1 mg to 0.4 mg/day and psychostimulant vs placebo and psychostimulant	DB, MC, PC, RCT Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant therapy	N=198 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (hyperactivity and inattention), CPRS, CGI-S, CGI-I, PGA	Primary: At week five, study patients in the clonidine ER plus psychostimulant group experienced a greater improvement in ADHD-RS total score compared to patients in the placebo plus psychostimulant group (P=0.009). Secondary: Scores from baseline ADHD-RS hyperactivity and inattention subscale (P=0.014 and P=0.017, respectively), CPRS (P<0.062), CGI-S (P=0.021), CGI-I (P=0.006), and PGA (P=0.001) were significantly improved in the clonidine ER plus psychostimulant group compared to the placebo plus psychostimulant group. The most commonly treatment-emergent adverse event reported were mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Cutler et al.[74] (2022) Dextroamphetamine Transdermal System (d-ATS) 5, 10, 15, or 20 mg vs placebo	PC, RCT Children and adolescents 6 to 17 years of age with ADHD	N=107 5 week OL dose-optimization 2 week crossover, DB	Primary: SKAMP total score Secondary: Onset and duration of efficacy by SKAMP total score, Permanent Product Measure of Performance (PERMP) scores	Primary: Treatment with d-ATS resulted in significant improvements versus placebo in ADHD symptoms, as measured by SKAMP total score, with an overall least-squares mean difference for d-ATS over placebo of −5.87 (95% CI, 6.76 to −4.97; P<0.001). Secondary: Onset of efficacy was observed at 2 hours postdose (P<0.001), and duration of effect continued through 12 hours (patch removed at 9 hours), with significant differences between d-ATS and placebo at all time points from 2 hours onward (all P≤0.003). Significant improvements versus placebo in PERMP-A and PERMP-C scores were also observed from 2 to 12 hours postdose with d-ATS treatment.
Wigal et al.[75] (2004)	DB, MC, PC, RCT	N=132	Primary: SNAP-T	Primary: Both DXM and MPH-IR significantly improved SNAP-T scores compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DXM (Focalin®) 2.5 to 10 mg twice daily vs MPH-IR 5 to 20 mg twice daily vs placebo	Children six to 17 years of age diagnosed with ADHD (any subtype)	4 weeks	Secondary: SNAP-P, CGI-I Math test performance (clinic and home)	to placebo (P=0.004 and P=0.0042, respectively) Secondary: The DXM group decreased SNAP-P scores at both 3 and 6 PM assessments compared to placebo (P<0.0001 and P=0.0003 respectively). The MPH-IR group significantly decreased 3 PM SNAP-P assessments compared to the placebo group (P=0.0073) but did not reach statistical significance at the 6 PM assessment (P=0.064). Both DXM and MPH-IR improved CGI-I scores in significantly more patients than the placebo group (67% [P=0.0010] and 49% [P=0.0130] compared to 22%, respectively). Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (P=0.001 and P=0.0041 respectively). DXM significantly improved home-based math test scores compared to placebo (P=0.0236). MPH-IR did not reach statistical significance compared to placebo.
Greenhill et al.[76] (2006) DXM-XR (Focalin XR®) 5 to 30 mg daily vs placebo	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=97 7 weeks	Primary: CADS-T Secondary: CADS-P, CGI-I, CGI-S, CHQ (physical and psychosocial)	Primary: DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7; P<0.001). Secondary: DXM-XR significantly increased CADS-P scores from baseline compared to placebo (17.6 vs 6.5; P<0.001). DXM-XR improved overall CGI-I scores in a greater percent of patients compared to placebo (67.3 vs 13.3%; P<0.001). DXM-XR significantly improved CGI-S scores in a greater percent of patients than placebo (64.0 vs 11.9%; P<0.001). There was not a statistical difference between DXM-XR and placebo on the mean change in CHQ physical scores. DXM-XR did significantly improve mean CHQ psychosocial scores compared to placebo (11.9 vs 4.3; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spencer et al.[77] (2007) DXM-XR (Focalin XR®) 20 to 40 mg daily vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with ADHD (any subtype), childhood onset of symptoms, and a baseline ADHD-RS score ≥24	N=184 5 weeks	Primary: ADHD-RS Secondary: ADHD-RS, CGI-I, CGI-S, CAARS, Q-LES-Q	Primary: All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (P<0.05). Secondary: The 20 and 40 mg doses of DXM-XR achieved improved ADHD-RS scores ≥30% and were significant compared to placebo, the 30 mg group did not reach statistical significance. The percent of patients who achieved ≥30% were as follows: DXM-XR 20 mg, 57.9% (P=0.017); DXM-XR 30 mg, 53.7% (P=0.054); DXM-XR 40 mg, 61.1% (P=0.007); and placebo, 34.0%. All doses DXM-XR significantly improved CGI-I scores over placebo (P<0.05 for all). The 20 and 40 mg doses of DXM-XR improved CGI-S scores in a greater percent of patients compared to placebo, but the 30 mg group did not reach statistical significance. The percents of patients were as follows: 20 mg, 68.4% (P=0.09); 30 mg, 61.1% (P value not significant); 40 mg, 64.8% (P=0.031); and placebo, 41.5%. All doses of DXM-XR significantly improved CAARS scores compared to placebo (P<0.05 for all). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al.[78] (2009) DXM-XR (Focalin XR®) 20 to 40 mg/day vs placebo	DB, MC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=103 6 months	Primary: Long-term safety and tolerability Secondary: ADHD-RS, CGI-I	Primary: DXM-XR was well tolerated; the most common adverse events were headache (27.6%), insomnia (20.0%), and decreased appetite (17.6%). Most adverse events were considered mild or moderate by the study investigator. Secondary: Mean improvements in ADHD-RS scores were -10.2 for study patients switched from placebo to DXM-XR and -8.4 for those maintained on DXM-XR.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for six months.				Improvements in CGI-I scores were reported in 95.1% of study patients switched from placebo to DXM-XR and 95.0% of study patients maintained on DXM-XR.
Brams et al.[79] (2012) DXM-XR 20 mg daily vs DXM-XR 30 mg daily vs placebo	DB, RCT, XO Children 6 to 12 years of age with ADHD previously stabilized on MPH (40 mg to 60 mg/day) or DXM (20 mg to 30 mg/day)	N=165 3 weeks	Primary: Change in average SKAMP-combined score from pre-dose to 10, 11 and 12 hours post-dose Secondary: Not reported	Primary: The mean change from pre-dose in SKAMP-combined score was significantly greater in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group (-4.47 vs -2.02; P=0.002). Significantly greater improvement in ADHD symptoms was observed in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group at hours 10 through 12. Secondary: Not reported
Stein et al.[80] (2011) DXM-XR (Focalin XR®) 10 to 30 mg/day vs AMP-XR (Adderall XR®) 10 to 30 mg/day	DB, PC, RCT Patients nine to 17 years of age with ADHD	N=56 8 weeks	Primary: ADHD-RS, CGI-I, CGI-S, WFIS, SSERS Secondary: Not reported	Primary: There were significant dose-related decreases in total and hyperactive-impulsive symptom scores (P<0.001 and P<0.001, respectively) that did not differ by type of stimulant. There were significant dose-related decreases for Inattention symptoms (P<0.001) that were more modest and did not differ by type of stimulant. There were significant dose-related decreases in CGI-S scores (P<0.001) that did not differ by type of stimulant. There were significant effects of dose on the WFIS total score (P=0.008), on the Family (P=0.010), Learning (P=0.002), Social Activities (P=0.018), and Risk Taking (P=0.050) subscales, but not on the Living Skills or Self-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Esteem subscales. The most common adverse events were mild to moderate in severity and included decreased appetite and insomnia. Adverse events were more common at higher dose levels for both stimulants. Secondary: Not reported
Muniz et al.[81] (2008) DXM-XR (Focalin XR®) 20 mg/day vs DXM-XR (Focalin XR®) 30 mg/day vs MPH-ER (Concerta®) 36 mg/day vs MPH-ER (Concerta®) 54 mg/day vs placebo	DB, MC, RCT Children six to 12 years of age diagnosed with ADHD and stabilized on MPH ≥2 weeks	N=84 10 weeks	Primary: SKAMP Secondary: Not reported	Primary: Mean change in combined SKAMP score at two hours post-dose was significantly larger for MPH-ER 20 vs 36 mg/day (P<0.001). MPH-ER 20 and 30 mg doses have a more rapid onset and a greater effect in the morning relative to MPH-ER 36 and 54 mg doses while MPH-ER 36 and 54 mg had a greater effect at the end of the 12 hour day. All active treatments provided a significant benefit over placebo at most time points to 12 hours post-dosing. Secondary: Not reported
McCracken et al.[82]	DB, RCT	N=207	Primary:	Primary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Study Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>(2016)

DXM-XR 5 to 20 mg/day

vs

guanfacine 1 to 3 mg/day

vs

combination of DXM-XR and guanfacine

vs

placebo</td><td>Children seven to 14 years of age diagnosed with ADHD</td><td>8 weeks</td><td>ADHD-RS-IV

Secondary:
Safety</td><td><table><tr><th>ADHD-RS Total Score</th><th>Estimated Difference</th><th>P-value</th></tr><tr><td>COMB vs Placebo</td><td>−10.66±1.99</td><td><0.0001</td></tr><tr><td>COMB vs GUAN</td><td>−2.67±1.35</td><td>0.049</td></tr><tr><td>COMB vs DXM-XR</td><td>−2.89±1.56</td><td>0.065</td></tr><tr><td>GUAN vs DXM-XR</td><td>−0.21±1.31</td><td>0.87</td></tr><tr><td>GUAN vs Placebo</td><td>−7.99±1.22</td><td><0.0001</td></tr><tr><td>DXM-XR vs Placebo</td><td>−7.77±1.70</td><td><0.0001</td></tr></table>
Secondary:
Overall rates for any treatment-emergent adverse events (mild, moderate, and severe) were high, but did not differ between groups. No serious adverse events occurred during the trial. Discontinuation at any time due to treatment-emergent adverse events was low and equivalent across groups: 1.5% in guanfacine, 1.5% in DXM-XR, and 2.9% in combination. No serious cardiovascular events occurred. Sedation, somnolence, lethargy, and fatigue were greater in both guanfacine groups.</td></tr>
<tr><td>Scahill et al.[83] (2001)

Guanfacine 0.5 mg at bedtime, day four added 0.5 mg in the morning, day eight added 0.5 mg afternoon dose

vs

placebo</td><td>DB, PC, PG, RCT

Children seven to 15 years of age diagnosed with ADHD and tic disorder</td><td>N=34

8 weeks</td><td>Primary:
ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT

Secondary:
Not reported</td><td>Primary:
Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo (P<0.01).

Nine of 17 patients who received guanfacine were rated on the CGI-I as either much improved or very much improved, compared to 0 of 17 patients who received placebo.

The mean CPRS-R on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference.

Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group (P=0.05).

For CPT, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared to increases of 29% in</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				commission errors and of 31% in omission errors in the placebo group. No significant adverse events were observed; one study patient taking guanfacine withdrew with sedation. Guanfacine was associated with an insignificant decrease in BP and pulse. Secondary: Not reported
Kollins et al.[84] (2011) Guanfacine ER 1 to 3 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=182 6 weeks	Primary: CANTAB-CRT Secondary: CANTAB-SWM, DSST, PERMP	Primary: There were no significant differences between guanfacine ER and placebo groups on measures of psychomotor functioning or alertness on the CANTAB-CRT (mean difference, 2.5; P=0.8 for CRT, 2.5; P=0.84 for correct responses, 15.5; P=0.30 for movement time, and -8.2; P=0.72 for total time). Secondary: Guanfacine ER treatment was associated with significant improvement in ADHD symptoms (P=0.001) Most sedative adverse events were mild to moderate and occurred during dose titration, decreased with dose maintenance, and resolved during the study period.
Sallee et al.[85] (2009) Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=324 9 weeks	Primary: ADHD-RS-IV total score Secondary: CPRS-R, CGI-I, PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all guanfacine ER dose groups was -19.6 compared to -12.2 for the placebo group. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the guanfacine ER 1, 2, 3, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (P=0.002), -3.0 P=0.02), -3.5 (P=0.007), and -4.0 (P=0.002) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (P=0.028), -2.5 (P=0.03), -3.9 (P=0.001), and -4.0 (P=0.0008) for guanfacine ER 1, 2, 3, and 4 mg, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Using placebo-adjusted LSMD in change from baseline at endpoint in CPRS-R total scores, the 4 mg guanfacine ER dose demonstrated significant efficacy at eight hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R results at eight (-11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R scores at eight hours (-9.0; P=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at eight, 12, 14, and 24 hours were -12.8 (P=0.0004), -11.4 (P=0.002), -10.4 (P=0.0077), and -8.9 (P=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical improvement were 30% (placebo), 54% (guanfacine ER 1 mg; P=0.007 vs placebo), 43% (guanfacine ER mg; P=0.1404 vs placebo), 55% (guanfacine ER mg; P=0.006 vs placebo), and 56% (guanfacine ER mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (guanfacine ER 1 mg; P=0.030 vs placebo), 36% (guanfacine ER 2 mg; P=0.4982 vs placebo), 62% (guanfacine ER mg; P=0.002 vs placebo), and 57% (guanfacine ER 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events in patients taking guanfacine ER were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. There were no significant differences in sleepiness between the patients taking placebo and guanfacine ER. Guanfacine ER was not associated with abnormal changes in height or weight. SBP, DBP, and pulse rate decreased as the guanfacine ER dose increased and then increased during dose maintenance and tapering. The range of mean changes from baseline for seated SBP for the placebo group was -1.30 to -0.48 mm Hg and -7.38 to 0.54 mm Hg for the guanfacine ER randomized dose groups.
Sallee et al.[86] (2009)	ES, OL	N=257	Primary: ADHD-RS-IV,	Primary: Somnolence (30.5%), headache (24.3%), upper respiratory tract infection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Guanfacine ER 1 to 4 mg once daily	Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	24 months	CPRS-R, CGI-I, CHQ-PF50, CTRS-R, PGA Secondary: Not reported	(17.8%), nasopharyngitis (14.3%), fatigue (13.9%), upper abdominal pain (12.7%) and sedation (11.2%) were the most frequently reported adverse events. The majority of somnolence, sedation, or fatigue events was moderate or mild in severity and resolved by end of treatment. Hypotension was reported in 5.0% of patients. Decreased DBP was found in 3.5% of patients, decreased BP in 2.7% of patients, and decreased SBP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common treatment-emergent adverse events that differed in the subgroup coadministered psychostimulants relative to monotherapy or the overall safety population. Mean changes in ADHD-RS-IV total score from baseline to end point showed significant improvement: overall, -20.1 (P<0.001), and for all guanfacine ER dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1, 2, 3, and 4 mg dose groups, respectively (P<0.001 for each). CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (-18.2; P<0.001). The overall mean change from baseline demonstrated significant improvement in CPRS-R scores at each postdose assessment (P<0.001). Investigator-rated CGI-I scores at end point showed that investigators rated the majority of patients very much improved (29.3%) or much improved (28.8%). For the PGA, 59.7% of patients were rated as very much or much improved at end point. Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. CHQ-PF50 Psychosocial Summary Scores demonstrated significant improvement from baseline to end point for the overall full analysis set (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Sallee et al.[87] (2012) Guanfacine ER 1 to 4 mg daily vs placebo	DB, PC, RCT (Post-hoc analysis) Patients 6 to 17 years of age with ADHD	N=631 Variable duration	Primary: Change in ADHD-RS total scores Secondary: Not reported	Primary: For patients with the predominantly inattentive subtype of ADHD, patients treated with guanfacine ER achieved significantly greater mean reductions from baseline in ADHD-RS total scores compared to placebo ($P \leq 0.020$). For patients with combined-type ADHD, patients treated with guanfacine ER achieved significantly greater reductions in ADHD-RS total score from baseline compared to placebo at treatment weeks one through five and at study end ($P \leq 0.011$). Secondary: Not reported
Connor et al.[88] (2010) Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms	N=217 9 weeks	Primary: Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	Primary: The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving guanfacine ER and -6.8 for those receiving placebo ($P<0.001$). The mean percentage reductions from baseline were 56.3% with guanfacine ER and 33.4% with placebo ($P<0.001$). Secondary: The mean decrease from baseline to endpoint in ADHD-RS-IV total score was 23.8 points for guanfacine ER compared to 11.5 for placebo ($P<0.001$). The mean percentage reductions from baseline were 56.7% with guanfacine ER and 26.5% with placebo ($P<0.001$). Adverse events were reported in 84.6% of those receiving guanfacine ER group and 60.3% of those receiving placebo. Treatment-emergent adverse events occurred more frequently with guanfacine ER than with placebo (83.8 vs 57.7%, respectively). The most common treatment-emergent adverse events in the guanfacine ER group were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Biederman et al.[89] (2008) Guanfacine ER 2 to 4 mg once daily	DB, MC, PC, RCT Patients six to 17 years of age with ADHD combined	N=345 8 weeks	Primary: ADHD-RS-IV total score observed during the last treatment week of	Primary: The mean reduction in ADHD-RS-IV score at end point across all guanfacine ER groups was -16.7 compared to -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the guanfacine ER 2, 3, and 4 mg groups were -7.70 ($P=0.0002$), -7.95 ($P=0.0001$), and -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype		the dosage escalation period (weeks one to five) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during the last treatment week of the dosage escalation period (weeks one to five)	10.39 (P<0.0001), respectively. Mean changes from baseline in hyperactivity/impulsivity in the placebo and guanfacine ER 2, 3, and 4 mg groups were -3.51, -7.33 (P=0.0002 vs placebo), -7.32 (P=0.0002 vs placebo), and -9.31, (P<0.0001 vs placebo) respectively. Mean changes from baseline in inattentiveness were -4.92, -8.7 (P=0.0011 vs placebo), -9.11 (P=0.0006 vs placebo), and -9.44 (P=0.0002 vs placebo), respectively. Secondary: Significant improvement in CGI-I scores at end point was shown in 25.64, 55.95, 50.00, and 55.56% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. Improvement in CGI-I scores was significant in the guanfacine ER 2 mg group compared to the placebo group by week two (P=0.0194) and in all guanfacine ER groups by week three continuing through week five (P<0.05). Significant improvement in PGA scores at end point was shown in 23.08, 62.12, 50.82, and 66.10% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were -6.55 in the 2 mg group (P=0.0448), -7.36 in the 3 mg group (P=0.0242), and -12.70 in the 4 mg group (P<0.0001). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were -11.57 (P<0.0001), -13.48 (P<0.0001), and -12.53 (P<0.0001), for the 2, 3, and 4 mg doses, respectively. The most commonly reported treatment-emergent adverse events were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving guanfacine ER 1, 2, 3, and 4 mg doses was 12.7, 11.4, 20.9, and 17.5%, respectively. SBP, DBP, and pulse rate decreased as guanfacine ER dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks three and five), and -10.1 mm Hg (week four) and -7.1 mm Hg (week four), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -5.7 beats per minute (week three), -8.1 beats per minute (week three), and -8.0 beats per minute (week four), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Iwanami et al.[90] (2020) Guanfacine ER 2 mg to 6 mg/day vs placebo	DB, PC RCT Adults ≥18 years of age currently diagnosed with ADHD who had a total score ≥24 on the ADHD-RS-IV and a score ≥4 on the CGI-S	N=201 12 weeks (5 weeks dose-optimization, 5 weeks dose-maintenance and 2 weeks dose taper)	Primary: Change from baseline in total score of the ADHD-RS-IV at week 10 Secondary: ADHD-RS-IV subscales, CGI-I, Patient Global Impression-Improvement and treatment-emergent adverse event	Primary: At week 10, the LS mean ±SE change from baseline in ADHD-RS-IV total score was greater with guanfacine ER (-11.55±1.10) than with placebo (-7.27±1.07) with LS mean difference of-4.28 (95% CI, -6.67 to -1.88; P=0.0005). Secondary: There were greater improvements in guanfacine ER compared to placebo for ADHD-RS-IV inattention (-7.39±0.79 vs -4.89±0.76; P=0.0032) and hyperactivity-impulsivity (-3.84±0.54 vs -2.10±0.52; P=0.0021) subscale scores, CGI-I scores (48.1% vs 22.6%; P=0.0007), and Patient Global Impression-Improvement scores (25.3% vs 11.8%; P=0.0283). More patients in the guanfacine ER versus the placebo group reported treatment-emergent adverse events (81.2% vs 62.0%) and discontinued due to treatment-emergent adverse events (19.8% vs 3.0%). The main treatment-emergent adverse event in the guanfacine ER group were somnolence, thirst, blood pressure decrease, nasopharyngitis, postural dizziness and constipation; most treatment-emergent adverse events were mild to moderate in severity.
Newcorn et al.[91] (2016) Guanfacine ER vs placebo Participants who	DB, MC, randomized-withdrawal study Children and adolescents (six to 17 years of age) with ADHD and an ADHD-RS-IV score ≥32 and CGI-S	N=316 7 weeks: OL dose optimization 6 weeks: OL maintenance phase	Primary: Percentage of treatment failures at the end of the randomized-withdrawal phase, defined as ≥50% increase in ADHD-RS-IV total score and a 2 or	Primary: A significantly smaller proportion of participants failed treatment with guanfacine ER (49.3%) than with placebo (64.9%; difference −15.6, 95% CI, −26.6 to −4.5; P=0.006). Secondary: The median time to treatment failure was 56.0 days (95% CI, 44.0 to 97.0) for the placebo group. The difference in time to treatment failure between the guanfacine ER and placebo groups was statistically significant (P=0.003). The median time to treatment failure in the guanfacine ER

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
met the response criteria in the OL phase, defined as at ≥30% reduction in ADHD-RS-IV total score and a CGI-S score of 1 or 2 at both Weeks 12 and 13, were entered into the 26-week, randomized-withdrawal phase	score ≥4	26 weeks: DB, randomized-withdrawal phase	more point increase in CGI-S score Secondary: Time to treatment failure	group could not be calculated, as less than half the participants failed treatment.
Hervas et al.[92] (2014) Guanfacine ER vs placebo An atomoxetine arm was included to provide reference data against placebo.	DB, MC, PC, PG, RCT Patients six to 17 years of age with a diagnosis of ADHD of at least moderate severity	N=337 10 to 13 weeks: 4 to 7 weeks of dose optimization, 6 weeks of DB maintenance, 2 week tapering, follow up 1 week after last dose	Primary: ADHD-RS Secondary: CGI-I, WFIS-parent report	Primary: The placebo-adjusted difference in LS mean change from baseline in ADHD-RS total score for guanfacine ER was −8.9 (95% CI, −11.9 to −5.8; P<0.001). Secondary: Compared with placebo, the difference in the percentage of patients showing improvement in CGI-I rating was 23.7 (95% CI, 11.1 to 36.4; P<0.001) for guanfacine ER and 12.1 (−0.9 to 25.1; P=0.024) for atomoxetine. The placebo-adjusted difference in LS mean change from baseline in WFIRS-parent report learning and school domain at study end for guanfacine ER was −0.22 (95% CI, −0.36 to −0.08; P=0.003) and for WFIRS-parent score family domain at study end was −0.21 (95% CI, −0.36 to −0.06; P=0.006). The corresponding values for atomoxetine were −0.16 (95% CI, −0.31 to −0.02; P=0.026) and −0.09 (95% CI, −0.24 to −0.06; P=0.242), respectively.
Biederman et al.[93] (2008) Guanfacine ER 2 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD combined subtype,	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. Changes from baseline to endpoint in SBP, DBP, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute, respectively. Mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype			changes in pulse rate and QRS intervals were generally unchanged across study visits. Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7.0% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported. Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; P<0.001 vs baseline). Mean reductions in ADHD-RS-IV scores were significant for both the inattention (-9.5; P<0.001 vs baseline) and the hyperactivity/impulsivity (-8.5; P<0.001 vs baseline) subscales. For PGA scores, 58.6% of patients were 'improved' at endpoint compared to baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group.
Spencer et al.[94] (2009) Guanfacine ER 1 mg to 4 mg once daily added to existing stimulant therapy	MC, OL Patients six to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of	N=75 9 weeks	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA Secondary: Not reported	Primary: The most common treatment-related adverse events were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most adverse events were mild to moderate in severity. The incidences of the treatment-emergent adverse events were comparable between both psychostimulant subgroups except for fatigue (28.6% in the guanfacine ER plus MPH subgroup vs 18.2% in the guanfacine ER plus AMP subgroup) and irritability (14.3% in the guanfacine ER plus MPH subgroup vs 33.3% in the guanfacine ER plus AMP subgroup).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms			Twenty patients have a decrease in BP judged to be of clinical interest. Twelve patients exhibited orthostatic BP decreases. None of the patients with BP decreases reported syncope or lightheadedness. At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1). During treatment, there was an increase from screening in the number of patients reporting clinically significant dullness, tiredness, and listlessness on the PSERS. There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall, -16.1; guanfacine ER plus MPH group, -17.8; guanfacine ER plus AMP group, -13.8; $P<0.0001$ for all). The mean percentage reduction from baseline to end point in ADHD-RS-IV score overall was 56.0%. Improvement was significant for the mean day CPRS-R total score (-19.8; $P<0.0001$), as well as for all three time points (-23.2 at 12 hours postdose, -18.5 at 14 hours postdose, and -17.8 at 24 hours postdose; $P<0.0001$ for all). The percentage of patients showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of patients showed improvement. No significant improvement occurred at end point in the CHQ-PF50 physical summary score. Mean improvement for the CHQ-PF50 psychosocial score was 10.2 ($P<0.0001$). Secondary: Not reported
Wilens et al.[95] (2012)	DB, MC, PC, RCT	N=461	Primary: ADHD-RS	Primary: At the end of the study, guanfacine ER treatment groups showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Guanfacine ER 1 to 4 mg/day in the morning and placebo at bedtime vs placebo in the morning and guanfacine ER 1 mg to 4 mg/day in the afternoon vs placebo Patients continued stable dose of psychostimulant given in the morning.	Children and adolescents six to 17 years of age diagnosed with ADHD	9 weeks	Secondary: CGI-S, CGI-I	significantly greater improvement from baseline ADHD-RS total scores compared to placebo plus psychostimulant (guanfacine ER in the morning; P=0.002; guanfacine ER in the evening; P<0.001). Secondary: Significant benefits of guanfacine ER treatment compared to placebo plus psychostimulant were observed on the CGI-S (guanfacine ER in the morning; P=0.013, guanfacine ER in the evening; P<0.001) and CGI-I (guanfacine ER in the morning; P=0.024, guanfacine ER in the evening; P=0.003). At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group. The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections.
Cutler et al.[96] (2014) Guanfacine ER 1 to 4 mg/day in the morning and placebo at bedtime vs placebo in the morning and guanfacine ER 1 mg to 4 mg/day	Post hoc analysis of Wilens et al, 2012 Children and adolescents six to 17 years of age diagnosed with ADHD	N=461 9 weeks	Primary: Response (≥40% or ≥50% reduction in ADHD-RS scores), remission (symptomatic: ADHD-RS score ≤18; syndromal: ADHD-RS score ≤18 and CGI-S score ≤2) Secondary: Not reported	Primary: With response defined as ≥40% reduction, 69.8% of participants in the guanfacine ER morning group and 70.3% of participants in the guanfacine ER evening group achieved response, vs 57.9% of placebo participants. The percentage of responders in both guanfacine ER groups was higher (P=0.032 for the morning group; P=0.026 for the evening group) compared with placebo. With response defined as ≥50%, response rates were 63.1% for the guanfacine ER morning group, 64.9% for the guanfacine ER evening group, and 43.4% for placebo (P<0.001 for the morning group; P<0.001 for the evening group compared with placebo). At final on-treatment assessment, more participants receiving morning guanfacine ER (61.1%; P=0.010) and evening guanfacine ER (62.2%; P=0.005) achieved symptomatic remission compared with the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in the afternoon vs placebo Patients continued stable dose of psychostimulant given in the morning.				group (46.1%). Similarly, more participants receiving guanfacine ER (morning group [40.3%; P=0.053] or evening group [46.6%; P=0.002]) achieved syndromal remission compared with participants receiving placebo (29.6%). Secondary: Not reported
Faraone et al.[97] (2010) Guanfacine ER 1 to 4 mg once daily	MA Patients six to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models Secondary: Not reported	Primary: Actual Dose Model The presence or absence of ADHD symptoms was influenced by the actual doses of medication received by the participants (P=0.006). In participants with residual ADHD symptoms, greater total ADHD-RS symptom scores were significantly related to shorter treatment duration (P<0.001) and higher baseline total ADHD-RS symptom scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). mg/kg Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the dose of medication received by the participant as expressed in mg/kg (P=0.001). Treatment duration (P<0.001) and baseline total ADHD-RS symptom scores (P<0.001) were predictors of weekly total ADHD-RS symptom scores. The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Titration Rate Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (P=0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The number of symptoms was significantly influenced by treatment duration (P<0.001) and baseline total ADHD-RS scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Secondary: Not reported
Adler et al.[98] (2013) LDX 30 to 70 mg daily vs placebo	DB, PC, RCT Adults 18 to 55 years of age with a primary diagnosis of ADHD and executive function deficits (assessed by baseline BRIEF-A GEC T-scores ≥65)	N=161 10 weeks	Primary: BRIEF-A scales (GEC, index and clinical subscales) Secondary: Not reported	Primary: At week 10 or early termination, treatment with LDX was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores compared to placebo (P<0.0001) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index scales (metacognition scale) and all nine clinical subscales (P≤0.0056 for all). At week 10 or early termination, patients treated with LDX had mean T-scores for BRIEF-A indices and clinical subscales that were below levels of clinically significant deficits in executive function. The mean GEC T-scores were 57.2 and 68.3 for the LDX and placebo groups, respectively. Secondary: Not reported
Babcock et al.[99] (2012) LDX 30 to 70 mg daily vs placebo	DB, MC, RCT (Post-hoc analysis) Adults with ADHD who remained symptomatic on AMP therapy prior to enrollment in a four-week trial	N=36 4 weeks	Primary: Mean change in ADHD-RS score from baseline Secondary: Change in CGI-S, CGI-I	Primary: At study end, the change from baseline in mean ADHD-RS scores for LDX-treated patients was similar in the AMP group and the overall study group. The prior AMP non-responders in the placebo group had a change from baseline in ADHD-RS total score of -13.5. In the overall efficacy population, the placebo group experienced a change from baseline of -7.8. Secondary: Mean CGI scores were similar between the prior AMP subgroup and overall efficacy population in the LDX groups. In addition, the percentage of clinical responders and symptomatic remitters was comparable at all time points assessed in both LDX groups.
Biederman et al.[100] (2007) LDX 30 to 70 mg	DB, MC, PC, RCT Children six to 12 years of age	N=209 4 weeks	Primary: ADHD-RS Secondary:	Primary: ADHD-RS scores were significantly greater with each of the three LDX doses compared to placebo (P<0.001). The greatest efficacy was seen in the 70 mg group with a mean ADHD-RS change of -4.91 from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs placebo	diagnosed with ADHD and with an ADHD-RS score ≥28		CPRS-R, CGI-S, CGI-I	between the 30 and 70 mg groups (P<0.05). Secondary: Each LDX group significantly improved CPRS-R scores throughout the day compared to the placebo group (P<0.01 for all). Mean CGI-S scale scores significantly improved from baseline to treatment end point for all LDX groups compared to the placebo group (P<0.001 for all). CGI-I ratings were either "very much improved" or "much improved" in ≥70% of patients in the LDX groups compared to 18% of patients in the placebo group (P<0.001 for all).
Biederman et al.[101] (2007) LDX 30 to 70 mg daily vs placebo (AMP-XR 10 to 30 mg was used as a control arm)	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=52 12 weeks	Primary: SKAMP scale Secondary: PERMP, CGI-I	Primary: SKAMP scores significantly improved in both the LDX and AMP-XR groups compared to the placebo group (P<0.0001 for both). Secondary: PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (P<0.0001 for both). The CGI-I scores significantly improved in the both LDX and AMP-XR groups compared to the placebo group (P<0.0001).
Brams et al.[102] (2012) LDX 30 to 70 mg daily vs placebo	DB, RCT Withdrawal study Adults 18 to 55 years of age with baseline ADHD-RS with adult prompt total scores <22 and CGI-S ratings of 1, 2 or 3	N=116 6 weeks	Primary: Proportion of patients with symptom relapse (≥50% increase in ADHD-RS score and ≥2 rating-point increase in CGI-S score)	Primary: At study end, 8.9% of patients in the LDX group and 75.0% of patients in the placebo group experienced symptom relapse (P<0.0001), with most patients showing relapse after one and two weeks of the randomized withdrawal period. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Coghill et al.[103] (2013) LDX 30 to 70 mg daily vs MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, MC, PC, PG, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=336 7 weeks	Primary: ADHD-RS Secondary: CGI-I	Primary: The LS mean change from baseline in ADHD-RS total score was significantly greater for patients treated with LDX (-24.3±1.2) and MPH-ER (-18.7±1.1) compared to placebo (-5.7±1.1; P<0.001 for both). The LS mean change from baseline in ADHD-RS total score was significantly greater with LDX or MPH-ER compared to placebo at every time point evaluated (P<0.001 for all visits). Effect sizes based on the difference in LS mean change in ADHD-RS total score from baseline to endpoint were 1.80 and 1.26 for LDX and MPH-ER, respectively. The decreases in both the ADHD-RS hyperactivity/impulsivity and inattention subscale scores from baseline were also significantly greater for patients treated with LDX or MPH-ER compared to placebo. The LS mean change from baseline to endpoint in hyperactivity/impulsivity was significantly greater with LDX compared to placebo (-8.7; 95% CI -10.3 to -7.2; P<0.001) as was the change in inattention score (-9.9; 95% CI, -11.5 to -8.3; P<0.001). The LS mean change from baseline to endpoint significantly favored MPH-ER compared to placebo for hyperactivity/impulsivity (-6.0; 95% CI, -7.5 to -4.5; P<0.001) and inattention (-7.0; 95% CI, -8.6 to -5.4; P<0.001) scores. Secondary: The proportions of patients with a CGI-I rating of 'very much improved' or 'much improved' after seven weeks of treatment were 78 and 61% for patients treated with LDX or MPH-ER, respectively, compared to 14% of patients treated with placebo (P<0.001 for both).
Findling et al.[104] (2011) LDX 30 to 70 mg daily vs	DB, PC, RCT Adolescents 13 to 17 years of age diagnosed with ADHD	N=314 4 weeks	Primary: ADHD-RS Secondary: CGI-I, YQOL-R, treatment-emergent adverse events	Primary: Differences in ADHD-RS total scores favored all LDX doses compared to placebo at all weeks (P<0.0076). Secondary: Patients were rated much or very much improved at the end of the study with all doses of LDX (69.1%) compared to placebo (39.5%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				YQOL-R scores at the end of the study indicated improvement with LDX treatment, but did not result in significant differences compared to placebo. The most common treatment-emergent adverse events for all combined LDX doses included decreased appetite, headache, insomnia, decreased weight, and irritability. The severity of treatment-emergent adverse events was generally mild or moderate Clinically insignificant mean increases in pulse, BP and ECG changes were noted with LDX.
Findling et al.[105] (2008) LDX 30 to 70 mg daily	MC, OL, SA Children six to 12 years of age diagnosed with ADHD	N=274 12 months	Primary: ADHD-RS Secondary: CGI-S	Primary: Mean ADHD-RS total score improved by 27.2 points (P<0.001). Mean ADHD-RS inattentive subscale score improved by 13.4 points (P<0.001). Mean ADHD-RS hyperactivity score improved by 13.8 points (P<0.001). After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment. Secondary: Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved. Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or electrocardiographic parameters.
Jain et al.[106] (2013) LDX 20 to 70 mg daily vs placebo	OL, PC, RCT, SA, XO (Post-hoc analysis) Children 6 to 12 years of age with ADHD and baseline ADHD-RS IV total score ≥28 who had received MPH	N=150 Variable duration	Primary: Study 1 Change in ADHD-RS total score from baseline Study 2 Mean SKAMP-D subscore over the course of a laboratory school	Study 1 Primary: Of patients treated with LDX, the mean change from baseline in ADHD-RS total score was similar for the overall study population and the prior MPH group, with a 64.9% improvement observed in the prior MPH group. Secondary: Of patients treated with LDX, the mean change in BRIEF scores from baseline were similar for the overall study population and the prior MPH group. The mean change in CGI-I scores, EESC total scores and the BRIEF

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	within six months of study enrollment		day Secondary: Study 1 CGI-S, EESC, BRIEF-Parent form Study 2 SKAMP-A, PERMP math scores, ADHD-RS and CGI scores	index subscale scores from baseline were similar between the overall study population and the prior MPH group. In addition, the BRIEF index subscale scores were normalized at endpoint. The rates of symptomatic remission were similar between the overall study population and the prior MPH group; however, the prior MPH group had numerically lower remission rates compared to the overall group. A clinical response was achieved in 89.6% and 86.7% of the overall population and the prior MPH group, respectively. Study 2 Primary: Improvements in SKAMP-D subscores were similar for both the overall study population and the prior MPH group. For both groups, SKAMP-D scores were improved at all post-dose time points from 1.5 hours to 13 hours with LDX vs placebo ($P \leq 0.0046$ and $P \leq 0.0284$ for all time points in the overall study population and prior MPH group, respectively). Secondary: Improvements in SKAMP-A scores were similar in the overall study population and prior MPH group from 1.5 hours to 13 hours post-dose with LDX vs placebo ($P<0.0001$ and $P \leq 0.0114$ for all time points in the overall study population and prior MPH group, respectively). The PERMP-A and PERMP-C scores were improved to a similar degree in both the overall study population and the prior MPH group at all post-dose time points from 1.5 to 13.0 hours with LDX vs placebo ($P<0.0001$ for all time points in the overall study population and prior MPH group, respectively, for both PERMP-A and PERMP-C). The change from baseline in mean ADHD-RS total scores for the overall study population and the prior MPH groups were similar when taking LDX and placebo during the XO phase (57.1 and 18.1% for patients who had previously received MPH in the LDX group and the placebo group, respectively). At visit five during the XO period, mean CGI-I scores were 1.7 and 3.5 for patients taking LDX and placebo, respectively, for the overall study population and 1.7 and 3.7, respectively, for the prior MPH group who had received $\geq$1 mg/kg/day of MPH.
Mattingly et al.[107]	Post-hoc analysis of	N=345	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) LDX 30 to 70 mg daily vs placebo	Weisler et al. Adults aged 18 to 55 years of age diagnosed with ADHD who had completed ≥2 weeks of treatment with LDX	12 months	ADHD-RS-IV Secondary: Not reported	Baseline ADHD-RS-IV total scores were lower in the predominantly inattention and hyperactivity/impulsivity symptom cluster subgroups. LDX decreased ADHD-RS-IV total scores in all predominant symptom cluster subgroups. Mean percent reduction from baseline to endpoint was 55.9, 71.0, and 62.6% for the predominantly inattention, hyperactivity/impulsivity, and combined symptom cluster subgroups, respectively, and was 61.1% for the overall population. At trial end, 285/345 patients were classified as clinical responders (ADHD-RS-IV total score decrease of ≥30% from baseline and CGI-I score of one or two). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders. Secondary: Not reported
Weisler et al.[108] (2009) LDX 30 to 70 mg daily	DB, PC, RCT, SA Adults aged 18 to 55 years of age diagnosed with ADHD	N=349 12 months	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Mean ADHD-RS total scores improved at week one of treatment and sustained throughout the eleven month treatment period (P<0.001). Mean ADHD-RS total scores improved by 24.8 points from baseline to study endpoint (P<0.001). Secondary: All study patients rated as moderately ill with a mean CGI-S of 4.8 with improvement in their mean score of 1.7 at endpoint. At weeks one, two, three, and four, the proportion of study patients rated as improved on the CGI-I was 43.9, 68.3, 83.4 and 89.1%, respectively. At month 12, 92.6% were improved on the CGI-I. Common adverse events included upper respiratory tract infection, insomnia, headache, dry mouth, decreased appetite and irritability. Most adverse events were considered mild or moderate by the study investigator.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Small but statistically significant increases in pulse and BP noted at treatment endpoint.
Dittmann et al.[109] (2013) LDX 30 to 70 mg/day vs atomoxetine 40 to 100 mg/day (or weight-based dosing if patient <70 kg)	AC, DB, RCT Patients aged six to 17 years of age with an ADHD-RS-IV total score ≥28 and an inadequate response to MPH treatment	N=262 9 weeks	Primary: Days to first clinical response (defined as CGI-I score of 1 or 2) Secondary: Proportion of responders at each study visit and the change from baseline in ADHD-RS-IV and CGI-Severity scores	Primary: The median time to first clinical response was shorter for patients receiving LDX (12.0 days; 95% CI, 8.0 to 16.0) than those receiving atomoxetine (21.0 days; 95% CI, 15.0 to 23.0; P=0.001). Secondary: Significantly greater proportions of patients receiving LDX than of those receiving atomoxetine responded to treatment at each study visit (all P<0.01). By visit nine, 81.7% (95% CI, 75.0 to 88.5) of patients receiving LDX had responded compared with 63.6% (55.4 to 71.8) of those receiving atomoxetine (P=0.001). The proportion of patients with a decrease of at least one category from baseline in CGI-S score was greater in the LDX treatment group than in the atomoxetine treatment group by visit four (LDX, 92.3%; 95% CI, 87.5 to 97.1; atomoxetine, 81.3%; 95% CI, 74.4 to 88.2; P<0.05) and by visit nine (LDX, 92.3%; 95% CI, 87.5 to 97.1; ATX, 79.7%; 95% CI, 72.6 to 86.8; P<0.01). Reductions from baseline in mean ADHD-RS-IV total scores were observed in both treatment groups; by visit nine, the mean ADHD-RS-IV total score was 16.3 in the LDX group and 22.5in the atomoxetine group. Treatment-emergent adverse events were reported by 71.9 and 70.9% of patients receiving LDX and atomoxetine, respectively.
Wigal et al.[110] (2011) MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, PC, RCT Children nine to 12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest Secondary: Not reported	Primary: MPH-ER significantly improved performance on the number of problems attempted and number of problems correctly answered on the PERMP compared to placebo (P<0.001). MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (P<0.001) as compared to placebo. Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (P<0.000). MPH-ER significantly improved performance on memory as compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or moderate by the study investigator. Secondary: Not reported
Casas et al.[111] (2011) MPH-ER (Concerta®) 54 mg to 72 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 65 years of age diagnosed with ADHD	N=279 13 weeks	Primary: CAARS-Inv: SV Secondary: CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA-A	Primary: Improvements in CAARS-Inv:SV were significantly greater with MPH-ER 72 mg compared to placebo (P=0.0024). There was no significant difference between MPH-ER 54 mg and placebo. Secondary: Mean improvement in CGI-S score was significantly greater with MPH-ER 72 mg than placebo (P<0.001); however, there was no significant difference with MPH-ER 54 mg compared to placebo. Median improvement in CGI-C score was significantly greater with MPH-ER 72 mg (2.0) compared to placebo (3.0; P=0.0018); however, there was no significant difference with MPH-ER 54 mg (2.5) compared to placebo. CAARS-Self:SV scores decreased significantly compared to placebo in both MPH-ER treatment groups (P<0.05). There was no significant change in SDS score from baseline in either treatment group. Significant benefit compared to placebo was observed on several AIM-A subscales, which included performance and daily functioning, communication and relationships, living with ADHD and general well-being. The most common adverse events with MPH-ER were mild to moderate in severity and included headache, decreased appetite, dry mouth and nausea.
Wigal et al.[112] (2017)	DB, PC, RCT	N=90	Primary: Average of all the	Primary: Treatment with MPH-ER chewable tablet was associated with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-ER chewable tablet 20 to 60 mg daily vs placebo	Children six to 12 years of age diagnosed with ADHD	1 week (after 6-week dose-optimization)	postdose SKAMP-Combined scores assessed during visit nine (the classroom study day) Secondary: Onset and duration of clinical efficacy; safety	statistically significant reduction in ADHD symptoms compared with placebo based on the primary efficacy endpoint (12.1 vs 19.1, respectively; P<0.001). Secondary: There were significant differences in SKAMP-Combined scores between MPH-ER and placebo from two hours postdose and continuing through eight hours postdose after adjusting for the prespecified fixed-sequence testing procedure (P<0.001 at two, four, and eight hours postdose). The 10-hour comparison did not reach statistical significance (P=0.133), and all subsequent comparisons in the fixed sequence (12-, 13-, and 0.75-hour time points) were considered nonsignificant. The only treatment-emergent adverse event reported by more than one subject receiving MPH-ER in the double-blind period was upper respiratory tract infection, reported by three (7%) subjects in each treatment group. No severe adverse events or serious adverse events were reported, and no deaths occurred at any time during the study.
Childress et al.[113] (2017) MPH-ER ODT 20 to 60 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD	N=87 1 weeks (after 5-week dose-optimization and stabilization)	Primary: SKAMP-Combined postdose score averaged across the seven postdose measurements over the classroom day Secondary: Onset and duration of effect; safety	Primary: The postdose SKAMP-Combined scores averaged over the classroom testing day for participants on MPH XR-ODT (LS mean, 14.3; 95% CI, 12.2 to 16.4) were significantly lower (improved) than for participants on placebo (LS mean, 25.3; 95% CI, 23.0 to 27.6; P<0.0001). The LS means difference was −11.0 (95% CI, −13.9 to −8.2). Secondary: The onset and duration of efficacy were assessed by comparing the SKAMP-Combined scores for participants on MPH XR-ODT versus placebo at one, three, five, seven, 10, 12, and 13 hours postdose on the classroom study day. The MPH XR-ODT-treated group demonstrated significantly lower scores than placebo at one hour postdose (LS means difference, −10.7; 95% CI, −13.6 to −7.9; P<0.0001). The difference between the two groups continued to be statistically significant at each assessment through 12 hours postdose (P<0.0001 at three, five, and seven hours; P=0.0024 at 10 hours; and P=0.0262 at 12 hours). The most common (occurred in >5% of the participants) adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				during the open-label dose optimization/stabilization periods were decreased appetite, upper abdominal pain, headache, insomnia, upper respiratory tract infection, affect lability, irritability, cough, and vomiting. The only adverse event that occurred in >5% of participants during the double-blind period was upper respiratory tract infection.
Goodman et al.[114] (2017) MPH OROS 18 to 72 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of ADHD and a baseline AISRS score >24	N=357 6 weeks	Primary: Change from baseline to end point (week 6 or study discontinuation) in the investigator-rated AISRS, with remission defined as an AISRS score of <18 Secondary: CGI-S, CGI-I, adverse events	Primary: The mean AISRS score at baseline was 37.8 for the OROS methylphenidate group and 37.0 for the placebo group. At end point, subjects receiving MPH OROS had a greater change from baseline (−17.1) than placebo subjects (−11.7). Treatment difference was larger for the MPH OROS–treated group with a LS mean difference of −5.0 (−16.9 and −12.0, respectively; P<0.001]. Remission (i.e., AISRS score of <18) was attained by a significantly greater percentage of MPH OROS–treated than placebo-treated subjects (45.0 vs 30.8%; P=0.0008). Secondary: In the investigator-rated assessments, OROS methylphenidate–treated subjects exhibited greater illness improvement (CGI-I; P<0.001) and a greater decrease in illness severity (CGI-S; P<0.001) compared to placebo treated-subjects. Any treatment-emergent adverse event occurred in 72.4% of the MPH OROS patients and 49.7% of placebo patients. Severe events were reported in six subjects treated with OROS methylphenidate (3.4%; anxiety, restlessness, tension headache, fatigue, nervousness and feeling jittery, and gastroenteritis) and in three placebo-treated subjects (1.7%; headache and fatigue, insomnia, and increased blood pressure). One placebo-treated subject experienced a serious adverse event of suicidal ideation.
Wigal et al.[115] (2013) MPH-ER suspension (Quillivant XR®) 20 to 60 mg daily	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=45 2 weeks	Primary: SKAMP combined score Secondary: Onset of action and duration of clinical effect, subscale	Primary: Children treated with MPH-ER suspension experienced a statistically significant improvement in SKAMP combined score at four hours post-dose compared to children treated with placebo. The LS mean SKAMP combined score was 7.12 in children receiving MPH-ER suspension compared to 19.58 in children receiving placebo (LS mean difference, -12.46; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			scores for SKAMP, PERMP, CGI-S and CGI-I	Secondary: There were statistically significant improvements from baseline with MPH-ER suspension compared to placebo at each time point tested (45 minutes, two, four, eight, 10 and 12 hours), with the onset of action at 45 minutes post-dose and a duration of effect continuing to be significant compared to placebo at 12 hours post-dose. The results of the remaining secondary endpoints were not presented in this study.
Wigal et al.[116] (2015) MPH-ER (Aptensio XR®) 10, 15, 20, or 40 mg once daily vs placebo	DB, MC, PC, RCT Children and adolescents six to 18 years of age with ADHD	N=221 Four study phases: (1) 4-week screening/ baseline; (2) 1-week, DB treatment; (3) 11-week, OL, dose-optimization period; (4) 30-day follow-up call	Primary: Change from baseline to end of DB treatment in ADHD-RS-IV total score Secondary: Changes in ADHD-RS-IV subscales and CGI-I at the end of the DB treatment phase	Primary: The mean decrease in ADHD-RS-IV total score from baseline was -5.0 in the placebo group and -9.1, -10.2, -12.0, and -12.6 in the MPH-ER 10, 15, 20, and 40 mg groups, respectively. The 20 and 40 mg doses were statistically different (P=0.0145 and P=0.0011, respectively) from placebo. Secondary: Subset analyses that examined the decrease in ADHD-RS-IV total score over the DB period revealed no difference among treatment groups for all sites, all age groups, and all races. Females responded differently than males (P=0.0238); there was a significant difference among treatments for males but not for females, partly because only one-third of subjects were females and partly because some females who received placebo had considerable improvement during the DB phase. CGI-I scores at the end of the DB phase also showed more improvement as the dose of MPH-ER increased. Pairwise difference from placebo was significant for both the 20 mg (P=0.0311) and 40 mg (P=0.0072) doses but not for the 10 mg (P=0.7391) or the 15 mg (P=0.5518) doses.
Childress et al.[117] (2021) MPH-ER (Adhansia XR®) 25, 35, 45, 55, 70, 85, or 100 mg/day vs	DB, MC, PC, PG, RCT Adults 18 to 60 years of age with ADHD and an ADHD Rating Scale IV (ADHD-RS-IV) score ≥28 at baseline	N=288 7 week OL dose-optimization 1 week DB treatment period	Primary: Permanent Product Measure of Performance-Total (PERMP-T) score Secondary: Time to onset and duration of efficacy based on PERMP-	Primary: Subjects treated with MPH-ER had a higher LS mean PERMP-T score than those treated with placebo when averaged over 16 hours after dosing (302.9 vs. 286.6; LS mean difference, 16.3; 95% CI, 7.6 to 24.9; P=0.0003). Secondary: Post-dose LS mean PERMP-T scores were higher in the MPH-ER group than in the placebo group at every time point from 1 hour through 16 hours (all P<0.05). The LS mean change from pre-dose PERMP-T score

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			T score after dosing, SKAMP-C	averaged over 16 hours after dosing was 35.9 for MPH-ER and 19.7 for placebo. During the full-day adult laboratory classroom visit, subjects treated with MPH-ER had a significantly lower (better) LS mean SKAMP-C score than those treated with placebo when averaged over 16 hours after dosing (9.1 vs. 11.4; LS mean difference, −2.3; 95% CI, −3.1 to −1.5; P<0.0001). Moreover, post-dose LS mean SKAMP-C scores were significantly lower in the MPH-ER group than in the placebo group at every time point from 1 hour through 16 hours (all P<0.05).
Weiss et al.[118] (2021) MPH-ER (Adhansia XR®) 25, 45, 70, or 85 mg once daily vs placebo	DB, MC, PC, PG, RCT Adolescents 12 to ≤17 years who met DSM-5 criteria for ADHD and had a baseline ADHD Rating Scale DSM-5 (ADHD-5-RS) score ≥24	N=354 4 weeks	Primary: Change from baseline in least-squares mean clinician-rated ADHD-5-RS total score Secondary: Change in parent-rated ADHD-5-RS scores, Conners 3rd Edition: Self-Report (C3SR) Short Form	Primary: Compared with participants receiving placebo, participants receiving MPH-ER (all doses combined) showed improvement in ADHD symptoms as measured by ADHD-5-RS total score at the end of DB treatment (mean decrease from baseline 40.8% vs. 29.8%; LS mean change from baseline −15.17 vs. −10.98; LS mean difference for MPH-ER vs. placebo −4.2; P=0.0067). For all individual doses of MPH-ER, improvements in ADHD-5-RS total score from baseline were significant (P<0.0001). Compared with placebo, improvements were higher for the 45 mg (P=0.0155) and 70 mg (P=0.0401) MPH-ER doses, but not for 25 or 85 mg. Secondary: Improvement in parent-rated ADHD-5-RS total score at the end of double-blind treatment was higher for MPH-ER (all doses combined) than for placebo (LS mean change from baseline −11.29 vs. −7.54, P=0.0221). As with clinician-rated ADHD-5-RS total score, significant improvements versus placebo were observed for the 45 mg (P=0.0192) and 70 mg (P=0.0127) MPH-ER doses, but not for 25 or 85 mg. Of the five subscales measured by the C3SR, the greatest improvements with MPH-ER (all doses combined) relative to placebo were on the Inattention subscale (LS mean change from baseline −11.7 vs. −7.3; P=0.0168) and the Hyperactivity-Impulsivity subscale (LS mean change from baseline −9.6 vs. −6.6; P=0.0798). For the Inattention subscale, significant improvements versus placebo were observed for the 45 mg (P=0.0135), 70 mg (P=0.0203), and 85 mg (P=0.0128) MPH-ER doses, but not for 25 mg. For the Hyperactivity-Impulsivity subscale, significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improvements versus placebo were observed for the 45 mg (P=0.0465) and 70 mg (P=0.0246) doses, but not for the 25 mg and 85 mg doses. Significant differences for MPH-ER (all doses combined) versus placebo were not observed for the Learning Problems, Defiance/Aggression, and Family Relations subscales (P=0.3458, 0.6079, and 0.0945, respectively).
Matthijssen et al.[119] (2019) MPH-ER 36 mg or 54 mg/day (continue same maintenance dose) vs placebo (gradual withdrawal over three weeks, then four weeks of placebo)	DB, MC, PC, randomized discontinuation study Children eight to 18 years of age who had been using MPH as prescribed in clinical practice in any dosage or form for two years or longer	N=94 7 weeks	Primary: ADHD-RS Secondary: CGI-I and CTRS-RS	Primary: The mean ADHD-RS scores at baseline for the continuation and discontinuation groups, respectively, were 21.4 (SD=9.7) and 19.6 (SD=8.9). After seven weeks, the mean scores were 21.9 (SD=10.8) and 24.7 (SD=11.4), with a significant between-group difference in change over time of -4.6 (95% CI, -8.7 to -0.56) in favor of the group that continued MPH-ER treatment. The ADHD-RS inattention subscale also deteriorated significantly more in the discontinuation placebo group. Secondary: The CGI-I scores indicated worsening in overall functioning in 19 of the 47 patients (40.4%) in the discontinuation placebo group, compared with seven of the 47 patients (15.9%) in the continuation group, with a significant between-group difference (χ^2=6.7, degrees of freedom=1, P=0.01). The analyses for the CTRS-RS showed significant differences with regard to the ADHD index (P<0.001) and the hyperactivity subscale score (P=0.001). The mean change from baseline was significantly larger among patients assigned to the discontinuation group than among those receiving MPH-ER, with medium effect sizes.
Wilens et al.[120] (2004) MPH-ER (Concerta®) 18 to 54 mg daily	MC, OS, PRO Children six to 13 years of age diagnosed with ADHD	N=432 1 year	Primary: HR and BP after one year Secondary: Not reported	Primary: Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, DBP elevations (1.5 mm Hg; P<0.001), SBP elevations (3.3 mm Hg; P<0.001) and HR (3.9 beats per minute; P<0.0001) at the 12-month end point. Secondary: Not reported
Mattos et al.[121] (2012) MPH-ER (Concerta®)	MC, OL Men and women 18 to 65 years of age diagnosed with	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAMD, CGI-I	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline to weeks four, eight, and 12 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
18 mg to 72 mg/day	ADHD		Secondary: Not reported	AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001), significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAMD, scores were observed (P<0.0001). The most common adverse events included appetite changes (25%), dry mouth (16.7%), headache (11.7%), irritability (5%) and insomnia (5%). Adverse events were mild to moderate in severity as reported by the study investigators. Secondary: Not reported
Cox et al.[122] (2006) MPH-ER (Concerta®) 36 mg once daily on days one to five, then 72 mg once daily on days 6 to 17 vs AMP-XR (Adderall XR®) 15 mg once daily on days one to five, then 30 mg once daily on days 6 to 17 vs placebo	DB, PC, RCT, XO Adolescents 16 to 19 years of age diagnosed with ADHD and licensed to drive	N=35 21 to 38 days	Primary: IDS, assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators Secondary: Not reported	Primary: Overall IDS values were significantly better than with placebo with MPH-ER (P<0.001), but not with AMP-ER (P=0.24). Simulator-rated driving performance as indicated by IDS was also significantly better in the MPH-ER group than in those receiving AMP-ER (P=0.03). MPH-ER was significantly better than placebo in the categories off-road excursions (P=0.02), speeding (P=0.01), SD speed (P=0.02), and time at a stop sign deciding where to turn (P=0.003). AMP-ER was significantly better than placebo in the category of inappropriate braking (P=0.04). Subjective ratings of driving performance by participants and investigators rated MPH-ER as better for driving performance (P=0.008). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Yang et al.[123] (2011) MPH-ER 18 mg to 54 mg/day vs atomoxetine 0.5 mg to 1.4 mg/kg/day	RCT, SB Children and adolescents seven to 14 years of age diagnosed with ADHD	N=142 4 to 6 weeks	Primary: RCFT, Digit span, Stroop color word test Secondary: Not reported	Primary: Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time. Visual and verbal memory was not significantly different from the control group at post-treatment assessment (P>0.05). Although word interference time was more improved than the control group, there was no statistically significant difference (P>0.05). Secondary: Not reported
Su et al.[124] (2016) MPH OROS 18 to 54 mg daily vs atomoxetine 0.5 mg to 1.4 mg/kg/day	RCT Chinese children and adolescents, six to 16 years of age, diagnosed with ADHD	N=237 4 weeks (maintenance period) 1 year (adherence)	Primary: Investigator-rated ADHD Rating Scale-IV Secondary: CGI-ADHD-S. adherence	Primary: The ADHD-RS-IV total scores were significantly lower at each post-treatment assessment (the ends of the week one, titration period, and maintenance period) compared with pretreatment for both OROS MPH and atomoxetine (P<0.001). The difference between the two medication groups was not significant. Secondary: The CGI-ADHD-S scores were significantly lower at each post-treatment assessment compared with pretreatment for both OROS MPH and atomoxetine (P<0.001). The difference between the two medication groups was not significant. Adherence rates to both medications were low. Subjects were adherent to OROS MPH treatment for a mean of 20.66 weeks, as compared with a mean of 10.92 weeks for atomoxetine during one year (P<0.001). For both medications, adverse effects and lack of efficacy were the primary reasons reported. At one year follow-up, 78.2% of the total patients were not compliant with OROS MPH treatment; in 31.9% and 20.2% of patients this was because of adverse effects and lack of efficacy, respectively. For those assigned to the atomoxetine group, 96.6% of patients were not compliant; in 36.4% and 33.9% of patients this was because of adverse effects and lack of efficacy, respectively.
Wolraich et al.[125] (2001)	DB, PC, PG, RCT	N=282	Primary: Iowa Conners I/O	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-IR 5 to 15 mg three times daily vs placebo	Children six to 12 years of age diagnosed with ADHD (any subtype)	28 days	and O/D rating scale (parents and teachers) Secondary: SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week one and at the end of the study (P<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR groups at week one (P=0.838) or at the end of the study (P=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (P<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups. CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared to the placebo group (P<0.001). Both the parent and teacher global assessment of efficacy scores were significantly higher with the MPH-ER and MPH-IR groups than the placebo group (P<0.001).
Pelham et al.[126] (2001) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-IR 5 to 15 mg three times daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to study entry	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary: Not reported	Primary: MPH-ER and MPH-IR were better than placebo in the Iowa Conners I/O and O/D rating scale scores from teachers and parents (P<0.05). MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (P<0.05). In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy, but both were significantly better than placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gau et al.[127] (2006) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-IR 5 to 10 mg three times daily	OL, RCT Children six to 15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10 to 40 mg/day)	N=64 28 days	Primary: CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D Secondary: SAICA, CGI	Primary: Each of the four groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (P<0.001 for all) compared to baseline, but there were no significant differences between the groups (P>0.05 for all). Secondary: Patients in both the MPH-XR and MPH-IR groups experienced significant improvements from baseline in academic performance and less severe problems at school (P<0.05). Patients in the MPH-XR group also significantly improved from baseline in attitude toward their teachers, school social interaction, and relationships with peers and siblings (P<0.05). The MPH-XR group had a significantly greater number of patients being very much or much improved (84.4%) than the MPH-IR group (56.3%) (P=0.014) based on the CGI score.
Lopez et al.[128] (2003) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-XR (Ritalin LA®) 20 mg daily vs placebo	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID)	N=36 28 days	Primary: SKAMP scales Secondary: Not reported	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (P<0.001). Secondary: Not reported
Swanson et al.[129] (2004)	DB, MC, PC, RCT, XO	N=184 7 weeks	Primary: SKAMP scales, PERMP	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (P<0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	Children six to 12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10 to 60 mg/day		Secondary: Not reported	Secondary: Not reported
Silva et al.[130] (2005) MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg vs MPH ER 20 mg vs MPH ER 40 mg vs placebo	MC, RCT, SB, XO Children six to 12 years of age diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day)	N=54 6 weeks	Primary: SKAMP-A rating subscale Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	Primary: All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (P<0.038). ER-MPH 20 and 40 mg showed significantly greater differences from predose on the SKAMP-A than did MPH ER, 36 mg at two hours postdose, and also when scores were integrated over zero to four hours (P=0.022 for the 20 mg dose and P=0.001 for the 40 mg dose), but showed no significant improvement over eight to 12 hours. Secondary: Single morning doses of ER-MPH and MPH ER were effective in improving SKAMP-D scores and academic productivity for the majority of the 12-hour classroom session.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All medications were dosed once per study day (six consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday.				
Jahromi et al.[131] (2009) MPH-IR 0.125 mg/kg/dose twice daily for one week (low dose) vs MPH-IR 0.25 mg/kg/dose twice daily for one week (medium dose) vs MPH-IR 0.50 mg/kg/dose twice daily for one week (high dose)	DB, RCT, XO Children five to 13 years of age with PDD and hyperactivity	N=33 4 weeks	Primary: JAMES, Caregiver-Child Interaction measure (competing demands and clean-up task) captured social communication, self-regulation and affective behavior Secondary: Not reported	Primary: Significant positive effect of MPH was seen on social communication (P<0.05); comparing each of the three MPH doses of MPH compared to placebo, the low dose showed significant improvement compared to placebo (P<0.05); no significant differences found between placebo and the medium or high doses. No significant improvement in self-regulation for the competing demands task when comparing best dose MPH to placebo (P=0.09); significant improvement in self-regulation behaviors comparing low dose MPH (P<0.05) and medium dose effect (P<0.01) compared to placebo; no improvement found in high dose MPH over placebo. No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared to placebo, or between placebo and the best dose of MPH (P>0.05). Significant improvement in affective behavior for the competing demands task when comparing medium MPH dose (P <0.05) and high MPH dose compared to placebo (P<0.05); no improvement found in best dose of MPH compared to placebo (P=0.09); or low dose (P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for one week				No significant improvement on affective behavior for the clean-up task and any MPH dose (P>0.05). Secondary: Not reported
Spencer et al.[132] (2011) MPH-IR three times daily vs MPH-ER once daily (OROS-MPH)	PG, RCT, SB Patients 19 to 60 years of age diagnosed with ADHD who were on stable therapy with MPH-IR	N=61 6 weeks	Primary: AISRS Secondary: Not reported	Primary: MPH-IR responders randomized to MPH-IR or MPH-ER had no effect on AISRS score at the study endpoint (11.2 vs 10.7; P=0.80). Study patients stabilized on MPH-IR and switched to MPH-ER remained satisfied over 71% of the time. MPH-IR treatment group missed significantly more doses than the MPH-ER treatment group (7.3 vs 3.3; P=0.02). Secondary: Not reported
Efron et al.[133] (1997) MPH-IR 0.3 mg/kg/dose twice daily vs DEX-IR 0.15 mg/kg/dose twice daily Patients received one drug for two weeks then crossed over to the other stimulant for two weeks.	DB, RCT, XO Children five to 15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19; P=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73; P<0.01). A majority of parents rated their children as improved compared to their “usual selves” in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pelham et al.[134] (1990) MPH-IR 10 mg twice daily vs MPH-SR (Ritalin SR®) 20 mg daily vs DEX-SR (Dexedrine®) 10 mg daily vs pemoline 56.25 mg daily vs placebo	DB, PC, RCT, XO Males eight to 13 years of age diagnosed with ADHD	N=22 8 weeks	Primary: Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task Secondary: Not reported	Primary: Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment (P<0.05). DEX-SR and pemoline tended to produce the most consistent effects. The continuous performance task results showed that all four medications had an effect within two hours, and the effects lasted for nine hours vs placebo (P<0.025). Secondary: Not reported
Palumbo et al.[135] (2008) MPH-IR 5 mg to 60 mg/day vs clonidine 0.05 mg to 0.6 mg/day	DB, MC, PC, RCT Children seven to 12 years of age diagnosed with ADHD	N=122 16 weeks	Primary: CASQ-T Secondary: CASQ-P, CGAS	Primary: For CASQ-T, clonidine did not improve ADHD symptoms. Study patients treated with MPH showed significant improvement compared to those not treated with MPH. Secondary: Study patients treated with clonidine had greater improvements on the CASQ-P and CGAS, but a higher rate of sedation compared to patients not treated with clonidine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs MPH-IR and clonidine vs placebo				
Huss et al.[136] (2014) MPH-LA 40 mg/day vs MPH-LA 60 mg/day vs MPH-LA 80 mg/day vs placebo	DB, MC, PC, RCT Adult patients 18 to 60 years of age with a diagnosis of ADHD	N=725 40 weeks (9 week double-blind dose-confirmation phase; 5 week real-life dose-optimization phase; 6 month double-blind maintenance of effect phase)	Primary: ADHD-RS, SHS, percentage of treatment failures Secondary: CGI-I, CGI-S, CAARS- observer, ASRS	Primary: Improvement from baseline in ADHD-RS (P<0.0001 for all comparisons) and SDS (40 mg, P=0.0003; 60 mg, P=0.0176; 80 mg, P<0.0001) total scores was significantly greater vs placebo for all MPH-LA doses. Treatment failure rate was significantly lower with MPH-LA (21.3%) versus placebo (49.6%) during the six-month maintenance of effect phase. By the end of the nine-week double-blind dose-confirmation phase, improvement from baseline in ADHD-RS total score for all MPH-LA dose levels was significantly greater than placebo (all comparisons: P<0.0001). Similarly, functional improvement, as assessed by change from baseline in the SDS total score, was significantly greater for all MPH-LA dose levels compared to placebo (40 mg, P=0.0003; 60 mg, P=0.0176; 80 mg, P<0.0001). During the six-month double-blind maintenance of effect phase, significantly less patients treated with MPH-LA were required to discontinue the study due to treatment failure (21.3%, n=75) compared to those treated with placebo (49.6%, n=57). Patients treated with placebo had more than three times higher chance of being required to discontinue the study due to treatment failure compared to patients treated with MPH-LA (OR, 0.3; 95% CI, 0.2 to 0.4). Secondary: The percentage of patients with improvement on the CGI-I scale for all three MPH-LA dose levels was significantly higher compared to placebo. Similarly, the percentage of patients with improvement for all three MPH-LA dose levels on CGI-S was significantly higher compared to the placebo group. Consistent results were seen for the observer-rated CAARS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and self-rated ASRS: improvement from baseline for all dose levels of MPH-LA was significantly greater than placebo.
Ginsberg et al.[137] (2014) MPH-LA (40 to 80 mg/day)	ES (of Huss et al, 2014), OL Adult patients 18 to 60 years of age with a diagnosis of ADHD	N=298 1 year (6 month double-blind maintenance of effect phase and 6 month extension)	Primary: Safety Secondary: Efficacy (ADHD-RS, SDS, CGI-I, CGI-S)	Primary: Overall, the incidence of adverse events was comparable between patients receiving placebo (79.3%) and those receiving MPH-LA (81.0%) during the maintenance of effect phase of the core study. The incidence of adverse events occurring in the extension study was 69.8%. Incidence of adverse events was comparable between MPH-LA mean daily dosage groups (69.4; 75.0; and 65.1% in the ≤40, >40 to 60, and >60 mg dosage groups, respectively). Secondary: The mean improvement in total score of ADHD-RS from the maintenance of effect phase baseline to the end of the extension study was 0.9. The mean improvement in SDS total score from the maintenance of effect phase baseline to the end of the extension study was 1.4. A total of 91 (31.4%) patients showed improvement in CGI-S score from the maintenance of effect phase baseline to the end of the extension study (MPH-LA, 32.1%; placebo, 29.5%). The mean improvement in total score of ADHD-RS and SDS from extension baseline to the end of the study was 7.2 and 4.8, respectively. Overall, 69.4% of patients showed improvement in CGI-I rating (MPH-LA, 65.3%; placebo, 80.2%), and 52.1% of patients showed improvement in CGI-S scale (MPH-LA, 42.9%; placebo, 76.9%) from the extension study baseline to the end of the study.
Greenhill et al.[138] (2002) MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT Children six to 16 years of age diagnosed with ADHD	N=321 3 weeks	Primary: CGI-S (teacher) Secondary: CGI-S (parents), CGI-I scores, adverse events	Primary: CGI-S teacher scores significantly improved in the MPH-XR group (12.7±7.2 to 4.9±4.7) compared to the placebo group (11.5±7.3 to 10.3±6.9; P<0.001). Secondary: CGI-S parent scores significantly improved from 13.6±6.6 to 7.4±5.9 with MPH-XR vs 12.9±7.6 to 10.1±6.7 with placebo (P<0.001 for both scales). Eighty-one percent of the patients in the MPH-XR group compared to 50% of the patients in the placebo group were classified as responders

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				based on their CGI-I scores (P<0.001). In the MPH-XR group, 52% of children reported at least one adverse event vs 38% from the placebo group (P=0.014). The rate of anorexia was more significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; P=0.007).
McGough et al.[139] (2006) MPH transdermal system 10 to 27 mg daily vs standard current therapy	OL, RCT (first five weeks) then DB, PC Children six to 12 years of age diagnosed with ADHD	N=80 7 weeks	Primary: Evaluate time course effects of MPH transdermal patch vs placebo transdermal patch via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MPH transdermal patch	Primary: Mean SKAMP-D scores were improved with MPH transdermal patch vs placebo (mean score, 3.2 vs 8.0) and at all time points assessed including 12 hours post-application (P<0.01). Mean (SKAMP-A) scores were improved with MPH transdermal patch vs placebo (6.2±0.50 vs 9.9±0.50, respectively; P<0.0001). PERMP scale results: Mean number of math problems attempted and math problems correct were significantly higher with MPH transdermal patch vs placebo (113.8 vs 86.2 and 109.4 vs 80.7, respectively; P<0.0001). Across the double-blind period, mean scores for the ADHD-RS-IV and CPRS-R scales were significantly improved with MPH transdermal patch vs placebo (P<0.0001). Those in the MPH transdermal patch group (79.8%) were more likely to be deemed improved on clinician rated CGI-I scores vs those in the placebo group (79.85 and 11.6%, respectively; P<0.0001). Statistically significant differences were observed with PGA ratings; 71.1% of MPH transdermal patch participants and 15.8% of placebo participants were rated as improved (P<0.0001). Secondary: More treatment-emergent adverse events were recorded with MPH transdermal patch therapy (39 events, 24 participants) vs placebo therapy (25 events, 18 participants). The most common treatment-related adverse events were decreased appetite, anorexia, headache, insomnia, and upper abdominal pain, all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported by less than 5% of study participants.
Pelham et al.[140] (2005) MPH transdermal patches: 6.25 cm^2 (0.45 mg/hour), 12.5 cm^2 (0.9 mg/hour) and 25 cm^2 (1.8 mg/hour), worn for at least 12 hours daily Each participant received single applications of MPH transdermal patches 6.25 cm^2, 12.5 cm^2 or 25 cm^2 patches or placebo in a random order on separate days and at two time points (6:00 AM or 7:00 AM).	DB, DR, MC, RCT Children seven to 12 years of age diagnosed with ADHD	N=36 8 days	Primary: MPH transdermal patch efficacy and influence of exposure time on morning effects Secondary: Not reported	Primary: All doses of MPH transdermal patches were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior (P<0.05). Beneficial effects of MPH transdermal patches were observed at all time points after application of the patch and were still seen for three hours after the patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40 to 50%. Secondary: Not reported
Pelham et al.[141] (2005) MPH transdermal patches: 12.5 cm^2, 25 cm^2 and 37.5 cm^2 plus behavior modification Each participant had two days on each treatment	DR, RCT Children aged six to 12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card scores Secondary: Not reported	Primary: The percentage of individualized target criteria met by children in their Daily Report Card assessment was significantly (P<0.05 for all) higher with MPH transdermal patch 12.5, 25, and 37.5 cm^2 vs placebo, both without behavior modification (41.9, 63.1, and 66.2 vs 20.8%) and with behavior modification (73.7, 87.5, and 86.2 vs 54.7%; all P<0.05). Response rates were higher in the MPH transdermal patches 25 cm^2 group than in the 12.5 cm^2 group, both with and without behavior modification (P<0.05 for both); increasing the size of the patch to 37.5 cm^2 added no further advantage.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
without concomitant plus behavior modification and four days on each treatment with plus behavior modification.				Secondary: Not reported
Faraone et al.[142] (2009) MPH transdermal patches 10 to 30 mg daily worn for nine hours per day or MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)	N=268 5 weeks	Primary: CSHQ Secondary: Not reported	Primary: No significant difference in the severity of sleep problems was observed among the treatment and placebo groups (P≥0.233). No significant differences in the numbers of sleep problems were observed between MPH transdermal patch/MPH-ER and placebo (P≥0.554). There was no significant effect of MPH dosage on sleep problems (P=0.135). The effects of each MPH treatment and the various doses of these treatments on each CSHQ subscale were identical to the effects observed for the total CSHQ scale. Secondary: Not reported
Findling et al.[143] (2008) MPH transdermal system 10 to 30 mg daily or OROS-MPH 18 to 54 mg daily	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD	N=282 7 weeks	Primary: ADHD-RS Secondary: CTRS-R, CPRS-R, CGI-S, CGI-I	Primary: Mean total ADHD-RS scores were similar between MPH transdermal patch, MPH-ER, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and MPH-ER compared to patients receiving placebo (P<0.001). There was a two-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				MPH transdermal patch and MPH-ER showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MPH transdermal patch and MPH-ER compared to placebo were rated as improved by clinicians and parents (P<0.001). Adverse events included decreased appetite, nausea, vomiting and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Chou et al.[144] (2012) MPH-ER (Concerta®) 18, 36, or 54 mg once daily	OS Children six to 19 years of age with ADHD who have received MPH-IR for ≥1 month	N=521 10 weeks (six weeks forced-titration phase to achieve remission, followed by a four week maintenance phase)	Primary: Symptomatic remission Secondary: Changes in efficacy and satisfaction, safety	Primary: Using the forced-titration of MPH-ER dosage to increase the dosage during the first six weeks, the remission rate significantly increased with time from 4.8% (at baseline), 25% (week two), 44.2% (week four), 58.8% (week six), up to 59.6% (week 10) among 507 ITT patients. Among 439 patients who completed the 10 week follow-up assessments, 290 (66.1%) patients achieved symptomatic remission (95% CI, 61.6 to 70.5). The non-remission group had higher mean daily doses compared to the remission group from visit two to trial end. Secondary: Among the 439 patients who completed the treatment, there was a significant decrease in the total score and three sub-scores of the Chinese SNAP-IV (P<0.001), CGI-ADHD-S (P<0.001), and CGI-ADHD-I (P<0.001) as intra-individual comparison from the baseline to each visit through the trial period. Among the items on the Barkley SERS, poor appetite was the only one exacerbated on visit three, but improved on later visits. The other side effects gradually decreased in intensity throughout the trial period, and the difference from baseline reached significance from visit three to trial end. At trial end, there was a decrease in both mean body weight (-0.85 kg) and mean respiratory rate (-0.44/minute), and an increase in mean pulse rate (5.09 beats per minute) in comparison with baseline with significance (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Five percent of patients withdrew from the trial because of adverse events, and these patients mostly left due to poor appetite and insomnia. Three patients experienced at least one serious adverse event that was not deemed to be treatment-related.
Kollins et al.[145] (2021) Serdexmethylphenidate/dexmethylphenidate (SDX/d-MPH) capsules (Azstarys®) vs placebo	DB, MC, PC, RCT Children six to 12 years of age with ADHD	N=149 3-week OL, dose-optimization 1 week DB treatment phase	Primary: SKAMP and Permanent Product Measure of Performance (PERMP) Secondary: Adverse events	Primary: The mean postdose change from baseline in SKAMP-Combined scores averaged over the laboratory classroom day was improved with SDX/d-MPH versus placebo (least-squares mean treatment difference, -5.41; 95% CI, -7.10 to -3.71; P<0.001). A significant treatment effect for SDX/d-MPH compared with placebo was observed from 1 to 10 hours postdose. Both average postdose PERMP-Attempted and PERMP-Correct score changes from baseline were improved among those treated with SDX/d-MPH versus placebo (P<0.001 for both). Secondary: No serious adverse events were reported in this study. In the open-label Dose Optimization Phase, approximately two-thirds of subjects (67.1%) experienced at least one treatment-emergent adverse event, with a majority of treatment-emergent adverse events rated as mild (56.8%) or moderate (29.7%) in severity. The most common treatment-emergent adverse events in this phase were decreased appetite (24.5%), insomnia (15.5%), affect lability (11.6%), upper abdominal pain (9.7%), headache (7.7%), and irritability (7.7%). Four subjects experienced adverse events leading to drug discontinuation in this phase. Treatment-emergent adverse events (>2% incidence) during the Treatment Phase that occurred more frequently in the SDX/d-MPH versus placebo group included headache (5.4%), upper abdominal pain (4.1%), insomnia (2.7%), and pharyngitis (2.7%).
Nasser et al.[146] (2020) Viloxazine 100 mg QD or viloxazine 200 mg	DB, MC, PC, PG, RCT Children six to 11 years of age with ADHD and an ADHD-RS-5 score ≥28 and CGI-S score ≥4	N=477 6 weeks	Primary: Change from baseline in ADHD-RS-5 score Secondary: CGI-I at endpoint, change from baseline in	Primary: At six weeks, the change from baseline in ADHD-RS-5 was statistically significantly greater for patients treated with both viloxazine 100 mg and 200 mg compared to placebo (-16.6 vs -17.7 vs -10.9, respectively; 95% CI, -8.9 to -2.6 and -10.0 to -3.8; P=0.0004 and P <0.0001, respectively). Secondary: CGI-I score was significantly lower (improved) in viloxazine-treated patients compared to placebo (P=0.0020 and P<0.0001). The responder

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo			Conners 3–PS Composite T-score and WFIRS–P total average score	rate based on CGI-I score (i.e., percent of subjects with a CGI-I score of 1 or 2) was also significantly higher at the endpoint in both treatment groups compared to placebo (45% and 51% vs 30%, respectively; P=0.0065 and P=0.0002). The change from baseline in the Conners 3−PS Composite T-score at the endpoint was significantly reduced (improved) in both treatment groups compared to placebo (-9.1 vs -9.2 vs -4.8; P=0.0003 and P=0.0002, respectively). The change from baseline in WFIRS–P Total average score at the endpoint was significantly reduced (improved) in both treatment groups compared to placebo (-0.36 vs -0.39 vs -0.22; P=0.0019 and P=0.0002, respectively).
Nasser et al.[147] (2021) Viloxazine 200 mg QD or viloxazine 400 mg QD vs placebo	DB, MC, PC, PG, RCT Children six to 11 years of age with ADHD and an ADHD-RS-5 score ≥28 and CGI-S score ≥4	N=313 8 weeks	Primary: Change from baseline in ADHD-RS-5 score Secondary: CGI-I at endpoint, change from baseline in Conners 3–PS Composite T-score and WFIRS–P total average score	Primary: At eight weeks, the change from baseline in ADHD-RS-5 was statistically significantly greater for patients treated with both viloxazine 200 mg and 400 mg compared to placebo (-17.6 vs -17.5 vs -11.7, respectively; 95% CI, -10.0 to -1.9 and -9.9 to -1.7; P=0.0038 and 0.0063, respectively). Secondary: CGI-I score was significantly lower (improved) in viloxazine-treated patients compared to placebo (P=0.0028 and P=0.0099). The responder rate based on CGI-I score (i.e., percent of subjects with a CGI-I score of 1 or 2) was also significantly higher at various timepoints compared to placebo, but not at the endpoint. The change from baseline in the Conners 3−PS Composite T-score at the endpoint was significantly reduced (improved) in the 200 mg treatment group compared to placebo (-9.1 vs -5.3; P=0.0064, respectively). The change from baseline in WFIRS-P Total average score at the endpoint was not significantly reduced in either treatment group compared to placebo (P=0.0651 and P=0.1680, respectively).
Nasser et al.[148] (2021)	DB, MC, PC, PG, RCT	N=310 6 weeks	Primary: Change from baseline in ADHD-	Primary: In the 200 mg and 400 mg treatment groups, a significant improvement was found in the change from baseline at end of study in ADHD Rating

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Viloxazine 200 mg QD or viloxazine 400 mg QD vs placebo	Adolescents 12 to 17 years of age with ADHD		RS-5 score Secondary: CGI-I at endpoint, Conners score	Scale-5 Total (P=0.0232, P=0.0091) and Inattention (P=0.0424, P=0.0390) and Hyperactivity/Impulsivity (P=0.0069, P=0.0005) subscale scores versus placebo. Secondary: CGI-I score was also improved in viloxazine-treated patients compared to placebo (P=0.0042 in the 200 mg group, P=0.0003 in the 400 mg group). The Conners 3-Parent Short Form composite T-score and Weiss Functional Impairment Rating Scale-Parent Total average score exhibited improvement in both viloxazine groups; however, the difference versus placebo was not statistically significant.
Nasser et al.[149] (2022) Viloxazine ER (flexible dose of 200 to 600 mg/day) vs placebo	DB, PC, RCT Adults 18 to 65 years of age with ADHD	N=374 6 weeks	Primary: Change from baseline at end of study (week 6) in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score Secondary: Change from baseline at end of study in the Clinical Global Impressions-Severity of Illness (CGI-S) score and additional subscales	Primary: The reduction in the change from baseline at end of study AISRS total score (least-square means ± standard error) was significantly greater in subjects treated with viloxazine ER (-15.5 ± 0.91) compared with placebo (-11.7 ± 0.90), P=0.0040. Secondary: The reduction in the CGI-S score was also significantly greater in subjects treated with viloxazine ER (-1.4 ± 0.10) compared with placebo (-1.0 ± 0.10), P=0.0023. The viloxazine ER group demonstrated significantly greater improvements in the AISRS Inattention (P=0.0015) and Hyperactivity/Impulsivity (P=0.0380) subscales, the CGI-I (P=0.0076), and the BRIEF-A Global Executive Composite (P=0.0468) and Metacognition Index (P=0.0100). Analysis of categorical secondary endpoints revealed that the viloxazine ER group had a significantly higher AISRS 30% response rate compared with placebo (P=0.0395); all other comparisons were not significant.
Faraone et al.[150] (2006) AMP-IR, AMP-XR, atomoxetine,	MA (29 trials) Patients diagnosed with ADHD	N=2,988 Variable duration	Primary: Effect sizes Secondary: Not reported	Primary: All of the drugs groups produced a significant measure of effect compared to the placebo group (P<0.0001). The effect sizes for non-stimulant medications were significantly less than those for immediate-release stimulants (P<0.0001) or long-acting

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bupropion, DEX-IR, DEX-ER, DEX-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MPH transdermal patches, pemoline				stimulants (P=0.0008). The two classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14). Secondary: Not reported
Schelleman et al.[151] (2011) ADHD medications vs nonusers	RETRO Children three to 17 years of age who were dispensed a prescription for an AMP, atomoxetine, or MPH	N=241,417 Variable duration	Primary: Sudden cardiac death, or ventricular arrhythmia, stroke, MI Secondary: All-cause death	Primary and Secondary: No statistically significant difference between incident users and nonusers was observed in the rate of validated sudden death or ventricular arrhythmia (HR, 1.6; 95% CI, 0.19 to 13.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in study patients who used ADHD medication. No statistically significant difference between prevalent users and nonusers was observed for validated sudden death or ventricular arrhythmia (HR, 1.43; 95% CI, 0.31 to 6.61); stroke (HR, 0.89; 95% CI, 0.11 to 7.11); stroke/MI (HR, 0.72; 95% CI, 0.09 to 5.57); or all-cause death (HR, 0.77; 95% CI, 0.56 to 1.07).
Olfson et al.[152] (2012) AMP and MPH vs nonusers	RETRO Patients six to 21 years of age diagnosed with ADHD who were prescribed AMP or MPH	N=171,126 Variable duration	Primary: Cardiac events (inpatient diagnosis of chest pain, cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia, palpitations, or	Primary: There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use. Current stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI, 0.42 to 1.12). Past stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 1.18; 95% CI, 0.83 to 1.66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			syncope) Secondary: Not reported	The adjusted ORs for cardiac symptoms were 1.18 (95% CI, 0.89 to 1.59) for current and 0.93 (95% CI, 0.71 to 1.21) for past stimulant use when compared to no stimulant use. Current and past stimulant use was not associated with cardiac symptoms. No significant differences were observed in risks of cardiovascular events (adjusted OR, 2.14; 95% CI, 0.82 to 5.63) or symptoms (adjusted OR, 1.08; 95% CI, 0.66 to 1.79) for current MPH use compared to AMP use. Secondary: Not reported
Schelleman et al.[153] (2012) AMP, atomoxetine, MPH	RETRO Patients three to 17 years of age with a prescription for an AMP, atomoxetine, or MPH	N=219,954 Variable duration	Primary: Sudden death, ventricular arrhythmia, stroke, MI Secondary: Not reported	Primary: No significant difference between incident users and nonusers was observed in the rate of sudden death or ventricular arrhythmia (HR, 1.60; 95% CI, 0.19 to 3.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in ADHD medication users. No significant difference between prevalent users and nonusers was observed (HR for validated sudden death or ventricular arrhythmia, 1.43; 95% CI, 0.31 to 6.61; stroke, 0.89; 95% CI, 0.11 to 7.11; stroke/MI, 0.72; 95% CI, 0.09 to 5.57; and all-cause death, 0.77; 95% CI, 0.56 to 1.07). Secondary: Not reported
Hanwella et al.[154] (2011) Atomoxetine vs MPH	MA (five trials) Children and adolescents six to 16 years of age diagnosed with ADHD	N=2,762 Variable duration	Primary: ADHD-RS Secondary: Not reported	Primary: The MA did not find a significant difference in efficacy between MPH and atomoxetine when comparing SMD in ADHD-RS scores (SMD, 0.09; 95% CI, -0.08 to 0.26). There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment effects between the formulations of MPH showed a significant SMD in ADHD-RS favoring OROS-MPH (SMD, 0.32; 95% CI, 0.12 to 0.53). MPH-IR was not superior to atomoxetine (SMD, -0.04; 95% CI, -0.19 to 0.12). There was no significant difference in acceptability between atomoxetine and MPH (RR, 1.22; 95% CI, 0.87 to 1.71). Secondary: Not reported
Bloch et al.[155] (2009) ADHD medications	MA (11 trials) Children diagnosed with ADHD and Tourette's	N=77 Variable duration	Primary: ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and GTSS) Secondary: Not reported	Primary: MPH, α-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics. α-2 agonists and atomoxetine significantly improved co-morbid tic symptoms. There was evidence that supratherapeutic doses of DXM worsened tics; however, there was no evidence that MPH worsened tic severity in the short term. Secondary: Not reported
Binge Eating Disorder				
McElroy et al.[156] (2015) LDX 30 mg/day vs LDX 50 mg/day vs LDX 70 mg/day vs placebo	DB, PC, PG, RCT Adults 18 to 55 years of age with moderate to severe binge eating disorder, as indicated by at least three binge eating days per week for the two weeks before the baseline visit	N=260 11 weeks	Primary: Number of binge eating days per week Secondary: Number of binge eating episodes per week, one-week binge eating response status, four-week cessation from binge eating, CGI-I	Primary: The mean (SD) changes from baseline to week 11 or early termination in nontransformed binge eating days per week for the placebo and the 30, 50, and 70 mg treatment groups were −3.3 (2.04), −3.5 (1.95), −4.1 (1.52), and −4.1 (1.57), respectively. The primary efficacy end point was significantly decreased in the 50 and 70 mg treatment groups but not in the 30 mg treatment group compared with the placebo group. Secondary: The LS mean change from baseline to week 11 of binge eating episodes per week was significantly decreased for the 50 and 70 mg treatment groups. At week 11 or early termination, the one-week response status was improved in the 50 and 70 mg treatment groups compared with the placebo group, and the four-week binge eating cessation response status was improved in the 50 and 70 mg treatment groups compared with the placebo group. Greater proportions of participants receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				lisdexamfetamine were rated improved (CGI-I rating, one or two) compared with those receiving placebo at week 11 or early termination.
Hudson et al.[157] (2017) LDX 50 or 70 mg/day vs placebo	DB, MC, randomized withdrawal study Adults 18 to 55 years of age meeting DSM-IV-R binge-eating disorder criteria with moderate to severe binge eating disorder (≥3 binge-eating days per week for 14 days before OL baseline; CGI-S scores ≥4 [moderate severity] at screening and OL baseline)	N=275 LDX responders 26 weeks	Primary: Time to relapse (≥2 binge-eating days per week for 2 consecutive weeks and ≥2-point CGI-S score increases from randomized withdrawal baseline) Secondary: Binge-eating days per week, CGI-S scores, and Yale-Brown Obsessive Compulsive Scale modified for Binge Eating scores	Primary: The observed percentage of participants meeting relapse criteria was 32.1% with placebo and 3.7% with lisdexamfetamine (P<0.001). Secondary: The LS mean treatment difference for the change from randomized withdrawal baseline in binge-eating days per week indicated that there was an increase for placebo compared with LDX (−0.61; 95% CI, −0.81 to −0.42; nominal P<0.001). CGI-S score distributions differed between treatment groups (nominal P<0.001), with placebo scores skewed toward more severe illness than LDX scores. The LS mean treatment difference for the change from randomized withdrawal baseline indicated that there were total score increases for placebo compared with LDX on the Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (−5.6; 95% CI, −7.2 to −3.9; nominal P<0.001).
Gasior et al.[158] (2017) LDX 50 or 70 mg/day	ES, MC, OL Adults 18 to 55 years of age meeting DSM-IV-R binge-eating disorder criteria who completed one of three antecedent studies	N=604 52 weeks (4 week dose optimization and 48 week dose maintenance)	Primary: Adverse events Secondary: CGI-I, Eating Disorder Examination Questionnaire	Primary: Most participants reported treatment-emergent adverse events (84.5%), and most of the reported treatment-emergent adverse events were of mild or moderate intensity. There were no deaths during the study. Cholecystitis was the only serious adverse event reported in more than one participant (n=3). A detailed review of these events did not suggest a direct association with LDX, and none was considered to be related to LDX by the investigator. The only serious adverse events considered to be related to LDX by the investigator were coincident events of supraventricular tachycardia (mild intensity) and acute coronary syndrome (moderate intensity) reported in one participant who indicated that a double dose of 50-mg LDX may have been taken on the day of the events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most frequently reported treatment-emergent adverse events (occurring in ≥10% of participants) were dry mouth (27.2%), headache (13.2%), insomnia (12.4%), and upper respiratory tract infection (11.4%). Secondary: During the study, more than half of the participants in the full analysis set were categorized as improved on the CGI-I. At week 52/end-of-treatment, 89.8% (536/597) of the participants were categorized as improved on the CGI-I, with most participants having scores of one ("very much improved," 67.0%). At week 52/end-of-treatment, four participants exhibited worsening on the CGI-I ("minimally worse," n=3; "much worse," n=1). Mean Eating Disorder Examination Questionnaire global and subscale scores and the number of binge eating days for the past 28 days at weeks 52 and 52/end-of-treatment were numerically lower than those at baseline.

Drug regimen abbreviations: AMP=mixed amphetamine salts, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, ODT=orally disintegrating tablet, OROS=osmotic-release oral system, SR=sustained release, XR=extended release
Study abbreviations: CI=confidence interval, DB=double blind, DR=dosing ranging, ES=extension study, FD=fixed dose, HR=hazard ratio, MA=meta-analysis, MC=multi-center, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, TB=triple blind, XO=crossover design
Other abbreviations: AAQoL=Adult ADHD quality of life scale, ADHD=attention deficit hyperactivity disorder, ADHD-RS=ADHD rating scale, AIM-A=ADHD impact module-adult, AISRS=Adult ADHD investigator system symptom report scale, ASRS=Adult self-rating scale, BFI=Brief Fatigue Inventory, BP=blood pressure, BRIEF=Behavior Rating Inventory of Executive Function, BRIEF-A=Behavior Rating Inventory of Executive Function-Adult Version, CAARS=Conner's adult ADHD rating scale, CAARS-Inv:SV=Conners' Adult ADHD Rating Scale–Investigator Rated: Screening Version, CAARS-Self:SV=Conners' Adult ADHD Rating Scale–Self Rated: Screening Version, CADS-P=Conners ADHD/DSM IV scale-parent version, CADS-T=Conners ADHD/DSM IV scale-teacher version, CANTAB-CRT=Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time, CANTAB-SWM=Cambridge Neuropsychological Test Automated Battery-Working Memory and Strategy Performance, CASQ-P=Conner's abbreviated symptom questionnaire for parents, CASQ-T=Conner's abbreviated symptom questionnaire for teachers, CBC=Conner's behavior checklist, CGAS=Children's Global Assessment Scale, CGI=clinical global impression CGI-C=clinical global impression of change, CGI-I=clinical global impression of improvement, CGI-S=clinical global impression of severity, CHIP-CE=Child Health and Illness Profile-Child Edition, CPRS=Conners parent rating scale, CHQ=child health questionnaire, CHQ-PF50=Child Health Questionnaire-Parent Form, CPRS=Conners parent rating scale, CPRS-R=Conners parent rating scale—revised, CPRS-R:S=Conners parent rating scale: short form, CPRS-R:L=Conners' parent rating scale-revised: long form, CPT=Continuous performance test, CSHQ=Children's Sleep Habits Questionnaire, CTRS-R=Conners teacher rating scale–revised, CTRS-R: S=Conners teacher rating scale-revised: short form, DBP=diastolic blood pressure, DSST=Digit Symbol Substitution Task/Coding Test, EESC=Expression and Emotion Scale for Children, FBIM=Family Burden of Illness Module, HAMA=Hamilton Anxiety Rating Scale, GEC=global executive composite, GTSS=Global tic severity scale, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, HMVTS=Hopkins motor/vocal tic scale, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, JAMES=Joint Attention Measure from the EScs (Early and Social Communication Scale), LS=least square, MI=myocardial infarction, O/D=oppositional/defiance, ODD=oppositional defiant disorder, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PSQ=parental satisfaction questionnaire, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, SAICA=Social Adjustment Scale for Children and Adolescents, SBP=systolic blood pressure, SD=standard deviation, SDS=Sheehan disability scale, SE=standard error, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SMD=standard mean difference, SNAP=Swanson, Nolan and Pelham, SNAP-ODD=Swanson, Nolan and Pelham-oppositional defiant disorder, SNAP-P=Swanson, Nolan and Pelham-parent rating scale, SNAP-T=Swanson, Nolan and Pelham-teacher rating scale, SSERS=Stimulant Side Effects Rating Scale, STAI=State and trait anxiety inventory, STSSS=Shapiro Tourette syndrome severity scale, TOVA=test of variables of attention, WFIS=Weiss Functional Impairment Scale, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale, YGTSS=Yale global tic severity scale, YQOL-R=Youth quality of life-research version

Additional Evidence

Dose Simplification
Once-daily formulations increase patient compliance and eliminate the need for medication use during school. Prescribing immediate-release stimulants that require dosing during school hours can be problematic, especially with controlled drugs which have the potential for abuse. A few studies have compared immediate-release formulations with extended-release products. Lage et al. evaluated a pharmacy claims database to assess medication compliance among patients who took methylphenidate three times daily compared to those taking an extended-release product (Concerta®).[159] The investigators found better compliance in patients taking the extended-release product, less likelihood of switching medications, and a lower probability of discontinuing the medication. The use of the extended-release product was associated with a lower rate of emergency-room visits and fewer physician visits.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 19. Relative Cost of the Cerebral Stimulants/Agents Used for Attention-Deficit/Hyperactivity Disorder

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Central Alpha-Agonists				
Clonidine	extended-release tablet	Kapvay®	N/A	$
Amphetamine Derivatives				
Amphetamine	extended-release orally disintegrating tablet, extended-release suspension, extended-release tablet, tablet	Adzenys XR-ODT®, Dyanavel XR®, Evekeo®*	$$$$$	$$$$$
Amphetamine aspartate, amphetamine sulfate,	extended-release capsule, tablet	Adderall®*, Adderall XR®*, Mydayis ER®	$$$$$	$$ to $$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
and dextroamphetamine				
Dextroamphetamine	sustained-release capsule, solution, tablet, transdermal patch	Dexedrine®*, ProCentra®*, Xelstrym®, Zenzedi®*	$$$$$	$
Lisdexamfetamine	capsule, chewable tablet	Vyvanse®	$$$$$	N/A
Methamphetamine	tablet	Desoxyn®*	$$$$$	$$$$$
Respiratory and CNS Stimulants				
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®*	$$$$$	$$$$
Methylphenidate	chewable tablet, extended-release capsule, extended-release chewable tablet, extended-release orally disintegrating tablet, extended-release solution, extended-release tablet, solution, tablet, transdermal patch	Adhansia XR®, Aptensio XR®*, Concerta®*, Cotempla XR-ODT®, Daytrana®*, Jornay PM®, Methylin®*, Quillichew ER®, Quillivant XR®, Relexxii ER®*, Ritalin®*, Ritalin LA®*	$$$$$	$$$
Serdexmethylphenidate and dexmethylphenidate	capsule	Azstarys®	$$$$$	N/A
Central Nervous System Agents, Miscellaneous				
Atomoxetine	capsule	Strattera®*	$$$$$	$$$
Guanfacine	extended-release tablet	Intuniv®*	$$$$$	$
Viloxazine	extended-release capsule	Qelbree ER®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The central nervous system agents that are included in this review are approved to treat attention deficit hyperactivity disorder (ADHD).[3-29] The cerebral stimulants are classified as Schedule II (amphetamines and methylphenidate derivatives) controlled substances. Atomoxetine, extended-release clonidine, extended-release guanfacine, and viloxazine are not cerebral stimulants; therefore, they are not classified as controlled substances. There is at least one short-acting, intermediate-acting, and long-acting central nervous system agent available in a generic formulation. Lisdexamfetamine, serdexmethylphenidate-dexmethylphenidate, and viloxazine are not available in a generic formulation.

Azstarys® (serdexmethylphenidate and dexmethylphenidate) is a central nervous system stimulant indicated for the treatment of ADHD in patients six years of age and older.[25] Azstarys® capsules are co-formulated to contain immediate-release dexmethylphenidate (30%) and serdexmethylphenidate (70%), a prodrug of dexmethylphenidate.[25] Qelbree® (viloxazine) is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in adults and pediatric patients six years of age and older.[28] The mechanism of viloxazine is similar to the norepinephrine modulation of atomoxetine, but with additional potential efficacy of serotonin modulation.[146-147] Viloxazine is approved with a Black Box Warning related to concerns and risks of suicidal ideation and behaviors.[28] Xelstrym® (dextroamphetamine) is indicated for the treatment of ADHD in adults and pediatric patients 6 years and older. Xelstrym® is the first-and-only FDA approved transdermal amphetamine patch.[10] There is also a methylphenidate patch (Daytrana®) approved for the treatment of ADHD. Rates of response to methylphenidate versus amphetamines are idiosyncratic, with approximately 40% of patients responding to either drug and approximately 40% responding to only one of the two.[74]

Guidelines recommend the use of an agent approved by the Food and Drug Administration (FDA) for the initial pharmacologic treatment of ADHD and they do not give preference to one agent over another.[32-34] The central nervous system agents have been shown to be effective for the treatment of ADHD in numerous clinical trials.[42-158] Although comparative trials have been conducted, it is difficult to interpret the results of these studies due to design flaws (small sample size, short duration, crossover design, variable outcomes, etc.).[43-45,60-65,67,75,80,122-129,133-135,143] Extended-release clonidine and extended-release guanfacine are approved for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulants.[2,30,73,82,94,95]

There are several factors to take into consideration when selecting a pharmacologic agent for the treatment of children and adolescents with ADHD. This includes the presence of comorbid conditions, patient/family preference, storage/administration at school, history of substance abuse, drug diversion, pharmacokinetics, and adverse events.[2,32-33] The advantage of a once-daily formulation is that the medication does not need to be taken during school hours, as is the case with the immediate-release formulations. Administration of medications during school hours, especially Schedule II controlled substances, can be difficult since the medication must be administered by a licensed school nurse. Atomoxetine, extended-release clonidine, extended-release guanfacine, and viloxazine are not controlled substances, which may be preferable to the stimulants in certain situations. In January 2022 labeling updates occurred for atomoxetine related to screening for bipolar disorder prior to starting treatment. Warnings have been added for the emergence of new psychotic or manic symptoms, for adequately screening for risk factors for bipolar disorder such as a personal or family history of mania and depression, and for the appearance or worsening of aggressive behavior or hostility.[26]

There is insufficient evidence to support that one brand cerebral stimulant/agent used for ADHD is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand cerebral stimulant/agent used for ADHD within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cerebral stimulant/agent used for ADHD is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost-effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
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I. Overview

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement sleep during wakefulness.[1] Obstructive sleep apnea is the most common form of breathing-related sleep disorder, which is caused by obstruction of the airway.[2] Individuals with obstructive sleep apnea often suffer from excessive daytime sleepiness, as well as other serious health conditions (e.g., depression, hypertension, and cardiovascular/cerebrovascular disease).[3] Circadian rhythm sleep disorder consists of a persistent/recurrent pattern of sleep interruption. The shift work type occurs in individuals who work non-standard hours (e.g., night work, early morning work, and rotating schedules), and is characterized by excessive sleepiness and/or insomnia.[2,4]

Modafinil and armodafinil (the longer half-life enantiomer of modafinil) are wakefulness promoting agents approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[5,6] The exact mechanism by which these two agents improve wakefulness is unknown; however, their actions are similar to other sympathomimetic agents. They have been shown to produce psychoactive and euphoric effects similar to stimulants, as well as alterations in mood, perception, thinking, and feelings.[5,6] As a result, these agents are classified as Schedule IV controlled substances.

Sodium oxybate is gamma-hydroxybutyric acid, a known drug of abuse.[7,8] It is classified as a miscellaneous central nervous system agent but included within this review as it is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The exact mechanism by which sodium oxybate reduces cataplexy and excessive daytime sleepiness in patients with narcolepsy is unknown. It is classified as a Schedule III controlled substance; however, non-medical uses of sodium oxybate are classified under Schedule I. In July 2020, a new oxybate product with a unique composition of cations resulting in 92 percent less sodium was approved under the brand name Xywav®.[7,8,11] While the labeling for Xyrem® carries a warning concerning the high salt content and consideration for patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), Xywav® does not.[7,8]

Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, is approved in adult patients with excessive daytime sleepiness associated with narcolepsy or excessive daytime sleepiness associated with obstructive sleep apnea in combination with continuous positive airway pressure therapy. The mechanism by which solriamfetol exerts its therapeutic effect is unknown. Solriamfetol is classified as a Schedule IV controlled substance.[9]

Pitolisant is a histamine H3 receptor antagonist/inverse agonist approved for excessive daytime sleepiness or cataplexy in adult patients with narcolepsy. The mechanism by which pitolisant exerts its therapeutic effect in narcolepsy is unknown but believed to be mediated through its H3 activity. Pitolisant is the only approved agent in this class that is not a controlled substance based on the potential for abuse or dependence.[10]

The wakefulness promoting agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. In terms of duration of action, modafinil, armodafinil, pitolisant and solriamfetol are all long-acting agents while sodium oxybate is a short-acting agent.[5-10] Armodafinil and modafinil are currently available generically. The agents in this class were last reviewed in May 2021.

Table 1. Wakefulness Promoting Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Armodafinil	tablet	Nuvigil®*	armodafinil
Modafinil	tablet	Provigil®*	modafinil
Pitolisant	tablet	Wakix®	none
Sodium oxybate	oral solution	Xyrem®, Xywav®	none
Solriamfetol	tablet	Sunosi®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the wakefulness promoting agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Wakefulness Promoting Agents

Clinical Guideline	Recommendation(s)

American Academy of Sleep Medicine: **Practice Guideline for the Treatment of Central Disorders of Hypersomnolence (2021)**[1]	Adult patients with narcolepsy
	• Modafinil, pitolisant, sodium oxybate, and solriamfetol are recommended for the treatment of narcolepsy in adults.
	• Armodafinil, dextroamphetamine, and methylphenidate are suggested for the treatment of narcolepsy in adults.
	
	Adult patients with idiopathic hypersomnia
	• Modafinil is recommended for the treatment of idiopathic hypersomnia in adults.
	• Clarithromycin, methylphenidate, pitolisant, and sodium oxybate are suggested for the treatment of idiopathic hypersomnia in adults.
	
	Adult patients with Kleine-Levin syndrome
	• Lithium is suggested for the treatment of Kleine-Levin syndrome in adults.
	
	Adult patients with hypersomnia due to medical conditions
	• Hypersomnia secondary to alpha-synucleinopathies
	  ○ Armodafinil is suggested for the treatment of hypersomnia secondary to dementia with Lewy bodies in adults.
	  ○ Modafinil and sodium oxybate are suggested for the treatment of hypersomnia secondary to Parkinson's disease in adults.
	• Posttraumatic hypersomnia
	  ○ Armodafinil and modafinil are suggested for the treatment of hypersomnia secondary to traumatic brain injury in adults.
	• Adult patients with genetic disorders associated with primary central nervous system somnolence
	  ○ Modafinil is suggested for the treatment of hypersomnia secondary to myotonic dystrophy in adults.
	• Adult patients with hypersomnia secondary to brain tumors, infections, or other central nervous system lesions
	  ○ Modafinil is suggested for the treatment of hypersomnia secondary to multiple sclerosis in adults.
	• Pediatric patients with narcolepsy
	  ○ Modafinil and sodium oxybate are suggested for the treatment of narcolepsy in pediatric patients.
	
	A "strong" recommendation (i.e., "is recommended…") is one that clinicians should follow under most circumstances. A "conditional" recommendation (i.e., "is suggested…") is one that requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action. Under each disorder, strong recommendations are listed in alphabetical order followed by the conditional recommendations in alphabetical order. The interventions in all the recommendation statements were compared to no treatment.

European Federation of Neurological Sciences:	Pathway for the management of narcolepsy – Pharmacological management in adults • Excessive daytime sleepiness unique/main symptom ○ First-line monotherapy: modafinil, pitolisant, or solriamfetol

Clinical Guideline	Recommendation(s)
Guidelines on Management of Narcolepsy in Adults and Children (2021)[12]	○ Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to another monotherapy, if not successful, change to second-line options ○ Second-line combination therapy: Pitolisant AND modafinil or solriamfetol; or sodium oxybate AND any wake-promoting agent (modafinil, solriamfetol, pitolisant, methylphenidate, amphetamines) ○ Second-line monotherapy: Sodium oxybate, methylphenidate, or amphetamines • Excessive daytime sleepiness and cataplexy ○ First-line monotherapy: Sodium oxybate or pitolisant ○ First-line combination therapies: venlafaxine/clomipramine AND a first-line wake-promoting agent; or sodium oxybate AND a first-line wake-promoting agent ○ Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to second-line options ○ Second-line combination therapy: Exchange sodium oxybate to venlafaxine/clomipramine (and vice-versa); or sodium oxybate, venlafaxine/clomipramine, and a first-line wake-promoting agent; or exchange venlafaxine/clomipramine to another antidepressant • Excessive daytime sleepiness, cataplexy, and disturbed nocturnal sleep ○ First-line monotherapy: sodium oxybate ○ First-line combination therapies: sodium oxybate and/or venlafaxine/clomipramine, and a first-line wake-promoting agent; or any wake-promoting agent, venlafaxine/clomipramine, and (only exceptionally and only short-term) z-drugs <u>Pathway for the management of narcolepsy – Pharmacological management in children</u> • Excessive daytime sleepiness unique/main symptom ○ First-line monotherapy: modafinil, methylphenidate, sodium oxybate, amphetamine derivatives, or pitolisant ○ Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to another monotherapy • Excessive daytime sleepiness and cataplexy ○ First-line monotherapy: Sodium oxybate ○ First-line combination therapy: modafinil or methylphenidate and sodium oxybate ○ Other combination therapies: modafinil, methylphenidate, and venlafaxine; or modafinil, methylphenidate, or pitolisant, and venlafaxine (or clomipramine or another antidepressant) and sodium oxybate ○ Consider optimal dosage and titration if not or only partially effective after four to six weeks: change to second-line options • Excessive daytime sleepiness, cataplexy, and disturbed nocturnal sleep ○ First-line monotherapy: sodium oxybate ○ First-line combination therapies: sodium oxybate and/or venlafaxine/clomipramine, and a first-line wake-promoting agent
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)[3]**	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective

Clinical Guideline	Recommendation(s)
	positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea. <u>Supplemental oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea. <u>Medical therapies intended to improve nasal patency</u> • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. <u>Positional therapies</u> • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position. vs
American Academy of Sleep Medicine: **Practice Parameters for the Evaluation and Treatment of Extrinsic Circadian Rhythm Sleep Disorders (2015)**[4]	<u>Shift work disorder</u> • Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. • Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the wakefulness promoting agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Wakefulness Promoting Agents[5-10,13-14]

Generic Name(s)	Armodafinil	Modafinil	Pitolisant	Sodium oxybate	Solriamfetol
Improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy	✔	✔			✔
Improve wakefulness in adult patients with excessive daytime sleepiness associated with obstructive sleep apnea	✔	✔			✔

Generic Name(s)	Armodafinil	Modafinil	Pitolisant	Sodium oxybate	Solriamfetol
Improve wakefulness in adult patients with excessive sleepiness associated with shift work disorder	✔	✔			
Treatment of cataplexy in narcolepsy			✔	✔	
Treatment of excessive daytime sleepiness in narcolepsy			✔	✔	
Treatment of idiopathic hypersomnia in adults				✔ (Xywav® only)	

IV. Pharmacokinetics

The pharmacokinetic parameters of the wakefulness promoting agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Wakefulness Promoting Agents[14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Armodafinil	Rapid	60	Liver (not reported)	Renal (not reported)	15
Modafinil	Rapid	60	Liver (90)	Renal (80) Feces (1)	15
Pitolisant	Not reported	91 to 96	Liver (not reported)	Renal (90) Feces (2.3)	20
Sodium oxybate	88	<1	Liver (not reported)	Renal (1 to 5)	<1
Solriamfetol	95	13.3 to 19.4	Minimal (not reported)	Renal (not reported)	7.1

V. Drug Interactions

Major drug interactions with the wakefulness promoting agents are listed in Table 5.

Table 5. Major Drug Interactions with the Wakefulness Promoting Agents[14]

Generic Name(s)	Interaction	Mechanism
Modafinil	Hormonal contraceptives	Concurrent use of modafinil and hormonal contraceptives may result in decreased plasma levels of hormonal contraceptives.
Modafinil	Tolvaptan	Concurrent use of modafinil and tolvaptan may result in decreased tolvaptan plasma concentrations.
Modafinil	Enzalutamide	Concurrent use of enzalutamide and modafinil may result in decreased enzalutamide plasma concentrations; decreased modafinil plasma concentrations.
Modafinil	Citalopram	Concurrent use of citalopram and modafinil may result in increased citalopram exposure and risk of QT interval prolongation.
Modafinil	Ifosfamide	Concurrent use of ifosfamide and modafinil may result in increased neurotoxic and nephrotoxic effects.
Pitolisant	Strong CYP2D6 inhibitors (i.e., paroxetine, fluoxetine, bupropion)	Concurrent use increases pitolisant exposure by 2.2-fold. Reduce pitolisant dose by half if used concomitantly.

Generic Name(s)	Interaction	Mechanism
Pitolisant	Strong CYP3A4 inducers (i.e., rifampin, carbamazepine)	Concurrent use decreases pitolisant exposure by 50%. Assess for loss of efficacy after initiation of a strong CYP3A4 inducer. Dose may be doubled for patients using 8.9 or 17.8 mg. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease pitolisant dosage by half. No recommendations regarding patients stabilized on 35.6 mg.
Pitolisant	Centrally acting H1 antagonist (i.e., pheniramine maleate, diphenhydramine, imipramine, promethazine, clomipramine, mirtazapine)	Concurrent use of H1 antagonists that cross the blood brain barrio may reduce the effectiveness of pitolisant. Avoid concomitant use.
Pitolisant	QT prolonging agents (i.e., quinidine, procainamide, disopyramide, amiodarone, sotalol, ziprasidone, chlorpromazine, thioridazine, moxifloxacin)	Concurrent use of drugs that prolong the QT interval may add to the QT effects of pitolisant and increase the risk of cardiac arrhythmia. Avoid concomitant use.
Pitolisant	CYP3A4 substrates (i.e., midazolam, hormonal contraceptives, cyclosporine)	Concurrent use with certain sensitive CYP3A4 substrates may result in reduced effectiveness of the substrates. The effectiveness of hormonal contraceptives may be reduced for 21 days after discontinuation of therapy. Non-hormonal contraceptives should be used.
Sodium oxybate	Barbiturates	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Benzodiazepines	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Central nervous system depressants	Concurrent use of sodium oxybate and central nervous system depressants may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Opioid analgesics	Concurrent use of sodium oxybate and opioid analgesics may result in additive respiratory depression.
Sodium oxybate	Sedative hypnotics	Concurrent use of sodium oxybate and sedative hypnotics may result in increased central nervous system depression.
Sodium oxybate	Selected antiepileptics (topiramate, perampanel, difenoxin)	Concurrent use of sodium oxybate and selected antiepileptics may result in increased central nervous system depression.
Sodium oxybate	Selected antipsychotics (loxapine, thioridazine, chlorpromazine)	Concurrent use of sodium oxybate and selected antipsychotics may result in increased central nervous system depression.
Sodium oxybate	Skeletal muscle relaxants	Concurrent use of sodium oxybate and skeletal muscle relaxants may result in increased central nervous system depression.
Sodium oxybate	Buspirone	Concurrent use of sodium oxybate and buspirone may result in an increase in sleep duration and central nervous system depression.
Solriamfetol	Monoamine oxidase inhibitors	Concurrent use may increase the risk of hypersensitivity reactions or hypertensive crisis. Concomitant use or use of a monoamine oxidase inhibitor within the preceding 14 days is contraindicated.
Solriamfetol	Drugs that increase blood pressure and/or heart rate	Concurrent use has not been evaluated and should be used with caution.

Generic Name(s)	Interaction	Mechanism
Solriamfetol	Dopaminergic drugs	Concurrent use has may result in pharmacodynamic interactions which have not been evaluated with solriamfetol and should be used with caution.

VI. Adverse Drug Events

The most common adverse drug events reported with the wakefulness promoting agents are listed in Table 6. The boxed warning for sodium oxybate is listed in Table 7. Sodium oxybate is a known drug of abuse and has been associated with central nervous system-related adverse reactions, including confusion, respiratory depression, profound decreases in consciousness, and death. As such, sodium oxybate is classified as a Schedule III controlled substance by federal regulation and is available through a centralized pharmacy. Modafinil and armodafinil may produce psychoactive and euphoric effects similar to stimulants and are therefore classified as Schedule IV controlled substances by federal regulation. Solriamfetol also has potential for abuse as a study demonstrated that solriamfetol produced Drug Liking scores similar to or lower than phentermine. As such, solriamfetol is also classified as a Schedule IV controlled substance by federal regulation. Pitolisant is not a controlled substance.

Table 6. Adverse Drug Events (%) Reported with the Wakefulness Promoting Agents [5-10,13]

Adverse Events	Armodafinil	Modafinil	Pitolisant	Sodium Oxybate (Xyrem®)	Sodium Oxybate (Xywav®)	Solriamfetol
Cardiovascular						
Angina	-	-	-	-	-	-
Cardiac arrhythmia	-	-	-	-	-	-
Chest discomfort	-	-	-	-	-	2
Chest pain	-	3	-	-	-	
Heart rate increase	-	-	3	-	-	-
Hypertension	-	3	-	✔	-	-
Hypotension	-	-	-	-	-	-
Myocardial infarction	-	-	-	-	-	-
Palpitations	2	2	-	-	-	2 to 3
Peripheral edema	-	-	-	3	-	-
Pulse increase/decrease	1	-	-	-	-	-
Raynaud's phenomenon	-	-	-	-	-	-
Sudden death	-	-	-	-	-	-
Systolic blood pressure increased	✔	-	-	-	-	-
Tachycardia	-	2	-	-	-	-
Vasodilation	-	2	-	-	-	-
Central Nervous System						
Abnormal dreams	-	-	-	-	-	-
Aggressive behavior	-	-	-	-	-	-
Agitation	1	1	-	-	-	-
Anxiety	4	5 to 21	5	1 to 2	5	4 to 6
Ataxia	-	-	-	-	-	-
Attention disturbance	1	-	-	0 to 4	-	-
Cerebral arteritis	-	-	-	-	-	-
Cerebral occlusion	-	-	-	-	-	-
Chills	-	-	-	-	-	-
Confusion	-	-	-	3 to 17	1	-
Depression	1 to 3	2	-	3 to 17	3	-
Disorientation	-	-	-	1 to 3	-	-
Dizziness	3 to 8	5	-	6 to 15	10	2
Drowsiness	-	-	-	8	2	-
Dyskinesia	-	1	-	-	-	-
Emotional instability	-	-	-	-	-	-
Fatigue/lethargy	2	-	-	-	4	-
Fever	1	-	-	-	-	-
Hallucinations	-	-	3	-	✔	-

Adverse Events	Armodafinil	Modafinil	Pitolisant	Sodium Oxybate (Xyrem®)	Sodium Oxybate (Xywav®)	Solriamfetol
Headache	14 to 23	34	18	≤	20	16
Hyperkinesia	-	1	-	-	-	-
Hypertonia	-	1	-	-	-	-
Insomnia	4 to 6	3 to 21	6	-	-	5
Irritability	-	-	3	0 to 3	3	3
Jittery feeling	-	-	-	-	-	3
Labile affect	-	-	-	-	-	-
Mania	-	✔	-	-	-	-
Migraine	1	-	-	-	-	-
Nervousness	1	7	-	-	-	-
Neuroleptic malignant syndrome	-	-	-	-	-	-
Nightmare	-	-	-	-	-	-
Overstimulation	-	1	-	-	-	-
Parasomnias	-	-	-	-	6	-
Paresthesia	1	2	-	1 to 3	3	-
Psychotic episodes	-	✔	-	-	-	-
Restlessness	-	-	-	-	-	-
Seizures	-	-	-	-	-	-
Sleep disorder	-	-	-	-	-	-
Sleep disturbance	-	-	3	-	-	-
Sleep paralysis	-	-	-	1 to 3	-	-
Sleep walking	-	-	-	0 to 3	-	-
Somnolence	-	2	-	1 to 8	-	-
Suicidal ideation	-	-	-	-	-	-
Syncope	-	-	-	-	-	-
Tic	-	-	-	-	-	-
Tourette's exacerbation	-	-	-	-	-	-
Toxic psychosis	-	-	-	-	-	-
Tremor	1	1	-	0 to 5	-	-
Vertigo	-	1	-	-	-	-
Dermatological						
Alopecia	-	-	-	-	-	-
Application site reaction	-	-	-	-	-	-
Dermatitis	1	-	-	-	-	-
Diaphoresis	-	1	-	-	6	-
Erythema	-	-	-	-	-	-
Erythema multiforme	-	✔	-	-	-	-
Exfoliative dermatitis	-	-	-	-	-	-
Hair loss	-	-	-	-	-	-
Herpes simplex	-	1	-	-	-	-
Hyperhidrosis	1	-	-	1 to 3	-	2
Rash	1 to 4	<1	2	-	-	-
Stevens-Johnson syndrome	✔	✔	-	-	-	-
Toxic epidermal necrolysis	-	-	-	-	-	-
Urticaria	-	-	-	-	-	-
Gastrointestinal						
Abdominal pain	2	-	3	1 to 3	-	3
Anorexia	1	4	-	-	-	-
Appetite decreased	1	-	3	✔	8	6 to 9
Bruxism	-	-	-	-	-	-
Constipation	1	2	-	-	-	3
Diarrhea	3 to 5	6	-	3 to 4	6	4
Dry mouth	2 to 7	4	2	1 to 2	4	4
Dyspepsia	2	5	-	-	-	-
Flatulence	-	1	-	-	-	-
Mouth ulceration	-	1	-	-	-	-

Adverse Events	Armodafinil	Modafinil	Pitolisant	Sodium Oxybate (Xyrem®)	Sodium Oxybate (Xywav®)	Solriamfetol
Nausea	7 to 14	11	6	8 to 20	13	7 to 8
Stomach cramps	-	-	-	-	-	-
Thirst	-	1	-	-	-	-
Unpleasant taste	-	1	-	-	-	-
Vomiting	1	-	-	2 to 16	5	-
Weight increase	-	-	-	-	-	-
Weight loss	-	-	-	≤	-	-
Genitourinary						
Abnormal urine	-	1	-	-	-	-
Enuresis	-	-	-	3 to 7	-	-
Erectile disturbance	-	-	-	-	-	-
Hematuria	-	1	-	-	-	-
Libido decreased	-	-	-	-	-	-
Polyuria	1	-	-	-	-	-
Pyuria	-	1	-	-	-	-
Urinary incontinence	-	-	-	3 to 18	4	-
Hematologic						
Agranulocytosis	-	✔	-	-	-	-
Anemia	-	-	-	-	-	-
Eosinophilia	-	1	-	-	-	-
Leukopenia	-	-	-	-	-	-
Pancytopenia	✔	-	-	-	-	-
Thrombocytopenic purpura	-	-	-	-	-	-
Hepatic						
Hepatic coma	-	-	-	-	-	-
Liver function test abnormalities	✔	2	-	-	-	-
Musculoskeletal						
Arthralgia	-	-	-	✔	-	-
Back pain	-	6	-	-	-	-
Cataplexy	-	-	2	1 to 2	-	-
Hypoesthesia	-	-	-	-	-	-
Muscle spasms	-	-	-	<1 to 2	-	-
Musculoskeletal pain	-	-	5	-	-	-
Pain in extremity	-	-	-	1 to 3	-	-
Weakness	-	-	-	-	-	-
Respiratory						
Bronchitis	-	-	-	-	-	-
Cough	-	-	-	-	-	-
Dyspnea	1	-	-	-	-	-
Epistaxis	-	1	-	-	-	-
Lung disorder	-	2	-	-	-	-
Nasal congestion	-	-	-	-	-	-
Pharyngitis	-	4	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	-	-
Rhinitis	-	7	-	-	-	-
Sinusitis	-	-	-	-	-	-
Upper respiratory tract infection	-	-	5	-	-	-
Special Senses						
Abnormal vision	-	1	-	-	-	-
Accommodation difficulties	-	1	-	-	-	-
Amblyopia	-	1	-	-	-	-
Blurred vision	-	1	-	✔	-	-
Dry eyes	-	-	-	-	-	-
Eye pain	-	1	-	-	-	-
Mydriasis	-	-	-	-	-	-

Adverse Events	Armodafinil	Modafinil	Pitolisant	Sodium Oxybate (Xyrem®)	Sodium Oxybate (Xywav®)	Solriamfetol
Tinnitus	-	-	-	-	-	-
Other						
Accidental injury	-	-	-	-	-	-
Anaphylaxis	✔	✔	-	-	-	-
Ear pain	-	-	-	-	-	-
Edema	-	1	-	0 to 3	-	-
Feeling drunk	-	-	-	0 to 3	-	-
Flu-like syndrome	1	4	-	-	-	-
Growth suppression	-	-	-	-	-	-
Hypersensitivity reactions	-	✔	-	-	-	-
Pain	1	-	-	<1 to 3	-	-
Thirst	1	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Boxed Warning for Sodium Oxybate[7,8]

WARNING
WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE Sodium oxybate is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in sodium oxybate-treated patients. Almost all of the patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants. The active moiety of oxybate salts (calcium, magnesium, potassium, and sodium) is oxybate or gamma hydroxybutyrate (GHB). Sodium oxybate is the sodium salt of GHB. Abuse of GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the XYWAV and XYREM REMS.

VII. Dosing and Administration

The usual dosing regimens for the wakefulness promoting agents are listed in Table 8.

Table 8. Usual Dosing Regimens for the Wakefulness Promoting Agents[5-10,13-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Armodafinil	Improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy: Table: 150 mg to 250 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea: Tablet: 150 mg to 250 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with shift work disorder: Tablet: 150 mg daily given one hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 50 mg 150 mg 200 mg 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Modafinil	Improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy: Tablet: 200 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea: Tablet: 200 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with shift work disorder: Tablet: 200 mg as a single dose one hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 100 mg 200 mg
Pitolisant	Cataplexy in narcolepsy and excessive daytime sleepiness in narcolepsy: Tablet: initial, 8.9 mg (two 4.45 mg tablets) once daily for one week then 17.8 mg once daily; may increase to 35.6 mg (two 17.8 mg tablets) once daily after one week; maximum, 35.6 mg once daily	Safety and efficacy in children have not been established.	Tablet: 4.45 mg 17.8 mg
Sodium oxybate	Cataplexy in narcolepsy and excessive daytime sleepiness in narcolepsy: Oral solution: initial, 4.5 g per night in two divided doses; first dose to be given at bedtime after the patient is in bed and second dose to be given 2.5 to four hours later; dose may be increased or adjusted in two-week intervals; maximum, 9 g per day Idiopathic hypersomnia: Oral solution (Xywav® only): initial, 4.5 g per night in two divided doses; first dose to be given at bedtime after the patient is in bed and second dose to be given 2.5 to four hours later; dose may be increased or adjusted in two-week intervals; maximum, 9 g per day; for once nightly dosing, begin with 3 g per night and increase or adjust dose weekly to a maximum total nightly dose of 6 g	Cataplexy in narcolepsy and excessive daytime sleepiness in narcolepsy in patients 7 years of age and older: Oral solution: administer orally twice nightly; the recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in the labeling	Oral solution: 500 mg/mL
Solriamfetol	Excessive daytime sleepiness associated with narcolepsy: Tablet: initial, 75 mg once daily; maintenance, 75 mg to 150 mg once daily; maximum, 150 mg once daily Excessive daytime sleepiness associated with obstructive sleep apnea: Tablet: initial, 37.5 mg once daily; maintenance, 37.5 mg to 150 mg once daily; maximum, 150 mg once daily	Safety and efficacy in children have not been established.	Tablet: 75 mg 150 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the wakefulness promoting agents are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Wakefulness Promoting Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Narcolepsy				
Harsh et al.[15] (2006) Armodafinil 150 to 250 mg once daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age diagnosed with narcolepsy	N=196 12 weeks	Primary: MWT 0900-1500 sleep latency, CGI-C Secondary: MWT 1500-1900 sleep latency, CGI-C, CDR, ESS, BFI	Primary: Mean MWT 0900–1500 sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group (P<0.01 for all comparisons). Secondary: Mean MWT 1500–1900 sleep latency increased 1.5, 1.6, and 1.6 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 minutes from baseline in the placebo group. The differences for the armodafinil combined group vs placebo and the 150 mg group vs the placebo group were significant (P<0.05 for both comparisons). The proportion of patients with at least minimal improvement in their CGI-C rating was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared to the placebo group (P<0.0001 for all comparisons). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21, 33, and 16%, respectively, for armodafinil 150 mg; 20, 35, and 18%, respectively, for armodafinil 250 mg; 20, 34, and 17%, respectively, for the armodafinil combined group; and 17, 12, and 3%, respectively, for placebo. Power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared to placebo at the final visit (P<0.05). There were not significant effects on mean continuity of attention between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Armodafinil demonstrated significantly greater improvements in quality of episodic secondary memory compared to placebo at the final visit (P<0.05). Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory compared to placebo at the final visit (P<0.05). Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared to placebo at weeks eight (P<0.01 for all comparisons) and 12 (P<0.01) and at the final visit (150 mg/day, -4.1; P=0.0044, 250 mg/day, -3.8; P=0.0015, and combined group, -3.9; P=0.0006). At the final visit, 21% of patients in the armodafinil 150 mg/day group (P=0.0312) and 28% of patients in the armodafinil 250 mg/day group (P=0.0023) had an ESS score <10, compared to only 7% of patients in the placebo group. Improvements in global fatigue were significantly greater with armodafinil compared to placebo at the final visit (150 mg/day, -1.5; P=0.0007; 250 mg/day, -1.3; P=0.0018; combined group, -1.4; P=0.0002; placebo, -0.3). Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil.
U.S. Modafinil in Narcolepsy Group[16] (1998) Modafinil 200 to 400 mg daily vs placebo	DB, MC, PC, RCT Adults 18 to 68 years of age diagnosed with narcolepsy	N=283 9 weeks	Primary: ESS Secondary: MSLT, MWT, CGI-C	Primary: Both modafinil treatment groups reduced mean ESS scores and subjective sleepiness at each time point (weeks three, six, and nine) compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. Secondary: Mean sleep latency for MSLT significantly increased in both modafinil groups compared to the placebo group (P<0.001). Modafinil groups did not differ from each other. Mean sleep latencies for MWT significantly increased in each of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				modafinil groups compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. There were significantly more patients with improved CGI-C scores in each of the modafinil groups compared to the placebo group (P<0.005), but the number of patients did not differ between modafinil groups.
U.S. Modafinil in Narcolepsy Group[17] (2000) Modafinil 200 to 400 mg daily vs placebo	DB, MC, PC, RCT Adults 17 to 67 years of age diagnosed with narcolepsy	N=271 9 weeks	Primary: MWT, CGI-C Secondary: MSLT, ESS	Primary: MWT improved for both modafinil groups vs the placebo group (P<0.001) at each follow-up visit (weeks three, six, nine). The percent of patients with improvement in CGI-C scores at week nine were as follows: modafinil 200 mg, 58%; modafinil 400 mg, 61%; and placebo, 38% (P<0.03). Secondary: MSLT increased by 5.1 minutes with modafinil 400 mg vs 3.5 minutes with placebo (P<0.001). The impact of the 200 mg modafinil dose was not significant. Mean ESS scores were reduced by both treatment groups (P<0.001) vs the placebo group.
Broughton et al.[18] (1997) Modafinil 200 to 400 mg daily vs placebo	MC, PC, RCT, XO Patients 27 to 59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness Secondary: ESS	Primary: MWT (sleep latency) increased by 40% with modafinil 200 mg (P<0.002) and by 54% with modafinil 400 mg (P<0.001) compared to placebo. There was not a significant difference between modafinil groups. Both modafinil groups significantly decreased the patient assessed mean number of involuntary sleep and somnolence episodes by 24% in the 200 mg group and 26% in the 400 mg group as compared to the placebo group (P<0.013 and P<0.007). Secondary: ESS was significantly decreased in modafinil 200 mg (P<0.018) and modafinil 400 mg (P<0.0009) groups compared to the placebo group.
Billiard et al.[19] (1994)	DB, MC, PC, RCT, XO	N=50	Primary: Results of sleep	Primary: In the patient sleep logs, the number of episodes of sleepiness and duration

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Modafinil 100 mg in the morning and 200 mg at noon (or vice versa) vs placebo	Patients 27 to 54 years of age diagnosed with narcolepsy	12 weeks	logs, CGI Secondary: MWT	of daytime total sleep time were significantly reduced in the modafinil groups compared to the placebo group (P=0.05, P=0.0002). The CGI scores were not statistically significantly different between the modafinil group and the placebo group (P=0.19). Secondary: MWT scores were significantly improved in the modafinil group compared to the placebo group (P<0.05).
Boivin et al.[20] (1993) Modafinil 200 mg in morning and 100 mg at noon vs placebo	DB, PC, RCT, XO Patients 31 to 61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT less than five minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (P<0.05) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT (P<0.05), but did not significantly reduce the mean reaction time over placebo (P=0.08). Modafinil did not statistically significantly decrease PLMs over placebo (P=0.06). Modafinil did not display negative effects on any of the nocturnal sleep parameters measured (P value not significant). Secondary: Not reported
Thorpy et al.[21] (2003) Modafinil 200 to 400 mg/day	OL, RCT Adults 17 to 65 years of age diagnosed with narcolepsy who had been receiving MPH for EDS for a month	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group. Headache was the most frequently reported adverse event during therapy, experienced by 42% of patients in the no-washout group, 36% of patients in the washout group, and 21% of patients in the taper/titrate group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dauvilliers et al.[22] (2013) Pitolisant hydrochloride QD (10, 20, or 40 mg) or modafinil QD (100, 200, 400 mg) vs placebo	AC, DB, MC, PC, PG, RCT Patents 18 years of age with a diagnosis of narcolepsy, mean sleep latency ≤8 minutes with two or more sleep onset rapid eye movement periods, and ESS score ≥14	N=94 8 weeks	Primary: Change in ESS score from baseline to week eight Secondary: Change from baseline to week eight in MWT, SART-NO GO, SART-GO, SART total, CGI-C, EQ-5D, and patient's global opinion of their treatment, and symptoms of cataplexy	Primary: The mean change in ESS scores from baseline to week eight was -3.4 (18.9 to 15.6) for placebo, -5.8 (17.8 to 12.0) for pitolisant and -6.9 (18.5 to 11.6) for modafinil. There was a statistically significant difference for pitolisant when compared to placebo (mean difference, -3.0; 95% CI, -5.6 to -0.4; P=0.024). When compared to modafinil, pitolisant was shown to be non-inferior (mean difference, 0.12; 95% CI, -2.5 to 2.7; P=0.25). Secondary: The mean change in MWT from baseline to week eight was 0.88 (8.4 to 7.6) for placebo, 1.32 (7.4 to 9.7) for pitolisant and 1.72 (8.8 to 15.1) for modafinil. There was a statistically significant difference for pitolisant when compared to placebo (mean difference, 1.47; 95% CI, 1.01 to 2.14; P=0.044). When compared to modafinil, pitolisant was shown to be non-inferior (mean difference, 0.173; 95% CI, 0.52 to 1.13; P=0.173). Mean change in SART-NO GO from baseline to week eight was 1.0 (8.0 to 8.1) for placebo, 0.82 (9.2 to 7.5) for pitolisant and 0.84 (8.5 to 7.1) for modafinil. There was a statistically significant difference for pitolisant when compared to placebo (mean difference, 0.81; 95% CI, 0.67 to 0.99; P=0.038). When compared to modafinil, pitolisant was shown to be non-inferior (mean difference, 0.97; 95% CI, 0.81 to 1.17; P=0.765). Mean change in SART-GO from baseline to week 8 was 0.76 (3.5 to 2.7) for placebo, 0.6 (3.5 to 2.1) for pitolisant and 0.79 (3.2 to 2.5) for modafinil. There was no statistically significant difference between pitolisant and either placebo or modafinil (P=0.176 and P=0.141, respectively). Mean change in SART-total from baseline to week eight was 1.0 (11.5 to 11.4) for placebo, 0.8 (12.5 to 10.0) for pitolisant and 0.89 (11.6 to 10.4) for modafinil. There was no statistically significant difference between pitolisant and either placebo or modafinil (P=0.053 and P=0.370, respectively). The proportion of patients for EDS improvement as assessed by the CGI-C after eight weeks of treatment was 56% (14/25) in the placebo group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				35% (19/26) in the pitolisant group and 86% (24/28) in the modafinil group (P values not reported). The proportion of patients that were cataplexy improvement as assessed by CGI-C after eight weeks of treatment was 24% (6/25) in the placebo group, 35% (9/26) in the pitolisant group and 29% (8/28) in the modafinil group (P values not reported). EQ-5D score changed from 64 to 70.2 in the placebo group, from 65.3 to 73.8 in the pitolisant group and from 58.7 to 72.6 in the modafinil group (P values not reported). The proportion of patients who considered themselves globally improved was 56% (14/25) in the placebo group, 81% (24/28) in the pitolisant group and 86% (24/28) in the modafinil group (P values not reported).
U.S. Xyrem Multicenter Study Group[23] (2004) <u>Phase One (Two weeks)</u> Continue sodium oxybate at the dose previously prescribed. <u>Phase Two (Two weeks)</u> Continue sodium oxybate treatment at previously prescribed dose vs conversion to	DB treatment withdrawal study design (alternative to conventional DB, PC, RCT) Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy who were previously stabilized on sodium oxybate 3 to 9 g/day	N=55 4 weeks	Primary: Cataplexy attacks, treatment-emergent adverse events Secondary: Not reported	Primary: During the two-week DB phase, the abrupt cessation of sodium oxybate therapy in the placebo study patients resulted in a significant increase in the number of cataplexy attacks (median, 21; P<0.001) compared to patients who remained on sodium oxybate (median, 0). Cataplexy attacks returned gradually with placebo study patients reporting a median of 4.2 and 11.7 cataplexy attacks during the first and second weeks, respectively. There were no symptoms of withdrawal reported by the study investigators. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Xyrem International Study Group[24] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: ESS, MWT, CGI-C Secondary: Not reported	Primary: Study patients displayed dose related decreases in median ESS scores and frequency of weekly inadvertent naps, which were significant at the 6 and 9 g doses (P<0.001 for each). Study patients treated with 9 g of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (P<0.001). Improvements in EDS were incremental in those study patients who received concomitant stimulants alone. Significant improvements in the CGI-C were observed for each group treated with sodium oxybate (P≤0.001). The most common adverse events were mild to moderate and included nausea, dizziness, and enuresis, which seemed to be dose related. Other adverse events less common included feeling drunk, contusion, back pain, muscle cramp, somnolence, disturbance in attention, dysarthria, tremor, disorientation, sleepwalking, dyspnea, and snoring. Secondary: Not reported
Xyrem International Study Group[25] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Narcolepsy symptoms, medication use, adverse events Secondary: Not reported	Primary: Compared to placebo, nightly doses of 4.5, 6, and 9 g of sodium oxybate for eight weeks resulted in significant decreases in weekly cataplexy attacks of 57.0 (P=0.003), 65.0 (P=0.002), and 84.7% (P<0.001), respectively. The decrease in cataplexy at the 4.5 g dose was significant compared to placebo at eight weeks of treatment (P=0.003). The reduction in the number of weekly cataplexy attacks was dependent on the length of time study patients received treatment and the amount of medication received. The weekly increase in sodium oxybate dose was associated with fewer adverse events than previously reported in double-blind sodium oxybate studies using fixed doses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common adverse events included nausea and dizziness, which demonstrated a clear dose–response relationship. Although greater than 5% of study patients reported emesis, this adverse event was not significantly different than placebo-treated patients. Secondary: Not reported
Black et al.[26] (2010) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, PC, PG, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Sleep architecture, narcolepsy symptoms and adverse events Secondary: Not reported	Primary: Following four (P<0.001) and eight weeks (P<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage three and four sleep, reaching a median increase of 52.5 minutes in patients receiving 9 g nightly. Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups. Stage one sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses. The changes in nocturnal sleep coincided with significant decreases in the severity and frequency of narcolepsy symptoms. The most common adverse events included nausea, headache, dizziness, nasopharyngitis, and enuresis with a statistically significant difference in nausea and dizziness compared to placebo. Adverse events were mild to moderate in severity and appeared to be dose-related as documented by study investigators. Secondary: Not reported
Bogan et al.[27] (2021) Lower sodium oxybate (LXB;	DB, MC, PC, RCT Adults 18 to 70 years of age with narcolepsy with	N=134 (efficacy population) 30-day	Primary: Change in weekly number of cataplexy attacks from during the 2	Primary: The median change in weekly number of cataplexy attacks was 2.35 in the placebo group versus 0.00 in the LXB group, which was associated with a significant (P<0.0001) location shift of −3.31 (95% CI, −6.04 to −1.50); mean (SD) change in weekly number of cataplexy attacks was 11.46

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Xywav®) vs placebo	cataplexy	screening 12-week OL optimization 2-week stable dose period 2-week DB, R, withdrawal period safety follow-up	weeks of stable dose period to during the 2 weeks of DB, R, withdrawal period, as determined from participants' daily cataplexy diaries Secondary: Change in the ESS score from the end of stable dose period to the end of the DB, R, withdrawal period	(24.751) in the placebo group versus 0.12 (5.772) in the LXB group. Secondary: As with cataplexy, there was worsening of excessive daytime sleepiness in participants randomized to placebo, and no change in participants randomized to LXB. At the end of DB, R, withdrawal period, the change in median ESS score from stable dose period was 2.0 for participants randomized to placebo and 0.0 for participants randomized to LXB, which was associated with a significant (P<0.0001) location shift of −2.0 (95% CI, −4.0 to −1.0); the change in mean (SD) ESS score was 3.0 (4.68) in the placebo group versus 0.0 (2.90) in the LXB group.
Weaver et al.[28] (2006) Sodium oxybate 4.5 to 9 g/day in two divided doses taken at bedtime and again 2.5 to 4 hours later vs placebo	DB, MC, RCT Patients 16 to 75 years of age with narcolepsy who were experiencing cataplexy and EDS with recurrent episodes for ≥3 months	N=285 4 weeks	Primary: FOSQ Secondary: Not reported	Primary: The nightly administration of sodium oxybate showed statistically significant dose-related improvements in functional status and quality of life as evidenced by the total FOSQ (P<0.001), as well as in the activity level (P<0.001), vigilance (P<0.001), general productivity (P=0.002), and social outcomes (P<0.001) subscales. Effect sizes escalated from small effects for the 6 g per day dose of sodium oxybate to large effects for the 9 g/day dose. Secondary: Not reported
Wang et al.[29] (2009) Sodium oxybate	RETRO Patients receiving sodium oxybate	N=~26,000 68 months	Primary: Occurrence of abuse/misuse of sodium oxybate Secondary: Not reported	Primary: During the study period, 3,781 adverse event reports were reported to the manufacturer worldwide. Overall, there were no new significant safety findings from the postmarketing adverse event profile compared to what was reported in clinical trials described in the product prescribing information.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Of those 26,000 patients, 0.2% reported ≥1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, four cases (0.016%) meeting DSM-IV dependence criteria, eight cases (0.031%, including three of the previous four) with withdrawal symptoms reported after discontinuation of sodium oxybate, two confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with one death known to be related to sodium oxybate, and three cases (0.01%) of traffic accidents involving drivers taking sodium oxybate. During the study period, approximately 600,000 bottles of sodium oxybate were distributed, and five incidents (0.0009%) of diversion were reported. Secondary: Not reported
Mamelak et al.[30] (2015) Sodium oxybate 3 to 9 g/night (titrated to clinical effect)	MC, OL Patients ≥16 years of age with a history of narcolepsy with cataplexy who were sodium oxybate-naïve or had participated in one of three randomized clinical trials of sodium oxybate and had not been titrated to adequate clinical effect	N=202 12 weeks	Primary: Adverse events Secondary: NSAQ	Primary: In total, 56% of patients reported adverse events. Nine patients discontinued due to a variety of adverse events that included psychosis, migraine headache, dizziness, nausea, anxiety, fatigue, insomnia, abdominal pain, shortness of breath, and depression. Five patients had serious adverse events, and two of these were serious adverse events were considered treatment related: headache in a patient taking 7.5 g/night who continued with study participation, and psychosis in a patient taking 9 g/night who discontinued treatment. The most common adverse events were nausea (10%), headache (7%), and dizziness (5%). Secondary: Based on the response criterion of "much improved" or "somewhat improved" relative to baseline for overall symptoms on the NSAQ, 92% of all patients were rated as treatment responders at week six, and 90% were responders at week 12. The response rate among patients across treatment doses was similar at the two time points. At week six, 54% of all patients reported being "much improved," and 60% at week 12.
Plazzie et al.[31] (2018) EXPRESS study	DB, MC, PC, randomized withdrawal trial	N=63 Up to one year	Primary: Change in weekly number of	Primary: Participants who were withdrawn from sodium oxybate treatment and randomly assigned to placebo during the DB treatment period had a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sodium oxybate, continuation of stable dose or titration to optimal dose vs placebo	Patients 7 to 16 years of age with a primary diagnosis of narcolepsy with cataplexy and were either being treated with sodium oxybate or were sodium oxybate-naive at entry	(3 to 10 week titration period, 2 week stable-dose period, DB randomized withdrawal period and OL sodium oxybate treatment safety period)	cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period Secondary: Change in CGI-C for cataplexy severity and in ESS for Children and Adolescents from the end of the stable-dose period to the end of double-blind treatment period	significant increase in the number of weekly cataplexy attacks compared with participants who were randomly assigned to continue treatment with sodium oxybate. The median change from baseline in the weekly number of cataplexy attacks was 12.7 (Q1, Q3=3.4, 19.8) for participants randomly assigned to placebo and 0.3 (-1.0, 2.5) for participants randomly assigned to continue treatment with sodium oxybate (P<0.0001). Secondary: Participants who received placebo were rated as having worse cataplexy severity than were participants continuing sodium oxybate treatment. The mean change in CGI-C score for cataplexy severity for the placebo group was -1.5 (SD=1.2) versus -0.4 (SD=1.1) for the sodium oxybate group (P=0.0006). The median change from baseline in ESS for Children and Adolescents scores was greater in the placebo group (3.0 [Q1, Q3=1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; P=0.0004).
Thorpy et al.[32] (2019) TONES 2 Solriamfetol 75 mg QD or solriamfetol 150 mg QD (75 mg QD on day one to three) or solriamfetol 300 mg QD (150 mg	DB, MC, PC, PG, RCT Patents 18 to 75 years of age with a diagnosis of type 1 or type 2 narcolepsy according to the ICSD-3 or DSM-5, mean sleep latency <25 minutes on the first four trials of a 5-trial MWT, baseline ESS score ≥10, usual nightly total sleep time ≥6 hours, and a BMI between 18 and 45	N=236 12 weeks	Primary: Change in MWT mean sleep latency on the first four trials of the MWT from baseline to week 12 and change in ESS score from baseline to week 12 Secondary: Proportion of patients who reported improvement on the PGI-C at week 12; change in sleep	Primary: The treatment difference in least squares mean change in MWT from baseline to week 12 when compared to placebo was 2.67 (95% CI, -1.04 to 6.28; P=0.1595) for solriamfetol 75 mg, 7.65 (95% CI, 3.99 to 11.31; P<0.0001) for solriamfetol 150 mg, and 10.14 (95% CI, 6.39 to 13.90; P<0.0001). There were significant differences in the solriamfetol 150 mg and 300 mg groups when compared to placebo. The treatment difference in least square mean change in ESS score from baseline to week 12 when compared to placebo was -2.2 (95% CI, -4.0 to -0.3; P=0.0211) for solriamfetol 75 mg, -3.8 (95% CI, -5.6 to -2.0; P<0.0001) for solriamfetol 150 mg, and -4.7 (95% CI, -6.6 to -2.9; P<0.0001). Secondary: The proportion of patients reporting an improvement on PGI-C at week 12 was 39.7% for placebo, 67.8% for solriamfetol 75 mg, 78.2% for solriamfetol 150 mg and 84.7% for solriamfetol 300 mg. When compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD on day one to three) vs placebo	kg/m^2		latency on each of the five MWT trials; change in mean sleep latency from baseline to week four; change in ESS from baseline to weeks one, four, and eight; percentage of patients who reported improvement on PGI-C at weeks one, four, and eight; and the percentage of patients who reported improvement on the CGI-C at weeks 1, 4, 8 and 12.	to placebo, there was a statistically significant difference in favor of the solriamfetol 75 mg (P<0.05), solriamfetol 150 mg (P<0.0001) and solriamfetol 300 mg (P<0.0001). Treatment difference in the proportion of patients who. The degrees of improvement were not reported. The proportion of patients who reported improvement on PGI-C at weeks one, four and eight was 53.4%, 53.4% and 44.8% for placebo, respectively; 71.2%, 71.2% and 66.1% for solriamfetol 75 mg, respectively; 84.9%, 89.1%, 83.6% for solriamfetol 150 mg, respectively; and 84.7%, 88.1%, 88.1% and 84.7% for solriamfetol 300 mg, respectively. When compared with placebo there were statistically significant differences between all solriamfetol groups at all time points (P<0.05 or P<0.0001). The degrees of improvement were not reported. The least square mean changes from baseline to week four in MWT mean sleep latency was 2.2 for placebo, 4.7 for solriamfetol 75 mg, 9.2 for solriamfetol 150 mg and 13.1 for solriamfetol 300 mg. When compared to placebo there was a statistically significant difference in favor of solriamfetol 150 mg (treatment difference 7.0; P<0.0001) and solriamfetol 300 mg (treatment difference 10.9; P<0.0001). The least square mean changes from baseline in ESS at weeks one, four and eight were -2.7, -2.2, and -2.1 for placebo; -3.2, -3.3, and -3.4 for solriamfetol 75 mg; -5.5, -5.6, -5.2 for solriamfetol 150 mg; -6.7, -5.6, -6.4 for solriamfetol 300 mg. When compared to placebo there were no statistically significant differences for solriamfetol 75 mg. When compared to placebo, were statistically significant differences for solriamfetol 150 mg at weeks one, four and eight (P<0.05, P<0.0001, P<0.05) and solriamfetol 300 mg at weeks one, four and eight (P<0.0001 for all time points). The proportion of patients with reported improvement on CGI-C at weeks one, four and eight and 12 was 50.0%, 55.2%, 48.3% and 41.4% for placebo, respectively; 67.8%, 67.8%, 66.1% and 69.5 for solriamfetol 75 mg, respectively; 81.8%, 90.9%, 90.9%, and 83.6% for solriamfetol 150 mg, respectively; and 88.1%, 89.8%, 89.8% and 83.1% for solriamfetol 300 mg, respectively. When solriamfetol 75 mg is compared to placebo,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				there was a statistically significant difference only at week 12 (P<0.05). When solriamfetol 150 mg and 300 mg were compared to placebo, there were statistically significant differences between groups at all time points (P<0.05 or P<0.0001). The degrees of improvement were not reported. Least square mean changes in sleep latency on each of the 5 MWT trials was statistically significant begging at one hour post-dose and maintained through nine hours post-dose (P<0.05 or P<0.001 for various time points). There was no significant difference between placebo or solriamfetol 75 mg at any time point.
Black et al.[33] (2006) Sodium oxybate 6 to 9 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 to 9 g/day and modafinil 200 to 600 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS	N=270 8 weeks	Primary: MWT Secondary: ESS, CGI-C	Primary: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after eight weeks (P<0.001). In the sodium oxybate group, there was no decrease in sleep latency, suggesting that this medication was as efficacious in treating EDS as previously administered modafinil. In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 to 13.15 minutes (P<0.001), suggesting that this combination of drugs produced an additive effect. Secondary: The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (P<0.001). The sodium oxybate plus modafinil group showed a decreased in median average EES scores from 15 to 11 (P<0.001). Treatment with sodium oxybate, alone (P=0.002) and together with modafinil (P=0.023), showed significant overall clinical improvements as compared to the placebo-treated study patients. The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
Black et al.[34]	DB, PC, RCT	N=278	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Sodium oxybate 6 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 g/day and modafinil 200 to 600 mg/day vs placebo	Patients ≥18 years of age with narcolepsy taking modafinil 200 to 600 mg/day for the treatment of EDS	8 weeks	Sleep architecture, MWT Secondary: Not reported	Following eight weeks of treatment, there was no significant change in total sleep time for any group. Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate plus modafinil included a median increase in Stage three and four sleep (43.5 and 24.25 minutes, respectively; P<0.001 for each) and delta power (P<0.001 for each) and significant decrease in the number of nocturnal awakenings in sodium oxybate (P=0.008) and sodium plus modafinil (P=0.014) treated study patients. No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone. Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at eight weeks (P<0.001) once they had been switched to placebo following stable chronic modafinil treatment. A slight worsening of EDS indicated by increased ESS scores, was noted in placebo-treated patients (P=0.011) after stopping baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment. Sodium oxybate-treated patients and sodium oxybate plus modafinil-treated patients experienced significant improvements in ESS scores (P<0.001 for each). There was no change in ESS scores in the group maintained on modafinil alone. Secondary: Not reported
Obstructive Sleep Apnea				
Hirshkowitz et al.[35] (2007) Armodafinil 150 mg/day	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of OSA/hypopnea	N=263 12 weeks	Primary: MWT, CGI-C Secondary: CDR, ESS, BFI	Primary: Armodafinil significantly improved wakefulness compared to placebo. The mean MWT sleep latency increased from baseline by 2.3 minutes in the armodafinil group and decreased by 1.3 minutes in the placebo group (P=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	syndrome who complained of residual excessive sleepiness during CPAP therapy			Armodafinil significantly improved MWT sleep latency compared to placebo at each visit (P<0.01 for all). The proportion of patients with at least ‘‘minimal improvement’’ on the CGI-C scale was greater for armodafinil than placebo (71 vs 53%; P=0.0069). Secondary: As assessed on the CDR, armodafinil significantly improved the quality of episodic secondary memory compared to placebo. The quality of episodic secondary memory increased by 7.6 points from baseline to the final visit for patients in the armodafinil group and decreased by 7.0 points for those in the placebo group (P=0.0102). The mean change from baseline in ESS total score was significantly greater for patients receiving armodafinil than for those receiving placebo (P<0.01 for all). As assessed on the BFI, armodafinil significantly reduced global fatigue and worst fatigue in the past 24 hours at weeks four and 12 and at the final visit compared to placebo (P<0.05 for all).
Roth et al.[36] (2006) Armodafinil 150 to 250 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of moderate OSA/ hypopnea syndrome and residual excessive sleepiness despite effective, regular, and stable use of CPAP treatment	N=395 12 weeks	Primary: MWT, CGI-C Secondary: ESS, CDR, BFI	Primary: The mean changes in MWT sleep latency across the first four tests were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group at the final visit (P<0.001 for all). There was no difference between the two modafinil doses. The proportions of patients who had at least minimal improvement on the CGI-C were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.001 for all). There was no difference between the two modafinil doses. Secondary: The mean change in ESS total score was significantly greater in the armodafinil combined group compared to the placebo group at the final visit (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean changes in global fatigue scores were significantly greater in the armodafinil combined group compared to the placebo group at all visits (P<0.05 for all). The mean change in score for worst fatigue during the past 24 hours was statistically greater in the armodafinil combined group compared to placebo at week eight (P<0.05). Mean changes in quality of episodic secondary memory score were significantly greater with armodafinil 150 and 250 mg/day compared to placebo at week four (both, P<0.05) and with armodafinil 250 mg/day vs placebo at week eight (P<0.01). No significant differences in speed of memory or power of attention were found between the armodafinil combined and placebo groups across the first four or last three sessions at any assessment. At weekeight8, mean changes in continuity of attention across the first four sessions were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.05 for all). The most frequently reported adverse event was headache, occurring in 17.6% of patients in the armodafinil combined group and 8.5% of patients in the placebo group (P<0.05). The severity of adverse events was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Krystal et al.[37] (2010) Armodafinil 200 mg/day vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age diagnosed with obstructive sleep apnea	N=249 18 months	Primary: CGI-C as related to sleepiness, mean change from baseline in MWT to mean sleep latency at final visit Secondary:	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group compared to the placebo group (69 vs 53%; P=0.012). Mean MWT sleep latency was increased following armodafinil (2.6 minutes) compared to placebo (1.1 minutes), but was not statistically significant (P=0.30). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ESS	Mean ESS scores were significantly reduced in study patients treated with armodafinil compared to patients treated with placebo (-6.3 vs -4.8; P=0.003). The most common adverse effects included headache, dry mouth and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Black et al.[38] (2005) Modafinil 200 to 400 mg/day vs placebo	DB, MC, PC, RCT Adults 18 to 70 years of age with OSA/ hypopnea syndrome and having residual excessive sleepiness during CPAP therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, FOSQ	Primary: Modafinil significantly improved mean sleep latency on the MWT compared to placebo (P<0.001). Modafinil significantly decreased the ESS scores compared to placebo (P<0.001). There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (P>0.15 for each). Secondary: At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (P<0.001). Modafinil improved mean FOSQ scores compared to placebo (P<0.02) for vigilance, general productivity, and activity level.
Weaver et al.[39] (2009) Modafinil 200 to 400 mg/day vs placebo	2 DB, MC, PC, RCT (Pooled analysis) Patients 24 to 76 years of age diagnosed with OSA and residual excessive sleepiness associated with CPAP	N=480 4 to 12 weeks	Primary: FOSQ Secondary: Not reported	Primary: After treatment with modafinil, there were greater improvements from baseline in the total FOSQ score (P<0.0001) as well as activity level (P=0.002), productivity level (P=0.007), intimacy and sexual relationships (P=0.01) and vigilance (P<0.001) compared to treatment with placebo. A greater proportion of patients who received modafinil were considered responders compared to patients who received placebo (45 vs 25%; P<0.001). Analysis based on the individual FOSQ questions demonstrated that 18 of the 30 questions increased at least one point for significantly more patients who received modafinil (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Williams et al.[40] (2010) Modafinil 200 mg/day vs placebo	DB, RCT, XO Men diagnosed with OSA who were modafinil-naïve	N=21 2 days	Primary: Driving simulation, subjective sleepiness Secondary: Not reported	Primary: During CPAP withdrawal, severe sleep-disordered breathing was evident and administration of modafinil improved simulated driving performance (steering variability; P<0.0001, mean reaction time; P<0.0002, lapses on a current task; P<0.01), psychomotor vigilance task (mean one/reaction time and lapses, both P<0.0002), and subjective sleepiness (P<0.01). Secondary: Not reported
Schweizer et al.[41] (2019) TONES 3 Solriamfetol 37.5 mg QD or solriamfetol 75 mg QD or solriamfetol 150 mg QD (75 mg QD on days 1 to 3) or solriamfetol 300 mg QD (150 mg QD on days 1 to 3)	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a diagnosis of EDS associated with OSA according to the ICSD-3, current or previous use of a primary OSA therapy including PAP, mandibular advancement device or surgical intervention to treat underlying obstruction or have been tried to use a primary OSA therapy for at least one month with at least one documented adjustment to therapy, ESS score	N=474 12 weeks	Primary: Change from baseline to week 12 in mean sleep latency derived from the first four trials of a five-trial 40-minute MWT and change from baseline to week 12 in ESS score Secondary: Change from baseline to week 12 in sleep latency for each of the five individual MWT trials, proportion of patients reporting any improvement on the PGI-C at week 12, proportion of patients with any improvement on	Primary: The LS mean difference in change from baseline to week 12 for sleep latency derived from MWT when compared to placebo was 4.5 (95% CI, 1.2 to 7.9; P=0.0086) for solriamfetol 37.5 mg, 8.9 (95% CI, 5.6 to 12.1; P<0.0001) for solriamfetol 75 mg, 10.7 (95% CI, 8.1 to 13.4; P<0.0001) for solriamfetol 150 mg, and 12.8 (95% CI, 10.0 to 15.6; P<0.0001) for solriamfetol 300 mg. The LS mean difference in change from baseline to week 12 for ESS when compared to placebo was -1.9 (95% CI, -3.4 to -0.3; P=0.0161) for solriamfetol 37.5 mg, -1.7 (95% CI, -3.2 to -0.2; P=0.0233) for solriamfetol 75 mg, -4.5 (95% CI, -5.7 to -3.2; P<0.0001) for solriamfetol 150 mg, and -4.7 (95% CI, -5.9 to -3.4; P<0.0001) for solriamfetol 300 mg. Secondary: The difference in the proportion of patients reporting any improvement on the PGI-C when compared to placebo was 6.2% (95% CI, -9.7 to 22.2; P=0.4447) for solriamfetol 37.5 mg, 23.3% (95% CI, 8.6 to 38.0; P=0.0035) for solriamfetol 75 mg, 40.5% (95% CI, 29.8 to 51.3; P<0.0001) for solriamfetol 150 mg and 39.6% (95% CI, 28.7 to 50.4; P<0.0001) for solriamfetol 300 mg. There was a statistically significant difference in favor of the solriamfetol 75 mg, 150 mg and 300 mg groups when compared to placebo. Change from baseline in sleep latency on each of the five individual MWT

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	≥10, baseline sleep latency <30 minutes for the first four of a five-trial 40-minute MWT, and usual nightly sleep time greater than or equal to six hours		the CGI-C at week 12	trials at week 12 was significantly greater with solriamfetol 75-, 150-, and 300-mg doses compared with placebo from one to nine hours after dosing (P<0.05 or P<0.0001). The 37.5-mg dose showed a significant difference relative to placebo for trial 2 only (P<0.05), based on the prespecified testing sequence. The proportion of patients with reported improvement on CGI-C at week 12 was 49.1%, 58.9%, 70.7%, 90.5% and 88.7% for the placebo and solriamfetol 37.5 mg, 75 mg, 150 mg and 300 mg groups, respectively. When compared to placebo, there was a statistically significant difference between the solriamfetol 75 mg group (P<0.05) and solriamfetol 150 and 300 mg groups (P<0.0001 for both). There was no significant difference between placebo and solriamfetol 37.5 mg. The following secondary and exploratory endpoints were not noted, but results were not included: 10-item functional outcomes of sleep questionnaire, work productivity and activity impairment questionnaire: specific health problems, 36-item short form health survey version two, five-dimension five-level EuroQoL, and change in primary OSA therapy use.
Strollo et al.[42] (2018) TONES 4 Solriamfetol (75, 150 or 300 mg) QD vs placebo	MC, PC, RCT, Withdrawal Patients 18 to 75 years of age with OSA who had current or prior primary OSA therapy, BMI 18 to <45 kg/m2, baseline ESS score ≥10, mean sleep latency <30 minutes on the first four trials of a five-trial, 40-minute MWT, and usual nightly sleep time	N=174 6 weeks	Primary: Change from week four to week six in MWT mean sleep latency and ESS score Secondary: Proportion of patients who reported worsening of their condition on the PGI-C from week four to week six, proportion of patients who worsened from	Primary: The LS mean changes in MWT mean sleep latency from week four to week six were -1.0 for solriamfetol and -12.1 for placebo, representing a statistically significant difference in favor of placebo (treatment difference, 11.2 minutes; 95% CI, 7.8 to 14.6; P<0.0001). The LS mean changes in ESS score from week four to week six were 4.5 for placebo and -0.1 for solriamfetol resulting a statistically significant difference in favor of placebo (treatment difference, -4.6; 95% CI, −6.4 to −2.8; P<0.0001). Secondary: The proportion of patients who reported worsening of during the withdrawal phase (weeks four to six) on the ePGI-C was 50.0% for patients randomized to placebo and 20.0% for patients who remained on solriamfetol (treatment difference, -30.0%; 95% CI, -46.0 to -14.0; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥6 hours		week four to week six by CGI-C	The proportion of patients who worsened from week four to week six by CGI-C was 59.0% of patients randomized to placebo and 21.7% who continued solriamfetol (treatment difference, -37.3%; 95% CI, -53.50 to -21.19; P<0.0001).
Shift Work Sleep Disorder				
Czeisler et al.[43] (2009) Armodafinil 150 mg daily administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age who exhibited signs and symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of four or higher for sleepiness on work nights, including the commute to and from work	N=254 12 weeks	Primary: MSLT, CGI-C Secondary: KSS, CDR	Primary: Armodafinil improved mean nighttime sleep latency (2 to 8 AM) by 3.1 to 5.3 minutes compared to an increase of 0.4 to 2.8 minutes at in patients receiving placebo at the final visit (P<0.001). Of the patients who received armodafinil, 79% were rated as improved in the CGI-C ratings compared to 59% of the patients who received placebo at the final visit (P=0.001). Secondary: Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits. Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and mean number of mistakes, accidents, or near misses compared to placebo. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared to placebo at each visit (P<0.001 at weeks four and eight; P=0.002 at week 12; P<0.001 at final visit) and during the first four tests on the final night shift (P=0.002 at 12:30 AM; P<0.001 at 2:30 AM; P=0.02 at 4:30 AM; P=0.006 at 6:30 AM). Armodafinil significantly improved speed of memory from baseline compared to placebo at week eight (armodafinil, -240.9 milliseconds; placebo, -6.5 milliseconds; P=0.02) and week 12 (armodafinil, -307.7 milliseconds; placebo, -115.2 milliseconds; P=0.01). However, this was not significant at the final visit (armodafinil, -257.2 milliseconds; placebo. -140.4 milliseconds; P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Armodafinil significantly improved mean power of attention at each study visit (P=0.005 at week four; P=0.006 at week eight; P=0.005 at week 12; P=0.001 at final visit) and during the first four tests on the final night shift compared to placebo (P=0.002 at 12:30 AM; P=0.006 at 2:30 AM; P=0.004 at 4:30 AM; P=0.03 at 6:30 AM). Continuity of attention improved at the final visit in patients who received armodafinil compared to those who received placebo (P<0.001). Adverse events included headache, nausea, nasopharyngitis and anxiety. Most adverse events were considered mild or moderate by the investigator.
Tembe et al.[44] (2011) Armodafinil 150 mg administered one hour prior to night shift vs modafinil 200 mg administered one hour prior to night shift	DB, MC, RCT Patients 18 to 60 years of age suffering from excessive sleepiness associated with SWD	N=211 12 weeks	Primary: Proportion of patients showing ≥2 grades of improvement (responder) based on SSS in both groups Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy and safety	Primary: Responder rates with armodafinil (72.12%) and modafinil (74.29%) were comparable (P=0.76). Secondary: Armodafinil and modafinil significantly improved mean sleepiness grades as compared to baseline (P<0.0001). At the end of therapy, compliance in both modafinil group (99.31%) and armodafinil group (99.13%) was found to be comparable (P=0.63). Both physicians' and patients' assessment of efficacy was comparable among the treatment groups. Adverse events were similar with modafinil (40.57%) and armodafinil (42.87%; P=0.78). The most commonly treatment-emergent adverse events reported were mild to moderate in severity and included headache, nausea, and dry mouth.
Erman et al. (abstract)[45] (2012) Armodafinil 150 mg administered one hour prior to	DB, MC, PC, PG, RCT Patients 18 to 65 years of age suffering from excessive sleepiness	N=383 6 weeks	Primary: SDS-M and FOSQ-10 Secondary: Not reported	Primary: Patients treated with armodafinil experienced significantly greater improvements in SDS-M composite scores at final visit compared to patients treated with placebo (-6.8 vs -4.5, respectively; P=0.0027). Patients in the armodafinil treatment group demonstrated a greater improvement in total FOSQ-10 score from baseline to six weeks compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
night shift vs placebo	associated with SWD			to placebo (3.6 vs 2.7; P=0.0351); however, there was no difference between treatments at the final visit (3.4 vs 2.7; P=0.0775). Secondary: Not reported
Erman et al.[46] (2011) Armodafinil 150 mg administered one hour prior to night shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: CGI-C Secondary: GAF and KSS	Primary: Significantly more patients treated with armodafinil experienced an improvement in CGI-C compared to placebo at three weeks (78 vs 51%; P<0.0001) and at six weeks (80 vs 56%; P<0.0001). Similarly, more patients treated with armodafinil experienced an improvement in late-in-shift CGI-C at the final visit compared to placebo (77 vs 57%; P<0.0001). At the final visit, most patients in the armodafinil group were categorized as 'much improved' (33%) or 'very much improved' (24%) on the late-in-shift CGI-C rating scale. For patients treated with placebo, 38% had 'no change' in their condition compared to only 19% of patients in the armodafinil group. Secondary: The mean (±SD) improvement from baseline in GAF score at the final visit was significantly greater in the armodafinil group compared to the placebo group (9.4 vs 5.0; P<0.0001). Improvements in GAF scores were also significantly greater for armodafinil-treated patients at three weeks (6.9 vs 3.7; P<0.0001) and six weeks (9.8 vs 4.9; P<0.0001) compared to patients treated with placebo. A higher proportion of patients treated with armodafinil had GAF scores greater than 70 ("normal function") at each visit, with almost twice as many patients receiving armodafinil reaching GAF scores greater than 70 at final visit compared to placebo (51 vs 28%; P value not reported). The improvements in KSS scores from baseline to the final visit were significantly greater for armodafinil-treated patients compared to patients receiving placebo (-2.8 vs -1.8; P<0.0001). The KSS scores were also significantly improved in the armodafinil group compared to the placebo group at three weeks (-2.6 vs -1.6; P<0.0001) and six weeks (-2.9 vs -1.8; P<0.0001).
Czeisler et al.[47]	DB, MC, PC, RCT	N=204	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Modafinil 200 mg daily administered 30 to 60 minutes before the start of work shift vs placebo	Adults 18 to 60 years of age diagnosed with SWD and worked each month at least five night shifts for ≤12 hours, with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively	3 months	MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	The modafinil group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (P=0.002). The modafinil group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared to 36% in the placebo group (P<0.001). The modafinil group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline vs the placebo group (P=0.005). Secondary: Not reported
Miscellaneous				
Black et al.[48] (2010) Armodafinil 100 to 250 mg/day (OSA) or 100 to 250 mg/night 30 minutes to one hour before night shift but no later than 23:00 (SWD)	DB, MC, OL Men and women 18 to 65 years of age with a diagnosis of OSA, SWD, or narcolepsy	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI) Secondary: Not reported	Primary: Discontinuations due to adverse events occurred in 13% of study patients during the initial study period. Most adverse events were mild to moderate in severity and included headache (25%), nasopharyngitis (17%), and insomnia (14%). Small increases were observed in BP (3.6/2.3 mm Hg), HR (6.7 beats per minute) across all study patient groups with most of the changes occurring by month three. Greater improvement, compared to baseline, on the CGI-C was reported in the three study groups (75 to 92%) at the final visit with the SWD group reporting the greatest improvement. Study patients reported significant improvement at the final visit by 65% with treated OSA (95% CI, 60.2 to 68.9), 88% with SWD (95% CI, 81.3 to 93.9), and 62% with narcolepsy (95% CI, 54.2 to 69.8). Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The level of fatigue and its impact on daily activities was consistently reduced from baseline, at all visits, in each of the study groups, measured by BFI scores. Secondary: Not reported
Schwartz et al.[49] (2010) Armodafinil 100 to 250 mg/day (OSA and narcolepsy) or 100 to 250 mg/day 30 minutes to one hour before the start of night shift but no later than 23:00 (SWD)	MC, OL Patients 18 to 65 years of age who had a complaint of excessive sleepiness associated with OSA, SWD, or narcolepsy	N=328 12 months	Primary: CGI, ESS, adverse events Secondary: Not reported	Primary: At the final visit, 80% (95% CI, 74.1 to 86.7) of patients with OSA and 84% (95% CI, 72.7 to 94.8) of patients with narcolepsy were rated with the CGI-I scale as at least minimally improved with regard to overall clinical condition. Armodafinil improved EES scores in study patients treated with OSA (-7.3; 95% CI, -8.39 to -6.30) and narcolepsy (-4.7; 95% CI, -7.41 to -1.93). A total of 98% (95% CI, 95.2 to 100.0) of patients with SWD were rated as improved with regard to sleepiness during night shifts, including the commute to and from work. Across the diagnosis groups, the most commonly occurring adverse event was headache (14 to 24%). The adverse event was mild to moderate in severity as noted by the study investigators. Secondary: Not reported
Jean-Pierre et al.[50] (2010) Modafinil 200 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with cancer with a survival expectancy >6 months	N=877 4.5 years	Primary: BFI question 3, ESS, POMS-DD Secondary: Not reported	Primary: Patients with severe fatigue at baseline benefited from modafinil (P=0.033) whereas patients with mild (P=0.09) to moderate (P=0.41) fatigue did not benefit from modafinil as compared to placebo. Daytime sleepiness improved significantly in the modafinil group (P=0.002). Modafinil had no statistically significant effect on depression (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Orlikowski et al.[51] (2009) Modafinil 300 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with myotonic muscular dystrophy type one experiencing hypersomnia	N=28 2.5 years	Primary: MWT Secondary: MSLT, ESS, global assessment (patient and physician), HAMD, SF-36	Primary: At four weeks, the mean MWT score was 16.4 minutes in the modafinil group and 15.8 minutes in the placebo group (P=0.71). Secondary: There were no significant differences between the treatment groups in MSLT latency, ESS or treatment efficacy scores. There were no significant differences between the groups in disturbances of personality and mood or quality-of-life. A total of eight patients reported at least one adverse event, including digestive, neurologic and skin symptoms. The adverse events were considered mild or moderate by the study investigator.

Study abbreviations: DB=double blind, CI=confidence interval, MC=multi-center, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SD=standard deviation, XO=crossover design

Other abbreviations: BFI=Brief Fatigue Inventory, CDR=Cognitive Drug Research, CGI-C=clinical global impression of change, CGI-S=clinical global impression of severity, CPAP=continuous positive airway pressure, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, EDS=excessive daytime sleepiness, EQ-5D=European quality-of-life questionnaire, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FOSQ=Functional outcomes of sleep questionnaire, GAF=Global Assessment of Functioning, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, ICSD-3=International Classification of Sleep Disorders Third Edition, KSS=Karolinska Sleepiness Scale, MPH=methylphenidate, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, NSAQ=Narcolepsy Symptom Assessment Questionnaire, OSA=obstructive sleep apnea, PGI-C=Patient Global Impression of Change, PLM=periodic leg movements, POMS-DD=depression-dejection subscale of profile of mood states, PSG=Polysomnogram, REM=rapid eye movement, SART=Sustained attention to response task, SDS-M=modified Sheehan Disability Scale, SF-36=36-item Short Form Health Survey, SSS=Stanford sleepiness score, SWD=shift work disorder

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Wakefulness Promoting Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Armodafinil	tablet	Nuvigil®*	$$$$$	$$$
Modafinil	tablet	Provigil®*	$$$$$	$
Pitolisant	tablet	Wakix®	$$$$$	N/A
Sodium oxybate	oral solution	Xyrem®, Xywav®	$$$$$	N/A
Solriamfetol	tablet	Sunosi®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The agents included in this review are approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, shift work sleep disorder, and idiopathic hypersomnia.[5-10,13-14] Armodafinil, modafinil and solriamfetol are Schedule IV controlled substances. Sodium oxybate is a central nervous system depressant and is classified as a Schedule III controlled substance. Pitolisant is the only agent in this review that is not a controlled substance. Armodafinil, modafinil, pitolisant and solriamfetol are long-acting agents while sodium oxybate is a short-acting agent. Armodafinil and modafinil are available in generic formulations.[5-10]

The American Academy of Sleep Medicine guidelines for the treatment of central disorders of hypersomnolence state that modafinil, pitolisant, sodium oxybate, and solriamfetol are recommended for the treatment of narcolepsy in adults. Armodafinil, dextroamphetamine, and methylphenidate are suggested for the treatment of narcolepsy in adults.[1] Modafinil is recommended for the treatment of idiopathic hypersomnia in adults.[1] Modafinil is also recommended as one of several initial treatment options for individuals with excessive sleepiness due to obstructive sleep apnea and shift work sleep disorder.[3,4] Armodafinil, modafinil, pitolisant, solriamfetol and sodium oxybate have been shown to be more effective than placebo in patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder[15-27,31-43,45-47]

There is insufficient evidence to support that one brand wakefulness promoting agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand wakefulness promoting agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand wakefulness promoting agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost-effective products and possibly designate one or more preferred brands.

XII. References

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