

2019

Nelson's Pediatric Antimicrobial Therapy

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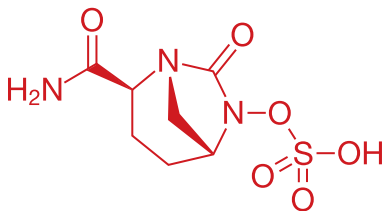


American Academy of Pediatrics

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25th Edition

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Introduction

We are now in our 25th edition of *Nelson's Pediatric Antimicrobial Therapy*, a tribute to John Nelson's belief that advice on treatment of children with infections should be clear and concise! Although no new oral anti-infective agents have been approved in the United States recently, several antibiotics in many classes that completed adult studies are now entering pediatric clinical trials, particularly those for multidrug-resistant Gram-negative bacilli. The contributing editors, all very active in clinical work, have updates in their sections with relevant new recommendations based on current published data, guidelines, and clinical experience. We hope that the reference list for each chapter provides the available evidence to support our recommendations, for those who wish to see the data.

For those who use the *Nelson's* app, you may have noticed a new "feel" to the app, which is now written in one of the Apple programming languages by Dr Howard Smart, a full-time office-based pediatrician and the chief of pediatrics at the Sharp Rees-Stealy multispecialty medical group in San Diego, CA. With the support of the American Academy of Pediatrics (AAP) (particularly Peter Lynch) and the editors, we are putting more of Howard's enhancements in this 2019 edition. So substantial are his contributions to the app, the book (from the perspective of an office-based pediatrician), and the development of future *Nelson's* digital versions that the editors and the AAP have unanimously asked Howard to join us officially as a contributing editor. We believe that his skills (clinical and digital) are an essential part of what we all hope the AAP *Nelson's* book can and should be.

Recognizing the talent in collaborators/colleagues of the editors and their substantial and ongoing contributions to the quality of the material that is presented in this book, we wish to continue to acknowledge their advice each year in this Introduction. We continue to receive valuable suggestions from Drs John van den Anker and Pablo Sanchez on antimicrobial therapy of the newborn, in support of the work done by JB Cantey and Jason Sauberan in Chapter 5.

A pediatric hospital medicine consulting editor who is with us again this year is Dr Brian Williams, a pediatric/adult hospitalist who trained with us at the University of California, San Diego, School of Medicine/Rady Children's Hospital San Diego and is now in Madison, WI. His continuing advice on organizing information for both the book and the app has been invaluable. He is focused, practical, and very collaborative.

We continue to harmonize the *Nelson's* book with *Red Book: 2018–2021 Report of the Committee on Infectious Diseases*, 31st Edition (easy to understand, given that Dr David Kimberlin is also the editor of the *Red Book*). We are virtually always in sync but often with additional explanations (that do not necessarily represent AAP policy) to allow the reader to understand the basis for recommendations.

We continue to provide grading of our recommendations—our assessment of how strongly we feel about a recommendation and the strength of the evidence to support our recommendation (noted in the Table).

Strength of Recommendation	Description
A	Strongly recommended
B	Recommended as a good choice
C	One option for therapy that is adequate, perhaps among many other adequate therapies
Level of Evidence	Description
I	Based on well-designed, prospective, randomized, and controlled studies in an appropriate population of children
II	Based on data derived from prospectively collected, small comparative trials, or noncomparative prospective trials, or reasonable retrospective data from clinical trials in children, or data from other populations (eg, adults)
III	Based on case reports, case series, consensus statements, or expert opinion for situations in which sound data do not exist

As we state each year, many of the recommendations by the editors for specific situations have not been systematically evaluated in controlled, prospective, comparative clinical trials. Many of the recommendations may be supported by published data, but the data may never have been presented to or reviewed by the US Food and Drug Administration (FDA) and, therefore, are not in the package label. We all find ourselves in this situation frequently. Many of us are working closely with the FDA to try to narrow the gap in our knowledge of antimicrobial agents between adults and children; the FDA pediatric infectious diseases staff is providing an exceptional effort to shed light on the doses that are safe and effective for neonates, infants, and children, with major efforts to place important new data on safety and efficacy in the antibiotic package labels for all to use in clinical practice.

Barrett Winston, our primary AAP editorial contact for the past few years, has done an amazing job of organizing all the AAP staff, as well as the contributing and consulting editors, but has now moved to other responsibilities within the AAP and is turning over the editorial tasks to Mary Kelly, who has an impressive track record in publications. Mary will now keep us all moving forward with the 2019 edition upgrades and enhancements as we keep looking to the long-term future of the book in partnership with the

AAP. Peter Lynch continues to work on developing *Nelson's* online, as well as the app, and has shared considerable AAP resources with us. We continue to appreciate the teamwork of all those at the AAP who make sure this book gets to all the clinicians who may benefit. Thanks to Mark Grimes, vice president, Publishing, and our steadfast friends and supporters in AAP Membership, Marketing, and Publishing—Jeff Mahony, director, professional and consumer publishing; Linda Smessaert, senior marketing manager, professional resources; and the entire staff—who make certain that the considerable information in *Nelson's* makes it to those who are actually caring for children.

We are still very interested to learn from readers/users if there are new chapters or sections you wish for us to develop—and whether you find certain sections particularly helpful, so we don't change or delete them! From the feedback we have received, the chapter on adverse drug reactions is no longer included in this edition. We are focusing on more common antimicrobial drug issues, such as dosing in obesity. Please send your suggestions to nelsonabx@aap.org.

John S. Bradley, MD

Notable Changes to 2019 Nelson's Pediatric Antimicrobial Therapy, 25th Edition

Nelson's Pediatric Antimicrobial Therapy has been updated to incorporate new approaches to treatment based on clinical guidelines and new publications, as well as to be consistent with *Red Book: 2018–2021 Report of the Committee on Infectious Diseases*, 31st Edition. Color has been added throughout to improve navigation and help you find the best treatment options quickly.

Antimicrobials, Antifungals, Antivirals, and Antiparasitics

- Updates to tables for susceptibility of bacterial, fungal, viral, and parasitic pathogens. Tables are now color coded to make it easier to instantly find the best treatment options by pathogen.
- Presents new safety data on fluoroquinolones (including moxifloxacin) in children, supporting current policy that these drugs are appropriate for situations in which no other drug is active against the bacterial pathogen.
- Updates for doxycycline dosing, which has been converted to kilogram-based dosing to be consistent with US Food and Drug Administration (FDA) package label dosing.
- Provides extensive explanations of the new beta-lactam/beta-lactamase inhibitor combinations. At least 4 new antibiotics are under investigation in children, mostly for multidrug-resistant Gram-negative bacilli. Specific, new, and evolving recommendations about antifungal therapeutic drug levels for several invasive fungal infections are clarified, particularly in immunocompromised children.
- Adds *Candida auris* as a newly emergent fungal pathogen.
- Incorporates new coccidioidomycosis guidelines to updated recommendations.
- Includes new approaches to mucormycosis, a devastating infection, based on published data, animal models, and the extensive experience of William J. Steinbach, MD.
- Reorganizes antiviral table into 2 tables for easier reading: common viral pathogens are in one table, and HIV, hepatitis B, and hepatitis C are in a second table.
- Updates to babesiosis to include a recent publication supporting the choice of azithromycin and atovaquone for both mild to moderate and severe infection.
- Updates, including new information on drug therapy and steroid therapy, for neurocysticercosis incorporating the Infectious Diseases Society of America (IDSA) and American Society of Tropical Medicine and Hygiene guidelines.
- Updates for *Giardia*, including tinidazole and nitazoxanide as drugs of choice, based on the IDSA guidelines for clinical management of diarrhea.

- Updates for Chagas disease to include benznidazole, which was approved by the FDA for use in children 2 to 12 years of age and is no longer available through the Centers for Disease Control and Prevention (CDC). Nifurtimox continues to be available only through the CDC.

Antimicrobial Therapy for Newborns

- Updates to the management of newborns exposed to HIV, including links to the National Institutes of Health Web site that is continuously updated.
- Options for treatment of increasing resistance in *Escherichia coli* for urinary tract infections.
- Guidance to achieve similar antibacterial activity in similar tissue sites, with a similar safety profile, in the neonate during the ongoing cefotaxime shortage.

1. Choosing Among Antibiotics Within a Class: Beta-lactams and Beta-lactamase Inhibitors, Macrolides, Aminoglycosides, and Fluoroquinolones

New drugs should be compared with others in the same class regarding (1) antimicrobial spectrum; (2) degree of antibiotic exposure (a function of the pharmacokinetics of the nonprotein-bound drug at the site of infection and the pharmacodynamic properties of the drug); (3) demonstrated efficacy in adequate and well-controlled clinical trials; (4) tolerance, toxicity, and side effects; and (5) cost. If there is no substantial benefit for efficacy or safety for one antimicrobial over another for the isolated or presumed bacterial pathogen(s), one should opt for using an older, more extensively used agent (with presumably better-defined efficacy and safety) that is usually less expensive and preferably with a narrower spectrum of activity.

Beta-lactams and Beta-lactamase Inhibitors

Beta-lactam (BL)/Beta-lactamase Inhibitor (BLI) Combinations. Increasingly studied and approved by the US Food and Drug Administration (FDA) are BL/BLI combinations that target antibiotic resistance based on the presence of a pathogen's beta-lactamase. The BL antibiotic may demonstrate activity against a pathogen, but if a beta-lactamase is present in that pathogen, it will hydrolyze the BL ring structure and inactivate the antibiotic. The BLI is usually a BL structure, which explains why it binds readily to certain beta-lactamases and can inhibit their activity; however, the BLI usually does not demonstrate direct antibiotic activity itself. As amoxicillin and ampicillin were used extensively against *Haemophilus influenzae* following their approval, resistance to both antibiotics increased, based on the presence of a beta-lactamase that hydrolyzes the BL ring of amoxicillin/ampicillin (up to 40% resistance in some regions). Clavulanate, a BLI that binds to and inactivates the beta-lactamase, allows amoxicillin/ampicillin to "survive" and inhibit cell wall formation, leading to the death of the organism. The oral BL/BLI combination of amoxicillin/clavulanate, originally known as Augmentin, has been very effective. Similar combinations, primarily intravenous (IV), have now been studied, pairing penicillins, cephalosporins, and carbapenems with other BLIs such as tazobactam, sulbactam, and avibactam. Under investigation in children are the IV BL/BLI combinations ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam, and imipenem relebactam.

Beta-lactam Antibiotics

Oral Cephalosporins (cephalexin, cefadroxil, cefaclor, cefprozil, cefuroxime, cefixime, cefdinir, cefpodoxime, cefditoren [tablet only], and cefibuten). As a class, the oral cephalosporins have the advantage over oral penicillins of somewhat greater spectrum of activity. The serum half-lives of cefpodoxime, cefibuten, and cefixime are greater than 2 hours. This pharmacokinetic feature accounts for the fact that they may be given in 1 or 2 doses per day for certain indications, particularly otitis media, where the middle ear fluid half-life is likely to be much longer than the serum half-life. For more resistant pathogens, twice daily is preferred (see Chapter 3). The spectrum of activity increases for

Gram-negative organisms as one goes from the first-generation cephalosporins (cephalexin and cefadroxil), to the second generation (cefaclor, cefprozil, and cefuroxime) that demonstrates activity against *Haemophilus influenzae* (including beta-lactamase-producing strains), to the third-generation agents (cefdinir, cefixime, cefpodoxime, and ceftibuten) that have enhanced coverage of many enteric Gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp). However, ceftibuten and cefixime, in particular, have a disadvantage of less activity against *Streptococcus pneumoniae* than the others, particularly against penicillin (BL) non-susceptible strains. No oral fourth- or fifth-generation cephalosporins (see the Parenteral Cephalosporins section) currently exist (no activity against *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* [MRSA]). The palatability of generic versions of these products may not have the same better-tasting characteristics as the original products.

Parenteral Cephalosporins. First-generation cephalosporins, such as cefazolin, are used mainly for treatment of Gram-positive infections caused by *S aureus* (excluding MRSA) and group A streptococcus and for surgical prophylaxis; the Gram-negative spectrum is limited but more extensive than ampicillin. Cefazolin is well tolerated on intramuscular or IV injection.

A second-generation cephalosporin (cefuroxime) and the cephamycins (cefoxitin and cefotetan) provide increased activity against many Gram-negative organisms, particularly *Haemophilus* and *E coli*. Cefoxitin has, in addition, activity against approximately 80% of strains of *Bacteroides fragilis* and can be considered for use in place of the more active agents, like metronidazole or carbapenems, when that organism is implicated in nonserious disease.

Third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) all have enhanced potency against many enteric Gram-negative bacilli. As with all cephalosporins, at readily achievable serum concentrations, they are less active against enterococci and *Listeria*; only ceftazidime has significant activity against *Pseudomonas*. Cefotaxime and ceftriaxone have been used very successfully to treat meningitis caused by pneumococcus (mostly penicillin-susceptible strains), *H influenzae* type b, meningococcus, and susceptible strains of *E coli* meningitis. These drugs have the greatest usefulness for treating Gram-negative bacillary infections due to their safety, compared with other classes of antibiotics (including aminoglycosides). Because ceftriaxone is excreted, to a large extent, via the liver, it can be used with little dosage adjustment in patients with renal failure. With a serum half-life of 4 to 7 hours, it can be given once a day for all infections, including meningitis, that are caused by susceptible organisms.

Cefepime, a fourth-generation cephalosporin approved for use in children in 1999, exhibits (1) enhanced antipseudomonal activity over ceftazidime; (2) the Gram-positive activity of second-generation cephalosporins; (3) better activity against Gram-negative enteric bacilli; and (4) stability against the inducible ampC beta-lactamases of *Enterobacter* and *Serratia* (and some strains of *Proteus* and *Citrobacter*) that can hydrolyze third-generation cephalosporins. It can be used as single-drug antibiotic therapy against

these pathogens, rather than paired with an aminoglycoside, as is commonly done with third-generation cephalosporins to decrease the emergence of ampC-resistant clones.

Ceftaroline is a fifth-generation cephalosporin, the first of the cephalosporins with activity against MRSA. Ceftaroline was approved by the FDA in December 2010 for adults and approved for children in June 2016 for treatment of complicated skin infections (including MRSA) and community-acquired pneumonia. The pharmacokinetics of ceftaroline have been evaluated in all pediatric age groups, including neonates and children with cystic fibrosis; clinical studies for pediatric community-acquired pneumonia and complicated skin infection have now been published.¹ Based on these published data, review by the FDA, and post-marketing experience for infants and children 2 months and older, ceftaroline should be as effective and safer than vancomycin for treatment of MRSA infections. Just as BLs are preferred over vancomycin for methicillin-susceptible *S aureus* infections, ceftaroline should be considered preferred treatment over vancomycin for MRSA infection. Neither renal function nor drug levels need to be followed with ceftaroline therapy.

Penicillinase-Resistant Penicillins (dicloxacillin [capsules only]; nafcillin and oxacillin [parenteral only]). “Penicillinase” refers specifically to the beta-lactamase produced by *S aureus* in this case and not those produced by Gram-negative bacteria. These antibiotics are active against penicillin-resistant *S aureus* but not against MRSA. Nafcillin differs pharmacologically from the others in being excreted primarily by the liver rather than by the kidneys, which may explain the relative lack of nephrotoxicity compared with methicillin, which is no longer available in the United States. Nafcillin pharmacokinetics are erratic in persons with liver disease, and the drug is often painful with IV infusion.

Antipseudomonal and Anti-enteric Gram-negative BLs (piperacillin/tazobactam, aztreonam, ceftazidime, cefepime, meropenem, and imipenem). Piperacillin/tazobactam (Zosyn), ceftolozane/tazobactam (Zerbaxa), and ceftazidime/avibactam (Avycaz) represent BL/BLI combinations, as noted previously. The BLI (clavulanic acid, tazobactam, or avibactam in these combinations) binds irreversibly to and neutralizes specific beta-lactamase enzymes produced by the organism. The combination only adds to the spectrum of the original antibiotic when the mechanism of resistance is a beta-lactamase enzyme and only when the BLI is capable of binding to and inhibiting that particular organism's beta-lactamase enzyme(s). The combinations extend the spectrum of activity of the primary antibiotic to include many beta-lactamase-positive bacteria, including some strains of enteric Gram-negative bacilli (*E coli*, *Klebsiella*, and *Enterobacter*), *S aureus*, and *B fragilis*. Piperacillin/tazobactam, ceftolozane/tazobactam, and ceftazidime/avibactam may still be inactive against *Pseudomonas* because their BLIs may not effectively inhibit all the many relevant beta-lactamases of *Pseudomonas*.

Pseudomonas has an intrinsic capacity to develop resistance following exposure to any BL, based on the activity of several inducible chromosomal beta-lactamases, upregulated efflux pumps, and changes in the permeability of the cell wall, as well as mutational changes in the antibacterial target sites. Because development of resistance during therapy

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is not uncommon (particularly beta-lactamase-mediated resistance against piperacillin or ceftazidime), an aminoglycoside such as tobramycin is often used in combination, assuming that the tobramycin may kill strains developing resistance to the BLs. Cefepime, meropenem, and imipenem are relatively stable to the beta-lactamases induced while on therapy and can be used as single-agent therapy for most *Pseudomonas* infections, but resistance may still develop to these agents based on other mechanisms of resistance. For *Pseudomonas* infections in compromised hosts or in life-threatening infections, these drugs, too, should be used in combination with an aminoglycoside or a second active agent. The benefits of the additional antibiotic should be weighed against the potential for additional toxicity and alteration of host flora.

Aminopenicillins (amoxicillin and amoxicillin/clavulanate [oral formulations only, in the United States], ampicillin [oral and parenteral], and ampicillin/sulbactam [parenteral only]). Amoxicillin is very well absorbed, good tasting, and associated with very few side effects. Augmentin is a combination of amoxicillin and clavulanate (as noted previously) that is available in several fixed proportions that permit amoxicillin to remain active against many beta-lactamase-producing bacteria, including *H influenzae* and *S aureus* (but not MRSA). Amoxicillin/clavulanate has undergone many changes in formulation since its introduction. The ratio of amoxicillin to clavulanate was originally 4:1, based on susceptibility data of pneumococcus and *Haemophilus* during the 1970s. With the emergence of penicillin-resistant pneumococcus, recommendations for increasing the dosage of amoxicillin, particularly for upper respiratory tract infections, were made. However, if one increases the dosage of clavulanate even slightly, the incidence of diarrhea increases dramatically. If one keeps the dosage of clavulanate constant while increasing the dosage of amoxicillin, one can treat the relatively resistant pneumococci while not increasing gastrointestinal side effects of the combination. The original 4:1 ratio is present in suspensions containing 125-mg and 250-mg amoxicillin/5 mL and the 125-mg and 250-mg chewable tablets. A higher 7:1 ratio is present in the suspensions containing 200-mg and 400-mg amoxicillin/5 mL and in the 200-mg and 400-mg chewable tablets. A still higher ratio of 14:1 is present in the suspension formulation Augmentin ES-600 that contains 600-mg amoxicillin/5 mL; this preparation is designed to deliver 90 mg/kg/day of amoxicillin, divided twice daily, for the treatment of ear (and sinus) infections. The high serum and middle ear fluid concentrations achieved with 45 mg/kg/dose, combined with the long middle ear fluid half-life (4–6 hours) of amoxicillin, allow for a therapeutic antibiotic exposure to pathogens in the middle ear with a twice-daily regimen. However, the prolonged half-life in the middle ear fluid is not necessarily found in other infection sites (eg, skin, lung tissue, joint tissue), for which dosing of amoxicillin and Augmentin should continue to be 3 times daily for most susceptible pathogens.

For older children who can swallow tablets, the amoxicillin to clavulanate ratios are as follows: 500-mg tablet (4:1); 875-mg tablet (7:1); 1,000-mg tablet (16:1).

Sulbactam, another BLI like clavulanate, is combined with ampicillin in the parenteral formulation Unasyn. The cautions regarding spectrum of activity for piperacillin/tazobactam with respect to the limitations of the BLI in increasing the spectrum of

activity also apply to ampicillin/sulbactam, in which ampicillin does not even have the extended activity against the enteric bacilli seen with piperacillin or ceftazidime.

Carbapenems. Meropenem, imipenem, doripenem, and ertapenem are carbapenems with a broader spectrum of activity than any other class of BL currently available. Meropenem, imipenem, and ertapenem are approved by the FDA for use in children. At present, we recommend them for treatment of infections caused by bacteria resistant to standard therapy or for mixed infections involving aerobes and anaerobes. Imipenem has greater central nervous system (CNS) irritability compared with other carbapenems, leading to an increased risk of seizures in children with meningitis, but this is not clinically significant in children without underlying CNS inflammation. Meropenem was not associated with an increased rate of seizures, compared with cefotaxime in children with meningitis. Imipenem and meropenem are active against virtually all coliform bacilli, including cefotaxime-resistant (extended spectrum beta-lactamase-producing or ampC-producing) strains, against *Pseudomonas aeruginosa* (including most ceftazidime-resistant strains), and against anaerobes, including *B fragilis*. While ertapenem lacks the excellent activity against *P aeruginosa* of the other carbapenems, it has the advantage of a prolonged serum half-life, which allows for once-daily dosing in adults and children aged 13 years and older and twice-daily dosing in younger children. Newly emergent strains of *Klebsiella pneumoniae* contain *K pneumoniae* carbapenemases that degrade and inactivate all the carbapenems. These strains, as well as strains carrying the less common New Delhi metallo-beta-lactamase, which is also active against carbapenems, have begun to spread to many parts of the world, reinforcing the need to keep track of your local antibiotic susceptibility patterns. Carbapenems that have been paired with BLIs, as noted previously, may only inhibit one type of carbapenemase.

Macrolides

Erythromycin is the prototype of macrolide antibiotics. Almost 30 macrolides have been produced, but only 3 are FDA approved for children in the United States: erythromycin, azithromycin (also called an azalide), and clarithromycin, while a fourth, telithromycin (also called a ketolide), is approved for adults and only available in tablet form. As a class, these drugs achieve greater concentrations intracellularly than in serum, particularly with azithromycin and clarithromycin. As a result, measuring serum concentrations is usually not clinically useful. Gastrointestinal intolerance to erythromycin is caused by the breakdown products of the macrolide ring structure. This is much less of a problem with azithromycin and clarithromycin. Azithromycin, clarithromycin, and telithromycin extend the clinically relevant activity of erythromycin to include *Haemophilus*; azithromycin and clarithromycin also have substantial activity against certain mycobacteria. Azithromycin is also active in vitro and effective against many enteric Gram-negative pathogens, including *Salmonella* and *Shigella*.

Aminoglycosides

Although 5 aminoglycoside antibiotics are available in the United States, only 3 are widely used for systemic therapy of aerobic Gram-negative infections and for synergy

in the treatment of certain Gram-positive and Gram-negative infections: gentamicin, tobramycin, and amikacin. Streptomycin and kanamycin have more limited utility due to increased toxicity compared with the other agents. Resistance in Gram-negative bacilli to aminoglycosides is caused by bacterial enzymes that adenylate, acetylate, or phosphorylate the aminoglycoside, resulting in inactivity. The specific activities of each enzyme against each aminoglycoside in each pathogen are highly variable. As a result, antibiotic susceptibility tests must be done for each aminoglycoside drug separately. There are small differences in toxicities to the kidneys and eighth cranial nerve hearing/vestibular function, although it is uncertain whether these small differences are clinically significant. For all children receiving a full treatment course, it is advisable to monitor peak and trough serum concentrations early in the course of therapy, as the degree of drug exposure correlates with toxicity and elevated trough concentrations may predict impending drug accumulation. With amikacin, desired peak concentrations are 20 to 35 mcg/mL and trough drug concentrations are less than 10 mcg/mL; for gentamicin and tobramycin, depending on the frequency of dosing, peak concentrations should be 5 to 10 mcg/mL and trough concentrations less than 2 mcg/mL. Children with cystic fibrosis require greater dosages to achieve equivalent therapeutic serum concentrations due to enhanced clearance. Inhaled tobramycin has been very successful in children with cystic fibrosis as an adjunctive therapy of Gram-negative bacillary infections. The role of inhaled aminoglycosides in other Gram-negative pneumonias (eg, ventilator-associated pneumonia) has not yet been defined.

Once-Daily Dosing of Aminoglycosides. Once-daily dosing of 5 to 7.5 mg/kg gentamicin or tobramycin has been studied in adults and in some neonates and children; peak serum concentrations are greater than those achieved with dosing 3 times daily. Aminoglycosides demonstrate concentration-dependent killing of pathogens, suggesting a potential benefit to higher serum concentrations achieved with once-daily dosing. Regimens giving the daily dosage as a single infusion, rather than as traditionally split doses every 8 hours, are effective and safe for normal adult hosts and immune-compromised hosts with fever and neutropenia and may be less toxic. Experience with once-daily dosing in children is increasing, with similar encouraging results as noted for adults. A recent Cochrane review for children (and adults) with cystic fibrosis comparing once-daily with 3-times-daily administration found equal efficacy with decreased toxicity in children.² Once-daily dosing should be considered as effective as multiple, smaller doses per day and is likely to be safer for children; therefore, it should be the preferred regimen for treatment.

Fluoroquinolones

More than 40 years ago, fluoroquinolone (FQ) toxicity to cartilage in weight-bearing joints in experimental juvenile animals was documented to be dose and duration of therapy dependent. Pediatric studies were, therefore, not initially undertaken with ciprofloxacin or other FQs. However, with increasing antibiotic resistance in pediatric pathogens and an accumulating database in pediatrics suggesting that joint toxicity may be uncommon, the FDA allowed prospective studies to proceed in 1998. As of July 2018,

no cases of documented FQ-attributable joint toxicity have occurred in children with FQs that are approved for use in the United States. Limited published data are available from prospective, blinded studies to accurately assess this risk, although some uncontrolled retrospective published data are reassuring. A prospective, randomized, double-blind study of moxifloxacin for intra-abdominal infection, with 1-year follow-up specifically designed to assess tendon/joint toxicity, demonstrated no concern for toxicity.³ Unblinded studies with levofloxacin for respiratory tract infections and unpublished randomized studies comparing ciprofloxacin versus other agents for complicated urinary tract infection suggest the possibility of an uncommon, reversible, FQ-attributable arthralgia, but these data should be interpreted with caution. The use of FQs in situations of antibiotic resistance where no other active agent is available is reasonable, weighing the benefits of treatment against the low risk of toxicity of this class of antibiotics. The use of an oral FQ in situations in which the only alternative is parenteral therapy is also justified.⁴

Ciprofloxacin usually has very good Gram-negative activity (with great regional variation in susceptibility) against enteric bacilli (*E coli*, *Klebsiella*, *Enterobacter*, *Salmonella*, and *Shigella*) and against *P aeruginosa*. However, it lacks substantial Gram-positive coverage and should not be used to treat streptococcal, staphylococcal, or pneumococcal infections. Newer-generation FQs are more active against these pathogens; levofloxacin has documented efficacy and safety in pediatric clinical trials for respiratory tract infections, acute otitis media, and community-acquired pneumonia. Children with any question of joint/tendon/bone toxicity in the levofloxacin studies were followed up to 5 years after treatment, with no difference in outcomes in these randomized studies, compared with the standard FDA-approved antibiotics used in these studies.⁵ None of the newer-generation FQs are significantly more active against Gram-negative pathogens than ciprofloxacin. Quinolone antibiotics are bitter tasting. Ciprofloxacin and levofloxacin are currently available in a suspension form; ciprofloxacin is FDA approved in pediatrics for complicated urinary tract infections and inhalation anthrax, while levofloxacin is approved for inhalation anthrax only, as the sponsor chose not to apply for approval for pediatric respiratory tract infections. For reasons of safety and to prevent the emergence of widespread resistance, FQs should still not be used for primary therapy of pediatric infections and should be limited to situations in which safe and effective oral therapy with other classes of antibiotics does not exist.

2. Choosing Among Antifungal Agents: Polyenes, Azoles, and Echinocandins

Separating antifungal agents by class, much like navigating the myriad of antibacterial agents, allows one to best understand the underlying mechanisms of action and then appropriately choose which agent would be optimal for empirical therapy or a targeted approach. There are certain helpful generalizations that should be considered; for example, echinocandins are fungicidal against yeasts and fungistatic against molds, while azoles are the opposite. Coupled with these concepts is the need for continued surveillance for fungal epidemiology and resistance patterns. While some fungal species are inherently or very often resistant to specific agents or even classes, there are also an increasing number of fungal isolates that are developing resistance due to environmental pressure or chronic use in individual patients. Additionally, new (often resistant) fungal species emerge that deserve special attention, such as *Candida auris*, which can be multi-drug resistant. In 2019, there are 14 individual antifungal agents approved by the US Food and Drug Administration (FDA) for systemic use, and several more in development. This chapter will focus only on the most commonly used systemic agents and will not highlight the many anticipated new agents until they are approved for use in patients. For each agent, there are sometimes several formulations, each with unique pharmacokinetics that one must understand to optimize the agent, particularly in patients who are critically ill. Therefore, it is more important than ever to establish a firm foundation in understanding how these antifungal agents work to optimize pharmacokinetics and where they work best to target fungal pathogens most appropriately.

Polyenes

Amphotericin B (AmB) is a polyene antifungal antibiotic that has been available since 1958. A *Streptomyces* species, isolated from the soil in Venezuela, produced 2 antifungals whose names originated from the drug's amphoteric property of reacting as an acid as well as a base. Amphotericin A was not as active as AmB, so only AmB is used clinically. Nystatin is another polyene antifungal, but, due to systemic toxicity, it is only used in topical preparations. AmB remains the most broad-spectrum antifungal available for clinical use. This lipophilic drug binds to ergosterol, the major sterol in the fungal cell membrane, and creates transmembrane pores that compromise the integrity of the cell membrane and create a rapid fungicidal effect through osmotic lysis. Toxicity is likely due to the cross-reactivity with the human cholesterol bi-lipid membrane, which resembles ergosterol. The toxicity of the conventional formulation, AmB deoxycholate (AmB-D)—the parent molecule coupled with an ionic detergent for clinical use—can be substantial from the standpoints of systemic reactions (fever, rigors) and acute and chronic renal toxicity. Premedication with acetaminophen, diphenhydramine, and meperidine has historically been used to prevent systemic reactions during infusion. Renal dysfunction manifests primarily as decreased glomerular filtration with a rising serum creatinine concentration, but substantial tubular nephropathy is associated with potassium and magnesium wasting, requiring supplemental potassium for many neonates and children, regardless

of clinical symptoms associated with infusion. Fluid loading with saline pre- and post-AmB-D infusion seems to mitigate renal toxicity.

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Choosing Among Antifungal Agents: Polyenes, Azoles, and Echinocandins

Three lipid preparations approved in the mid-1990s decrease toxicity with no apparent decrease in clinical efficacy. Decisions on which lipid AmB preparation to use should, therefore, largely focus on side effects and costs. Two clinically useful lipid formulations exist: one in which ribbonlike lipid complexes of AmB are created (amphotericin B lipid complex [ABLC]), Abelcet, and one in which AmB is incorporated into true liposomes (liposomal amphotericin B [L-AmB]), AmBisome. The classic clinical dosage used of these preparations is 5 mg/kg/day, in contrast to the 1 mg/kg/day of AmB-D. In most studies, the side effects of L-AmB were somewhat less than those of ABLC, but both have significantly fewer side effects than AmB-D. The advantage of the lipid preparations is the ability to safely deliver a greater overall dose of the parent AmB drug. The cost of conventional AmB-D is substantially less than either lipid formulation. A colloidal dispersion of AmB in cholesteryl sulfate, Amphotec, which is no longer available in the United States, with decreased nephrotoxicity but infusion-related side effects, is closer to AmB-D than to the lipid formulations and precludes recommendation for its use. The decreased nephrotoxicity of the 3 lipid preparations is thought to be due to the preferential binding of its AmB to high-density lipoproteins, compared with AmB-D binding to low-density lipoproteins. Despite *in vitro* concentration-dependent killing, a clinical trial comparing L-AmB at doses of 3 mg/kg/day versus 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity.¹ Recent pharmacokinetic analyses of L-AmB found that while children receiving L-AmB at lower doses exhibit linear pharmacokinetics, a significant proportion of children receiving L-AmB at daily doses greater than 5 mg/kg/day exhibit nonlinear pharmacokinetics with significantly higher peak concentrations and some toxicity.^{2,3} Therefore, it is generally not recommended to use any lipid AmB preparations at very high dosages (>5 mg/kg/day), as it will likely only incur greater toxicity with no real therapeutic advantage. There are reports of using higher dosing in very difficult infections where a lipid AmB formulation is the first-line therapy (eg, mucormycosis), and while experts remain divided on this practice, it is clear that at least 5 mg/kg/day of a lipid AmB formulation should be used. AmB has a long terminal half-life and, coupled with the concentration-dependent killing, the agent is best used as single daily doses. These pharmacokinetics explain the use in some studies of once-weekly, or even once every 2 weeks,⁴ AmB for antifungal prophylaxis or preemptive therapy, albeit with mixed clinical results. If the overall AmB exposure needs to be decreased due to toxicity, it is best to increase the dosing interval (eg, 3 times weekly) but retain the full mg/kg dose for optimal pharmacokinetics.

AmB-D has been used for nonsystemic purposes, such as in bladder washes, intraventricular instillation, intrapleural instillation, and other modalities, but there are no firm data supporting those clinical indications, and it is likely that the local toxicities outweigh the theoretic benefits. One exception is aerosolized AmB for antifungal prophylaxis (not treatment) in lung transplant recipients due to the different pathophysiology of invasive aspergillosis (often originating at the bronchial anastomotic site, more so than

parenchymal disease) in that specific patient population. Due to the lipid chemistry, the L-AmB does not interact well with renal tubules and L-AmB is recovered from the urine at lower levels than AmB-D, so there is a theoretic concern with using a lipid formulation, as opposed to AmB-D, when treating isolated urinary fungal disease. This theoretic concern is likely outweighed by the real concern of toxicity with AmB-D. Most experts believe AmB-D should be reserved for use in resource-limited settings in which no alternative agents (eg, lipid formulations) are available. An exception is in neonates, where limited retrospective data suggest that the AmB-D formulation had better efficacy for invasive candidiasis.⁵ Importantly, there are several pathogens that are inherently or functionally resistant to AmB, including *Candida lusitanae*, *Trichosporon* spp, *Aspergillus terreus*, *Fusarium* spp, and *Pseudallescheria boydii* (*Scedosporium apiospermum*) or *Scedosporium prolificans*.

Azoles

This class of systemic agents was first approved in 1981 and is divided into imidazoles (ketoconazole), triazoles (fluconazole, itraconazole), and second-generation triazoles (voriconazole, posaconazole, and isavuconazole) based on the number of nitrogen atoms in the azole ring. All the azoles work by inhibition of ergosterol synthesis (fungal cytochrome P450 [CYP] sterol 14-demethylation) that is required for fungal cell membrane integrity. While the polyenes are rapidly fungicidal, the azoles are fungistatic against yeasts and fungicidal against molds. However, it is important to note that ketoconazole and fluconazole have no mold activity. The only systemic imidazole is ketoconazole, which is primarily active against *Candida* spp and is available in an oral formulation. Three azoles (itraconazole, voriconazole, posaconazole) need therapeutic drug monitoring with trough levels within the first 4 to 7 days (when patient is at pharmacokinetic steady state); it is unclear at present if isavuconazole will require drug-level monitoring. It is less clear if therapeutic drug monitoring is required during primary azole prophylaxis, although low levels have been associated with a higher probability of breakthrough infection.

Fluconazole is active against a broader range of fungi than ketoconazole and includes clinically relevant activity against *Cryptococcus*, *Coccidioides*, and *Histoplasma*. The pediatric treatment dose is 12 mg/kg/day, which targets exposures that are observed in critically ill adults who receive 800 mg of fluconazole per day. Like most other azoles, fluconazole requires a loading dose on the first day, and this approach is routinely used in adult patients. A loading dose of 25 mg/kg on the first day has been nicely studied in infants⁶ and is likely also beneficial, but has not been definitively studied yet, in all children. The exception is children on extracorporeal membrane oxygenation, for whom, because of the higher volume of distribution, a higher loading dose (35 mg/kg) is required to achieve comparable exposure.⁷ Fluconazole achieves relatively high concentrations in urine and cerebrospinal fluid (CSF) compared with AmB due to its low lipophilicity, with urinary concentrations often so high that treatment against even “resistant” pathogens that are isolated only in the urine is possible. Fluconazole remains one of the most active and, so far, one of the safest systemic antifungal agents for the treatment of most *Candida*

infections. *Candida albicans* remains generally sensitive to fluconazole, although resistance is increasingly present in many non-*albicans* *Candida* spp as well as in *C. albicans* in children repeatedly exposed to fluconazole. For instance, *Candida krusei* is considered inherently resistant to fluconazole, *Candida glabrata* demonstrates dose-dependent resistance to fluconazole (and usually voriconazole), *Candida tropicalis* is developing more resistant strains, and the newly identified *Candida auris* is generally fluconazole resistant. Fluconazole is available in parenteral and oral (with >90% bioavailability) formulations and toxicity is unusual and primarily hepatic.

Itraconazole is active against an even broader range of fungi and, unlike fluconazole, includes molds such as *Aspergillus*. It is currently available as a capsule or oral solution (the intravenous [IV] form was discontinued); the oral solution provides approximately 30% higher and more consistent serum concentrations than capsules and should be used preferentially. Absorption using itraconazole oral solution is improved on an empty stomach and not influenced by gastric pH (unlike the capsule form, which is best administered under fed conditions or with a more acidic cola beverage to increase absorption), and monitoring itraconazole serum concentrations, like most azole antifungals, is a key principal in management (generally, itraconazole serum trough levels should be 1–2 mcg/mL; trough levels >5 mcg/mL may be associated with increased toxicity). Concentrations should be checked after 5 days of therapy to ensure adequate drug exposure. When measured by high-pressure liquid chromatography, itraconazole and its bioactive hydroxy-itraconazole metabolite are reported, the sum of which should be considered in assessing drug levels. In adult patients, itraconazole is recommended to be loaded at 200 mg twice daily for 2 days, followed by 200 mg daily starting on the third day. Loading dose studies have not been performed in children. Dosing itraconazole in children requires twice-daily dosing throughout treatment, compared with once-daily maintenance dosing in adults, and the key to treatment success is following drug levels. Limited pharmacokinetic data are available in children; itraconazole has not been approved by the FDA for pediatric indications. Itraconazole is indicated in adults for therapy of mild/moderate disease with blastomycosis, histoplasmosis, and others. Although it possesses antifungal activity, itraconazole is not indicated as primary therapy against invasive aspergillosis, as voriconazole is a far superior option. Itraconazole is not active against *Zygomycetes* (eg, mucormycosis). Toxicity in adults is primarily hepatic.

Voriconazole was approved in 2002 and is only FDA approved for children 12 years and older, although there are now substantial pharmacokinetic data and experience for children aged 2 to 12 years.⁸ Voriconazole is a fluconazole derivative, so think of it as having the greater tissue and CSF penetration of fluconazole but the added antifungal spectrum to include molds. While the bioavailability of voriconazole in adults is approximately 96%, multiple studies have shown that it is only approximately 50% to 60% in children, requiring clinicians to carefully monitor voriconazole trough concentrations in patients taking the oral formulation, further complicated by great inter-patient variability in clearance. Voriconazole serum concentrations are tricky to interpret, but monitoring concentrations is essential to using this drug, like all azole antifungals, and especially important in

circumstances of suspected treatment failure or possible toxicity. Most experts suggest voriconazole trough concentrations of 2 mcg/mL (at a minimum, 1 mcg/mL) or greater, which would generally exceed the pathogen's minimum inhibitory concentration, but, generally, toxicity will not be seen until concentrations of approximately 6 mcg/mL or greater. Trough levels should be monitored 2 to 5 days after initiation of therapy and repeated the following week to confirm the patient remains in the therapeutic range or repeated 4 days after change of dose. One important point is the acquisition of an accurate trough concentration, one obtained just before the next dose is due and not obtained through a catheter infusing the drug. These simple trough parameters will make interpretation possible. The fundamental voriconazole pharmacokinetics are different in adults versus children; in adults, voriconazole is metabolized in a nonlinear fashion, whereas in children, the drug is metabolized in a linear fashion. This explains the increased pediatric starting dosing for voriconazole at 9 mg/kg/dose versus loading with 6 mg/kg/dose in adult patients. Younger children, especially those younger than 3 years, require even higher dosages of voriconazole and also have a larger therapeutic window for dosing. However, many studies have shown an inconsistent relationship, on a population level, between dosing and levels, highlighting the need for close monitoring after the initial dosing scheme and then dose adjustment as needed in the individual patient. For children younger than 2 years, some have proposed 3-times-daily dosing to achieve sufficient serum levels.⁹ Given the poor clinical and microbiological response of *Aspergillus* infections to AmB, voriconazole is now the treatment of choice for invasive aspergillosis and many other invasive mold infections (eg, pseudallescheriasis, fusariosis). Importantly, infections with *Zygomycetes* (eg, mucormycosis) are resistant to voriconazole. Voriconazole retains activity against most *Candida* spp, including some that are fluconazole resistant, but it is unlikely to replace fluconazole for treatment of fluconazole-susceptible *Candida* infections. Importantly, there are increasing reports of *C glabrata* resistance to voriconazole. Voriconazole produces some unique transient visual field abnormalities in about 10% of adults and children. There are an increasing number of reports, seen in as high as 20% of patients, of a photosensitive sunburn-like erythema that is not aided by sunscreen (only sun avoidance). In some rare long-term (mean of 3 years of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity. The rash is the most common indication for switching from voriconazole to posaconazole/isavuconazole if a triazole antifungal is required. Hepatotoxicity is uncommon, occurring only in 2% to 5% of patients. Voriconazole is CYP metabolized (CYP2C19), and allelic polymorphisms in the population could lead to personalized dosing.¹⁰ Results have shown that some Asian patients will achieve higher toxic serum concentrations than other patients. Voriconazole also interacts with many similarly P450 metabolized drugs to produce some profound changes in serum concentrations of many concurrently administered drugs.

Posaconazole, an itraconazole derivative, was FDA approved in 2006 as an oral suspension for adolescents 13 years and older. An extended-release tablet formulation was approved in November 2013, also for adolescents 13 years and older, and an IV

formulation was approved in March 2014 for patients 18 years and older. Effective absorption of the oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The tablet formulation has significantly better absorption due to its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient can take the (relatively large) tablets, the extended-release tablet is the preferred form due to the ability to easily obtain higher and more consistent drug levels. Due to the low pH (<5) of IV posaconazole, a central venous catheter is required for administration. The IV formulation contains only slightly lower amounts of the cyclodextrin vehicle than voriconazole, so similar theoretic renal accumulation concerns exist. The exact pediatric dosing for posaconazole has not been completely determined and requires consultation with a pediatric infectious diseases expert. The pediatric oral suspension dose recommended by some experts for treating invasive disease is at least 18 mg/kg/day divided 3 times daily, but the true answer is likely higher and serum trough level monitoring is recommended. A study with a new pediatric formulation for suspension, essentially the tablet form that is able to be suspended, has recently been completed, and results are pending. Importantly, the current tablet cannot be broken for use due to its chemical coating. Pediatric dosing with the current IV or extended-release tablet dosing is completely unknown, but adolescents can likely follow the adult dosing schemes. In adult patients, IV posaconazole is loaded at 300 mg twice daily on the first day, and then 300 mg once daily starting on the second day. Similarly, in adult patients, the extended-release tablet is dosed as 300 mg twice daily on the first day, and then 300 mg once daily starting on the second day. In adult patients, the maximum amount of posaconazole oral suspension given is 800 mg per day due to its excretion, and that has been given as 400 mg twice daily or 200 mg 4 times a day in severely ill patients due to saturable absorption and findings of a marginal increase in exposure with more frequent dosing. Greater than 800 mg per day is not indicated in any patient. Like voriconazole and itraconazole, trough levels should be monitored, and most experts feel that posaconazole levels for treatment should be greater than or equal to 1 mcg/mL (and greater than 0.7 mcg/mL for prophylaxis). Monitor posaconazole trough levels 5 days after initiation of therapy. The in vitro activity of posaconazole against *Candida* spp is better than that of fluconazole and similar to voriconazole. Overall in vitro antifungal activity against *Aspergillus* is also equivalent to voriconazole, but, notably, it is the first triazole with substantial activity against some *Zygomycetes*, including *Rhizopus* spp and *Mucor* spp, as well as activity against *Coccidioides*, *Histoplasma*, and *Blastomyces* and the pathogens of phaeohyphomycosis. Posaconazole treatment of invasive aspergillosis in patients with chronic granulomatous disease appears to be superior to voriconazole in this specific patient population for an unknown reason. Posaconazole is eliminated by hepatic glucuronidation but does demonstrate inhibition of the CYP3A4 enzyme system, leading to many drug interactions with other P450 metabolized drugs. It is currently approved for prophylaxis of *Candida* and *Aspergillus* infections in high-risk adults and for treatment of *Candida* oropharyngeal disease or esophagitis in adults. Posaconazole, like itraconazole, has generally poor CSF penetration.

Isavuconazole is a new triazole that was FDA approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis with oral (capsules only) and IV formulations. Isavuconazole has a similar antifungal spectrum as voriconazole and some activity against *Zygomycetes* (yet, potentially, not as potent against *Zygomycetes* as posaconazole). A phase 3 clinical trial in adult patients demonstrated non-inferiority versus voriconazole against invasive aspergillosis and other mold infections,¹¹ and an open-label study showed activity against mucormycosis.¹² Isavuconazole is actually dispensed as the prodrug isavuconazonium sulfate. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to 372-mg isavuconazonium sulfate) every 8 hours for 2 days (6 doses), followed by 200 mg once daily for maintenance dosing. The half-life is long (>5 days), there is 98% bioavailability in adults, and there is no reported food effect with oral isavuconazole. The manufacturer suggests no need for therapeutic drug monitoring, but some experts suggest trough levels may be needed in difficult-to-treat infections and, absent well-defined therapeutic targets, the mean concentrations from phase II/III studies suggest a range of 2 to 3 mcg/mL after day 5 is adequate exposure. The IV formulation does not contain the vehicle cyclodextrin, unlike voriconazole, which could make it more attractive in patients with renal failure. Early experience suggests a much lower rate of photosensitivity and skin disorders as well as visual disturbances compared with voriconazole. No specific pediatric dosing data exist for isavuconazole yet, but studies have already begun.

Echinocandins

This class of systemic antifungal agents was first approved in 2001. The echinocandins inhibit cell wall formation (in contrast to acting on the cell membrane by the polyenes and azoles) by noncompetitively inhibiting beta-1,3-glucan synthase, an enzyme present in fungi but absent in mammalian cells. These agents are generally very safe, as there is no beta-1,3-glucan in humans. The echinocandins are not metabolized through the CYP system, so fewer drug interactions are problematic, compared with the azoles. There is no need to dose-adjust in renal failure, but one needs a lower dosage in the setting of very severe hepatic dysfunction. As a class, these antifungals generally have poor CSF penetration, although animal studies have shown adequate brain parenchyma levels, and do not penetrate the urine well. While the 3 clinically available echinocandins each individually have some unique and important dosing and pharmacokinetic parameters, especially in children, efficacy is generally equivalent. Opposite the azole class, the echinocandins are fungicidal against yeasts but fungistatic against molds. The fungicidal activity against yeasts has elevated the echinocandins to the preferred therapy against invasive candidiasis. Echinocandins are thought to be best utilized against invasive aspergillosis only as salvage therapy if a triazole fails or in a patient with suspected triazole resistance, but never as primary monotherapy against invasive aspergillosis or any other invasive mold infection. Improved efficacy with combination therapy with the echinocandins and triazoles against *Aspergillus* infections is unclear, with disparate results in multiple smaller studies and a definitive clinical trial demonstrating minimal benefit over voriconazole monotherapy in only certain patient populations. Some experts have used combination

therapy in invasive aspergillosis with a triazole plus echinocandin only during the initial phase of waiting for triazole drug levels to be appropriately high. There are reports of echinocandin resistance in *Candida* spp, as high as 12% in *C. glabrata* in some studies, and the echinocandins as a class have previously been shown to be somewhat less active against *Candida parapsilosis* isolates (approximately 10%–15% respond poorly, but most are still susceptible, and guidelines still recommend echinocandin empiric therapy for invasive candidiasis).

Caspofungin received FDA approval for children aged 3 months to 17 years in 2008 for empiric therapy of presumed fungal infections in febrile, neutropenic children; treatment of candidemia as well as *Candida* esophagitis, peritonitis, and empyema; and salvage therapy of invasive aspergillosis. Due to its earlier approval, there are generally more reports with caspofungin than the other echinocandins. Caspofungin dosing in children is calculated according to body surface area, with a loading dose on the first day of 70 mg/m², followed by daily maintenance dosing of 50 mg/m², and not to exceed 70 mg regardless of the calculated dose. Significantly higher doses of caspofungin have been studied in adult patients without any clear added benefit in efficacy, but if the 50 mg/m² dose is tolerated and does not provide adequate clinical response, the daily dose can be increased to 70 mg/m². Dosing for caspofungin in neonates is 25 mg/m²/day.

Micafungin was approved in adults in 2005 for treatment of candidemia, *Candida* esophagitis and peritonitis, and prophylaxis of *Candida* infections in stem cell transplant recipients, and in 2013 for pediatric patients aged 4 months and older. Micafungin has the most pediatric and neonatal data available of all 3 echinocandins, including more extensive pharmacokinetic studies surrounding dosing and several efficacy studies.^{13–15} Micafungin dosing in children is age dependent, as clearance increases dramatically in the younger age groups (especially neonates), necessitating higher doses for younger children. Doses in children are generally thought to be 2 mg/kg/day, with higher doses likely needed for younger patients, and preterm neonates dosed at 10 mg/kg/day. Adult micafungin dosing (100 or 150 mg once daily) is to be used in patients who weigh more than 40 kg. Unlike the other echinocandins, a loading dose is not required for micafungin.

Anidulafungin was approved for adults for candidemia and *Candida* esophagitis in 2006 and is not officially approved for pediatric patients. Like the other echinocandins, anidulafungin is not P450 metabolized and has not demonstrated significant drug interactions. Limited clinical efficacy data are available in children, with only some pediatric pharmacokinetic data suggesting weight-based dosing (3 mg/kg/day loading dose, followed by 1.5 mg/kg/day maintenance dosing).¹⁶ This dosing achieves similar exposure levels in neonates and infants.¹⁶ The adult dose for invasive candidiasis is a loading dose of 200 mg on the first day, followed by 100 mg daily.

3. How Antibiotic Dosages Are Determined Using Susceptibility Data, Pharmacodynamics, and Treatment Outcomes

Factors Involved in Dosing Recommendations

Our view of the optimal use of antimicrobials is continually changing. As the published literature and our experience with each drug increases, our recommendations for specific dosages evolve as we compare the efficacy, safety, and cost of each drug in the context of current and previous data from adults and children. Every new antibiotic that treats infections that occur in both adults and children must demonstrate some degree of efficacy and safety in adults with antibiotic exposures that occur at specific dosages, which we duplicate in children as closely as possible. Occasionally, due to unanticipated toxicities and unanticipated clinical failures at a specific dosage in children that should have been effective, we will modify our initial recommendations for an antibiotic.

Important considerations in any recommendations we make include (1) the susceptibilities of pathogens to antibiotics, which are constantly changing, are different from region to region, and are often hospital- and unit-specific; (2) the antibiotic concentrations achieved at the site of infection over a 24-hour dosing interval; (3) the mechanism of how antibiotics kill bacteria; (4) how often the dose we select produces a clinical and microbiological cure; (5) how often we encounter toxicity; (6) how likely the antibiotic exposure will lead to antibiotic resistance in the treated child and in the population in general; and (7) the effect on the child's microbiome.

Susceptibility

Susceptibility data for each bacterial pathogen against a wide range of antibiotics are available from the microbiology laboratory of virtually every hospital. This antibiogram can help guide you in antibiotic selection for empiric therapy while you wait for specific susceptibilities to come back from your cultures. Many hospitals can separate the inpatient culture results from outpatient results, and many can give you the data by hospital ward (eg, pediatric ward vs neonatal intensive care unit vs adult intensive care unit). Susceptibility data are also available by region and by country from reference laboratories or public health laboratories. The recommendations made in *Nelson's Pediatric Antimicrobial Therapy* reflect overall susceptibility patterns present in the United States. Tables A and B in Chapter 7 provide some overall guidance on susceptibility of Gram-positive and Gram-negative pathogens, respectively. Wide variations may exist for certain pathogens in different regions of the United States and the world. New techniques for rapid molecular diagnosis of a bacterial, mycobacterial, fungal, or viral pathogen based on polymerase chain reaction or next-generation sequencing may quickly give you the name of the pathogen, but with current molecular technology, susceptibility data are usually not available.

Drug Concentrations at the Site of Infection

With every antibiotic, we can measure the concentration of antibiotic present in the serum. We can also directly measure the concentrations in specific tissue sites, such as spinal fluid or middle ear fluid. Because “free,” nonprotein-bound antibiotic is required to

inhibit and kill pathogens, it is also important to calculate the amount of free drug available at the site of infection. While traditional methods of measuring antibiotics focused on the peak concentrations in serum and how rapidly the drugs were excreted, complex models of drug distribution in plasma and tissue sites (eg, cerebrospinal fluid, urine, peritoneal fluid) and elimination from plasma and tissue compartments now exist. Antibiotic exposure to pathogens at the site of infection can be described mathematically in many ways: (1) the percentage of time in a 24-hour dosing interval that the antibiotic concentrations are above the minimum inhibitory concentration (MIC; the antibiotic concentration required for inhibition of growth of an organism) at the site of infection ($\%T > MIC$); (2) the mathematically calculated area below the serum concentration-versus-time curve (area under the curve [AUC]); and (3) the maximal concentration of drug achieved at the tissue site (C_{max}). For each of these 3 values, a ratio of that value to the MIC of the pathogen in question can be calculated and provides more useful information on specific drug activity against a specific pathogen than simply looking at the MIC. It allows us to compare the exposure of different antibiotics (that achieve quite different concentrations in tissues) to a pathogen (where the MIC for each drug may be different) and to assess the activity of a single antibiotic that may be used for empiric therapy against the many different pathogens (potentially with many different MICs) that may be causing an infection at that tissue site.

Pharmacodynamics

Pharmacodynamic descriptions provide the clinician with information on *how* the bacterial pathogens are killed (see Suggested Reading). Beta-lactam antibiotics tend to eradicate bacteria following prolonged exposure of relatively low concentrations of the antibiotic to the pathogen at the site of infection, usually expressed as the percent of time over a dosing interval that the antibiotic is present at the site of infection in concentrations greater than the MIC ($\%T > MIC$). For example, amoxicillin needs to be present at the site of pneumococcal infection (eg, middle ear) at a concentration above the MIC for only 40% of a 24-hour dosing interval. Remarkably, neither higher concentrations of amoxicillin nor a more prolonged exposure will substantially increase the cure rate. On the other hand, gentamicin's activity against *Escherichia coli* is based primarily on the absolute concentration of free antibiotic at the site of infection, in the context of the MIC of the pathogen ($C_{max}:MIC$). The more antibiotic you can deliver to the site of infection, the more rapidly you can sterilize the tissue; we are only limited by the toxicities of gentamicin. For fluoroquinolones like ciprofloxacin, the antibiotic exposure best linked to clinical and microbiologic success is, like aminoglycosides, concentration-dependent. However, the best mathematical correlate to microbiologic (and clinical) outcomes for fluoroquinolones is the AUC:MIC, rather than $C_{max}:MIC$. All 3 metrics of antibiotic exposure should be linked to the MIC of the pathogen to best understand how well the antibiotic will eradicate the pathogen causing the infection.

Assessment of Clinical and Microbiological Outcomes

In clinical trials of anti-infective agents, most adults and children will hopefully be cured, but a few will fail therapy. For those few, we may note unanticipated inadequate drug exposure (eg, more rapid drug elimination in a particular patient; the inability of a particular antibiotic to penetrate to the site of infection in its active form, not bound to salts or proteins) or infection caused by a pathogen with a particularly high MIC. By analyzing the successes and the failures based on the appropriate exposure parameters outlined previously (%T>MIC, AUC:MIC, or Cmax:MIC), we can often observe a particular value of exposure, above which we observe a higher rate of cure and below which the cure rate drops quickly. Knowing this target value in adults (the “antibiotic exposure break point”) allows us to calculate the dosage that will create treatment success in most children. We do not evaluate antibiotics with study designs that have failure rates in children sufficient to calculate a pediatric exposure break point. It is the adult *exposure value* that leads to success that we all (including the US Food and Drug Administration [FDA] and pharmaceutical companies) subsequently share with you, a pediatric health care practitioner, as one likely to cure your patient. US FDA-approved break points that are reported by microbiology laboratories (S, I, and R) are now determined by outcomes linked to drug pharmacokinetics and exposure, the MIC, and the pharmacodynamic parameter for that agent. Recommendations to the FDA for break points for the United States often come from “break point organizations,” such as the US Committee on Antimicrobial Susceptibility Testing (www.uscast.org) or the Clinical and Laboratory Standards Institute Subcommittee on Antimicrobial Susceptibility Testing (<https://clsi.org/education/microbiology/ast>).

Suggested Reading

Bradley JS, et al. *Pediatr Infect Dis J*. 2010;29(11):1043–1046 PMID: 20975453

Drusano GL. *Clin Infect Dis*. 2007;45(Suppl 1):S89–S95 PMID: 17582578

Onufrak NJ, et al. *Clin Ther*. 2016;38(9):1930–1947 PMID: 27449411

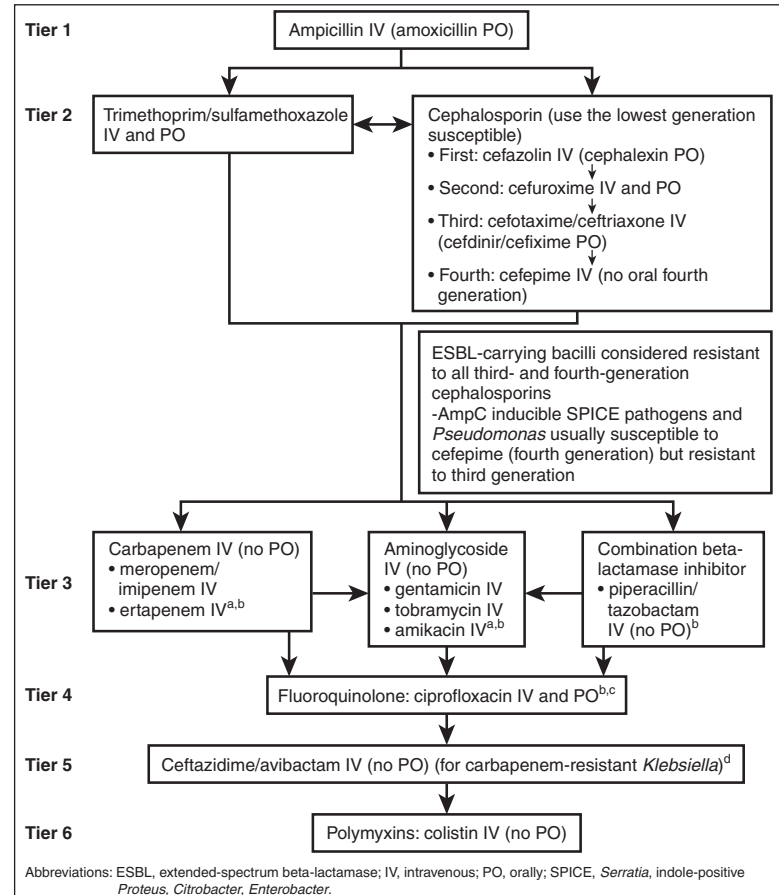
4. Approach to Antibiotic Therapy of Drug-Resistant Gram-negative Bacilli and Methicillin-Resistant *Staphylococcus aureus*

Multidrug-Resistant Gram-negative Bacilli

Increasing antibiotic resistance in Gram-negative bacilli, primarily the enteric bacilli, *Pseudomonas aeruginosa* and *Acinetobacter* spp, has caused profound difficulties in management of patients around the world; some of the pathogens are now resistant to all available agents. At this time, a limited number of pediatric tertiary care centers in North America have reported isolated outbreaks, but sustained transmission of completely resistant organisms has not yet been reported in children, likely due to the critical infection control strategies in place to prevent spread within pediatric health care institutions. However, for complicated hospitalized neonates, infants, and children, multiple treatment courses of antibiotics for documented or suspected infections can create substantial resistance to many classes of agents, particularly in *P aeruginosa*. These pathogens have the genetic capability to express resistance to virtually any antibiotic used, as a result of more than one hundred million years of exposure to antibiotics elaborated by other organisms in their environment. Inducible enzymes to cleave antibiotics and modify binding sites, efflux pumps, and Gram-negative cell wall alterations to prevent antibiotic penetration (and combinations of mechanisms) all may be present. Some mechanisms of resistance, if not intrinsic, can be acquired from other bacilli. By using antibiotics, we “awaken” resistance; therefore, only using antibiotics when appropriate limits the selection, or induction, of resistance for both that child and for all children. Community prevalence, as well as health care institution prevalence of resistant organisms, such as extended-spectrum beta-lactamase (ESBL)-containing *Escherichia coli*, is increasing.

In Figure 4-1, we assume that the clinician has the antibiotic susceptibility report in hand (or at least a local antibiogram). Each tier provides increasingly broader spectrum activity, from the narrowest of the Gram-negative agents to the broadest (and most toxic), colistin. Tier 1 is ampicillin, safe and widely available but not active against *Klebsiella*, *Enterobacter*, or *Pseudomonas* and only active against about half of *E coli* in the community setting. Tier 2 contains antibiotics that have a broader spectrum but are also very safe and effective (trimethoprim/sulfamethoxazole [TMP/SMX] and cephalosporins), with decades of experience. In general, use an antibiotic from tier 2 before going to broader spectrum agents. Please be aware that many enteric bacilli (the SPICE bacteria, *Enterobacter*, *Citrobacter*, *Serratia*, and indole-positive *Proteus*) have inducible beta-lactam resistance (active against third-generation cephalosporins cefotaxime, ceftriaxone, and ceftazidime, as well as the fifth-generation cephalosporin ceftaroline), which may manifest only after exposure of the pathogen to the antibiotic. Tier 3 is made up of very broad-spectrum antibiotics (carbapenems, piperacillin/tazobactam) and aminoglycosides (with significantly more toxicity than beta-lactam antibacterial agents, although we have used them safely for decades). Use any antibiotic from tier 3 before going to broader spectrum agents. Tier 4 is fluoroquinolones, to be used only when lower-tier antibiotics cannot be used due to potential (and not yet verified in children) toxicities. Tier 5 is represented by a new

Figure 4-1. Enteric Bacilli: Bacilli and *Pseudomonas* With Known Susceptibilities
(See Text for Interpretation)



^a Ertapenem is the only carbapenem *not* active against *Pseudomonas*. Ertapenem and amikacin can be given once daily as outpatient IV/intramuscular (IM) therapy for infections where these drugs achieve therapeutic concentrations (eg, urinary tract). Some use once-daily gentamicin or tobramycin.

^b For mild to moderate ESBL infections caused by organisms susceptible only to IV/IM beta-lactam or aminoglycoside therapy but also susceptible to fluoroquinolones, oral fluoroquinolone therapy is preferred over IV/IM therapy for infections amenable to treatment by oral therapy.

^c If you have susceptibility to only a few remaining agents, consider combination therapy to prevent the emergence of resistance to your last-resort antibiotics (no prospective, controlled data in these situations).

^d Active against carbapenem-resistant *Klebsiella pneumoniae* strains; US Food and Drug Administration approved for adults; pharmacokinetic data published for children.

set of beta-lactam/beta-lactamase inhibitor combinations, represented by ceftazidime/avibactam, which is active against certain carbapenem-resistant *Klebsiella* spp and *E coli*; it is approved for adults, with phase 3 clinical trials now completed in children. Tier 6 is colistin, one of the broadest-spectrum agents available. Colistin was US Food and Drug Administration (FDA) approved in 1962 with significant toxicity and limited clinical experience in children. Many newer drugs for multidrug-resistant Gram-negative organisms are currently investigational for adults and children.

Investigational Agents Recently Approved for Adults That Are Being Studied in Children

Ceftazidime and avibactam. Familiar ceftazidime, a third-generation cephalosporin active against many strains of *Pseudomonas*, is paired with avibactam allowing for activity against ESBL-producing enteric bacilli, and against the *Klebsiella pneumoniae* serine carbapenemase (KPC) but not metallo-carbapenemases.

Ceftolozane and tazobactam. Ceftolozane represents a more active cephalosporin agent against *Pseudomonas aeruginosa*, paired with tazobactam allowing for activity against ESBL-producing enteric bacilli.

Meropenem and vaborbactam. Meropenem, a familiar broad-spectrum aerobic/anaerobic coverage carbapenem that is already stable to ESBL beta-lactamases, is now paired with vaborbactam allowing for activity against the KPC but not metallo-carbapenemases.

Plazomicin. A new aminoglycoside antibiotic that is active against many of the gentamicin-, tobramycin-, and amikacin-resistant enteric bacilli and *Pseudomonas*.

Community-Associated Methicillin-Resistant *Staphylococcus aureus*

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a community pathogen for children (that can also spread from child to child in hospitals) that first appeared in the United States in the mid-1990s and currently represents 30% to 80% of all community isolates in various regions of the United States (check your hospital microbiology laboratory for your local rate); it is increasingly present in many areas of the world, with some strain variation documented. Notably, we have begun to see a decrease in invasive MRSA infections in some institutions, as documented in Houston, TX, by Hultén and Mason.¹ CA-MRSA is resistant to beta-lactam antibiotics, except for ceftaroline, a fifth-generation cephalosporin antibiotic FDA approved for pediatrics in June 2016 (see Chapter 1).

There are an undetermined number of pathogenicity factors that make CA-MRSA more aggressive than methicillin-susceptible *S aureus* (MSSA) strains. CA-MRSA seems to cause greater tissue necrosis, an increased host inflammatory response, an increased rate of complications, and an increased rate of recurrent infections compared with MSSA. Response to therapy with non-beta-lactam antibiotics (eg, vancomycin, clindamycin) seems to be inferior compared with the response of MSSA to oxacillin/nafticillin or cefazolin, but it is unknown whether poorer outcomes are due to a hardier, better-adapted, more

aggressive CA-MRSA or whether these alternative agents are just not as effective against MRSA as beta-lactam agents are against MSSA. Studies in children using ceftaroline to treat skin infections (many caused by MRSA) were conducted using a non-inferiority clinical trial design, compared with vancomycin, with the finding that ceftaroline was equivalent to vancomycin. Guidelines for management of MRSA infections (2011) and management of skin and soft tissue infections (2014) have been published by the Infectious Diseases Society of America² and are available at www.idsociety.org, as well as in *Red Book: 2018–2021 Report of the Committee on Infectious Diseases*.

Antimicrobials for CA-MRSA

Vancomycin (intravenous [IV]) has been the mainstay of parenteral therapy of MRSA infections for the past 4 decades and continues to have activity against more than 98% of strains isolated from children. A few cases of intermediate resistance and “hetero-resistance” (transient moderately increased resistance likely to be based on thickened staphylococcal cell walls) have been reported, most commonly in adults who are receiving long-term therapy or who have received multiple exposures to vancomycin. Unfortunately, the response to therapy using standard vancomycin dosing of 40 mg/kg/day in the treatment of many CA-MRSA strains has not been as predictably successful as in the past with MSSA. Increasingly, data in adults suggest that serum trough concentrations of vancomycin in treating serious CA-MRSA infections should be kept in the range of 15 to 20 mcg/mL, which frequently causes toxicity in adults. For children, serum trough concentrations of 15 to 20 mcg/mL can usually be achieved using the old pediatric “meningitis dosage” of vancomycin of 60 mg/kg/day but are also associated with renal toxicity. Although no prospectively collected data are available, it appears that this dosage in children is reasonably effective and not associated with the degree of nephrotoxicity observed in adults. For vancomycin efficacy, the ratio of the area under the serum concentration curve to minimum inhibitory concentration (AUC:MIC) appears to be the best exposure metric to predict a successful outcome, with better outcomes achieved with an AUC:MIC of about 400 or greater (see Chapter 3 for more on the AUC:MIC). This ratio is achievable for CA-MRSA strains with in vitro MIC values of 1 mcg/mL or less but difficult to achieve for strains with 2 mcg/mL or greater.³ Recent data suggest that vancomycin MICs may actually be decreasing in children for MRSA, causing bloodstream infections as they increase for MSSA.⁴ Strains with MIC values of 4 mcg/mL or greater should be considered resistant to vancomycin. When using these higher “meningitis” treatment dosages, one needs to follow renal function carefully for the development of toxicity and subsequent need to switch classes of antibiotics.

Clindamycin (oral [PO] or IV) is active against approximately 70% to 90% of strains of either MRSA or MSSA, with great geographic variability (again, check with your hospital laboratory).⁵ The dosage for moderate to severe infections is 30 to 40 mg/kg/day, in 3 divided doses, using the same mg/kg dose PO or IV. Clindamycin is not as bactericidal as vancomycin but achieves higher concentrations in abscesses (based on high intracellular concentrations in neutrophils). Some CA-MRSA strains are susceptible to clindamycin on initial testing but have inducible clindamycin resistance (methylase-mediated) that

is usually assessed by the “D-test” and, more recently, in automated multi-well microtiter plates. Within each population of CA-MRSA organisms, a rare organism (between 1 in 10^9 and 10^{11} organisms) will have a mutation that allows for constant (rather than induced) resistance.⁶ Although still somewhat controversial, clindamycin should be effective therapy for infections that have a relatively low organism load (cellulitis, small or drained abscesses) and are unlikely to contain a significant population of these constitutive methylase-producing mutants that are truly resistant (in contrast to the strains that are not already producing methylase and, in fact, are actually poorly induced by clindamycin). Infections with a high organism load (empyema) may have a greater risk of failure (as a large population is more likely to have a significant number of truly resistant organisms), and clindamycin should not be used as the preferred agent for these infections. Many laboratories no longer report D-test results but simply call the organism “resistant,” prompting the use of alternative therapy that may not be needed.

Clindamycin is used to treat most CA-MRSA infections that are not life-threatening, and, if the child responds, therapy can be switched from IV to PO (although the oral solution is not very well tolerated). *Clostridium difficile* enterocolitis is a concern; however, despite a great increase in the use of clindamycin in children during the past decade, recent published data do not document a clinically significant increase in the rate of this complication in children.

Trimethoprim/sulfamethoxazole (TMP/SMX) (PO, IV), Bactrim/Septa, is active against CA-MRSA in vitro. Prospective comparative data on treatment of skin or skin structure infections in adults and children document efficacy equivalent to clindamycin.⁷ Given our current lack of prospective, comparative information in MRSA bacteremia, pneumonia, and osteomyelitis (in contrast to skin infections), TMP/SMX should not be used routinely to treat these more serious infections at this time.

Linezolid (PO, IV), active against virtually 100% of CA-MRSA strains, is another reasonable alternative but is considered bacteriostatic and has relatively frequent hematologic toxicity in adults (neutropenia, thrombocytopenia) and some infrequent neurologic toxicity (peripheral neuropathy, optic neuritis), particularly when used for courses of 2 weeks or longer (a complete blood cell count should be checked every week or 2 in children receiving prolonged linezolid therapy). The cost of linezolid is substantially more than clindamycin or vancomycin.

Daptomycin (IV), FDA approved for adults for skin infections in 2003 and, subsequently, for bacteremia/endocarditis, was approved for use for children with skin infections in April 2017. It is a unique class of antibiotic, a lipopeptide, and is highly bactericidal. Daptomycin became generic in 2017 and should be considered for treatment of skin infection and bacteremia in failures with other, better studied antibiotics. **Daptomycin should not be used to treat pneumonia**, as it is inactivated by pulmonary surfactant. Pediatric studies for skin infections and bacteremia have been completed and published,^{8,9} and those for osteomyelitis have concluded but have not been presented. Some newborn animal neurologic toxicity data suggest additional **caution for the use of daptomycin in**

infants younger than 1 year, prompting a warning in the package label. Pediatric clinical trial investigations in young infants are not proceeding at this time.

Tigecycline and fluoroquinolones, both of which may show in vitro activity, are not generally recommended for children if other agents are available and are tolerated due to potential toxicity issues for children with tetracyclines and fluoroquinolones and rapid emergence of resistance with fluoroquinolones.

4

Approach to Antibiotic Therapy of Drug-Resistant Gram-negative Bacilli and Methicillin-Resistant *Staphylococcus aureus*

Ceftaroline, a fifth-generation cephalosporin antibiotic, the first FDA-approved beta-lactam antibiotic to be active against MRSA, was approved for children in June 2016. The Gram-negative coverage is similar to cefotaxime, with no activity against *Pseudomonas*. Published data are available for pediatric pharmacokinetics, as well as for prospective, randomized comparative treatment trials of skin and skin structure infections¹⁰ and community-acquired pneumonia.^{11,12} The efficacy and toxicity profile in adults is what one would expect from most cephalosporins. Based on these published data and review by the FDA, for infants and children 2 months and older, ceftaroline should be effective and safer than vancomycin for treatment of MRSA infections. Just as beta-lactams are preferred over vancomycin for MSSA infections, ceftaroline should be considered preferred treatment over vancomycin for MRSA infections. Neither renal function nor drug levels need to be followed with ceftaroline therapy. Since pediatric approval in mid-2016, there have been no reported post-marketing adverse experiences in children; recommendations may change if unexpected clinical data on lack of efficacy or unexpected toxicity (beyond what may be expected with beta-lactams) should be presented.

Combination therapy for serious infections, with vancomycin and rifampin (for deep abscesses) or vancomycin and gentamicin (for bacteremia), is often used, but no prospective, controlled human clinical data exist on improved efficacy over single antibiotic therapy. Some experts use vancomycin and clindamycin in combination, particularly for children with a toxic-shock clinical presentation. Ceftaroline has also been used in combination therapy with other agents in adults, but no prospective, controlled clinical data exist to assess benefits.

Investigational Agents Recently Approved for Adults That Are Being Studied in Children

Dalbavancin and Oritavancin. Both antibiotics are IV glycopeptides, structurally very similar to vancomycin but with enhanced in vitro activity against MRSA and a much longer serum half-life, allowing once-weekly dosing or even just a single dose to treat skin infections.

Telavancin. A glycolipopeptide with mechanisms of activity that include cell wall inhibition and cell membrane depolarization, telavancin is administered once daily.

Tedizolid. A second-generation oxazolidinone like linezolid, tedizolid is more potent in vitro against MRSA than linezolid, with somewhat decreased toxicity to bone marrow in adult clinical studies.

Recommendations for Empiric Therapy of Suspected MRSA Infections

Life-threatening and Serious Infections. If any CA-MRSA is present in your community, empiric therapy for presumed staphylococcal infections that are life-threatening or infections for which any risk of failure is unacceptable (eg, meningitis) should follow the recommendations for CA-MRSA and include *high-dose* vancomycin, clindamycin, or linezolid, in addition to nafcillin or oxacillin (beta-lactam antibiotics are considered better than vancomycin or clindamycin for MSSA). Ceftaroline is now another option for possible MRSA infections, particularly for children with some degree of renal injury, and will replace vancomycin in the near future if safety and efficacy are confirmed.

Moderate Infections. If you live in a location with greater than 10% methicillin resistance, consider using the CA-MRSA recommendations for hospitalized children with presumed staphylococcal infections of any severity, and start empiric therapy with clindamycin (usually active against >80% of CA-MRSA), ceftaroline, vancomycin, or linezolid IV.

In skin and skin structure abscesses, drainage of the abscess may be completely curative in some children, and antibiotics may not be necessary following incision and drainage.

Mild Infections. For nonserious, presumed staphylococcal infections in regions with significant CA-MRSA, empiric topical therapy with mupirocin (Bactroban) or retapamulin (Altabax) ointment, or oral therapy with TMP/SMX or clindamycin, is preferred. For older children, doxycycline and minocycline are also options based on data in adults.

Prevention of Recurrent Infections

For children with problematic, recurrent infections, no well-studied, prospectively collected data provide a solution. Bleach baths (one-half cup of bleach in a full bathtub)¹³ seems to be able to transiently decrease the numbers of colonizing organisms but was not shown to decrease the number of infections in a prospective, controlled study in children with eczema. Similarly, a regimen to decolonize with twice-weekly bleach baths in an attempt to prevent recurrent infection did not lead to a statistically significant decrease.¹⁴ Bathing with chlorhexidine (Hibiclens, a preoperative antibacterial skin disinfectant) daily or 2 to 3 times each week should provide topical anti-MRSA activity for several hours following a bath. Treating the entire family with decolonization regimens will provide an additional decrease in risk of recurrence for the index child.¹⁵ Nasal mupirocin ointment (Bactroban) designed to eradicate colonization may also be used. All these measures have advantages and disadvantages and need to be used together with environmental measures (eg, washing towels frequently, using hand sanitizers, not sharing items of clothing). Helpful advice can be found on the Centers for Disease Control and Prevention Web site at www.cdc.gov/mrsa (accessed September 26, 2018).

Vaccines are being investigated but are not likely to be available for several years.

5. Antimicrobial Therapy for Newborns

NOTES

- Prospectively collected data in newborns continue to become available, thanks in large part to federal legislation (including the US Food and Drug Administration [FDA] Safety and Innovation Act of 2012 that mandates neonatal studies). In situations of inadequate data, suggested doses are based on efficacy, safety, and pharmacological data from older children or adults. These may not account for the effect of developmental changes (effect of ontogeny) on drug metabolism that occur during early infancy and among preterm and full-term newborns.¹ These values may vary widely, particularly for the unstable preterm newborn. Oral convalescent therapy for neonatal infections has not been well studied but may be used cautiously in non-life-threatening infections in adherent families with ready access to medical care.²
- The recommended antibiotic dosages and intervals of administration are given in the tables in this chapter.
- **Adverse drug reaction:** Neonates should not receive intravenous (IV) ceftriaxone while receiving IV calcium-containing products, including parenteral nutrition, by the same or different infusion lines, as fatal reactions with ceftriaxone-calcium precipitates in lungs and kidneys in neonates have occurred. There are no data on interactions between IV ceftriaxone and oral calcium-containing products or between intramuscular ceftriaxone and IV or oral calcium-containing products.³ Cefotaxime or other cephalosporins with similar microbiologic activity are preferred over ceftriaxone for neonates.⁴
- **Abbreviations:** 3TC, lamivudine; ABLC, lipid complex amphotericin; ABR, auditory brainstem response; ALT, alanine transaminase; AmB, amphotericin B; AmB-D, AmB deoxycholate; amox/clav, amoxicillin/clavulanate; AOM, acute otitis media; AST, aspartate transaminase; AUC, area under the curve; bid, twice daily; CBC, complete blood cell count; CDC, Centers for Disease Control and Prevention; CLD, chronic lung disease; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; div, divided; ECMO, extracorporeal membrane oxygenation; ESBL, extended spectrum beta-lactamase; FDA, US Food and Drug Administration; GA, gestational age; GBS, group B streptococcus; G-CSF, granulocyte colony stimulating factor; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IAI, intra-abdominal infection; ID, infectious diseases; IM, intramuscular; IUGR, intrauterine growth restriction; IV, intravenous; IVIG, intravenous immune globulin; L-AmB, liposomal AmB; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NVP, nevirapine; PCR, polymerase chain reaction; pip/tazo, piperacillin/tazobactam; PMA, post-menstrual age; PNA, postnatal age; PO, orally; RAL, raltegravir; RSV, respiratory syncytial virus; spp, species; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; UCSF, University of California, San Francisco; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VDRL, Venereal Disease Research Laboratories; ZDV, zidovudine.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
Conjunctivitis		
– Chlamydial ^{5–8}	Azithromycin 10 mg/kg/day PO for 1 day, then 5 mg/kg/day PO for 4 days (AII), or erythromycin ethylsuccinate PO for 10–14 days (AII)	Macrolides PO preferred to topical eye drops to prevent development of pneumonia; association of erythromycin and pyloric stenosis in young neonates. ⁹ Alternative: 3-day course of higher-dose azithromycin at 10 mg/kg/dose once daily, although safety not well defined in neonates (CIII). Oral sulfonamides may be used after the immediate neonatal period for infants who do not tolerate erythromycin.
– Gonococcal ^{10–14}	Ceftriaxone or cefotaxime 25–50 mg/kg (max 125 mg) IV, IM once, AND azithromycin 10 mg/kg PO q24h for 5 days (AIII)	Cephalosporins no longer recommended as single agent therapy due to increasing resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose given is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia ⁴ and those at risk for calcium drug interactions (see Table 5B). Saline irrigation of eyes. Evaluate for chlamydial infection. All neonates born to mothers with untreated gonococcal infection (regardless of symptoms) require therapy. Cefixime and ciprofloxacin no longer recommended for empiric maternal therapy.
– <i>Staphylococcus aureus</i> ^{15–17}	Topical therapy sufficient for mild <i>S aureus</i> cases (AII), but oral or IV therapy may be considered for moderate to severe conjunctivitis. MSSA: oxacillin/nafticillin IV or cefazolin (for non-CNS infections) IM, IV for 7 days. MRSA: vancomycin IV or clindamycin IV, PO.	Neomycin or erythromycin (BIII) ophthalmic drops or ointment No prospective data for MRSA conjunctivitis (BIII) Cephalexin PO for mild to moderate disease caused by MSSA Increased <i>S aureus</i> resistance with ciprofloxacin/levofloxacin ophthalmic formulations (AII)

– <i>Pseudomonas aeruginosa</i> ^{18–20}	Ceftazidime IM, IV AND tobramycin IM, IV for 7–10 days (alternatives: meropenem, cefepime, pipo/tazo) (BIII)	Aminoglycoside or polymyxin B-containing ophthalmic drops or ointment as adjunctive therapy
– Other Gram-negative	Aminoglycoside or polymyxin B-containing ophthalmic drops or ointment if mild (AII) Systemic therapy if moderate to severe or unresponsive to topical therapy (AIII)	Duration of therapy is dependent on clinical course and may be as short as 5 days if clinically resolved.
Cytomegalovirus		
– Congenital ^{21–25}	For moderately to severely symptomatic neonates with congenital CMV disease: oral valganciclovir at 16 mg/kg/dose PO bid for 6 mo ²⁴ (AI); IV ganciclovir 6 mg/kg/dose IV q12h can be used for some of or all the first 6 wk of therapy if oral therapy not advised, but provides no added benefit over oral valganciclovir (AII). An “induction period” starting with IV ganciclovir is not recommended if oral valganciclovir can be tolerated.	Benefit for hearing loss and neurodevelopmental outcomes (AI). Treatment recommended for neonates with moderate or severe symptomatic congenital CMV disease, with or without CNS involvement. Treatment is not routinely recommended for “mildly symptomatic” neonates congenitally infected with CMV (eg, only 1 or perhaps 2 manifestations of congenital CMV infection, which are mild in scope [eg, isolated IUGR, mild hepatomegaly] or transient and mild in nature [eg, a single platelet count of 80,000 or an ALT of 130, with these numbers serving only as examples]), as the risks of treatment may not be balanced by benefits in mild disease. ²⁵ This includes neonates who are asymptomatic except for sensorineural hearing loss. Treatment for asymptomatic neonates congenitally infected with CMV is not recommended. Neutropenia develops in 20% (oral valganciclovir) to 68% (IV ganciclovir) of neonates on long-term therapy (responds to G-CSF or temporary discontinuation of therapy). Treatment for congenital CMV should start within the first month after birth. There are no data currently on starting therapy beyond the first month after birth. CMV-IVIg not recommended for infants.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) See Tables 5B–D for neonatal dosages.	Comments
– Perinatally or postnatally acquired ²³	Ganciclovir 12 mg/kg/day IV div q12h for 14–21 days (AIII)	Antiviral treatment has not been studied in this population but can be considered in patients with acute, severe, visceral (end-organ) disease, such as pneumonitis, hepatitis, encephalitis, necrotizing enterocolitis, or persistent thrombocytopenia. If such patients are treated with parenteral ganciclovir, a reasonable approach is to treat for 2 wk and then reassess responsiveness to therapy. If clinical and laboratory data suggest benefit of treatment, an additional 1 wk of parenteral ganciclovir can be considered if symptoms and signs have not fully resolved. Oral valganciclovir is not recommended in these more severe disease presentations. Observe for possible relapse after completion of therapy (AIII).

Fungal infections (See also Chapter 8.)

– Candidiasis ^{26–35}	<p>Treatment</p> <p>AmB-D (1 mg/kg/day) is recommended therapy (All).</p> <p>Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative if patient has not been on fluconazole prophylaxis (All).²⁶</p> <p>For treatment of neonates and young infants (<120 days) on ECMO, fluconazole loading dose is 35 mg/kg on day 1, then 12 mg/kg q24h (BII).^{36,37}</p> <p>Lipid formulation AmB is an alternative but carries a theoretical risk of less urinary tract penetration compared with AmB-D (CIII).³⁷</p>	<p>Neonates are at high risk of urinary tract and CNS infection, problematic for echinocandins with poor penetration at those sites; therefore, AmB-D is preferred, followed by fluconazole, and echinocandins discouraged, despite their fungicidal activity. Evaluate for other sites of infection: CSF analysis, echocardiogram, abdominal ultrasound to include bladder; retinal eye examination. Length of therapy dependent on disease (BIII), usually 2 wk after all clearance.</p> <p>Antifungal susceptibility testing is suggested with persistent disease. <i>Candida krusei</i> inherently resistant to fluconazole; <i>Candida parapsilosis</i> may be less susceptible to echinocandins; increasing resistance of <i>Candida glabrata</i> to fluconazole and echinocandins. No proven benefit for combination antifungal therapy in candidiasis. Change from AmB or fluconazole to echinocandin if cultures persistently positive (BIII).</p> <p>Although fluconazole prophylaxis has been shown to reduce colonization, it has not reduced mortality.²⁹</p>
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Duration of therapy for candidemia without obvious metastatic complications is for 2 wk after documented clearance and resolution of symptoms (therefore generally 3 wk total).

Prophylaxis

In nurseries with high rates of candidiasis (>10%),³⁸ IV or oral fluconazole prophylaxis (AI) (3–6 mg/kg twice weekly for 6 wk) in high-risk neonates (birth weight <1,000 g) is recommended. Oral nystatin, 100,000 units tid for 6 wk, is an alternative to fluconazole in neonates with birth weights <1,500 g if availability or resistance preclude fluconazole use (CII).

Prophylaxis of neonates and children on ECMO: fluconazole 12 mg/kg on day 1, followed by 6 mg/kg/day (BII).

Lumbar puncture and dilated retinal examination recommended in neonates with cultures positive for *Candida* spp from blood (AIII). Same recommended for all infants with birth weight <1,500 g with candiduria with or without candidemia (AIII).

CT or ultrasound imaging of genitourinary tract, liver, and spleen should be performed if blood culture results are persistently positive (AIII).

Meningoencephalitis in the neonate occurs at a higher rate than in older children/adults.

Central venous catheter removal strongly recommended.

Infected CNS devices, including ventriculostomy drains and shunts, should be removed, if possible.

See Skin and soft tissues later in this Table for management of congenital cutaneous candidiasis.

Echinocandins should be used with caution and generally limited to salvage therapy or situations in which resistance or toxicity preclude use of AmB-D or fluconazole (CIII).

Role of flucytosine in neonates with meningitis is questionable and not routinely recommended due to toxicity concerns. The addition of flucytosine (100 mg/kg/day div q6h) may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent (CIII).

Serum flucytosine concentrations should be obtained after 3–5 days to achieve a 2-h post-dose peak <100 mcg/mL (ideally 30–80 mcg/mL) to prevent neutropenia.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
– Aspergillosis (usually cutaneous infection with systemic dissemination) ^{24,39–41}	<p>Voriconazole dosing never studied in neonates but likely initial dosing same or higher as pediatric ≥ 2 y: 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose. Continued dosing is guided by monitoring of trough serum concentrations (AII).</p> <p>When stable, may switch from voriconazole IV to voriconazole PO 18 mg/kg/day div bid (AII). Unlike in adults, PO bioavailability in children is only approximately 60%. PO bioavailability in neonates has never been studied. Trough monitoring is crucial after switch.²³</p> <p>Alternatives for primary therapy when voriconazole cannot be administered: L-AmB 5 mg/kg/day (AII). ABLC is another possible alternative. Echinocandin primary monotherapy should not be used for treating invasive aspergillosis (CII). AmB-D should be used only in resource-limited settings in which no alternative agent is available (AII).</p>	<p>Aggressive antifungal therapy, early debridement of skin lesions, as this is common presenting finding in neonatal aspergillosis (AIII).</p> <p>Voriconazole is preferred primary antifungal therapy for all clinical forms of aspergillosis (AI). Early initiation of therapy in patients with strong suspicion of disease is important while a diagnostic evaluation is conducted.</p> <p>Therapeutic voriconazole trough serum concentrations of 2–5 mg/L are important for success. It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability.²⁵ Low voriconazole concentrations are a leading cause of clinical failure.</p> <p>Neonatal and infant voriconazole dosing is not well defined, but doses required to achieve therapeutic troughs are generally higher than in children >2 y (AIII).</p> <p>No experience with posaconazole or isavuconazole in neonates. Total treatment course is for a minimum of 6–12 wk, largely dependent on the degree and duration of immunosuppression and evidence of disease improvement.</p> <p>Salvage antifungal therapy options after failed primary therapy include a change of antifungal class (using L-AmB or an echinocandin), switching to posaconazole (trough concentrations >1 mcg/mL (see Chapter 11 for pediatric dosing), or using combination antifungal therapy.</p> <p>Combination therapy with voriconazole + an echinocandin may be considered in select patients.²⁶</p> <p>In vitro data suggest some synergy with 2 (but not 3) drug combinations: an azole + an echinocandin is the most well studied. If combination therapy is employed, this is likely best done initially when voriconazole trough concentrations may not yet be therapeutic.</p>

Routine susceptibility testing is not recommended but is suggested for patients suspected of having an azole-resistant isolate or who are unresponsive to therapy.

Azole-resistant *Aspergillus fumigatus* is increasing. If local epidemiology suggests >10% azole resistance, empiric initial therapy should be voriconazole + echinocandin OR + L-AmB, and subsequent therapy guided based on antifungal susceptibilities.⁴² Micafungin likely has equal efficacy to caspofungin against aspergillosis.²⁷

Gastrointestinal infections

– NEC or peritonitis secondary to bowel rupture ^{43–48}	Ampicillin IV AND gentamicin AND metronidazole IM, IV for ≥ 10 days (AII). Clindamycin may be used in place of metronidazole (AII). Alternatives: meropenem (BI); pip/tazo \pm gentamicin (AII). ADD fluconazole if known to have gastrointestinal colonization with susceptible <i>Candida</i> species (BIII).	Surgical drainage (AII). Definitive antibiotic therapy based on blood-culture results (aerobic, anaerobic, and fungal); meropenem or cefepime if ceftazidime-resistant Gram-negative bacilli isolated. Vancomycin rather than ampicillin if MRSA prevalent. <i>Bacteroides</i> colonization may occur as early as the first week after birth (AIII). ⁴⁸ Duration of therapy dependent on clinical response and risk of persisting intra-abdominal abscess (AIII). Probiotics may prevent NEC in preterm neonates born 1–1.5 kg, but the optimal strain(s), dose, and safety are not fully known. ^{45,48,49}
– <i>Salmonella</i> (non-typhi and typhi) ⁵⁰	Ampicillin IM, IV (if susceptible) OR cefotaxime/cefepime IM, IV for 7–10 days (AII)	Observe for focal complications (eg, meningitis, arthritis) (AIII). TMP/SMX for focal gastrointestinal infection and low risk for unconjugated hyperbilirubinemia due to interaction between sulfa and bilirubin-albumin binding.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
Herpes simplex infection		
– CNS and disseminated disease ^{51–53}	Acyclovir 60 mg/kg/day div q8h IV for 21 days (All) (if eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel) (All). Infuse IV doses over 1 h in a well-hydrated infant to decrease risk of renal toxicity.	For babies with CNS involvement, perform CSF HSV PCR near end of 21 days of therapy and continue acyclovir until PCR negative. Serum AST/ALT may help identify early disseminated infection. An ophthalmologist should be involved in management and treatment of acute neonatal ocular HSV disease. Foscarnet for acyclovir-resistant disease. Acyclovir PO (300 mg/m ² /dose tid) suppression for 6 mo recommended following parenteral therapy (AI). ⁵⁴ Monitor for neutropenia during suppressive therapy. Different dosages than those listed in Table 5B have been modeled, but there are no safety or efficacy data in humans to support them. ⁵⁴
– Skin, eye, or mouth disease ^{51–53}	Acyclovir 60 mg/kg/day div q8h IV for 14 days (All) (if eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel) (All). Obtain CSF PCR for HSV to assess for CNS infection.	An ophthalmologist should be involved in management and treatment of acute neonatal ocular HSV disease. Acyclovir PO (300 mg/m ² /dose tid) suppression for 6 mo recommended following parenteral therapy (AI). ⁵⁵ Monitor for neutropenia during suppressive therapy. Different dosages than those listed in Table 5B have been modeled, but there are no safety or efficacy data in humans to support them. ⁵⁴
Human immunodeficiency virus prophylaxis following perinatal exposure^{56,57}		
– Prophylaxis following low-risk exposure (mother received antiretroviral therapy during pregnancy and had sustained viral suppression near delivery)	ZDV for the first 4 wk of age (AI). GA ≥35 wk: ZDV 8 mg/kg/day PO div q12h OR 6 mg/kg/day IV div q8h. GA 30–34 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 2 wk of age to 6 mg/kg/day PO (OR 4.5 mg/kg/day IV) div q12h.	For detailed information: https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/# (accessed September 27, 2018). UCSF Clinician Consultation Center (888/448-8765) provides free clinical consultation. Start prevention therapy as soon after delivery as possible but by 6–8 h of age for best effectiveness (All). Monitor CBC at birth and 4 wk (All).

GA \leq 29 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 4 wk of age to 6 mg/kg/day PO (OR 4.5 mg/kg/day IV) div q12h.

The preventive ZDV doses listed herein for neonates are also treatment doses for infants with diagnosed HIV infection.

Treatment of HIV-infected neonates should be considered only with expert consultation.

Perform HIV-1 DNA PCR or RNA assays at 14–21 days, 1–2 mo, and 4–6 mo (AI).

Initiate TMP/SMX prophylaxis for pneumocystis pneumonia at 6 wk of age if HIV infection not yet excluded (AII). TMP/SMX dosing is 2.5–5 mg/kg/dose of TMP component PO q12h.

– Prophylaxis following higher risk perinatal exposure (mothers who were not treated before delivery or who were treated but did not achieve undetectable viral load before delivery, especially if delivery was vaginal)

ZDV for 6 wk
AND

3 doses of NVP (first dose at 0–48 h; second dose 48 h later; third dose 96 h after second dose [AI]).

NVP dose (not per kg): birth weight 1.5–2 kg: 8 mg/dose PO; birth weight $>$ 2 kg: 12 mg/dose PO (AI).⁵⁸

OR

Empiric treatment with ZDV AND NVP AND 3TC (BII). Consider the addition of RAL in consultation with a pediatric ID specialist (CIII).

Delivery management of women with HIV who are receiving antiretroviral therapy and have viral loads between 50 and 999 copies/mL varies. Data do not show a clear benefit to IV ZDV and cesarean delivery for these women. Decisions about the addition of NVP, 3TC, or RAL for infants born to these mothers should be made in consultation with a pediatric ID specialist.

NVP dosing and safety not established for infants whose birth weight $<$ 1.5 kg.

There has been recent interest in using “treatment” antiretroviral regimens for high-risk, exposed neonates to achieve a remission or possibly even a cure. This was initially stimulated by the experience of a baby from Mississippi: high-risk neonate treated within the first 2 days after birth with subsequent infection documentation; off therapy at 18 mo of age without evidence of circulating virus until 4 y of age, at which point HIV became detectable.⁵⁹ A clinical trial is ongoing to study issues further.

When empiric treatment is used for high-risk infants and HIV infection is subsequently excluded, NVP, 3TC, and/or RAL can be discontinued and ZDV can be continued for 6 total wk.

If HIV infection is confirmed, see Chapter 9 for treatment recommendations.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) See Tables 5B–D for neonatal dosages.	Comments
Influenza A and B viruses ^{60–63}	<p>Oseltamivir:</p> <p>Preterm, <38 wk PMA: 1 mg/kg/dose PO bid</p> <p>Preterm, 38–40 wk PMA: 1.5 mg/kg/dose PO bid</p> <p>Preterm, >40 wk PMA: 3 mg/kg/dose PO bid⁶¹</p> <p>Term, birth–8 mo: 3 mg/kg/dose PO bid^{61,64}</p>	<p>Oseltamivir chemoprophylaxis not recommended for infants <3 mo unless the situation is judged critical because of limited safety and efficacy data in this age group.</p> <p>Parenteral peramivir is approved in the United States for use in children ≥2 y; no pharmacokinetic or safety data exist in neonates.⁶⁵</p>
Omphalitis and funisitis		
– Empiric therapy for omphalitis and necrotizing funisitis direct therapy against coliform bacilli, <i>S aureus</i> (consider MRSA), and anaerobes ^{66–68}	Cefotaxime/cefepime OR gentamicin, AND clindamycin for ≥10 days (All)	<p>Need to culture to direct therapy.</p> <p>Alternatives for coliform coverage if resistance likely: cefepime, meropenem.</p> <p>For suspect MRSA: ADD vancomycin.</p> <p>Alternative for combined MSSA and anaerobic coverage: pip/tazo.</p> <p>Appropriate wound management for infected cord and necrotic tissue (AllI).</p>
– Group A or B streptococci ⁶⁹	Penicillin G IV for ≥7–14 days (shorter course for superficial funisitis without invasive infection) (All)	Group A streptococcus usually causes “wet cord” without pus and with minimal erythema; single dose of benzathine penicillin IM adequate. Consultation with pediatric ID specialist is recommended for necrotizing fasciitis (All).
– <i>S aureus</i> ⁶⁸	<p>MSSA: oxacillin/nafticillin IV, IM for ≥5–7 days (shorter course for superficial funisitis without invasive infection) (AllI)</p> <p>MRSA: vancomycin (AllI)</p>	<p>Assess for bacteremia and other focus of infection.</p> <p>Alternatives for MRSA: linezolid, clindamycin (if susceptible).</p>
– <i>Clostridium</i> spp ⁷⁰	Clindamycin OR penicillin G IV for ≥10 days, with additional agents based on culture results (All)	<p>Crepitation and rapidly spreading cellulitis around umbilicus</p> <p>Mixed infection with other Gram-positive and Gram-negative bacteria common</p>

Osteomyelitis, suppurative arthritis^{70–73}

Obtain cultures (aerobic; fungal if NICU) of bone or joint fluid before antibiotic therapy.

Duration of therapy dependent on causative organism and normalization of erythrocyte sedimentation rate and C-reactive protein; minimum for osteomyelitis 3 wk and arthritis therapy 2–3 wk if no organism identified (AIII).

Surgical drainage of pus (AIII); physical therapy may be needed (BIII).

– Empiric therapy	Nafcillin/oxacillin IV (or vancomycin if MRSA is a concern) AND cefotaxime/cefepime OR gentamicin IV, IM (AIII)	
– Coliform bacteria (eg, <i>Escherichia coli</i> , <i>Klebsiella</i> spp, <i>Enterobacter</i> spp)	For <i>E coli</i> and <i>Klebsiella</i> : cefotaxime/cefepime OR gentamicin OR ampicillin (if susceptible) (AIII). For <i>Enterobacter</i> , <i>Serratia</i> , or <i>Citrobacter</i> : ADD gentamicin IV, IM to cefotaxime OR use cefepime or meropenem alone (AIII).	Meropenem for ESBL-producing coliforms (AIII)
– Gonococcal arthritis and tenosynovitis ^{11–14}	Ceftriaxone IV, IM OR cefotaxime IV AND azithromycin 10 mg/kg PO q24h for 5 days (AIII)	Ceftriaxone no longer recommended as single agent therapy due to increasing cephalosporin resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia ⁴ and those at risk for calcium drug interactions (see Table 5B).
– <i>S aureus</i>	MSSA: oxacillin/nafcillin IV (AII) MRSA: vancomycin IV (AIII)	Alternative for MSSA: cefazolin (AIII) Alternatives for MRSA: linezolid, clindamycin (if susceptible) (BIII) Addition of rifampin if persistently positive cultures
– Group B streptococcus	Ampicillin or penicillin G IV (AII)	
– <i>Haemophilus influenzae</i>	Ampicillin IV OR cefotaxime/cefepime IV, IM if ampicillin resistant	Start with IV therapy and switch to oral therapy when clinically stable. Amox/clav PO OR amoxicillin PO if susceptible (AIII).

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) See Tables 5B–D for neonatal dosages.	Comments
Otitis media ⁷⁴		
No controlled treatment trials in newborns; if no response, obtain middle ear fluid for culture.		
– Empiric therapy ⁷⁵	Oxacillin/nafticillin AND cefotaxime or gentamicin	Start with IV therapy and switch to amox/clav PO when clinically stable (AIII).
– <i>E coli</i> (therapy of other coliforms based on susceptibility testing)	Cefotaxime/cefepime OR gentamicin	Start with IV therapy and switch to oral therapy when clinically stable. In addition to pneumococcus and <i>Haemophilus</i> , coliforms and <i>S aureus</i> may also cause AOM in neonates (AIII). For ESBL-producing strains, use meropenem (AII). Amox/clav if susceptible (AIII).
– <i>S aureus</i>	MSSA: oxacillin/nafticillin IV MRSA: vancomycin or clindamycin IV (if susceptible)	Start with IV therapy and switch to oral therapy when clinically stable. MSSA: cephalexin PO for 10 days or cloxacillin PO (AIII). MRSA: linezolid PO or clindamycin PO (BIII).
– Group A or B streptococci	Penicillin G or ampicillin IV, IM	Start with IV therapy and switch to oral therapy when clinically stable. Amoxicillin 30–40 mg/kg/day PO div q8h for 10 days.
Parotitis, suppurative ⁷⁶	Oxacillin/nafticillin IV AND gentamicin IV, IM for 10 days; consider vancomycin if MRSA suspected (AIII).	Usually staphylococcal but occasionally coliform. Antimicrobial regimen without incision/drainage is adequate in >75% of cases.
Pulmonary infections		
– Empiric therapy of the neonate with early onset of pulmonary infiltrates (within the first 48–72 h after birth)	Ampicillin IV, IM AND gentamicin or cefotaxime/cefepime IV, IM for 10 days; consider treating low-risk neonates for ≤7 days (see Comments).	For newborns with no additional risk factors for bacterial infection (eg, maternal chorioamnionitis) who (1) have negative blood cultures, (2) have no need for >8 h of oxygen, and (3) are asymptomatic at 48 h into therapy, 4 days may be sufficient therapy, based on limited, uncontrolled data. ⁷⁷

– Aspiration pneumonia ⁷⁸	Ampicillin IV, IM AND gentamicin IV, IM for 7–10 days (AIII)	Early onset neonatal pneumonia may represent aspiration of amniotic fluid, particularly if fluid is not sterile. Mild aspiration episodes may not require antibiotic therapy.
– <i>Chlamydia trachomatis</i> ⁷⁹	Azithromycin PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII)	Association of erythromycin and azithromycin with pyloric stenosis in infants treated <6 wk of age ⁸⁰
– <i>Mycoplasma hominis</i> ^{81,82}	Clindamycin PO, IV for 10 days (Organisms are resistant to macrolides.)	Pathogenic role in pneumonia not well defined and clinical efficacy unknown; no association with bronchopulmonary dysplasia (BIII)
– Pertussis ⁸³	Azithromycin 10 mg/kg PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII)	Association of erythromycin and azithromycin with pyloric stenosis in infants treated <6 wk of age Alternatives: for >1 mo of age, clarithromycin for 7 days; for >2 mo of age, TMP/SMX for 14 days
– <i>P aeruginosa</i> ⁸⁴	Ceftazidime IV, IM AND tobramycin IV, IM for 10–14 days (AIII)	Alternatives: cefepime or meropenem, OR pip/tazo AND tobramycin

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
– Respiratory syncytial virus ⁸⁵	<p>Treatment: see Comments.</p> <p>Prophylaxis: palivizumab (a monoclonal antibody) 15 mg/kg IM monthly (maximum: 5 doses) for the following high-risk infants (AI):</p> <p>In first year after birth, palivizumab prophylaxis is recommended for infants born before 29 wk 0 days' gestation.</p> <p>Palivizumab prophylaxis is not recommended for otherwise healthy infants born at ≥ 29 wk 0 days' gestation.</p> <p>In first year after birth, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at < 32 wk 0 days' gestation and a requirement for $> 21\%$ oxygen for at least 28 days after birth.</p> <p>Clinicians may administer palivizumab prophylaxis in the first year after birth to certain infants with hemodynamically significant heart disease.</p>	<p>Aerosol ribavirin (6-g vial to make 20-mg/mL solution in sterile water), aerosolized over 18–20 h daily for 3–5 days (BII), provides little benefit and should only be considered for use in life-threatening RSV infection. Difficulties in administration, complications with airway reactivity, concern for potential toxicities to health care workers, and lack of definitive evidence of benefit preclude routine use.</p> <p>Palivizumab does not provide benefit in the treatment of an active RSV infection.</p> <p>Palivizumab prophylaxis may be considered for children < 24 mo who will be profoundly immunocompromised during the RSV season.</p> <p>Palivizumab prophylaxis is not recommended in the second year after birth except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical support (supplemental oxygen, chronic corticosteroid therapy, or diuretic therapy) during the 6-mo period before the start of the second RSV season.</p> <p>Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.</p> <p>Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year after birth.</p> <p>Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.</p> <p>The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native populations and possibly in selected other American Indian populations.^{86,87}</p> <p>Palivizumab prophylaxis is not recommended for prevention of health care–associated RSV disease.</p>

– <i>S aureus</i> ^{17,88–90}	MSSA: oxacillin/naftillin IV (AIII). MRSA: vancomycin IV OR clindamycin IV if susceptible (AIII). Duration of therapy depends on extent of disease (pneumonia vs pulmonary abscesses vs empyema) and should be individualized with therapy up to 21 days or longer.	Alternative for MSSA: cefazolin IV Addition of rifampin or linezolid if persistently positive cultures (AIII) Thoracostomy drainage of empyema
– Group B streptococcus ^{91,92}	Penicillin G IV OR ampicillin IV, IM for 10 days (AIII)	For serious infections, ADD gentamicin for synergy until clinically improved. No prospective, randomized data on the efficacy of a 7-day treatment course.
– <i>Ureaplasma</i> spp (<i>urealyticum</i> or <i>parvum</i>) ^{93,94}	Azithromycin ⁹⁵ PO, IV 20 mg/kg once daily for 3 days (BII)	Pathogenic role of <i>Ureaplasma</i> not well defined and no prophylaxis recommended for CLD Many <i>Ureaplasma</i> spp resistant to erythromycin Association of erythromycin and pyloric stenosis in young infants
Sepsis and meningitis ^{90,96,97}		
Duration of therapy: 10 days for sepsis without a focus (AIII); minimum of 21 days for Gram-negative meningitis (or at least 14 days after CSF is sterile) and 14–21 days for GBS meningitis and other Gram-positive bacteria (AIII). There are no prospective, controlled studies on 5- or 7-day courses for mild or presumed sepsis.		
– Initial therapy, organism unknown	Ampicillin IV AND a second agent, either cefotaxime/cefepime IV or gentamicin IV, IM (AII)	Cephalosporin preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII). For locations with a high rate ($\geq 10\%$) of ESBL-producing <i>E coli</i> , and meningitis is suspected, empiric therapy with meropenem is preferred over cephalosporins. For empiric therapy of sepsis without meningitis, in areas with a high rate of ESBL <i>E coli</i> , gentamicin is preferred. Initial empiric therapy of nosocomial infection should be based on each hospital's pathogens and susceptibilities. Always narrow antibiotic coverage once susceptibility data are available.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) See Tables 5B–D for neonatal dosages.	Comments
– <i>Bacteroides fragilis</i>	Metronidazole or meropenem IV, IM (AIII)	Alternative: clindamycin, but increasing resistance reported
– <i>Enterococcus</i> spp	Ampicillin IV, IM AND gentamicin IV, IM (AIII); for ampicillin-resistant organisms: vancomycin AND gentamicin IV (AIII)	Gentamicin needed with ampicillin or vancomycin for bactericidal activity; continue until clinical and microbiological response documented (AIII). For vancomycin-resistant enterococci that are also ampicillin resistant: linezolid (AIII).
– Enterovirus	Supportive therapy; no antivirals currently FDA approved	Pocapavir PO is currently under investigation for enterovirus (poliovirus). See Chapter 9. As of November 2018, it is not available for compassionate use. Pleconaril PO is currently under consideration for submission to FDA for approval for treatment of neonatal enteroviral sepsis syndrome. ⁹⁸ As of November 2018, it is not available for compassionate use.
– <i>E coli</i> ^{96,97}	Cefotaxime/cefepime IV or gentamicin IV, IM (AII)	Cephalosporins preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII). For locations with a high rate ($\geq 10\%$) of ESBL-producing <i>E coli</i> , and meningitis is suspected, empiric therapy with meropenem is preferred over cephalosporins.
– Gonococcal ^{11–14}	Ceftriaxone IV, IM OR cefotaxime IV, IM, AND azithromycin 10 mg/kg PO q24h for 5 days (AIII)	Cephalosporins no longer recommended as single agent therapy due to increasing resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia ⁴ and those at risk for calcium drug interactions (see Table 5B).
– <i>Listeria monocytogenes</i> ⁹⁹	Ampicillin IV, IM AND gentamicin IV, IM (AIII)	Gentamicin is synergistic in vitro with ampicillin. Continue until clinical and microbiological response documented (AIII).
– <i>P aeruginosa</i>	Ceftazidime IV, IM AND tobramycin IV, IM (AIII)	Meropenem, cefepime, and tobramycin are suitable alternatives (AIII). Pip/tazo should not be used for CNS infection.

– <i>S aureus</i> ^{17,88–90,100,101}	MSSA: oxacillin/nafticillin IV, IM or cefazolin IV, IM (All) MRSA: vancomycin IV (All)	Alternatives for MRSA: clindamycin, linezolid, ceftaroline
– <i>Staphylococcus epidermidis</i> (or any coagulase-negative staphylococci)	Vancomycin IV (All)	If organism susceptible and infection not severe, oxacillin/nafticillin or cefazolin are alternatives for methicillin-susceptible strains. Cefazolin does not enter CNS. Add rifampin if cultures persistently positive. ¹⁰² Alternatives: linezolid, ceftaroline.
– Group A streptococcus	Penicillin G or ampicillin IV (All)	
– Group B streptococcus ⁹¹	Ampicillin or penicillin G IV AND gentamicin IV, IM (All)	Continue gentamicin until clinical and microbiological response documented (All). Duration of therapy: 10 days for bacteremia/sepsis (All); minimum of 14 days for meningitis (All).
Skin and soft tissues		
– Breast abscess ¹⁰³	Oxacillin/nafticillin IV, IM (for MSSA) or vancomycin IV (for MRSA). ADD cefotaxime/cefepime OR gentamicin if Gram-negative rods seen on Gram stain (All).	Gram stain of expressed pus guides empiric therapy; vancomycin if MRSA prevalent in community; alternative to vancomycin: clindamycin, linezolid, ceftaroline; may need surgical drainage to minimize damage to breast tissue. Treatment duration individualized until clinical findings have completely resolved (All).
– Congenital cutaneous candidiasis ¹⁰⁴	AmB for 14 days, or 10 days if CSF culture negative (All). Fluconazole alternative if <i>Candida albicans</i> or known sensitive <i>Candida</i> .	Treat promptly when rash presents with full IV dose, not prophylactic dosing or topical therapy. Diagnostic workup includes aerobic cultures of skin lesions, blood, and CSF. Pathology examination of placenta and umbilical cord if possible.
– Erysipelas (and other group A streptococcal infections)	Penicillin G IV for 5–7 days, followed by oral therapy (if bacteremia not present) to complete a 10-day course (All).	Alternative: ampicillin. GBS may produce similar cellulitis or nodular lesions.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
– Impetigo neonatorum	MSSA: oxacillin/nafticillin IV, IM OR cephalexin (AIII) MRSA: vancomycin IV for 5 days (AIII)	Systemic antibiotic therapy usually not required for superficial impetigo; local chlorhexidine cleansing may help with or without topical mupirocin (MRSA) or bacitracin (MSSA). Alternatives for MRSA: clindamycin IV, PO or linezolid IV, PO.
– <i>S aureus</i> ^{17,88,90,105}	MSSA: oxacillin/nafticillin IV, IM (AII) MRSA: vancomycin IV (AIII)	Surgical drainage may be required. MRSA may cause necrotizing fasciitis. Alternatives for MRSA: clindamycin IV, linezolid IV, or ceftaroline IV. Convalescent oral therapy if infection responds quickly to IV therapy.
– Group B streptococcus ⁹¹	Penicillin G IV OR ampicillin IV, IM	Usually no pus formed Treatment course dependent on extent of infection, 7–14 days

Syphilis, congenital (<1 mo of age)¹⁰⁶

During periods when availability of penicillin is compromised, contact CDC.

Evaluation and treatment do not depend on mother's HIV status.

Obtain follow-up serology every 2–3 mo until nontreponemal test nonreactive or decreased 4-fold.

– Proven or highly probable disease: (1) abnormal physical examination; (2) serum quantitative nontreponemal serologic titer 4-fold higher than mother's titer; or (3) positive dark field or fluorescent antibody test of body fluid(s)	Aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (AII)	Evaluation to determine type and duration of therapy: CSF analysis (VDRL, cell count, protein), CBC, and platelet count. Other tests, as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmologic examination, and hearing test (ABR). If CSF positive, repeat spinal tap with CSF VDRL at 6 mo and, if abnormal, re-treat. If >1 day of therapy is missed, entire course is restarted.
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<p>– Normal physical examination, serum quantitative nontreponemal serologic titer \leq maternal titer, and maternal treatment was (1) none, inadequate, or undocumented; (2) erythromycin, azithromycin, or other non-penicillin regimen; or (3) <4 wk before delivery.</p>	<p>Evaluation abnormal or not done completely: aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (All) Evaluation normal: aqueous penicillin G 50,000 U/kg/dose q12h (day after birth 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days; OR benzathine penicillin G 50,000 units/kg/dose IM in a single dose (All)</p>	<p>Evaluation: CSF analysis, CBC with platelets, long-bone radiographs. If >1 day of therapy is missed, entire course is restarted. Reliable follow-up important if only a single dose of benzathine penicillin given.</p>
<p>– Normal physical examination, serum quantitative nontreponemal serologic titer \leq maternal titer, mother treated adequately during pregnancy and >4 wk before delivery; no evidence of reinfection or relapse in mother</p>	<p>Benzathine penicillin G 50,000 units/kg/dose IM in a single dose (All)</p>	<p>No evaluation required. Some experts would not treat but provide close serologic follow-up.</p>

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) <i>See Tables 5B–D for neonatal dosages.</i>	Comments
– Normal physical examination, serum quantitative nontreponemal serologic titer \leq maternal titer, mother's treatment adequate before pregnancy	No treatment	No evaluation required. Some experts would treat with benzathine penicillin G 50,000 U/kg as a single IM injection, particularly if follow-up is uncertain.
Syphilis, congenital (>1 mo of age) ¹⁰⁶	Aqueous crystalline penicillin G 200,000–300,000 U/kg/day IV div q4–6h for 10 days (All)	Evaluation to determine type and duration of therapy: CSF analysis (VDRL, cell count, protein), CBC and platelet count. Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and hearing evaluation. If no clinical manifestations of disease, CSF examination is normal, and CSF VDRL test result is nonreactive, some specialists would treat with up to 3 weekly doses of benzathine penicillin G 50,000 U/kg IM. Some experts would provide a single dose of benzathine penicillin G 50,000 U/kg IM after 10 days of parenteral treatment, but value of this additional therapy is not well documented.
Tetanus neonatorum ¹⁰⁷	Metronidazole IV, PO (alternative: penicillin G IV) for 10–14 days (All) Human TIG 3,000–6,000 U IM for 1 dose (All)	Wound cleaning and debridement vital; IVIG (200–400 mg/kg) is an alternative if TIG not available; equine tetanus antitoxin not available in the United States but is alternative to TIG.
Toxoplasmosis, congenital ^{108,109}	Sulfadiazine 100 mg/kg/day PO div q12h AND pyrimethamine 2 mg/kg PO daily for 2 days (loading dose), then 1 mg/kg PO q24h for 2–6 mo, then 3 times weekly (M–W–F) up to 1 y (All) Folinic acid (leucovorin) 10 mg 3 times weekly (All)	Corticosteroids (1 mg/kg/day div q12h) if active chorioretinitis or CSF protein >1 g/dL (All). Start sulfa after neonatal jaundice has resolved. Therapy is only effective against active trophozoites, not cysts.

Urinary tract infection¹¹⁰

No prophylaxis for grades 1–3 reflux.¹¹¹

In neonates with reflux, prophylaxis reduces recurrences but increases likelihood of recurrences being due to resistant organisms. Prophylaxis does not affect renal scarring.¹⁰⁶

– Initial therapy, organism unknown	Ampicillin AND gentamicin; OR ampicillin AND cefotaxime/cefepime pending culture and susceptibility test results for 7–10 days	Renal ultrasound and VCUG indicated after first UTI to identify abnormalities of urinary tract. Oral therapy acceptable once neonate asymptomatic and culture sterile.
– Coliform bacteria (eg, <i>E coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Serratia</i>)	Cefotaxime/cefepime IV, IM OR, in absence of renal or perinephric abscess, gentamicin IV, IM for 7–10 days (AII)	Ampicillin used for susceptible organisms.
– <i>Enterococcus</i>	Ampicillin IV, IM for 7 days for cystitis, may need 10–14 days for pyelonephritis, add gentamicin until cultures are sterile (AIII); for ampicillin resistance, use vancomycin, add gentamicin until cultures are sterile.	Aminoglycoside needed with ampicillin or vancomycin for synergistic bactericidal activity (assuming organisms susceptible to an aminoglycoside).
– <i>P aeruginosa</i>	Ceftazidime IV, IM OR, in absence of renal or perinephric abscess, tobramycin IV, IM for 7–10 days (AIII)	Meropenem or cefepime are alternatives.

A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

Condition	Therapy (evidence grade) See Tables 5B–D for neonatal dosages.	Comments
– <i>Candida</i> spp ^{31–33}	<p>AmB-D (1 mg/kg/day) is recommended therapy (AII).</p> <p>Lipid formulation AmB is an alternative but carries a theoretical risk of less urinary tract penetration compared with AmB-D (CIII).</p> <p>Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative if patient has not been on fluconazole prophylaxis (AII).^{26,112}</p> <p>Duration of therapy for candidemia without obvious metastatic complications is for 2 wk after documented clearance and resolution of symptoms.</p> <p>Echinocandins should be used with caution and generally limited to salvage therapy or to situations in which resistance or toxicity preclude the use of AmB-D or fluconazole (CIII).</p> <p>Role of flucytosine in neonates with meningitis is questionable and not routinely recommended due to toxicity concerns. The addition of flucytosine (100 mg/kg/day div q6h) may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent (CIII).</p> <p>Serum flucytosine concentrations should be obtained after 3–5 days to achieve a 2-h post-dose peak <100 mcg/mL (ideally 30–80 mcg/mL) to prevent neutropenia.</p>	<p>Neonatal <i>Candida</i> disease is usually systemic; isolated UTI is uncommon. Treat <i>Candida</i> identified in the urine as systemic infection until proven otherwise. See Fungal infections earlier in Table.</p> <p>Echinocandins are not renally eliminated and should not be used to treat isolated neonatal UTI.</p> <p>Central venous catheter removal strongly recommended.</p> <p>Length of therapy dependent on disease (BIII), usually 2 wk after all clearance.</p> <p>Antifungal susceptibility testing is suggested with persistent disease. (<i>C krusei</i> inherently resistant to fluconazole; <i>C parapsilosis</i> may be less susceptible to echinocandins; <i>C glabrata</i> demonstrates increasing resistance to fluconazole and echinocandins.)</p> <p>No proven benefit for combination antifungal therapy in candidiasis. Change from AmB or fluconazole to micafungin/caspofungin if cultures persistently positive (BIII).</p> <p>Although fluconazole prophylaxis has been shown to reduce colonization, it has not reduced mortality.²⁹</p> <p>Lumbar puncture and dilated retinal examination recommended in neonates with cultures positive for <i>Candida</i> spp from blood (AIII).</p> <p>Same recommended for all infants with birth weight <1,500 g with candiduria with or without candidemia (AIII).</p> <p>CT or ultrasound imaging of genitourinary tract, liver, and spleen should be performed if blood cultures are persistently positive (AIII).</p> <p>Meningoencephalitis in the neonate occurs at a higher rate than in older children/adults.</p> <p>Infected CNS devices, including ventriculostomy drains and shunts, should be removed, if possible.</p>

B. ANTIMICROBIAL DOSAGES FOR NEONATES—Lead author Jason Sauberan, assisted by the editors and John Van Den Anker

Dosages (mg/kg/day) and Intervals of Administration						
Antimicrobial	Route	Chronologic Age ≤28 days				Chronologic Age 29–60 days
		Body Weight ≤2,000 g		Body Weight >2,000 g		
		0–7 days old	8–28 days old	0–7 days old	8–28 days old	
NOTE: This table contains empiric dosage recommendations for each agent listed. See Table 5A (Recommended Therapy for Selected Newborn Conditions) for more details of dosages for specific pathogens in specific tissue sites and for information on anti-influenza and antiretroviral drug dosages.						
Acyclovir (treatment of acute disease)	IV	40 div q12h	60 div q8h	60 div q8h	60 div q8h	60 div q8h
Acyclovir (suppression following treatment for acute disease)	PO	—	900/m ² /day div q8h	—	900/m ² /day div q8h	900/m ² /day div q8h
Only parenteral acyclovir should be used for the treatment of acute neonatal HSV disease. Oral suppression therapy for 6 mo duration after completion of initial neonatal HSV treatment. See text in Table 5A, Herpes simplex infection.						
Amoxicillin-clavulanate ^a	PO	—	—	30 div q12h	30 div q12h	30 div q12h
Amphotericin B						
– deoxycholate	IV	1 q24h	1 q24h	1 q24h	1 q24h	1 q24h
– lipid complex	IV	5 q24h	5 q24h	5 q24h	5 q24h	5 q24h
– liposomal	IV	5 q24h	5 q24h	5 q24h	5 q24h	5 q24h
Ampicillin ^b	IV, IM	100 div q12h	150 div q12h	150 div q8h	150 div q8h	200 div q6h
Anidulafungin ^c	IV	1.5 q24h	1.5 q24h	1.5 q24h	1.5 q24h	1.5 q24h
Azithromycin ^d	PO	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
	IV	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h

B. ANTIMICROBIAL DOSAGES FOR NEONATES (continued)—Lead author Jason Sauberan, assisted by the editors and John Van Den Anker

		Dosages (mg/kg/day) and Intervals of Administration				
		Chronologic Age ≤28 days				Chronologic Age 29–60 days
		Body Weight ≤2,000 g		Body Weight >2,000 g		
Antimicrobial	Route	0–7 days old	8–28 days old	0–7 days old	8–28 days old	
Aztreonam	IV, IM	60 div q12h	90 div q8h ^e	90 div q8h	120 div q6h	120 div q6h
Caspofungin ^f	IV	25/m ² q24h	25/m ² q24h	25/m ² q24h	25/m ² q24h	25/m ² q24h
Cefazolin	IV, IM	50 div q12h	75 div q8h	100 div q12h	150 div q8h	100–150 div q6–8h
Cefepime	IV, IM	60 div q12h	60 div q12h	100 div q12h	100 div q12h	150 div q8h ^g
Cefotaxime	IV, IM	100 div q12h	150 div q8h	100 div q12h	150 div q6h	200 div q6h
Cefoxitin	IV, IM	70 div q12h	100 div q8h ^e	100 div q8h	100 div q8h	120 div q6h
Ceftaroline ¹¹³	IV, IM	12 div q12h	18 div q8h	18 div q8h	18 div q8h	18 div q8h
Ceftazidime	IV, IM	100 div q12h	150 div q8h ^e	100 div q12h	150 div q8h	150 div q8h
Ceftriaxone ^h	IV, IM	—	—	50 q24h	50 q24h	50 q24h
Cefuroxime	IV, IM	100 div q12h	150 div q8h ^e	100 div q12h	150 div q8h	150 div q8h
Chloramphenicol ⁱ	IV, IM	25 q24h	50 div q12h ^e	25 q24h	50 div q12h	50–100 div q6h
Clindamycin	IV, IM, PO	15 div q8h	15 div q8h	21 div q8h	27 div q8h	30 div q8h
Daptomycin (Potential neurotoxicity; use cautiously if no other options.)	IV	12 div q12h	12 div q12h	12 div q12h	12 div q12h	12 div q12h
Erythromycin	PO	40 div q6h	40 div q6h	40 div q6h	40 div q6h	40 div q6h

Fluconazole						
– treatment ^l	IV, PO	12 q24h	12 q24h	12 q24h	12 q24h	12 q24h
– prophylaxis	IV, PO	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly	6 mg/kg/dose twice weekly
Flucytosine ^k	PO	75 div q8h	100 div q6h ^e	100 div q6h	100 div q6h	100 div q6h
Ganciclovir	IV	Insufficient data	Insufficient data	12 div q12h	12 div q12h	12 div q12h
Linezolid	IV, PO	20 div q12h	30 div q8h	30 div q8h	30 div q8h	30 div q8h
Meropenem						
– sepsis, IAI ^l	IV	40 div q12h	60 div q8h ^l	60 div q8h	90 div q8h	90 div q8h
– meningitis	IV	80 div q12h	120 div q8h ^l	120 div q8h	120 div q8h	120 div q8h
Metronidazole ^m	IV, PO	15 div q12h	15 div q12h	22.5 div q8h	30 div q8h	30 div q8h
Micafungin	IV	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
Nafcillin, ⁿ oxacillin ⁿ	IV, IM	50 div q12h	75 div q8h ^e	75 div q8h	100 div q6h	150 div q6h
Penicillin G benzathine	IM	50,000 U	50,000 U	50,000 U	50,000 U	50,000 U
Penicillin G crystalline (GBS sepsis, congenital syphilis)	IV	100,000 U div q12h	150,000 U div q8h	100,000 U div q12h	150,000 U div q8h	200,000 U div q6h
Penicillin G crystalline (GBS meningitis)	IV	400,000 U div q6h	400,000 U div q6h	400,000 U div q6h	400,000 U div q6h	400,000 U div q6h
Penicillin G procaine	IM	50,000 U q24h	50,000 U q24h	50,000 U q24h	50,000 U q24h	50,000 U q24h
Piperacillin/tazobactam	IV	300 div q8h	320 div q6h ^o	320 div q6h	320 div q6h	320 div q6h
Rifampin	IV, PO	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h

B. ANTIMICROBIAL DOSAGES FOR NEONATES (continued)—Lead author Jason Sauberan, assisted by the editors and John Van Den Anker

		Dosages (mg/kg/day) and Intervals of Administration				
		Chronologic Age ≤28 days				Chronologic Age 29–60 days
		Body Weight ≤2,000 g		Body Weight >2,000 g		
Antimicrobial	Route	0–7 days old	8–28 days old	0–7 days old	8–28 days old	
Valganciclovir	PO	Insufficient data	Insufficient data	32 div q12h	32 div q12h	32 div q12h
Voriconazole ^p	IV	16 div q12h	16 div q12h	16 div q12h	16 div q12h	16 div q12h
Zidovudine	IV	3 div q12h ^a	3 div q12h ^a	6 div q12h	6 div q12h	See Table 5A, Human immuno- deficiency virus prophylaxis.
	PO	4 div q12h ^a	4 div q12h ^a	8 div q12h	8 div q12h	See Table 5A, Human immuno- deficiency virus prophylaxis.

^a 25- or 50-mg/mL formulation.^b 300 mg/kg/day for GBS meningitis div q8h for all neonates ≤7 days of age and q6h >7 days of age.^c Loading dose 3 mg/kg followed 24 h later by maintenance dose listed.^d See Table 5A for pathogen-specific dosing.^e Use 0–7 days old dosing until 14 days old if birth weight <1,000 g.^f Higher dosage of 50 mg/m² may be needed for *Aspergillus*.^g May require infusion over 3 h, or 200 mg/kg/day div q6h, to treat organisms with MIC ≥8 mg/L.^h Usually avoided in neonates. Can be considered for transitioning to outpatient treatment of GBS bacteremia in well-appearing neonates at low risk for hyperbilirubinemia. Contraindicated if concomitant IV calcium; see Notes section at beginning of chapter.ⁱ Desired serum concentration 15–25 mg/L.^j Loading dose 25 mg/kg followed 24 h later by maintenance dose listed.^k Desired serum concentrations peak 50–100 mg/L, trough 25–50 mg/L. Dose range 50–100 mg/kg/day.^l Adjust dosage after 14 days of age instead of after 7 days of age.^m Loading dose 15 mg/kg.ⁿ Double the dose for meningitis.^o When PMA reaches >30 weeks.^p Initial loading dose of 18 mg/kg div q12h on day 1. Desired serum concentrations, trough 2–5 mg/L. See text in Table 5A, Aspergillosis.^q Starting dose if GA <35+0 wk and PNA ≤14 days. See Table 5A, Human immunodeficiency virus prophylaxis, for ZDV dosage after 2 wk of age and for NVP and 3TC recommendations.

C. AMINOGLYCOSIDES

Empiric Dosage (mg/kg/dose) by Gestational and Postnatal Age

Medication	Route	<30 wk		30–34 wk		≥35 wk	
		0–14 days	>14 days	0–10 days	>10 days ^a	0–7 days	>7 days ^a
Amikacin ^b	IV, IM	15 q48h	15 q24h	15 q24h	15 q24h	15 q24h	17.5 q24h
Gentamicin ^c	IV, IM	5 q48h	5 q36h	5 q36h	5 q36h	4 q24h	5 q24h
Tobramycin ^c	IV, IM	5 q48h	5 q36h	5 q36h	5 q36h	4 q24h	5 q24h

^a If >60 days of age, see Chapter 11.

^b Desired serum concentrations: 20–35 mg/L or $>10 \times \text{MIC}$ (peak), <7 mg/L (trough).

^c Desired serum concentrations: 6–12 mg/L or $10 \times \text{MIC}$ (peak), <2 mg/L (trough). A 7.5 mg/kg dose q48h, or q36h if ≥ 30 wk GA and >7 days PNA, more likely to achieve desired concentrations if pathogen MIC = 1 mg/L.¹¹⁴

D. VANCOMYCIN^a

Empiric Dosage (mg/kg/dose) by Gestational Age and Serum Creatinine
(Begin with a 20 mg/kg loading dose.)

≤28 wk			>28 wk		
Serum Creatinine	Dose	Frequency	Serum Creatinine	Dose	Frequency
<0.5	15	q12h	<0.7	15	q12h
0.5–0.7	20	q24h	0.7–0.9	20	q24h
0.8–1.0	15	q24h	1.0–1.2	15	q24h
1.1–1.4	10	q24h	1.3–1.6	10	q24h
>1.4	15	q48h	>1.6	15	q48h

^a Serum creatinine concentrations normally fluctuate and are partly influenced by transplacental maternal creatinine in the first wk after birth. Cautious use of creatinine-based dosing strategy with frequent reassessment of renal function and vancomycin serum concentrations are recommended in neonates ≤7 days old. Desired serum concentrations; a 24-h AUC:MIC of 400 mg·h/L is recommended based on adult studies of invasive MRSA infections. The AUC is best calculated from 2 concentrations (ie, peak and trough) rather than 1 trough serum concentration measurement. In situations in which AUC calculation is not feasible, a trough concentration 10–12 mg/L is very highly likely (>90%) to achieve the goal AUC target in neonates when the MIC is 1 mg/L. If >60 days of age, see Chapter 11.

E. Use of Antimicrobials During Pregnancy or Breastfeeding

The use of antimicrobials during pregnancy and lactation should balance benefit to the mother with the risk of fetal and infant toxicity (including anatomic anomalies with fetal exposure). A number of factors determine the degree of transfer of antibiotics across the placenta: lipid solubility, degree of ionization, molecular weight, protein binding, placental maturation, and placental and fetal blood flow. The previous FDA labeling of 5 categories of risk will be phased out, replaced by narrative summaries of risks associated with the use of a drug during pregnancy and lactation for the mother, the fetus, and the breastfeeding child. The risk categories from A to X were felt to be too simplistic and are to be phased out by 2020. Risks are now all clearly noted, and for drugs with high fetal risk, black box warnings are included (eg, ribavirin).¹¹⁵

Fetal serum antibiotic concentrations (or cord blood concentrations) following maternal administration have not been systematically studied, but new pharmacokinetic models of transplacental drug transfer and fetal metabolism have recently been developed to provide some insight into fetal drug exposure.^{116–118} The following commonly used drugs appear to achieve fetal concentrations that are equal to or only slightly less than those in the mother: penicillin G, amoxicillin, ampicillin, sulfonamides, trimethoprim, tetracyclines, and oseltamivir. The aminoglycoside concentrations in fetal serum are 20% to 50% of those in maternal serum. Cephalosporins, carbapenems, nafcillin, oxacillin, clindamycin, and vancomycin penetrate poorly (10%–30%), and fetal concentrations of erythromycin and azithromycin are less than 10% of those in the mother.

The most current, updated information on the pharmacokinetics and safety of antimicrobials and other agents in human milk can be found at the National Library of Medicine LactMed Web site (<http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>; accessed September 27, 2018).¹¹⁹

In general, neonatal exposure to antimicrobials in human milk is minimal or insignificant. Aminoglycosides, beta-lactams, ciprofloxacin, clindamycin, macrolides, fluconazole, and agents for tuberculosis are considered safe for the mother to take during breastfeeding.^{120,121} The most common reported neonatal side effect of maternal antimicrobial use during breastfeeding is increased stool output.¹²² Clinicians should recommend mothers alert their pediatric health care professional if stool output changes occur. Maternal treatment with sulfa-containing antibiotics should be approached with caution in the breastfed infant who is jaundiced or ill.

6. Antimicrobial Therapy According to Clinical Syndromes

NOTES

- This chapter should be considered a rough guidance for a typical patient. Dosage recommendations are for patients with relatively normal hydration, renal function, and hepatic function. Because the dose required is based on the exposure of the antibiotic to the pathogen at the site of infection, higher dosages may be necessary if the antibiotic does not penetrate well into the infected tissue (eg, meningitis) or if the child eliminates the antibiotic from the body more quickly than average. Higher dosages/longer courses may also be needed if the child is immunocompromised and the immune system cannot help resolve the infection, as it is becoming clearer that the host contributes significantly to microbiologic and clinical cure above and beyond the antimicrobial-attributable effect.
- Duration of treatment should be individualized. Those recommended are based on the literature, common practice, and general experience. Critical evaluations of duration of therapy have been carried out in very few infectious diseases. In general, a longer duration of therapy should be used (1) for tissues in which antibiotic concentrations may be relatively low (eg, undrained abscess, central nervous system [CNS] infection); (2) for tissues in which repair following infection-mediated damage is slow (eg, bone); (3) when the organisms are less susceptible; (4) when a relapse of infection is unacceptable (eg, CNS infections); or (5) when the host is immunocompromised in some way. An assessment after therapy will ensure that your selection of antibiotic, dose, and duration of therapy were appropriate. Until prospective, comparative studies are performed for different durations, we cannot assign a specific increased risk of failure for shorter courses. We support the need for these studies in a controlled clinical research setting, either outpatient or inpatient.
- Our approach to therapy is continuing to move away from the concept that “one dose fits all,” as noted previously. In addition to the dose that provides antibiotic exposure and host immune competence, the concept of *target attainment* is being better defined. The severity of illness and the willingness of the practitioner to accept a certain rate of failure needs to be considered. Hence the use of broad-spectrum, high-dose treatment for a child in florid septic shock (where you need to be right virtually 100% of the time), compared with the child with impetigo where a treatment that is approximately 80% effective is acceptable, as you can just see the child back in the office in a few days and alter therapy as necessary.
- Diseases in this chapter are arranged by body systems. Please consult the index for the alphabetized listing of diseases and chapters 7 through 10 for the alphabetized listing of pathogens and for uncommon organisms not included in this chapter.
- A more detailed description of treatment options for methicillin-resistant *Staphylococcus aureus* (MRSA) infections and multidrug-resistant Gram-negative bacilli infections, including a stepwise approach to increasingly broad-spectrum agents, is

provided in Chapter 4. Although in the past, vancomycin has been the mainstay of therapy for invasive MRSA, it is nephrotoxic and ototoxic, and it requires monitoring renal function and serum drug concentrations. Its use in organisms with a minimal inhibitory concentration of 2 or greater may not provide adequate exposure for a cure with realistic pediatric doses. Alternatives now approved by the US Food and Drug Administration for children, particularly ceftaroline, are likely to be as effective, but are more likely to be safer, and should be considered.

- Therapy of *Pseudomonas aeruginosa* systemic infections has evolved from intravenous (IV) ceftazidime plus tobramycin to single-drug IV therapy with cefepime for most infections in immune-competent children, due to the relative stability of cefepime to beta-lactamases, compared with ceftazidime. Oral therapy with ciprofloxacin has replaced IV therapy in children who are compliant and able to take oral therapy, particularly for “step-down” therapy of invasive infections.
- **Abbreviations:** AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists; ADH, antidiuretic hormone; AFB, acid-fast bacilli; AHA, American Heart Association; ALT, alanine transaminase; AmB, amphotericin B; amox/clav, amoxicillin/clavulanate; AOM, acute otitis media; ARF, acute rheumatic fever; AST, aspartate transaminase; AUC:MIC, area under the serum concentration vs time curve: minimum inhibitory concentration; bid, twice daily; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; cap, capsule; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSD, cat-scratch disease; CSF, cerebrospinal fluid; CT, computed tomography; DAT, diphtheria antitoxin; div, divided; DOT, directly observed therapy; EBV, Epstein-Barr virus; ESBL, extended spectrum beta-lactamase; ESR, erythrocyte sedimentation rate; ETEC, enterotoxin-producing *Escherichia coli*; FDA, US Food and Drug Administration; GI, gastrointestinal; HACEK, *Haemophilus aphrophilus*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HUS, hemolytic uremic syndrome; I&D, incision and drainage; IDSA, Infectious Diseases Society of America; IM, intramuscular; INH, isoniazid; IV, intravenous; IVIG, intravenous immune globulin; KPC, *Klebsiella pneumoniae* carbapenemase; L-AmB, liposomal amphotericin B; LFT, liver function test; LP, lumbar puncture; MDR, multidrug resistant; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *S aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-susceptible *S aureus*; MSSE, methicillin-sensitive *S epidermidis*; ophth, ophthalmic; PCR, polymerase chain reaction; PCV13, Prevnar 13-valent pneumococcal conjugate vaccine; pen-R, penicillin-resistant; pen-S, penicillin-susceptible; PIDS, Pediatric Infectious Diseases Society; pip/tazo, piperacillin/tazobactam; PMA, post-menstrual age; PO, oral; PPD, purified protein derivative; PZA, pyrazinamide; qd, once daily; qid, 4 times daily; qod, every other day; RIVUR, Randomized Intervention for Children with Vesicoureteral Reflux; RSV,

respiratory syncytial virus; soln, solution; SPAG-2, small particle aerosol generator-2; spp, species; STEC, Shiga toxin-producing *E coli*; STI, sexually transmitted infection; tab, tablet; TB, tuberculosis; Td, tetanus, diphtheria; Tdap, tetanus, diphtheria, acellular pertussis; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; ULN, upper limit of normal; UTI, urinary tract infection; VDRL, Venereal Disease Research Laboratories; WBC, white blood cell.

A. SKIN AND SOFT TISSUE INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
<p>NOTE: CA-MRSA (see Chapter 4) is prevalent in most areas of the world but may now be decreasing, rather than increasing.¹ Recommendations for staphylococcal infections are given for 2 scenarios: standard MSSA and CA-MRSA. Antibiotic recommendations “for CA-MRSA” should be used for empiric therapy in regions with greater than 5% to 10% of invasive staphylococcal infections caused by MRSA, in situations where CA-MRSA is suspected, and for documented CA-MRSA infections, while “standard recommendations” refer to treatment of MSSA. During the past few years, clindamycin resistance in MRSA has increased to 40% in some areas but remained stable at 5% in others, although this increase may be an artifact of changes in reporting, with many laboratories now reporting all clindamycin-susceptible but D-test–positive strains as resistant. Please check your local susceptibility data for <i>Staphylococcus aureus</i> before using clindamycin for empiric therapy. For MSSA, oxacillin/nafticillin are considered equivalent agents.</p>		
<p>Adenitis, acute bacterial^{2–8} (<i>S aureus</i>, including CA-MRSA, and group A streptococcus; consider <i>Bartonella</i> [CSD] for subacute adenitis.)⁹</p>	<p>Empiric therapy Standard: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (AI), OR cephalexin 50–75 mg/kg/day PO div tid CA-MRSA: clindamycin 30 mg/kg/day IV or PO (AI) div q8h OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI), OR vancomycin 40 mg/kg/day IV q8h (BII), OR daptomycin: 1–<2 y, 10 mg/kg IV qd; 2–6 y, 9 mg/kg IV qd; 7–11 y, 7 mg/kg qd; 12–17 y, 5 mg/kg qd (BI) CSD: azithromycin 12 mg/kg qd (max 500 mg) for 5 days (BIII)</p>	<p>Avoid daptomycin in infants until 1 y due to potential toxicity. May need surgical drainage for staph/strep infection; not usually needed for CSD. Following drainage of mild to moderate suppurative adenitis caused by staph or strep, additional antibiotics may not be required. For oral therapy for MSSA: cephalexin or amox/clav. For CA-MRSA: clindamycin, TMP/SMX, or linezolid. For oral therapy of group A strep: amoxicillin or penicillin V. Total IV plus PO therapy for 7–10 days. For CSD: this is the same high dose of azithromycin that is recommended routinely for strep pharyngitis.</p>
<p>Adenitis, nontuberculous (atypical) mycobacterial^{10–13}</p>	<p>Excision usually curative (BII); azithromycin PO OR clarithromycin PO for 6–12 wk (with or without rifampin) if susceptible (BII)</p>	<p>Antibiotic susceptibility patterns are quite variable; cultures should guide therapy: excision >97% effective; medical therapy 60%–70% effective. No well-controlled trials available; risks are present with antimicrobials and surgery.</p>

Adenitis, tuberculous ^{14,15} <i>Mycobacterium tuberculosis</i> and <i>Mycobacterium bovis</i>	INH 10–15 mg/kg/day (max 300 mg) PO, IV qd, for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO, IV qd, for 6 mo AND PZA 20–40 mg/kg/day PO qd for first 2 mo therapy (BI); if suspected multidrug resistance, add ethambutol 20 mg/kg/day PO qd.	Surgical excision usually not indicated because organisms are treatable. Adenitis caused by <i>M bovis</i> (unpasteurized dairy product ingestion) is uniformly resistant to PZA. Treat 9–12 mo with INH and rifampin, if susceptible (BII). No contraindication to fine needle aspirate of node for diagnosis.
Anthrax, cutaneous ¹⁶	Empiric therapy: ciprofloxacin 20–30 mg/kg/day PO div bid OR doxycycline 4.4 mg/kg/day (max 200 mg) PO div bid (regardless of age) (AIII)	If susceptible, amoxicillin or clindamycin (BIII). Ciprofloxacin and levofloxacin are FDA approved for inhalational anthrax and should be effective for skin infection (BIII).
Bites, dog and cat ^{2,17–21} <i>Pasteurella multocida</i> ; <i>S aureus</i> , including CA-MRSA; <i>Streptococcus</i> spp, anaerobes; <i>Capnocytophaga canimorsus</i> , particularly in asplenic hosts)	Amox/clav 45 mg/kg/day PO div tid (amox/clav 7:1; see Chapter 1, Aminopenicillins) for 5–10 days (AII). For hospitalized children, use ampicillin AND clindamycin (BII) OR ceftriaxone AND clindamycin (BII) OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BIII).	Amox/clav has good <i>Pasteurella</i> , MSSA, and anaerobic coverage but lacks MRSA coverage. Ampicillin/amox plus clindamycin has good <i>Pasteurella</i> , MSSA, MRSA, and anaerobic coverage. Ceftaroline has good <i>Pasteurella</i> , MSSA, and MRSA coverage but lacks <i>Bacteroides fragilis</i> anaerobic coverage. ²² Ampicillin/sulbactam also lacks MRSA coverage. Consider rabies prophylaxis ²³ for bites from at-risk animals (observe animal for 10 days, if possible) (AI); CDC can provide advice on risk and management (www.cdc.gov/rabies/resources/contacts.html); consider tetanus prophylaxis. For penicillin allergy, ciprofloxacin (for <i>Pasteurella</i>) plus clindamycin (BIII). Doxycycline may be considered for <i>Pasteurella</i> coverage.

A. SKIN AND SOFT TISSUE INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Bites, human ^{2,20,24} (<i>Eikenella corrodens</i> ; <i>S aureus</i> , including CA-MRSA; <i>Streptococcus</i> spp, anaerobes)	Amox/clav 45 mg/kg/day PO div tid (amox/clav 7:1; see Chapter 1, Aminopenicillins) for 5–10 days (All). For hospitalized children, use ampicillin and clindamycin (BII) OR ceftriaxone and clindamycin (BII).	Human bites have a very high rate of infection (do not routinely close open wounds). Amox/clav has good <i>Eikenella</i> , MSSA, and anaerobic coverage but lacks MRSA coverage. Ampicillin/sulbactam also lacks MRSA coverage. For penicillin allergy, ciprofloxacin (for <i>Pasteurella</i>) plus clindamycin (BIII). Doxycycline and TMP/SMX may be considered for <i>Pasteurella</i> coverage.
Bullous impetigo ^{2,3,6,7} (usually <i>S aureus</i> , including CA-MRSA)	Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (CII) CA-MRSA: clindamycin 30 mg/kg/day PO div tid OR TMP/SMX 8 mg/kg/day of TMP PO div bid; for 5–7 days (CI)	For topical therapy if mild infection: mupirocin or retapamulin ointment
Cellulitis of unknown etiology (usually <i>S aureus</i> , including CA-MRSA, or group A streptococcus) ^{2–4,6–8,25–27}	Empiric IV therapy Standard: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BII) CA-MRSA: clindamycin 30 mg/kg/day IV div q8h OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI) OR vancomycin 40 mg/kg/day IV q8h (BII) OR daptomycin: 1–<2 y, 10 mg/kg IV qd; 2–6 y, 9 mg/kg IV qd; 7–11 y, 7 mg/kg qd; 12–17 y, 5 mg/kg qd (BI) For oral therapy for MSSA: cephalexin (All) OR amox/clav 45 mg/kg/day PO div tid (BII); for CA-MRSA: clindamycin (BII), TMP/SMX (All), or linezolid (BII)	For periorbital or buccal cellulitis, also consider <i>Streptococcus pneumoniae</i> or <i>Haemophilus influenzae</i> type b in unimmunized infants. Total IV plus PO therapy for 7–10 days. Since nonsuppurative cellulitis is most often caused by group A streptococcus, cephalexin alone is usually effective. In adults, a prospective, randomized study of non-purulent cellulitis did not find that the addition of TMP/SMX improved outcomes over cephalexin alone. ²⁷

Cellulitis, buccal (for unimmunized infants and preschool-aged children, <i>H influenzae</i> type b) ²⁸	Cefotaxime 100–150 mg/kg/day IV div q8h OR ceftriaxone 50 mg/kg/day (AI) IV, IM q24h; for 2–7 days parenteral therapy before switch to oral (BII)	Rule out meningitis (larger dosages may then be needed). For penicillin allergy, levofloxacin IV/PO covers pathogens, but no clinical data available. Oral therapy: amoxicillin if beta-lactamase negative; amox/clav or oral 2nd- or 3rd-generation cephalosporin if beta-lactamase positive.
Cellulitis, erysipelas (streptococcal) ^{2,3,8,29}	Penicillin G 100,000–200,000 U/kg/day IV div q4–6h (BII) initially, then penicillin V 100 mg/kg/day PO div qid (BIII) or tid OR amoxicillin 50 mg/kg/day PO div tid (BIII) for 10 days	Clindamycin and macrolides are also effective.
Gas gangrene (See Necrotizing fasciitis.)		
Impetigo (<i>S aureus</i> , including CA-MRSA; occasionally group A streptococcus) ^{2,3,7,8,30,31}	Mupirocin OR retapamulin topically (BII) to lesions tid; OR for more extensive lesions, oral therapy Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (AII) CA-MRSA: clindamycin 30 mg/kg/day (CII) PO div tid OR TMP/SMX 8 mg/kg/day TMP PO div bid (AI); for 5–7 days	Bacitracin ointment, widely available to treat skin infections, is inferior to cephalexin and mupirocin. ³¹
Ludwig angina ³²	Penicillin G 200,000–250,000 U/kg/day IV div q6h AND clindamycin 40 mg/kg/day IV div q8h (CIII)	Alternatives: ceftriaxone/clindamycin, meropenem, imipenem, pip/tazo if Gram-negative aerobic bacilli also suspected (CIII); high risk of respiratory tract obstruction from inflammatory edema
Lymphadenitis (See Adenitis, acute bacterial.)		
Lymphangitis (usually group A streptococcus) ^{2,3,8}	Penicillin G 200,000 U/kg/day IV div q6h (BII) initially, then penicillin V 100 mg/kg/day PO div qid OR amoxicillin 50 mg/kg/day PO div tid for 10 days	Cefazolin IV (for group A strep or MSSA) or clindamycin IV (for group A strep, most MSSA and MRSA) For mild disease, penicillin V 50 mg/kg/day PO div qid for 10 days Some recent reports of <i>S aureus</i> as a cause

A. SKIN AND SOFT TISSUE INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Myositis, suppurative ³³ (<i>S aureus</i> , including CA-MRSA; synonyms: tropical myositis, pyomyositis)	Standard: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (CII) CA-MRSA: clindamycin 40 mg/kg/day IV div q8h OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI) OR vancomycin 40 mg/kg/day IV q8h (CIII) OR daptomycin: 1–<2 y, 10 mg/kg IV qd; 2–6 y, 9 mg/kg IV qd; 7–11 y, 7 mg/kg qd; 12–17 y, 5 mg/kg qd (BIII)	Surgical debridement is usually necessary. For disseminated MRSA infection, may require aggressive, emergent debridement; use clindamycin to help decrease toxin production (BIII); consider IVIG to bind bacterial toxins for life-threatening disease (CIII); abscesses may develop with CA-MRSA while on therapy.
Necrotizing fasciitis (Pathogens vary depending on the age of the child and location of infection. Single pathogen: group A streptococcus; <i>Clostridia</i> spp, <i>S aureus</i> [including CA-MRSA], <i>Pseudomonas aeruginosa</i> , <i>Vibrio</i> spp, <i>Aeromonas</i> . Multiple pathogen, mixed aerobic/anaerobic synergistic fasciitis: any organism[s] above, plus Gram-negative bacilli, plus <i>Bacteroides</i> spp, and other anaerobes.) ^{2,34–37}	Empiric therapy: ceftazidime 150 mg/kg/day IV div q8h, or cefepime 150 mg/kg/day IV div q8h or cefotaxime 200 mg/kg/day IV div q6h AND clindamycin 40 mg/kg/day IV div q8h (BIII); OR meropenem 60 mg/kg/day IV div q8h; OR pip/tazo 400 mg/kg/day pip component IV div q6h (AIII). ADD vancomycin OR ceftaroline for suspect CA-MRSA, pending culture results (AIII). Group A streptococcal: penicillin G 200,000–250,000 U/kg/day div q6h AND clindamycin 40 mg/kg/day div q8h (AIII). Mixed aerobic/anaerobic/Gram-negative: meropenem or pip/tazo AND clindamycin (AIII).	Aggressive emergent wound debridement (AII). ADD clindamycin to inhibit synthesis of toxins during the first few days of therapy (AIII). If CA-MRSA identified and susceptible to clindamycin, additional vancomycin is not required. Consider IVIG to bind bacterial toxins for life-threatening disease (BIII). Value of hyperbaric oxygen is not established (CIII). ³⁸ Focus definitive antimicrobial therapy based on culture results.
Pyoderma, cutaneous abscesses (<i>S aureus</i> , including CA-MRSA; group A streptococcus) ^{3,4,6–8,25,26,39–41}	Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (BI) CA-MRSA: clindamycin 30 mg/kg/day PO div tid (BI) OR TMP/SMX 8 mg/kg/day of TMP PO div bid (AI)	I&D when indicated; IV for serious infections. For prevention of recurrent CA-MRSA infection, use bleach baths twice weekly (½ cup of bleach per full bathtub) (BI), OR bathe with chlorhexidine soap daily or qod (BIII). Decolonization with nasal mupirocin may also be helpful, as is decolonization of the entire family. ⁴²

Rat-bite fever (<i>Streptobacillus moniliformis</i> , <i>Spirillum minus</i>) ⁴³	Penicillin G 100,000–200,000 U/kg/day IV div q6h (BI) for 7–10 days; for endocarditis, ADD gentamicin for 4–6 wk (CIII). For mild disease, oral therapy with amox/clav (CIII).	Organisms are normal oral flora for rodents. High rate of associated endocarditis. Alternatives: doxycycline; 2nd- and 3rd-generation cephalosporins (CIII).
Staphylococcal scalded skin syndrome ^{7,44,45}	Standard: oxacillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (CII) CA-MRSA: clindamycin 30 mg/kg/day IV div q8h (CIII) OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI), OR vancomycin 40 mg/kg/day IV q8h (CIII) OR daptomycin: 1–<2 y, 10 mg/kg IV qd; 2–6 y, 9 mg/kg IV qd; 7–11 y, 7 mg/kg qd; 12–17 y, 5 mg/kg qd (BI)	Burow or Zephiran compresses for oozing skin and intertriginous areas. Corticosteroids are contraindicated.

B. SKELETAL INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
<p>NOTE: CA-MRSA (see Chapter 4) is prevalent in most areas of the world, although epidemiologic data suggest that MRSA infections are less common in skeletal infections than in skin infections. Recommendations are given for CA-MRSA and MSSA. Antibiotic recommendations for empiric therapy should include CA-MRSA when it is suspected or documented, while treatment for MSSA with beta-lactam antibiotics (eg, cephalexin) is preferred over clindamycin. During the past few years, clindamycin resistance in MRSA has increased to 40% in some areas but remained stable at 5% in others, although this increase may be an artifact of changes in reporting, with many laboratories now reporting all clindamycin-susceptible but D-test–positive strains as resistant. Please check your local susceptibility data for <i>Staphylococcus aureus</i> before using clindamycin for empiric therapy. For MSSA, oxacillin/nafticillin are considered equivalent agents. The first pediatric-specific PIDS/IDSA guidelines for bacterial osteomyelitis and bacterial arthritis are currently being written.</p>		
Arthritis, bacterial ^{46–51}	Switch to appropriate high-dose oral therapy when clinically improved, CRP decreasing (see Chapter 13). ^{48,52,53}	
– Newborns	See Chapter 5.	
<p>– Infants (<i>S aureus</i>, including CA-MRSA; group A streptococcus; <i>Kingella kingae</i>) (In unimmunized or immunocompromised children: pneumococcus, <i>Haemophilus influenzae</i> type b)</p> <p>– Children (<i>S aureus</i>, including CA-MRSA; group A streptococcus; <i>K kingae</i>)</p> <p>For Lyme disease and brucellosis, see Table L, Miscellaneous Systemic Infections.</p>	<p>Empiric therapy: clindamycin (to cover CA-MRSA unless clindamycin resistance locally is >10%, then use vancomycin).</p> <p>For serious infections, ADD cefazolin 100 mg/kg/day IV div q8h to provide better MSSA and <i>Kingella</i> coverage.</p> <p>See Comments for discussion of dexamethasone adjunctive therapy.</p> <p>For CA-MRSA: clindamycin 30 mg/kg/day IV div q8h (AI) OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI) OR vancomycin 40 mg/kg/day IV q8h (BI)</p> <p>For MSSA: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (AI).</p>	<p>Dexamethasone adjunctive therapy (0.15 mg/kg/dose every 6 h for 4 days in one study) demonstrated significant benefit in decreasing symptoms and earlier hospital discharge (but with some “rebound” symptoms).^{54,55}</p> <p>NOTE: children with rheumatologic, postinfectious, fungal/mycobacterial infections or malignancy are also likely to improve with steroid therapy despite ineffective antibiotics.</p> <p>Oral step-down therapy options:</p> <p>For CA-MRSA: clindamycin OR linezolid⁵⁰</p> <p>For MSSA: cephalexin OR dicloxacillin caps for older children</p> <p>For <i>Kingella</i>: most penicillins or cephalosporins (but not clindamycin)</p>

For *Kingella*: cefazolin 100 mg/kg/day IV div q8h OR ampicillin 150 mg/kg/day IV div q6h, OR ceftriaxone 50 mg/kg/day IV, IM q24h (All).
 For pen-S pneumococci or group A streptococcus: penicillin G 200,000 U/kg/day IV div q6h (BII).
 For pen-R pneumococci or *Haemophilus*: ceftriaxone 50–75 mg/kg/day IV, IM q24h, OR cefotaxime (BII).
 Total therapy (IV plus PO) for up to 21 days with normal ESR; low-risk, non-hip MSSA arthritis may respond to a 10-day course (All).⁵⁰

– Gonococcal arthritis or tenosynovitis ^{56,57}	Ceftriaxone 50 mg/kg IV, IM q24h (BII) for 7 days AND azithromycin 20 mg/kg PO as a single dose	Combination therapy with azithromycin to decrease risk of development of resistance. Cefixime 8 mg/kg/day PO as a single daily dose may not be effective due to increasing resistance. Ceftriaxone IV, IM is preferred over cefixime PO.
– Other bacteria	See Chapter 7 for preferred antibiotics.	
Osteomyelitis ^{46,48–50,58–63}	Step down to appropriate high-dose oral therapy when clinically improved (see Chapter 13). ^{48,50,52,61}	
– Newborns	See Chapter 5.	

B. SKELETAL INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– Infants and children, acute infection (usually <i>S aureus</i> , including CA-MRSA; group A streptococcus; <i>K kingae</i>)	<p>Empiric therapy: clindamycin (for coverage of MSSA and MRSA in most locations).</p> <p>For serious infections, ADD cefazolin to provide better MSSA and <i>Kingella</i> coverage (CIII).</p> <p>For CA-MRSA: clindamycin 30 mg/kg/day IV div q8h OR vancomycin 40 mg/kg/day IV q8h (BII), OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BI).</p> <p>For MSSA: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (AII).</p> <p>For <i>Kingella</i>: cefazolin 100 mg/kg/day IV div q8h OR ampicillin 150 mg/kg/day IV div q6h, OR ceftriaxone 50 mg/kg/day IV, IM q24h (BIII).</p> <p>Total therapy (IV plus PO) usually 4–6 wk for MSSA (with end-of-therapy normal ESR, radiograph to document healing) but may be as short as 3 wk for mild infection. May need longer than 4–6 wk for CA-MRSA (BII).</p> <p>Follow closely for clinical response to empiric therapy.</p>	<p>In children with open fractures secondary to trauma, add ceftazidime or cefepime for extended aerobic Gram-negative bacilli activity. <i>Kingella</i> is often resistant to clindamycin and vancomycin.</p> <p>For MSSA (BI) and <i>Kingella</i> (BIII), step-down oral therapy with cephalexin 100 mg/kg/day PO div tid. <i>Kingella</i> is usually susceptible to amoxicillin.</p> <p>Oral step-down therapy options for CA-MRSA include clindamycin and linezolid,⁶⁴ with insufficient data to recommend TMP/SMX.⁶⁰</p> <p>For prosthetic devices, biofilms may impair microbial eradication, requiring the addition of rifampin or other agents.⁶²</p>
– Acute, other organisms	See Chapter 7 for preferred antibiotics.	
– Chronic (staphylococcal)	<p>For MSSA: cephalexin 100 mg/kg/day PO div tid OR dicloxacillin caps 75–100 mg/kg/day PO div qid for 3–6 mo or longer (CIII)</p> <p>For CA-MRSA: clindamycin or linezolid (CIII)</p>	<p>Surgery to debride sequestrum is usually required for cure. For prosthetic joint infection caused by staphylococci, add rifampin (CIII).⁶²</p> <p>Watch for beta-lactam-associated neutropenia with high-dose, long-term therapy and linezolid-associated neutropenia/thrombocytopenia with long-term (>2 wk) therapy.⁶⁴</p>

Osteomyelitis of the foot ^{65,66} (osteochondritis after a puncture wound) <i>Pseudomonas aeruginosa</i> (occasionally <i>S aureus</i> , including CA-MRSA)	Cefepime 150 mg/kg/day IV div q8h (BIII); OR meropenem 60 mg/kg/day IV div q8h (BIII); OR ceftazidime 150 mg/kg/day IV, IM div q8h AND tobramycin 6–7.5 mg/kg/day IM, IV div q8h (BIII); ADD vancomycin 40 mg/kg/day IV q8h OR clindamycin 30 mg/kg/day IV div q8h for serious infection (for CA-MRSA), pending culture results.	Cefepime and meropenem will provide coverage for MSSA in addition to <i>Pseudomonas</i> . Thorough surgical debridement required for <i>Pseudomonas</i> (second drainage procedure needed in at least 20% of children); oral convalescent therapy with ciprofloxacin (BIII). ⁶⁷ Treatment course 7–10 days after surgery.
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C. EYE INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Cellulitis, orbital ^{68–70} (also called post-septal cellulitis; cellulitis of the contents of the orbit; may be associated with orbital abscess; usually secondary to sinus infection; caused by respiratory tract flora and <i>Staphylococcus aureus</i> , including CA-MRSA)	Cefotaxime 150 mg/kg/day div q8h or ceftriaxone 50 mg/kg/day q24h; ADD clindamycin 30 mg/kg/day IV div q8h (for <i>S aureus</i> , including CA-MRSA) OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BIII) OR vancomycin 40 mg/kg/day IV q8h (AIII). If MSSA isolated, use oxacillin/nafcillin IV OR cefazolin IV.	Surgical drainage of significant orbital or subperiosteal abscess if present by CT scan or MRI. Try medical therapy alone for small abscess (BIII). ⁷¹ Treatment course for 10–14 days after surgical drainage, up to 21 days. CT scan or MRI can confirm cure (BIII).
Cellulitis, periorbital ⁷² (preseptal cellulitis)	Periorbital tissues are TENDER with cellulitis. Periorbital edema with sinusitis can look identical but is NOT tender.	Oral antistaphylococcal antibiotic (eg, clindamycin) for empiric therapy of less severe infection; treatment course for 7–10 days
– Associated with entry site lesion on skin (<i>S aureus</i> , including CA-MRSA, group A streptococcus) in the fully immunized child	Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BII) CA-MRSA: clindamycin 30 mg/kg/day IV div q8h or ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BII)	

C. EYE INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– No associated entry site (in febrile, unimmunized infants): pneumococcal or <i>Haemophilus influenzae</i> type b	Ceftriaxone 50 mg/kg/day q24h OR cefotaxime 100–150 mg/kg/day IV, IM div q8h OR cefuroxime 150 mg/kg/day IV div q8h (AII)	Treatment course for 7–10 days; rule out meningitis if bacteremic with <i>H influenzae</i> . Alternative agents for beta-lactamase-positive strains of <i>H influenzae</i> : other 2nd-, 3rd-, or 4th-generation cephalosporins or amoxicillin/clavulanate.
– Periorbital, non-tender erythematous swelling (not true cellulitis, usually associated with sinusitis); sinus pathogens rarely may erode anteriorly, causing cellulitis.	Ceftriaxone 50 mg/kg/day q24h OR cefotaxime 100–150 mg/kg/day IV, IM div q8h OR cefuroxime 150 mg/kg/day IV div q8h (BIII). ADD clindamycin 30 mg/kg/day IV div q8h for more severe infection with suspect <i>S aureus</i> including CA-MRSA or for chronic sinusitis (covers anaerobes) (AIII).	For oral convalescent antibiotic therapy, see Sinusitis, acute; total treatment course of 14–21 days or 7 days after resolution of symptoms.
Conjunctivitis, acute (<i>Haemophilus</i> and pneumococcus predominantly) ^{73–75}	Polymyxin/trimethoprim ophth soln OR polymyxin/bacitracin ophth ointment OR ciprofloxacin ophth soln (BII), for 7–10 days. For neonatal infection, see Chapter 5. Steroid-containing therapy only if HSV ruled out.	Other topical antibiotics (gentamicin, tobramycin, erythromycin, besifloxacin, moxifloxacin, norfloxacin, ofloxacin, levofloxacin) may offer advantages for particular pathogens (CII). High rates of resistance to sulfacetamide.
Conjunctivitis, herpetic ^{76–79}	1% trifluridine or 0.15% ganciclovir ophth gel (AII) AND acyclovir PO (80 mg/kg/day div qid; max daily dose: 3,200 mg/day) has been effective in limited studies (BIII). Oral valacyclovir (60 mg/kg/day div tid) has superior pharmacokinetics to oral acyclovir and can be considered for systemic treatment, as can parenteral (IV) acyclovir if extent of disease is severe (CIII).	Refer to ophthalmologist. Recurrences common; corneal scars may form. Topical steroids for keratitis concurrent with topical antiviral soln or oral antiviral therapy. Long-term prophylaxis (≥ 1 y) for suppression of recurrent infection with oral acyclovir 300 mg/m ² /dose PO tid (max 400 mg/dose). Potential risks must balance potential benefits to vision (BIII).

Dacryocystitis	No antibiotic usually needed; oral therapy for more symptomatic infection, based on Gram stain and culture of pus; topical therapy as for conjunctivitis may be helpful.	Warm compresses; may require surgical probing of nasolacrimal duct.
Endophthalmitis ^{80,81}		
NOTE: Subconjunctival/sub-tenon antibiotics are likely to be required (vancomycin/ceftazidime or clindamycin/gentamicin); steroids commonly used (except for fungal infection); requires anterior chamber or vitreous tap for microbiological diagnosis. Listed systemic antibiotics to be used in addition to ocular injections.		Refer to ophthalmologist; vitrectomy may be necessary for advanced endophthalmitis. No prospective, controlled studies.
– Empiric therapy following open globe injury	Vancomycin 40 mg/kg/day IV div q8h AND cefepime 150 mg/kg/day IV div q8h (AIII)	
– Staphylococcal	Vancomycin 40 mg/kg/day IV div q8h pending susceptibility testing; oxacillin/nafticillin 150 mg/kg/day IV div q6h if susceptible (AIII)	Consider ceftaroline for MRSA treatment, as it may penetrate the vitreous better than vancomycin.
– Pneumococcal, meningococcal, <i>Haemophilus</i>	Ceftriaxone 100 mg/kg/day IV q24h; penicillin G 250,000 U/kg/day IV div q4h if susceptible (AIII)	Rule out meningitis; treatment course for 10–14 days.
– Gonococcal	Ceftriaxone 50 mg/kg q24h IV, IM AND azithromycin (AIII)	Treatment course 7 days or longer.
– <i>Pseudomonas</i>	Cefepime 150 mg/kg/day IV div q8h for 10–14 days (AIII)	Cefepime is preferred over ceftazidime for <i>Pseudomonas</i> based on decreased risk of development of resistance on therapy; meropenem IV or imipenem IV are alternatives (no clinical data). Very poor outcomes.

C. EYE INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
<p>– <i>Candida</i>⁸²</p>	<p>Fluconazole (25 mg/kg loading, then 12 mg/kg/day IV), OR voriconazole (9 mg/kg loading, then 8 mg/kg/day IV); for resistant strains, L-AmB (5 mg/kg/day IV). For chorioretinitis, systemic antifungals PLUS intravitreal amphotericin 5–10 mcg/0.1-mL sterile water OR voriconazole 100 mcg/0.1-mL sterile water or physiologic (normal) saline soln (AIII). Duration of therapy is at least 4–6 wk (AIII).</p>	<p>Echinocandins given IV may not be able to achieve adequate antifungal activity in the eye.</p>
Hordeolum (sty) or chalazion	None (topical antibiotic not necessary)	Warm compresses; I&D when necessary
Retinitis		
<p>– CMV^{83–85} For neonatal, see Chapter 5. For HIV-infected children, https://aidsinfo.nih.gov/guidelines/html/5/pediatric-opportunistic-infection/401/cytomegalovirus (accessed October 4, 2018).</p>	<p>Ganciclovir 10 mg/kg/day IV div q12h for 2 wk (BIII); if needed, continue at 5 mg/kg/day q24h to complete 6 wk total (BIII).</p>	<p>Neutropenia risk increases with duration of therapy. Foscarnet IV and cidofovir IV are alternatives but demonstrate significant toxicities. Oral valganciclovir has not been evaluated in HIV-infected children with CMV retinitis but is an option primarily for older children who weigh enough to receive the adult dose of valganciclovir (CIII). Intravitreal ganciclovir and combination therapy for non-responding, immunocompromised hosts; however, intravitreal injections may not be practical for most children.</p>

D. EAR AND SINUS INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Bullous myringitis (See Otitis media, acute.)	Believed to be a clinical presentation of acute bacterial otitis media	
Mastoiditis, acute (pneumococcus [less since introduction of PCV13], <i>Staphylococcus aureus</i> , including CA-MRSA; group A streptococcus; increasing <i>Pseudomonas</i> in adolescents, <i>Haemophilus rare</i>) ^{86–88}	Cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day q24h AND clindamycin 40 mg/kg/day IV div q8h (BIII) For adolescents: cefepime 150 mg/kg/day IV div q8h AND clindamycin 40 mg/kg/day IV div q8h (BIII)	Rule out meningitis; surgery as needed for mastoid and middle ear drainage. Change to appropriate oral therapy after clinical improvement.
Mastoiditis, chronic (See also Otitis, chronic suppurative.) (anaerobes, <i>Pseudomonas</i> , <i>S aureus</i> [including CA-MRSA]) ⁸⁷	Antibiotics only for acute superinfections (according to culture of drainage); for <i>Pseudomonas</i> : meropenem 60 mg/kg/day IV div q8h, OR pip/tazo 240 mg/kg/day IV div q4–6h for only 5–7 days after drainage stops (BIII)	Daily cleansing of ear important; if no response to antibiotics, surgery. Alternatives: cefepime IV or ceftazidime IV (poor anaerobic coverage with either antibiotic). Be alert for CA-MRSA.
Otitis externa		
Bacterial, swimmer's ear (<i>Pseudomonas aeruginosa</i> , <i>S aureus</i> , including CA-MRSA) ^{89,90}	Topical antibiotics: fluoroquinolone (ciprofloxacin or ofloxacin) with steroid, OR neomycin/polymyxin B/hydrocortisone (BII) Irrigation and cleaning canal of detritus important	Wick moistened with Burow (aluminum acetate topical) soln, used for marked swelling of canal; to prevent swimmer's ear, 2% acetic acid to canal after water exposure will restore acid pH.
– Bacterial, malignant otitis externa (<i>P aeruginosa</i>) ⁹¹	Cefepime 150 mg/kg/day IV div q8h (AIII)	Other antipseudomonal antibiotics should also be effective: ceftazidime IV AND tobramycin IV, OR meropenem IV or imipenem IV or pip/tazo IV. For more mild infection, ciprofloxacin PO.
– Bacterial furuncle of canal (<i>S aureus</i> , including CA-MRSA)	Standard: oxacillin/nafticillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BIII) CA-MRSA: clindamycin 30 mg/kg/day IV div q8h or vancomycin 40 mg/kg/day IV q8h (BIII)	I&D; antibiotics for cellulitis. Oral therapy for mild disease, convalescent therapy. For MSSA: cephalexin. For CA-MRSA: clindamycin, TMP/SMX, OR linezolid (BIII).

D. EAR AND SINUS INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– <i>Candida</i>	Fluconazole 6–12 mg/kg/day PO qd for 5–7 days (CIII)	May occur following antibiotic therapy of bacterial external otitis; debride canal.
Otitis media, acute		
<p>NOTE: The natural history of AOM in different age groups by specific pathogens has not been well defined; therefore, the actual contribution of antibiotic therapy on resolution of disease had also been poorly defined until 2 blinded, prospective studies using amox/clav vs placebo were published in 2011,^{92,93} although neither study used tympanocentesis to define a pathogen. The benefits and risks (including development of antibiotic resistance) of antibiotic therapy for AOM need to be further evaluated before the most accurate advice on the “best” antibiotic can be provided. However, based on available data, for most children, amoxicillin or amox/clav can be used initially. Considerations for the need for extended antimicrobial activity of amox/clav include severity of disease, young age of the child, previous antibiotic therapy within 6 months, and child care attendance, which address the issues of types of pathogens and antibiotic resistance patterns to expect. However, with universal PCV13 immunization, data suggest that the risk of antibiotic-resistant pneumococcal otitis has decreased but the percent of <i>Haemophilus</i> responsible for AOM have increased; therefore, some experts recommend use of amox/clav as first-line therapy for well-documented AOM. The most current AAP guidelines⁹⁴ and meta-analyses^{95,96} suggest the greatest benefit with therapy occurs in children with bilateral AOM who are younger than 2 years; for other children, close observation is also an option. AAP guidelines provide an option to treatment in non-severe cases, particularly disease in older children, to provide a prescription to parents but have them only fill the prescription if the child deteriorates.⁹⁴ Although prophylaxis is only rarely indicated, amoxicillin or other antibiotics can be used in half the therapeutic dose once or twice daily to prevent infections if the benefits outweigh the risks of development of resistant organisms for that child.⁹⁴</p>		
– Newborns	See Chapter 5.	
– Infants and children (pneumococcus, <i>Haemophilus influenzae</i> non-type b, <i>Moraxella</i> most common) ^{97–99}	<p>Usual therapy: amoxicillin 90 mg/kg/day PO div bid, with or without clavulanate; failures of amoxicillin in children not immunized with PCV13 will most likely be caused by beta-lactamase-producing <i>Haemophilus</i> (or <i>Moraxella</i>).</p> <p>a) For <i>Haemophilus</i> strains that are beta-lactamase positive, the following oral antibiotics offer better in vitro activity than amoxicillin: amox/clav, cefdinir, cefpodoxime, cefuroxime, ceftriaxone IM, levofloxacin.</p>	See Chapter 11 for dosages. Published data suggest continued presence of penicillin resistance in pneumococci isolated in the post-PCV13 era, ¹⁰⁰ high-dosage amoxicillin (90 mg/kg/day) should still be used for empiric therapy. The high serum and middle ear fluid concentrations achieved with 45 mg/kg/dose of amoxicillin, combined with a long half-life in middle ear fluid, allow for a therapeutic antibiotic exposure in the middle ear with only twice-daily dosing; high-dose amoxicillin

- b) For pen-R pneumococci: high-dosage amoxicillin achieves greater middle ear activity than oral cephalosporins. Options include ceftriaxone IM 50 mg/kg/day q24h for 1–3 doses; OR levofloxacin 20 mg/kg/day PO div bid for children ≤ 5 y and 10 mg/kg PO qd for children > 5 y; OR a macrolide-class antibiotic*: azithromycin PO at 1 of 3 dosages: (1) 10 mg/kg on day 1, followed by 5 mg/kg qd on days 2–5; (2) 10 mg/kg qd for 3 days; or (3) 30 mg/kg once.
- *Caution:** Up to 40% of pneumococci are macrolide resistant.
- (90 mg/kg/day) with clavulanate (Augmentin ES) is also available. If published data subsequently document decreasing resistance to amoxicillin, standard dosage (45 mg/kg/day) can again be recommended.
- Tympanocentesis should be performed in children who fail second-line therapy.

Otitis, chronic suppurative <i>(P aeruginosa, S aureus, including CA-MRSA, and other respiratory tract/skin flora)</i> ^{90,101,102}	<p>Topical antibiotics: fluoroquinolone (ciprofloxacin, ofloxacin, besifloxacin) with or without steroid (BIII)</p> <p>Cleaning of canal, view of tympanic membrane, for patency; cultures important</p>	<p>Presumed middle ear drainage through open tympanic membrane. Avoid aminoglycoside-containing therapy given risk of ototoxicity.¹⁰³</p> <p>Other topical fluoroquinolones with/without steroids available.</p>
Sinusitis, acute (<i>H influenzae</i> non-type b, pneumococcus, group A streptococcus, <i>Moraxella</i>) ^{104–108}	<p>Same antibiotic therapy as for AOM as pathogens similar: amoxicillin 90 mg/kg/day PO div bid, OR for children at higher risk of <i>Haemophilus</i>, amox/clav 14:1 ratio, with amoxicillin component at 90 mg/kg/day PO div bid (BIII).</p> <p>Therapy of 14 days may be necessary while mucosal swelling resolves and ventilation is restored.</p>	<p>IDSa sinusitis guidelines recommend amox/clav as first-line therapy,¹⁰⁷ while AAP guidelines (same pediatric authors) recommend amoxicillin.¹⁰⁵ Lack of data prevents a definitive evidence-based recommendation. The same antibiotic therapy considerations used for AOM apply to acute bacterial sinusitis.</p> <p>There is no controlled evidence to determine whether the use of antihistamines, decongestants, or nasal irrigation is efficacious in children with acute sinusitis.¹⁰⁶</p>

E. OROPHARYNGEAL INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Dental abscess (mixed aerobic/anaerobic oral flora) ^{109,110}	Clindamycin 30 mg/kg/day PO, IV, IM div q6–8h OR penicillin G 100–200,000 U/kg/day IV div q6h (AIII)	Amox/clav PO; amoxicillin PO is another option. Metronidazole has excellent anaerobic activity but no aerobic activity. Tooth extraction usually necessary. Erosion of abscess may occur into facial, sinusitis, deep head, and neck compartments.
Diphtheria pharyngitis ¹¹¹	Erythromycin 40–50 mg/kg/day PO div qid for 14 days OR penicillin G 150,000 U/kg/day IV div q6h; PLUS DAT (AIII)	DAT, a horse antisera, is investigational and only available from CDC Emergency Operations Center at 770/488-7100; www.cdc.gov/diphtheria/dat.html (accessed October 4, 2018).
Epiglottitis (supraglottitis; <i>Haemophilus influenzae</i> type b in an unimmunized child; rarely pneumococcus, <i>Staphylococcus aureus</i>) ^{112,113}	Ceftriaxone 50 mg/kg/day IV, IM q24h OR cefotaxime 150 mg/kg/day IV div q8h for 7–10 days	Emergency: provide airway. For <i>S aureus</i> (causes only 5% of epiglottitis), consider adding clindamycin 40 mg/kg/day IV div q8h.
Gingivostomatitis, herpetic ^{114–116}	Acyclovir 80 mg/kg/day PO div qid (max dose: 800 mg) for 7 days (for severe disease, use IV therapy at 30 mg/kg/day div q8h) (BIII); OR for infants ≥3 mo, valacyclovir 20 mg/kg/dose PO bid (max dose: 1,000 mg; instructions for preparing liquid formulation with 28-day shelf life included in package insert) (CIII). ¹¹⁶	Early treatment is likely to be the most effective. Start treatment as soon as oral intake is compromised. Valacyclovir is the prodrug of acyclovir that provides improved oral bioavailability compared with oral acyclovir. Extended duration of therapy may be needed for immunocompromised children. The oral acyclovir dose provided is safe and effective for varicella; 75 mg/kg/day div into 5 equal doses has been studied for HSV. ¹¹⁵ Maximum daily acyclovir dose should not exceed 3,200 mg.

Lemierre syndrome <i>(Fusobacterium necrophorum</i> primarily, new reports with MRSA) ^{117–121} (pharyngitis with internal jugular vein septic thrombosis, postanginal sepsis, necrobaecillosis)	Empiric: meropenem 60 mg/kg/day div q8h (or 120 mg/kg/day div q8h for CNS metastatic foci) (AIII) OR ceftriaxone 100 mg/kg/day q24h AND metronidazole 40 mg/kg/day div q8h or clindamycin 40 mg/kg/day div q6h (BIII). ADD empiric vancomycin if MRSA suspected.	Anecdotal reports suggest metronidazole may be effective for apparent failures with other agents. Often requires anticoagulation. Metastatic and recurrent abscesses often develop while on active, appropriate therapy, requiring multiple debridements and prolonged antibiotic therapy. Treat until CRP and ESR are normal (AIII).
Peritonsillar cellulitis or abscess (group A streptococcus with mixed oral flora, including anaerobes, CA-MRSA) ¹²²	Clindamycin 30 mg/kg/day PO, IV, IM div q8h; for preschool infants with consideration of enteric bacilli, ADD cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day IV q24h (BIII)	Consider incision and drainage for abscess. Alternatives: meropenem or imipenem or pip/tazo. Amox/clav for convalescent oral therapy (BIII). No controlled prospective data on benefits/risks of steroids. ¹²³
Pharyngitis (group A streptococcus primarily) ^{8,124–126}	Amoxicillin 50–75 mg/kg/day PO, either qd, bid, or tid for 10 days OR penicillin V 50–75 mg/kg/day PO, either div, bid, or tid, OR benzathine penicillin 600,000 units IM for children <27 kg, 1.2 million units IM if >27 kg, as a single dose (AII) For penicillin-allergic children: erythromycin (estolate at 20–40 mg/kg/day PO div bid to qid; OR 40 mg/kg/day PO div bid to qid) for 10 days; OR azithromycin 12 mg/kg qd for 5 days* (AII); OR clindamycin 30 mg/kg/day PO div tid *This is the dose investigated and FDA approved for chil- dren since 1994.	Although penicillin V is the most narrow spectrum treatment, amoxicillin displays better GI absorption than oral penicillin V; the suspension is better tolerated. These advantages should be balanced by the unnecessary increased spectrum of activity. Once-daily amoxicillin dosage: for children 50 mg/kg (max 1,000–1,200 mg). ⁸ Meta-analysis suggests that oral cephalosporins are more effective than penicillin for treatment of strep. ¹²⁷ A 5-day treatment course is FDA approved for azithromycin at 12 mg/kg/day for 5 days, and some oral cephalosporins have been approved (cefdinir, cefpodoxime), with rapid clinical response to treatment that can also be seen with other antibiotics; a 10-day course is preferred for the prevention of ARF, particularly areas where ARF is prevalent, as no data exist on efficacy of 5 days of therapy for prevention of ARF. ^{126,128}

E. OROPHARYNGEAL INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Retropharyngeal, parapharyngeal, or lateral pharyngeal cellulitis or abscess (mixed aerobic/anaerobic flora, now including CA-MRSA) ^{122,129–131}	Clindamycin 40 mg/kg/day IV div q8h AND cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day IV q24h	Consider I&D; possible airway compromise, mediastinitis. Alternatives: meropenem or imipenem (BIII); pip/tazo. Can step-down to less broad-spectrum coverage based on cultures. Amox/clav for convalescent oral therapy (but no activity for MRSA) (BIII).
Tracheitis, bacterial (<i>S aureus</i> , including CA-MRSA; group A streptococcus; pneumococcus; <i>H influenzae</i> type b, rarely <i>Pseudomonas</i>) ^{132,133}	Vancomycin 40 mg/kg/day IV div q8h or clindamycin 40 mg/kg/day IV div q8h AND ceftriaxone 50 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (BIII) OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h (BIII)	For susceptible <i>S aureus</i> , oxacillin/naftillin or cefazolin. May represent bacterial superinfection of viral laryngotracheobronchitis, including influenza.

F. LOWER RESPIRATORY TRACT INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Abscess, lung		
– Primary (severe, necrotizing community-acquired pneumonia caused by pneumococcus, <i>Staphylococcus aureus</i> , including CA-MRSA, group A streptococcus) ^{134–136}	Empiric therapy with ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND clindamycin 40 mg/kg/day div q8h or vancomycin 45 mg/kg/day IV div q8h for 14–21 days or longer (AIII) OR (for MRSA) ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII)	For severe CA-MRSA infections, see Chapter 4. Bronchoscopy may be necessary if abscess fails to drain; surgical excision rarely necessary for pneumococcus but may be important for CA-MRSA and MSSA. Focus antibiotic coverage based on culture results. For MSSA: oxacillin/naftillin or cefazolin.
– Secondary to aspiration (ie, foul smelling; polymicrobial infection with oral aerobes and anaerobes) ¹³⁷	Clindamycin 40 mg/kg/day IV div q8h or meropenem 60 mg/kg/day IV div q8h for 10 days or longer (AIII)	Alternatives: imipenem IV or pip/tazo IV (BIII) Oral step-down therapy with clindamycin or amox/clav (BIII)
Allergic bronchopulmonary aspergillosis ¹³⁸	Prednisone 0.5 mg/kg qd for 1–2 wk and then taper (BII) AND voriconazole 18 mg/kg/day PO div q12h load followed by 16 mg/kg/day div q12h (AIII) OR itraconazole 10 mg/kg/day PO div q12h (BII). Voriconazole and itraconazole require trough concentration monitoring.	Not all allergic pulmonary disease is associated with true fungal infection. Larger steroid dosages to control inflammation may lead to tissue invasion by <i>Aspergillus</i> . Corticosteroids are the cornerstone of therapy for exacerbations, and itraconazole has a demonstrable corticosteroid-sparing effect. Voriconazole not as well studied in allergic bronchopulmonary aspergillosis but is more active than itraconazole.

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Aspiration pneumonia (polymicrobial infection with oral aerobes and anaerobes) ¹³⁷	Clindamycin 40 mg/kg/day IV div q8h; ADD ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h for additional <i>Haemophilus</i> activity OR meropenem 60 mg/kg/day IV div q8h; for 10 days or longer (BIII).	Alternatives: imipenem IV or pip/tazo IV (BIII) Oral step-down therapy with clindamycin or amox/clav (BIII)
Atypical pneumonia (See <i>Mycoplasma pneumoniae</i> , Legionnaires disease.)		
Bronchitis (bronchiolitis), acute ¹³⁹	For bronchitis/bronchiolitis in children, no antibiotic needed for most cases, as disease is usually viral	Multicenter global studies with anti-RSV therapy are currently underway.
Community-acquired pneumonia		
(See Pneumonia: Community-acquired, bronchopneumonia; Pneumonia: Community-acquired, lobar consolidation.)		
Cystic fibrosis: Seek advice from experts in acute and chronic management. Larger than standard dosages of beta-lactam antibiotics are required in most patients with cystic fibrosis. ¹⁴⁰		
– Acute exacerbation (<i>Pseudomonas aeruginosa</i> primarily; also <i>Burkholderia cepacia</i> , <i>Stenotrophomonas maltophilia</i> , <i>S aureus</i> , including CA-MRSA, nontuberculous mycobacteria) ^{141–146}	Cefepime 150–200 mg/kg/day div q8h or meropenem 120 mg/kg/day div q6h AND tobramycin 6–10 mg/kg/day IM, IV div q6–8h for treatment of acute exacerbation (All); alternatives: imipenem, ceftazidime, or ciprofloxacin 30 mg/kg/day PO, IV div tid. May require vancomycin 60–80 mg/kg/day IV div q8h for MRSA, OR ceftaroline 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BIII). Duration of therapy not well defined: 10–14 days (BIII). ¹⁴²	Monitor concentrations of aminoglycosides, vancomycin. Insufficient evidence to recommend routine use of inhaled antibiotics for acute exacerbations. ¹⁴⁷ Cultures with susceptibility and synergy testing will help select antibiotics, as multidrug resistance is common, but synergy testing is not well standardized. ^{148,149} Combination therapy may provide synergistic killing and delay the emergence of resistance (BIII). Attempt at early eradication of new onset <i>Pseudomonas</i> may decrease progression of disease. ^{144,150} Failure to respond to antibacterials should prompt evaluation for appropriate drug doses and for invasive/allergic fungal disease.

– Chronic inflammation (Minimize long-term damage to lung.)	<p>Inhaled tobramycin 300 mg bid, cycling 28 days on therapy, 28 days off therapy, is effective adjunctive therapy between exacerbation (AI).^{148,151}</p> <p>Inhaled aztreonam¹⁵² provides an alternative to inhaled tobramycin (AI).</p> <p>Azithromycin adjunctive chronic therapy, greatest benefit for those colonized with <i>Pseudomonas</i> (AII).^{153,154}</p>	<p>Alternative inhaled antibiotics: aztreonam¹⁵⁴; colistin^{147,155} (BIII).</p> <p>Two newer powder preparations of inhaled tobramycin are available.</p>
Pertussis ^{156–158}	<p>Azithromycin: those ≥ 6 mo, 10 mg/kg/day for day 1, then 5 mg/kg/day for days 2–5; for those < 6 mo, 10 mg/kg/day for 5 days; or clarithromycin 15 mg/kg/day div bid for 7 days; or erythromycin (estolate preferable) 40 mg/kg/day PO div qid for 7–10 days (AII)</p> <p>Alternative: TMP/SMX 8 mg/kg/day TMP div bid for 14 days (BIII)</p>	<p>Azithromycin and clarithromycin are better tolerated than erythromycin; azithromycin is preferred in young infants to reduce pyloric stenosis risk (see Chapter 5). Provide prophylaxis to family members.</p> <p>Unfortunately, no adjunctive therapy has been shown beneficial in decreasing the cough.¹⁵⁹</p>
Pneumonia: Community-acquired, bronchopneumonia		
– Mild to moderate illness (overwhelmingly viral, especially in preschool children) ¹⁶⁰	No antibiotic therapy unless epidemiologic, clinical, or laboratory reasons to suspect bacteria or <i>Mycoplasma</i> .	Broad-spectrum antibiotics may increase risk of subsequent infection with antibiotic-resistant pathogens.

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
<p>– Moderate to severe illness (pneumococcus; group A streptococcus; <i>S aureus</i>, including CA-MRSA and for unimmunized children, <i>Haemophilus influenzae</i> type b; or <i>Mycoplasma pneumoniae</i>^{134,135,161–163}; and for those with aspiration and underlying comorbidities: <i>Haemophilus influenzae</i>, non-typable)</p>	<p>Empiric therapy For regions with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 150–200 mg/kg/day div q6h. For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AI). For suspected CA-MRSA: vancomycin 40–60 mg/kg/day (AIII)³ OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII).¹³⁶ For suspect <i>Mycoplasma</i>/atypical pneumonia agents, particularly in school-aged children, ADD azithromycin 10 mg/kg IV, PO on day 1, then 5 mg/kg qd for days 2–5 of treatment (AII).</p>	<p>Tracheal aspirate or bronchoalveolar lavage for Gram stain/culture for severe infection in intubated children. Check vancomycin serum concentrations and renal function, particularly at the higher dosage needed to achieve an AUC:MIC of 400 for CA-MRSA pneumonia. Alternatives to azithromycin for atypical pneumonia include erythromycin IV, PO, or clarithromycin PO, or doxycycline IV, PO for children >7 y, or levofloxacin. New data suggest that combination empiric therapy with a beta-lactam and a macrolide confers no benefit over beta-lactam monotherapy.^{164,165} Empiric oral outpatient therapy for less severe illness: high-dosage amoxicillin 80–100 mg/kg/day PO div tid (NOT bid) (BIII).</p>
Pneumonia: Community-acquired, lobar consolidation		
<p>Pneumococcus (May occur with non-vaccine strains, even if immunized for pneumococcus.)^{134,135,161–163}</p>	<p>Empiric therapy For regions with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 150–200 mg/kg/day div q6h. For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AI); for more severe disease ADD clindamycin 40 mg/kg/day div q8h or vancomycin</p>	<p>Change to PO after improvement (decreased fever, no oxygen needed); treat until clinically asymptomatic and chest radiography significantly improved (7–21 days) (BIII). No reported failures of ceftriaxone/cefotaxime for pen-R pneumococcus; no need to add empiric vancomycin for this reason (CIII). Oral therapy for pneumococcus and <i>Haemophilus</i> may also be successful with amox/clav, cefdinir, cefixime, cefpodoxime, or cefuroxime.</p>

	<p>40–60 mg/kg/day div q8h for suspect <i>S aureus</i> (AIII).³</p> <p>For suspect <i>Mycoplasma</i>/atypical pneumonia agents, particularly in school-aged children, ADD azithromycin 10 mg/kg IV, PO on day 1, then 5 mg/kg qd for days 2–5 of treatment (AII).</p> <p>Empiric oral outpatient therapy for less severe illness: high-dosage amoxicillin 80–100 mg/kg/day PO div tid (NOT bid); for <i>Mycoplasma</i>, ADD a macrolide as described previously (BIII).</p>	<p>Levofloxacin is an alternative, particularly for those with severe allergy to beta-lactam antibiotics (BI),¹⁶⁶ but, due to theoretical cartilage toxicity concerns for humans, should not be first-line therapy.</p>
– Pneumococcal, pen-S	<p>Penicillin G 250,000–400,000 U/kg/day IV div q4–6h for 10 days (BII) OR ampicillin 150–200 mg/kg/day IV div q6h</p>	<p>After improvement, change to PO amoxicillin 50–75 mg/kg/day PO div tid OR penicillin V 50–75 mg/kg/day div qid.</p>
– Pneumococcal, pen-R	<p>Ceftriaxone 75 mg/kg/day q24h, or cefotaxime 150 mg/kg/day div q8h for 10–14 days (BIII)</p>	<p>Addition of vancomycin has not been required for eradication of pen-R strains.</p> <p>For oral convalescent therapy, high-dosage amoxicillin (100–150 mg/kg/day PO div tid), clindamycin (30 mg/kg/day PO div tid), linezolid (30 mg/kg/day PO div tid), or levofloxacin PO.</p>
<i>Staphylococcus aureus</i> (including CA-MRSA) ^{3,7,134,161,167,168}	<p>For MSSA: oxacillin/nafticillin 150 mg/kg/day IV div q6h or cefazolin 100 mg/kg/day IV div q8h (AII).</p> <p>For CA-MRSA: vancomycin 60 mg/kg/day OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h; ≥6 mo, 45 mg/kg/day IV div q8h (max single dose 600 mg) (BII)¹³⁶; may need addition of rifampin, clindamycin, or gentamicin (AIII) (see Chapter 4).</p>	<p>Check vancomycin serum concentrations and renal function, particularly at the higher dosage designed to attain an AUC:MIC of 400, or serum trough concentrations of 15 mcg/mL for invasive CA-MRSA disease.</p> <p>For life-threatening disease, optimal therapy of CA-MRSA is not defined: add gentamicin and/or rifampin for combination therapy (CIII).</p> <p>Linezolid 30 mg/kg/day IV, PO div q8h is another option, more effective in adults than vancomycin for MRSA nosocomial pneumonia¹⁶⁹ (follow platelets and WBC count weekly).</p>

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Pneumonia: Immunosuppressed, neutropenic host ¹⁷⁰ <i>(P aeruginosa, other community-associated or nosocomial Gram-negative bacilli, S aureus, fungi, AFB, Pneumocystis, viral [adenovirus, CMV, EBV, influenza, RSV, others])</i>	Cefepime 150 mg/kg/day IV div q8h and tobramycin 6.0–7.5 mg/kg/day IM, IV div q8h (AII), OR meropenem 60 mg/kg/day div q8h (AII) ± tobramycin (BIII); AND if <i>S aureus</i> (including MRSA) is suspected clinically, ADD vancomycin 40–60 mg/kg/day IV div q8h (AIII) OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h; ≥6 mo, 45 mg/kg/day IV div q8h (max single dose 600 mg) (BIII).	Biopsy or bronchoalveolar lavage usually needed to determine need for antifungal, antiviral, antimycobacterial treatment. Antifungal therapy usually started if no response to antibiotics in 48–72 h (AmB, voriconazole, or caspofungin/micafungin—see Chapter 8). Amikacin 15–22.5 mg/kg/day is an alternative aminoglycoside. Use 2 active agents for definitive therapy for <i>Pseudomonas</i> for neutropenic hosts to assist clearing the pathogen; may decrease risk of resistance (BIII).
– Pneumonia: Interstitial pneumonia syndrome of early infancy	If <i>Chlamydia trachomatis</i> suspected, azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 OR erythromycin 40 mg/kg/day PO div qid for 14 days (BII)	Most often respiratory viral pathogens, CMV, or chlamydial; role of <i>Ureaplasma</i> uncertain
– Pneumonia, nosocomial (health care-associated/ventilator-associated) <i>(P aeruginosa, Gram-negative enteric bacilli [Enterobacter, Klebsiella, Serratia, Escherichia coli], Acinetobacter, Stenotrophomonas, and Gram-positive organisms including CA-MRSA and Enterococcus)</i> ^{171–173}	Commonly used regimens Meropenem 60 mg/kg/day div q8h, OR pipo-tazo 240–300 mg/kg/day div q6–8h, OR cefepime 150 mg/kg/day div q8h; ± gentamicin 6.0–7.5 mg/kg/day div q8h (AIII); ADD vancomycin 40–60 mg/kg/day div q8h for suspect CA-MRSA (AIII).	Empiric therapy should be institution specific, based on your hospital's nosocomial pathogens and susceptibilities. Pathogens that cause nosocomial pneumonia often have multidrug resistance. Cultures are critical. Empiric therapy also based on child's prior colonization/infection. Do not treat colonization, though. For MDR Gram-negative bacilli, IV therapy options include ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, or colistin. Aerosol delivery of antibiotics may be required for MDR pathogens, but little high-quality controlled data are available for children. ¹⁷⁴

<p>– Pneumonia: With pleural fluid/empyema (same pathogens as for community-associated bronchopneumonia) (Based on extent of fluid and symptoms, may benefit from chest tube drainage with fibrinolysis or video-assisted thorascopic surgery.)^{161,175–178}</p>	<p>Empiric therapy: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND vancomycin 40–60 mg/kg/day IV div q8h (BIII) OR ceftaroline as single drug therapy: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII)</p>	<p>Initial therapy based on Gram stain of empyema fluid; typically, clinical improvement is slow, with persisting but decreasing “spiking” fever for 2–3 wk.</p>
<p>– Group A streptococcal</p>	<p>Penicillin G 250,000 U/kg/day IV div q4–6h for 10 days (BII)</p>	<p>Change to PO amoxicillin 75 mg/kg/day div tid or penicillin V 50–75 mg/kg/day div qid to tid after clinical improvement (BIII).</p>
<p>– Pneumococcal</p>	<p>(See Pneumonia: Community-acquired, lobar consolidation.)</p>	
<p><i>S aureus</i> (including CA-MRSA)^{3,7,134,167}</p>	<p>For MSSA: oxacillin/naftillin or ceftazolin (AII). For CA-MRSA: use vancomycin 60 mg/kg/day (AIII) (designed to attain an AUC:MIC of 400, or serum trough concentrations of 15 mcg/mL); follow serum concentrations and renal function; OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII)¹³⁶; may need additional antibiotics (see Chapter 4).</p>	<p>For life-threatening disease, optimal therapy of CA-MRSA is not defined; add gentamicin and/or rifampin. For MRSA nosocomial pneumonia in adults, linezolid was superior to vancomycin.¹⁶⁹ Oral convalescent therapy for MSSA: cephalexin PO; for CA-MRSA: clindamycin or linezolid PO. Total course for 21 days or longer (AIII). For children infected who do not tolerate high-dose vancomycin, alternatives include ceftaroline, clindamycin, and linezolid. Do NOT use daptomycin for pneumonia.</p>
<p>Pneumonias of other established etiologies (See Chapter 7 for treatment by pathogen.)</p>		
<p>– <i>Chlamydia</i>¹⁷⁹ <i>pneumoniae</i>, <i>Chlamydophila psittaci</i>, or <i>Chlamydia trachomatis</i></p>	<p>Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 or erythromycin 40 mg/kg/day PO div qid; for 14 days</p>	<p>Doxycycline (patients >7 y). Levofloxacin should also be effective.</p>

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– CMV (immunocompromised host) ^{180,181} (See chapters 5 and 9 for CMV infection in newborns and older children, respectively.)	Ganciclovir IV 10 mg/kg/day IV div q12h for 2 wk (BIII); if needed, continue at 5 mg/kg/day q24h to complete 4–6 wk total (BIII).	Bone marrow transplant recipients with CMV pneumonia who fail to respond to ganciclovir therapy alone may benefit from therapy with IV CMV hyperimmunoglobulin and ganciclovir given together (BII). ^{182–184} Oral valganciclovir may be used for convalescent therapy (BIII). Foscarnet for ganciclovir-resistant strains.
– <i>E coli</i>	Ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AII)	For cephalosporin-resistant strains (ESBL producers), use meropenem, imipenem, or ertapenem (AIII). Use high-dose ampicillin if susceptible.
– <i>Enterobacter</i> spp	Cefepime 100 mg/kg/day div q12h or meropenem 60 mg/kg/day div q8h; OR ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h (AIII)	Addition of aminoglycoside to 3rd-generation cephalosporins may retard the emergence of ampC-mediated constitutive high-level resistance, but concern exists for inadequate aminoglycoside concentration in airways ¹⁷⁴ ; not an issue with beta-lactams (cefepime, meropenem, or imipenem).
– <i>Francisella tularensis</i> ¹⁸⁵	Gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h for 10 days or longer for more severe disease (AIII); for less severe disease, doxycycline PO for 14–21 days (AIII)	Alternatives for oral therapy of mild disease: ciprofloxacin or levofloxacin (BIII)
– Fungi (See Chapter 8.) Community-associated pathogens, vary by region (eg, <i>Coccidioides</i> , ^{186,187} <i>Histoplasma</i>) ^{188,189} <i>Aspergillus</i> , mucormycosis, other mold infections in immunocompromised hosts (See Chapter 8.)	For detailed pathogen-specific recommendations, see Chapter 8. For suspected endemic fungi or mucormycosis in immunocompromised host, treat empirically with a lipid AmB and not voriconazole; biopsy needed to guide therapy.	For normal hosts, triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) are better tolerated than AmB and equally effective for many community-associated pathogens (see Chapter 2). For dosage, see Chapter 8. Check voriconazole trough concentrations; need to be at least >2 mcg/mL.

	For suspected invasive aspergillosis, treat with voriconazole (AI) (load 18 mg/kg/day div q12h on day 1, then continue 16 mg/kg/day div q12h).	For refractory <i>Coccidioides</i> infection, posaconazole or combination therapy with voriconazole and caspofungin may be effective ¹⁸⁶ (AIII).
<ul style="list-style-type: none"> – Influenza virus^{190,191} – Recent seasonal influenza A and B strains continue to be resistant to adamantanes. 	<p>Empiric therapy, or documented influenza A or B</p> <p>Oseltamivir^{191,192} (AII):</p> <p><12 mo:</p> <p>Term infants 0–8 mo: 3 mg/kg/dose bid</p> <p>9–11 mo: 3.5 mg/kg/dose bid</p> <p>≥12 mo:</p> <p>≤15 kg: 30 mg PO bid</p> <p>>15–23 kg: 45 mg PO bid</p> <p>>23–40 kg: 60 mg PO bid</p> <p>>40 kg: 75 mg PO bid</p> <p>Zanamivir inhaled (AII): for those ≥7 y 10 mg (two 5-mg inhalations) bid</p> <p>Peramivir (BII):</p> <p>2–12 y: single IV dose of 12 mg/kg, up to 600 mg max</p> <p>13–17 y: Single IV dose of 600 mg</p> <p>Baloxavir (BI):</p> <p>≥12 y:</p> <p>40–79 kg: single PO dose of 40 mg</p> <p>≥80 kg: single PO dose of 80 mg</p>	<p>Check for antiviral susceptibility each season at www.cdc.gov/flu/professionals/antivirals/index.htm (updated June 28, 2018; accessed October 4, 2018).</p> <p>For children 12–23 mo, the unit dose of 30 mg/dose may provide inadequate drug exposure. 3.5 mg/kg/dose PO bid has been studied,¹⁹² but sample sizes have been inadequate to recommend weight-based dosing at this time.</p> <p>The adamantanes (amantadine and rimantadine) had activity against influenza A prior to the late 1990s, but all circulating A strains of influenza have been resistant for many years. Influenza B is intrinsically resistant to adamantanes.</p> <p>Limited data for preterm neonates.¹⁹¹</p> <p><38 wk PMA (gestational plus chronologic age):</p> <p>1.0 mg/kg/dose, PO bid.</p> <p>38–40 wk PMA: 1.5 mg/kg/dose, PO bid.</p> <p>Baloxavir under study in children <12 y.</p>
– <i>Klebsiella pneumoniae</i> ^{193,194}	Ceftriaxone 50–75 mg/kg/day IV, IM q24h OR cefotaxime 150 mg/kg/day IV, IM div q8h (AIII); for ceftriaxone-resistant strains (ESBL strains), use meropenem 60 mg/kg/day IV div q8h (AIII) or other carbapenem.	For <i>K pneumoniae</i> that contain ESBLs, piperacillin/tazobactam and fluoroquinolones are other options. New data presented in 2018 in adults suggest that outcomes with piperacillin/tazobactam are inferior to carbapenems. ¹⁹⁴ For KPC-producing strains that are resistant to meropenem: alternatives include ceftazidime/avibactam (FDA-approved for adults, pediatric studies in progress), fluoroquinolones, or colistin (BIII).

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– Legionnaires disease (<i>Legionella pneumophila</i>)	Azithromycin 10 mg/kg IV, PO q24h for 5 days (AIII)	Alternatives: clarithromycin, erythromycin, ciprofloxacin, levofloxacin, doxycycline
– Mycobacteria, nontuberculous (<i>Mycobacterium avium</i> complex most common) ¹⁹⁵	In a normal host: azithromycin PO or clarithromycin PO for 6–12 wk if susceptible For more extensive disease: a macrolide AND rifampin AND ethambutol; ± amikacin or streptomycin (AIII)	Highly variable susceptibilities of different nontuberculous mycobacterial species. Culture and susceptibility data are important for success. Check if immunocompromised: HIV or gamma-interferon receptor deficiency
– <i>Mycobacterium tuberculosis</i> (See Tuberculosis.)		
– <i>Mycoplasma pneumoniae</i> ^{161,196}	Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5, or clarithromycin 15 mg/kg/day div bid for 7–14 days, or erythromycin 40 mg/kg/day PO div qid for 14 days	<i>Mycoplasma</i> often causes self-limited infection and does not routinely require treatment (AIII). Little prospective, well-controlled data exist for treatment of documented mycoplasma pneumonia specifically in children. ¹⁹⁶ Doxycycline (patients >7 y) or levofloxacin. Macrolide-resistant strains have recently appeared worldwide. ¹⁹⁷
– <i>Paragonimus westermani</i>	See Chapter 10.	

<p>– <i>Pneumocystis jirovecii</i> (formerly <i>Pneumocystis carinii</i>)¹⁹⁸; disease in immunosuppressed children and those with HIV</p>	<p>Severe disease: preferred regimen is TMP/SMX, 15–20 mg TMP component/kg/day IV div q8h for 3 wk (AI).</p> <p>Mild to moderate disease: may start with IV therapy, then after acute pneumonitis is resolving, TMP/SMX 20 mg of TMP/kg/day PO div qid for 21 days (AI).</p> <p>Use steroid adjunctive treatment for more severe disease (AI).</p>	<p>Alternatives for TMP/SMX intolerant, or clinical failure: pentamidine 3–4 mg IV qd, infused over 60–90 min (AI); TMP AND dapson; OR primaquine AND clindamycin; OR atovaquone.</p> <p>Prophylaxis: TMP/SMX as 5 mg TMP/kg/day PO, divided in 2 doses, q12h, daily or 3 times/wk on consecutive days (AI); OR TMP/SMX 5 mg TMP/kg/day PO as a single dose, once daily, given 3 times/wk on consecutive days (AI); once-weekly regimens have also been successful¹⁹⁹; OR dapsone 2 mg/kg (max 100 mg) PO qd, or 4 mg/kg (max 200 mg) once weekly; OR atovaquone: 30 mg/kg/day for infants 1–3 mo, 45 mg/kg/day for infants 4–24 mo, and 30 mg/kg/day for children >24 mo.</p>
<p>– <i>P aeruginosa</i>^{174,200,201}</p>	<p>Cefepime 150 mg/kg/day IV div q8h ± tobramycin 6.0–7.5 mg/kg/day IM, IV div q8h (AI). Alternatives: meropenem 60 mg/kg/day div q8h, OR pip/tazo 240–300 mg/kg/day div q6–8h (AI) ± tobramycin (BII).</p>	<p>Ciprofloxacin IV, or colistin IV for MDR strains of <i>Enterobacteriaceae</i> or <i>Pseudomonas</i> (See Chapter 4.)²⁰²</p>
<p>RSV infection (bronchiolitis, pneumonia)²⁰³</p>	<p>For immunocompromised hosts, the only FDA-approved treatment is ribavirin aerosol: 6-g vial (20 mg/mL in sterile water), by SPAG-2 generator, over 18–20 h daily for 3–5 days, although questions remain regarding efficacy.</p> <p>Two RSV antivirals, ALS-008176 by Alios/J&J and GS-5806 by Gilead, are currently under investigation in children.</p>	<p>Treat only for severe disease, immunocompromised, severe underlying cardiopulmonary disease, as aerosol ribavirin only provides a small benefit. Airway reactivity with inhalation precludes routine use.</p> <p>Palivizumab (Synagis) is not effective for treatment of an active RSV infection, only cost-effective for prevention of hospitalization in high-risk patients.</p>

F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
—Tuberculosis		
– Primary pulmonary disease ^{14,15}	<p>INH 10–15 mg/kg/day (max 300 mg) PO qd for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd for 6 mo AND PZA 30–40 mg/kg/day (max 2 g) PO qd for first 2 mo therapy only (AII).</p> <p>If risk factors present for multidrug resistance, ADD ethambutol 20 mg/kg/day PO qd OR streptomycin 30 mg/kg/day IV, IM div q12h initially.</p>	<p>Obtain baseline LFTs. Consider monthly LFTs for at least 3 mo or as needed for symptoms. It is common to have mildly elevated liver transaminase concentrations (2–3 times normal) that do not further increase during the entire treatment interval. Obese children may have mild elevation when started on therapy.</p> <p>Contact TB specialist for therapy of drug-resistant TB. Fluoroquinolones may play a role in treating MDR strains. Bedaquiline, in a new drug class for TB therapy, was recently approved for adults with MDR TB, when used in combination therapy. Toxicities and lack of pediatric data preclude routine use in children.</p> <p>Directly observed therapy preferred; after 2 wk of daily therapy, can change to twice-weekly dosing double dosage of INH (max 900 mg), PZA (max 2 g), and ethambutol (max 2.5 g); rifampin remains same dosage (10–20 mg/kg/day, max 600 mg) (AII).</p> <p>LP ± CT of head for children ≤2 y to rule out occult, concurrent CNS infection; consider testing for HIV infection (AIII).</p> <p><i>Mycobacterium bovis</i> infection from unpasteurized dairy products is also called “tuberculosis” but rarely causes pulmonary disease; all strains of <i>M bovis</i> are PZA resistant.</p>

<p>– Latent TB infection¹⁵ (skin test conversion)</p>	<p>INH 10–15 mg/kg/day (max 300 mg) PO daily for 9 mo (12 mo for immunocompromised patients) (AIII); treatment with INH at 20–30 mg/kg twice weekly for 9 mo is also effective (AIII). Alternative (BII)²⁰⁴: for children ≥ 2 y, once-weekly DOT for 12 wk: INH (15 mg/kg/dose, max 900 mg), AND rifapentine: 10.0–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥ 50.0 kg: 900 mg (max)</p>	<p>Obtain baseline LFTs. Consider monthly LFTs or as needed for symptoms. Stop INH-rifapentine if AST or ALT ≥ 5 times the ULN even in the absence of symptoms or ≥ 3 times the ULN in the presence of symptoms. For children ≥ 2–12 y, 12 wk of INH and rifapentine may be used, but less data on safety and efficacy. Insufficient data for children < 2 y. For exposure to known INH-R but rifampin-S strains, use rifampin 6 mo (AIII).</p>
<p>– Exposed child < 4 y, or immunocompromised patient (high risk of dissemination)</p>	<p>Prophylaxis for possible infection with INH 10–15 mg/kg PO daily for 2–3 mo after last exposure with repeated skin test or interferon-gamma release assay test negative at that time (AIII). Also called “window prophylaxis.”</p>	<p>If PPD remains negative at 2–3 mo and child well, consider stopping empiric therapy. PPD may not be reliable in immunocompromised patients. Not much data to assess reliability of interferon-gamma release assays in very young infants or immunocompromised hosts, but not likely to be much better than the PPD skin test.</p>

G. CARDIOVASCULAR INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Bacteremia		
– Occult bacteremia (late-onset neonatal sepsis; fever without focus), infants <2 mo (group B streptococcus, <i>Escherichia coli</i> , <i>Listeria</i> , pneumococcus, meningococcus) ^{205–209}	In general, hospitalization for late-onset neonatal sepsis, with cultures of blood, urine, and CSF; start ampicillin 200 mg/kg/day IV div q6h AND cefotaxime 150 mg/kg/day IV div q8h (AII); higher dosages if meningitis is documented. In areas with low (<20%) ampicillin resistance in <i>E coli</i> , consider ampicillin and gentamicin (gentamicin will not cover CNS infection caused by ampicillin-resistant <i>E coli</i>).	Current data document the importance of ampicillin-resistant <i>E coli</i> in bacteremia in infants <90 days. ^{207,208,210} For a nontoxic, febrile infant with good access to medical care: cultures may be obtained of blood, urine, and CSF, ceftriaxone 50 mg/kg IM (lacks <i>Listeria</i> activity) given with outpatient follow-up the next day (Boston criteria) (BII); alternative is home without antibiotics if evaluation is negative (Rochester; Philadelphia criteria) ^{205,209} (BI).
– Occult bacteremia (fever without focus) in age 2–3 mo to 36 mo (<i>Haemophilus influenzae</i> type b, pneumococcus, meningococcus; increasingly <i>Staphylococcus aureus</i>) ^{208–210}	Empiric therapy: if unimmunized, febrile, mild to moderate toxic: after blood culture: ceftriaxone 50 mg/kg IM (BII). If fully immunized (<i>Haemophilus</i> and <i>Pneumococcus</i>) and nontoxic, routine empiric therapy of fever with antibiotics is no longer recommended, but follow closely in case of vaccine failure or meningococcal bacteremia (BIII).	Oral convalescent therapy is selected by susceptibility of blood isolate, following response to IM/IV treatment, with CNS and other foci ruled out by examination ± laboratory tests ± imaging. LP is not recommended for routine evaluation of fever. ²⁰⁵
– <i>H influenzae</i> type b, non-CNS infections	Ceftriaxone IM/IV OR, if beta-lactamase negative, ampicillin IV, followed by oral convalescent therapy (AII)	If beta-lactamase negative: amoxicillin 75–100 mg/kg/day PO div tid (AII) If positive: high-dosage cefixime, ceftibuten, cefdinir PO, or levofloxacin PO (CIII)
– Meningococcus	Ceftriaxone IM/IV or penicillin G IV, followed by oral convalescent therapy (AII)	Amoxicillin 75–100 mg/kg/day PO div tid (AIII)
– Pneumococcus, non-CNS infections	Ceftriaxone IM/IV or penicillin G/ampicillin IV (if pen-S), followed by oral convalescent therapy (AII)	If pen-S: amoxicillin 75–100 mg/kg/day PO div tid (AII). If pen-R: continue ceftriaxone IM or switch to clindamycin if susceptible (CIII); linezolid or levofloxacin may also be options (CIII).

- *S aureus*^{3,7,211–214} usually associated with focal infection

MSSA: nafcillin or oxacillin/naafcillin IV 150–200 mg/kg/day div q6h ± gentamicin 6 mg/kg/day div q8h (AII).
 MRSA: vancomycin 40–60 mg/kg/day IV div q8h OR ceftaroline: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg) (BIII) ± gentamicin 6 mg/kg/day div q8h ± rifampin 20 mg/kg/day div q12h (AIII).
 Treat for 2 wk (IV plus PO) from negative blood cultures unless endocarditis/endovascular thrombus present, which may require up to 6 wk of therapy (BIII).

For persisting bacteremia caused by MRSA, consider adding gentamicin, or changing from vancomycin to ceftaroline or daptomycin (but daptomycin will not treat pneumonia), particularly for MRSA with vancomycin MIC of >2 mcg/mL.

For toxic shock syndrome, clindamycin should be added for the initial 48–72 h of therapy to decrease toxin production (linezolid may also act in this way); IVIG may be added to bind circulating toxin (linezolid may also act in this way); no controlled data exist for these measures.

Watch for the development of metastatic foci of infection, including endocarditis.

If catheter-related, remove catheter.

Endocarditis: Surgical indications: intractable heart failure; persistent infection; large mobile vegetations; peripheral embolism; and valve dehiscence, perforation, rupture or fistula, or a large perivalvular abscess.^{215–219} Consider community versus nosocomial pathogens based on recent surgeries, prior antibiotic therapy, and possible entry sites for bacteremia (skin, oropharynx and respiratory tract, gastrointestinal tract). Children with congenital heart disease are more likely to have more turbulent cardiovascular blood flow, which increases risk of endovascular infection. Immunocompromised hosts may become bacteremic with a wide range of bacteria, fungi, and mycobacteria. Prospective, controlled data on therapy for endocarditis in neonates, infants, and children is quite limited, and many recommendations provided are extrapolations from adults, where some level of evidence exists, or from other invasive bacteremia infections.

– Native valve^{215–218}

- Empiric therapy for presumed endocarditis (viridans streptococci, *S aureus*, HACEK group)

Ceftriaxone IV 100 mg/kg q24h AND gentamicin IV, IM 6 mg/kg/day div q8h (AII).
 For more acute, severe infection, ADD vancomycin 40–60 mg/kg/day IV div q8h to cover *S aureus* (AIII).

Combination (ceftriaxone + gentamicin) provides bactericidal activity against most strains of viridans streptococci, the most common pathogens in infective endocarditis. Cefepime is recommended for adults,²¹⁵ but resistance data in enteric bacilli in children suggest that ceftriaxone remains a reasonable choice.

May administer gentamicin with a qd regimen (CIII).
 For beta-lactam allergy, use vancomycin 45 mg/kg/day IV div q8h and gentamicin 6 mg/kg/day IV div q8h.

G. CARDIOVASCULAR INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Culture-negative native valve endocarditis: treat 4–6 wk (please obtain advice from an infectious diseases specialist for an appropriate regimen that is based on likely pathogens). ²¹⁵		
– Viridans streptococci: Follow echocardiogram for resolution of vegetation (BIII); for beta-lactam allergy: vancomycin.		
Fully susceptible to penicillin	Ceftriaxone 50 mg/kg IV, IM q24h for 4 wk OR penicillin G 200,000 U/kg/day IV div q4–6h for 4 wk (BII); OR penicillin G or ceftriaxone AND gentamicin 6 mg/kg/day IM, IV div q8h (AII) for 14 days for adults (4 wk for children per AHA guidelines due to lack of data in children)	AHA recommends higher dosage of ceftriaxone similar to that for penicillin non-susceptible strains.
Relatively resistant to penicillin	Penicillin G 300,000 U/kg/day IV div q4–6h for 4 wk, or ceftriaxone 100 mg/kg IV q24h for 4 wk; AND gentamicin 6 mg/kg/day IM, IV div q8h for the first 2 wk (AIII)	Gentamicin is used for the first 2 wk of a total of 4 wk of therapy for relatively resistant strains. Vancomycin-containing regimens should use at least a 4-wk treatment course, with gentamicin used for the entire course.
– Enterococcus (dosages for native or prosthetic valve infections)		
Ampicillin-susceptible (gentamicin-S)	Ampicillin 300 mg/kg/day IV, IM div q6h or penicillin G 300,000 U/kg/day IV div q4–6h; AND gentamicin 6.0 mg/kg/day IV div q8h; for 4–6 wk (AII)	Combined treatment with cell-wall active antibiotic plus aminoglycoside used to achieve bactericidal activity. For beta-lactam allergy: vancomycin.
Ampicillin-resistant (gentamicin-S)	Vancomycin 40 mg/kg/day IV div q8h AND gentamicin 6.0 mg/kg/day IV div q8h; for 6 wk (AIII)	Little data exist in children for daptomycin or linezolid. For gentamicin-R strains, use streptomycin or other aminoglycoside if susceptible.
Vancomycin-resistant (gentamicin-S)	Daptomycin IV if also ampicillin-resistant (dose is age-dependent; see Chapter 11) AND gentamicin 6.0 mg/kg/day IV div q8h; for 4–6 wk (AIII)	

<p>– Staphylococci: <i>S aureus</i>, including CA-MRSA; <i>S epidermidis</i>^{7,212}</p> <p>Consider continuing therapy at end of 6 wk if vegetations persist on echocardiogram. The risk of persisting organisms in deep venous thromboses subsequent to bacteremia is not defined.</p>	<p>MSSA or MSSE: nafcillin or oxacillin/nafcillin 150–200 mg/kg/day IV div q6h for 4–6 wk AND gentamicin 6 mg/kg/day div q8h for first 14 days.</p> <p>CA-MRSA or MRSE: vancomycin 40–60 mg/kg/day IV div q8h AND gentamicin for 6 wk; consider for slow response, ADD rifampin 20 mg/kg/day IV div q8–12h.</p> <p>For vancomycin-resistant MRSA, please consult an infectious diseases specialist.</p>	<p>Surgery may be necessary in acute phase; avoid 1st-generation cephalosporins (conflicting data on efficacy).</p> <p>AHA suggests gentamicin for only the first 3–5 days for MSSA or MSSE and optional gentamicin for MRSA. For failures on therapy, or vancomycin-resistant MRSA, consider daptomycin (dose is age-dependent; see Chapter 11) AND gentamicin 6 mg/kg/day div q8h.</p>
<p>– Pneumococcus, gonococcus, group A streptococcus</p>	<p>Penicillin G 200,000 U/kg/day IV div q4–6h for 4 wk (BII); alternatives: ceftriaxone or vancomycin</p>	<p>Ceftriaxone plus azithromycin for suspected gonococcus until susceptibilities known.</p> <p>For penicillin non-susceptible strains of pneumococcus, use high-dosage penicillin G 300,000 U/kg/day IV div q4–6h or high-dosage ceftriaxone 100 mg/kg IV q24h for 4 wk.</p>
<p>HACEK (<i>Haemophilus</i>, <i>Aggregatibacter</i> [formerly <i>Actinobacillus</i>], <i>Cardiobacterium</i>, <i>Eikenella</i>, <i>Kingella</i> spp)</p>	<p>Usually susceptible to ceftriaxone 100 mg/kg IV q24h for 4 wk (BIII)</p>	<p>Some organisms will be ampicillin-susceptible. Usually do not require the addition of gentamicin.</p>
<p>– Enteric Gram-negative bacilli</p>	<p>Antibiotics specific to pathogen (usually ceftriaxone plus gentamicin); duration at least 6 wk (AIII)</p>	<p>For ESBL organisms, carbapenems or beta-lactam/beta-lactamase inhibitor combinations PLUS gentamicin, should be effective.</p>
<p>– <i>Pseudomonas aeruginosa</i></p>	<p>Antibiotic specific to susceptibility: cefepime or meropenem PLUS tobramycin</p>	<p>Cefepime and meropenem are both more active against <i>Pseudomonas</i> and less likely to allow beta-lactamase-resistant pathogens to emerge than ceftazidime.</p>
<p>– Prosthetic valve/material^{215,219}</p>	<p>Follow echocardiogram for resolution of vegetation. For beta-lactam allergy: vancomycin.</p>	

G. CARDIOVASCULAR INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– Viridans streptococci		
Fully susceptible to penicillin	Ceftriaxone 100 mg/kg IV, IM q24h for 6 wk OR penicillin G 300,000 U/kg/day IV div q4–6h for 6 wk (All); OR penicillin G or ceftriaxone AND gentamicin 6.0 mg/kg/day IM, IV div q8h for first 2 wk of 6 wk course (All)	Gentamicin is optional for the first 2 wk of a total of 6 wk of therapy for prosthetic valve/material endocarditis.
Relatively resistant to penicillin	Penicillin G 300,000 U/kg/day IV div q4–6h for 6 wk, or ceftriaxone 100 mg/kg IV q24h for 6 wk; AND gentamicin 6 mg/kg/day IM, IV div q8h for 6 wk (All)	Gentamicin is used for all 6 wk of therapy for prosthetic valve/material endocarditis caused by relatively resistant strains.
– Enterococcus (See dosages under native valve.) Treatment course is at least 6 wk, particularly if vancomycin is used. ^{215,219}		
– Staphylococci: <i>S aureus</i> , including CA-MRSA; <i>S epidermidis</i> ^{7,215} Consider continuing therapy at end of 6 wk if vegetations persist on echocardiogram.	MSSA or MSSE: nafcillin or oxacillin/nafcillin 150–200 mg/kg/day IV div q6h for ≥6 wk AND gentamicin 6 mg/kg/day div q8h for first 14 days. CA-MRSA or MRSE: vancomycin 40–60 mg/kg/day IV div q8h AND gentamicin for ≥6 wk; ADD rifampin 20 mg/kg/day IV div q8–12h.	For failures on therapy, consider daptomycin (dose is age-dependent; see Chapter 11) AND gentamicin 6 mg/kg/day div q8h.
– <i>Candida</i> ^{82,215,220}	AmB preparations have more experience (no comparative trials against echinocandins), OR caspofungin 70 mg/m ² load on day 1, then 50 mg/m ² /day or micafungin 2–4 mg/kg/day (BII). Do not use fluconazole as initial therapy because of inferior fungistatic effect.	Poor prognosis; please obtain advice from an infectious diseases specialist. Surgery may be required to resect infected valve. Long-term suppressive therapy with fluconazole. Suspect <i>Candida</i> vegetations when lesions are large on echocardiography.
– Culture-negative prosthetic valve endocarditis: treat at least 6 wk.		

Endocarditis prophylaxis^{213,217,221}: Given that (1) endocarditis is rarely caused by dental/GI procedures and (2) prophylaxis for procedures prevents an exceedingly small number of cases, the risks of antibiotics outweigh the benefits. Highest risk conditions currently recommended for prophylaxis: (1) prosthetic heart valve (or prosthetic material used to repair a valve); (2) previous endocarditis; (3) cyanotic congenital heart disease that is unrepaired (or palliatively repaired with shunts and conduits); (4) congenital heart disease that is repaired but with defects at the site of repair adjacent to prosthetic material; (5) completely repaired congenital heart disease using prosthetic material, for the first 6 mo after repair; or (6) cardiac transplant patients with valvulopathy. Routine prophylaxis no longer is required for children with native valve abnormalities. Assessment of new prophylaxis guidelines documents a possible increase in viridans streptococcal endocarditis in children 10–17 y old but not 0–9 y old.²²² However, no changes in prophylaxis recommendations are being made at this time.

– In highest risk patients: dental procedures that involve manipulation of the gingival or periodontal region of teeth	Amoxicillin 50 mg/kg PO 60 min before procedure OR ampicillin or ceftriaxone or cefazolin, all at 50 mg/kg IM/IV 30–60 min before procedure	If penicillin allergy: clindamycin 20 mg/kg PO (60 min before) or IV (30 min before); OR azithromycin 15 mg/kg or clarithromycin 15 mg/kg, 60 min before
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– Genitourinary and GI procedures	None	No longer recommended
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Lemierre syndrome

(*Fusobacterium necrophorum* primarily, new reports with MRSA)^{117–121} (pharyngitis with internal jugular vein septic thrombosis, postanginal sepsis, necrobaecillosis)

Empiric: meropenem 60 mg/kg/day div q8h (or 120 mg/kg/day div q8h for CNS metastatic foci) (AIII) OR ceftriaxone 100 mg/kg/day q24h AND metronidazole 40 mg/kg/day div q8h or clindamycin 40 mg/kg/day div q6h (BIII).
ADD empiric vancomycin if MRSA suspected.

Anecdotal reports suggest metronidazole may be effective for apparent failures with other agents. Often requires anticoagulation. Metastatic and recurrent abscesses often develop while on active, appropriate therapy, requiring multiple debridements and prolonged antibiotic therapy. Treat until CRP and ESR are normal (AIII).

Purulent pericarditis

– Empiric (acute, bacterial: *S aureus* [including MRSA], group A streptococcus, pneumococcus, meningococcus, *H influenzae* type b)^{223,224}

Vancomycin 40 mg/kg/day IV div q8h AND ceftriaxone 50–75 mg/kg/day q24h (AIII), OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h; ≥6 mo, 45 mg/kg/day IV div q8h (max single dose 600 mg) (BIII)

For presumed staphylococcal infection, ADD gentamicin (AIII). Increasingly uncommon with immunization against pneumococcus and *H influenzae* type b.²²⁴ Pericardiocentesis is essential to establish diagnosis. Surgical drainage of pus with pericardial window or pericardiectomy is important to prevent tamponade.

G. CARDIOVASCULAR INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– <i>S aureus</i>	For MSSA: oxacillin/naftillin 150–200 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h. Treat for 2–3 wk after drainage (BIII). For CA-MRSA: continue vancomycin or ceftaroline. Treat for 3–4 wk after drainage (BIII).	Continue therapy with gentamicin; consider use of rifampin in severe cases due to tissue penetration characteristics.
– <i>H influenzae</i> type b in unimmunized children	Ceftriaxone 50 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h; for 10–14 days (AIII)	Ampicillin for beta-lactamase–negative strains
– Pneumococcus, meningococcus, group A streptococcus	Penicillin G 200,000 U/kg/day IV, IM div q6h for 10–14 days OR ceftriaxone 50 mg/kg qd for 10–14 days (AIII)	Ceftriaxone or cefotaxime for penicillin non-susceptible pneumococci
– Coliform bacilli	Ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h for 3 wk or longer (AIII)	Alternative drugs depending on susceptibilities; for <i>Enterobacter</i> , <i>Serratia</i> , or <i>Citrobacter</i> , use cefepime or meropenem. For ESBL <i>E coli</i> or <i>Klebsiella</i> , use a carbapenem.
– Tuberculous ^{14,15}	INH 10–15 mg/kg/day (max 300 mg) PO, IV qd, for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd, IV for 6 mo. ADD PZA 20–40 mg/kg/day PO qd for first 2 mo therapy; if suspected multidrug resistance, also add ethambutol 20 mg/kg/day PO qd (AIII).	Current guidelines do not suggest a benefit from routine use of corticosteroids. However, for those at highest risk of restrictive pericarditis, steroid continues to be recommended. ¹⁴ For children: prednisone 2 mg/kg/day for 4 wk, then 0.5 mg/kg/day for 4 wk, then 0.25 mg/kg/day for 2 wk, then 0.1 mg/kg/day for 1 wk.

H. GASTROINTESTINAL INFECTIONS (See Chapter 10 for parasitic infections.)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Diarrhea/Gastroenteritis		
<p>Note on <i>Escherichia coli</i> and diarrheal disease: Antibiotic susceptibility of <i>E coli</i> varies considerably from region to region. For mild to moderate disease, TMP/SMX may be started as initial therapy, but for more severe disease and for locations with rates of TMP/SMX resistance greater than 10% to 20%, azithromycin, an oral 3rd-generation cephalosporin (eg, cefixime, cefdinir, ceftibuten), or ciprofloxacin should be used (AIII). Cultures and antibiotic susceptibility testing are recommended for significant disease (AIII).</p>		
<p>– Empiric therapy of community-associated diarrhea in the United States (<i>E coli</i> [STEC, including O157:H7 strains, and ETEC], <i>Salmonella</i>, <i>Campylobacter</i>, and <i>Shigella</i> predominate; <i>Yersinia</i> and parasites causing <5%; however, viral pathogens are far more common, especially for children <3 y.)^{225,226}</p>	<p>Azithromycin 10 mg/kg qd for 3 days (BII), OR cefixime 8 mg/kg/day PO qd (BII) for 5 days; OR ciprofloxacin 30 mg/kg/day PO div bid for 3 days</p>	<p>Alternatives: other oral 3rd-generation cephalosporins (eg, cefdinir, ceftibuten); or rifaximin 600 mg/day div tid for 3 days (for nonfebrile, non-bloody diarrhea for children >11 y).</p> <p>Controversy exists regarding treatment of O157:H7 strains and the prevention or increased incidence of HUS, with retrospective data to support either treatment, or withholding treatment. Some experts treat with antimicrobials and others prefer to use supportive care.^{227–231}</p>

H. GASTROINTESTINAL INFECTIONS (continued) (See Chapter 10 for parasitic infections.)

Clinical Diagnosis	Therapy (evidence grade)	Comments
<p>– Traveler's diarrhea: empiric therapy (<i>E coli</i>, <i>Campylobacter</i>, <i>Salmonella</i>, <i>Shigella</i>, plus many other pathogens, including protozoa)^{226,232–239}</p>	<p>Azithromycin 10 mg/kg qd for 1–3 days (All); OR rifaximin 200 mg PO tid for 3 days (age ≥ 12 y) (BII); OR ciprofloxacin (BII); OR rifaximin 200 mg tid for 3 days for age ≥ 12 y (BII)</p>	<p>Susceptibility patterns of <i>E coli</i>, <i>Campylobacter</i>, <i>Salmonella</i>, and <i>Shigella</i> vary widely by country; check country-specific data for departing or returning travelers. Azithromycin preferable to ciprofloxacin for travelers to Southeast Asia given high prevalence of quinolone-resistant <i>Campylobacter</i>.</p> <p>Rifaximin is less effective than ciprofloxacin for invasive bloody bacterial enteritis; rifaximin may also not be as effective for <i>Shigella</i>, <i>Salmonella</i>, and <i>Campylobacter</i> as other agents.</p> <p>Interestingly, for adults who travel and take antibiotics (mostly fluoroquinolones), colonization with ESBL-positive <i>E coli</i> is more frequent on return home.²⁴⁰</p> <p>Adjunctive therapy with loperamide (antimotility) is not recommended for children <2 y and should be used only in nonfebrile, non-bloody diarrhea.^{226,241,242}</p> <p>May shorten symptomatic illness by about 24 h.</p>
<p>– Traveler's diarrhea: prophylaxis^{232,233}</p>	<p>– Prophylaxis: Early self-treatment with agents listed previously is preferred over long-term prophylaxis, but may use prophylaxis for a short-term (<14 days) visit to very high-risk region: rifaximin (for older children), azithromycin, or bismuth subsalicylate (BIII).</p>	
<p>– <i>Aeromonas hydrophila</i>²⁴³</p>	<p>Ciprofloxacin 30 mg/kg/day PO div bid for 5 days OR azithromycin 10 mg/kg qd for 3 days OR cefixime 8 mg/kg/day PO qd (BIII)</p>	<p>Not all strains produce enterotoxins and diarrhea; role in diarrhea questioned.²⁴³ Resistance to TMP/SMX about 10%–15%. Choose narrowest spectrum agent based on in vitro susceptibilities.</p>
<p>– <i>Campylobacter jejuni</i>^{243–246}</p>	<p>Azithromycin 10 mg/kg/day for 3 days (BII) or erythromycin 40 mg/kg/day PO div qid for 5 days (BII)</p>	<p>Alternatives: doxycycline or ciprofloxacin (high rate of fluoroquinolone resistance in Thailand, India, and now the United States).</p> <p>Single-dose azithromycin (1 g, once) is effective in adults.</p>

– Cholera ^{237,247}	Azithromycin 20 mg/kg once; OR erythromycin 50 mg/kg/day PO div qid for 3 days; OR doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid, for all ages	Ciprofloxacin or TMP/SMX (if susceptible)
– <i>Clostridium difficile</i> (antibiotic-associated colitis) ^{248–253}	Metronidazole 30 mg/kg/day PO div qid OR vancomycin 40 mg/kg/day PO div qid for 7 days; for relapsing <i>C difficile</i> enteritis, consider pulse therapy (1 wk on/1 wk off for 3–4 cycles) or prolonged tapering therapy. ²⁴⁸ Stool transplantation for failure of medical therapy in recurrent enteritis.	Attempt to stop antibiotics that may have represented the cause of <i>C difficile</i> infection. Vancomycin is more effective for severe infection. ^{249,250} Fidaxomicin approved for adults; pediatric studies successfully completed with similar results to those in adults. ²⁵² Many infants and children may have asymptomatic colonization with <i>C difficile</i> . ²⁵⁰ Higher risk of relapse in children with multiple comorbidities.
– <i>E coli</i>		
Enterotoxigenic (etiology of most traveler's diarrhea) ^{226,233–236}	Azithromycin 10 mg/kg qd for 3 days; OR cefixime 8 mg/kg/day PO qd for 3 days; OR ciprofloxacin 30 mg/kg/day PO div bid for 3 days	Most illnesses brief and self-limited. Alternatives: rifaximin 600 mg/day div tid for 3 days (for nonfebrile, non-bloody diarrhea for children >11 y, as rifaximin is not absorbed systemically); OR TMP/SMX. Resistance increasing worldwide; check country-specific rates, if possible. ²³⁶
Enterohemorrhagic (O157:H7; STEC, etiology of HUS) ^{226–230}	Controversy on whether treatment of O157:H7 diarrhea results in more or less toxin-mediated renal damage. ^{226–230} For severe infection, treat as for enterotoxigenic strains as previously described, preferably with azithromycin that is associated with decreased toxin production in animal models. ²³⁰	Injury to colonic mucosa may lead to invasive bacterial colitis that does require antimicrobial therapy.

H. GASTROINTESTINAL INFECTIONS (continued) (See Chapter 10 for parasitic infections.)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Enteropathogenic	Neomycin 100 mg/kg/day PO div q6–8h for 5 days	Most traditional “enteropathogenic” strains are not toxigenic or invasive. Postinfection diarrhea may be problematic.
– Gastritis, peptic ulcer disease (<i>Helicobacter pylori</i>) ^{254–257}	Either triple agent therapy in areas of low clarithromycin resistance: clarithromycin 7.5 mg/kg/dose 2–3 times each day, AND amoxicillin 40 mg/kg/dose (max 1 g) PO bid AND omeprazole 0.5 mg/kg/dose PO bid 14 days (BII), OR quadruple therapy that includes metronidazole (15 mg/kg/day div bid) added to the regimen previously described. ²⁵⁸	New pediatric guidelines recommend some restriction of testing for those at high risk of complications. Resistance to clarithromycin is as high as 20% in some regions. ^{254,256,259} Current approach for empiric therapy if clarithromycin resistance may be present: high-dose triple therapy is recommended with proton pump inhibitor, amoxicillin, and metronidazole for 14 days ± bismuth to create quadruple therapy. ²⁵⁴
– Giardiasis (See Chapter 10.) (<i>Giardia intestinalis</i> , formerly <i>lamblia</i>) ²⁶⁰	Metronidazole 30–40 mg/kg/day PO div tid for 7–10 days (BII); OR tinidazole 50 mg/kg/day (max 2 g) for 1 day (BII); OR nitazoxanide PO (take with food), age 12–47 mo, 100 mg/dose bid for 7 days; age 4–11 y, 200 mg/dose bid for 7 days; age ≥ 12 y, 1 tab (500 mg)/dose bid for 7 days (BII)	If therapy is unsuccessful, another course of the same agent is usually curative. Alternatives: paromomycin OR albendazole (CII). Prolonged or combination drug courses may be needed for immunocompromised conditions (eg, hypogammaglobulinemia). Treatment of asymptomatic carriers not usually recommended.
– Salmonellosis ^{261–263} (See Chapter 10 for discussion of traveler’s diarrhea for typhoid infection outside of North America.)		
Non-typhoid strains ^{261–263}	Usually none for self-limited diarrhea in immunocompetent child (eg, diarrhea is often much improved by the time culture results are available). Treat those with persisting symptomatic infection and all infants <3 months: azithromycin 10 mg/kg PO qd for 3 days (AII); OR ceftriaxone 75 mg/kg/day IV, IM q24h for 5 days (AII); OR	Alternatives: ciprofloxacin 30 mg/kg/day PO div bid for 5 days (AI). Carriage of strains may be prolonged in treated children. For bacteremic infection, ceftriaxone IM/IV may be initially used until secondary sites of infection (bone/joint, liver/spleen, CNS) are ruled out.

	cefixime 20–30 mg/kg/day PO for 5–7 days (BII); OR for susceptible strains: TMP/SMX 8 mg/kg/day of TMP PO div bid for 14 days (AI).	
Typhoid fever ^{263–267}	Azithromycin 10 mg/kg qd for 5 days (AII); OR ceftriaxone 75 mg/kg/day IV, IM q24h for 5 days (AII); OR cefixime 20–30 mg/kg/day PO, div q12h for 14 days (BII); OR for susceptible strains: TMP/ SMX 8 mg/kg/day of TMP PO div bid for 10 days (AI)	Increasing cephalosporin resistance. For newly emergent MDR strains, may require prolonged IV therapy. Longer treatment courses for focal invasive disease (eg, osteomyelitis). Alternative: ciprofloxacin 30 mg/kg/day PO div bid for 5–7 days (AI).
– Shigellosis ^{268–270}	Cefixime 8 mg/kg/day PO qd for 5 days (AII); OR azithromycin 10 mg/kg/day PO for 3 days (AII); OR ciprofloxacin 30 mg/kg/day PO div bid for 3–5 days (BII)	Alternatives for susceptible strains: TMP/SMX 8 mg/kg/ day of TMP PO div bid for 5 days; OR ampicillin (<i>not</i> amoxicillin). Ceftriaxone 50 mg/kg/day IM, IV if parenteral therapy necessary, for 2–5 days. Avoid antiperistaltic drugs. Treatment for the improving child is not usually necessary to hasten recovery, but some experts would treat to decrease communicability.
– <i>Yersinia enterocolitica</i> ^{271–273}	Antimicrobial therapy probably not of value for mild disease in normal hosts. TMP/SMX PO, IV; OR ciprofloxacin PO, IV (BIII).	Alternatives: ceftriaxone or gentamicin. High rates of resistance to ampicillin. May mimic appendicitis in older children. Limited clinical data exist on oral therapy.

H. GASTROINTESTINAL INFECTIONS (continued) (See Chapter 10 for parasitic infections.)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Intra-abdominal infection (abscess, peritonitis secondary to bowel/appendix contents)		
<ul style="list-style-type: none"> Appendicitis; bowel-associated (enteric Gram-negative bacilli, <i>Bacteroides</i> spp, <i>Enterococcus</i> spp, increasingly <i>Pseudomonas</i>)^{274–279} 	<p>Source control is critical to curing this infection. Meropenem 60 mg/kg/day IV div q8h or imipenem 60 mg/kg/day IV div q6h; OR pip/tazo 240 mg pip/kg/day div q6h; for 4–5 days for patients with adequate source control,²⁷⁸ 7–10 days or longer if suspicion of persisting intra-abdominal abscess (AII).</p> <p><i>Pseudomonas</i> is found consistently in up to 30% of children)^{274–276,280} providing evidence to document the need for empiric use of an antipseudomonal drug (preferably one with anaerobic activity), such as a carbapenem or pip/tazo, <i>unless the surgery was highly effective at drainage/source control</i> (gentamicin is not active in an abscess), which may explain successful outcomes in retrospective studies that did not include antipseudomonal coverage.^{281–283}</p>	<p>Many other regimens may be effective, including ampicillin 150 mg/kg/day div q8h AND gentamicin 6–7.5 mg/kg/day IV, IM div q8h AND metronidazole 40 mg/kg/day IV div q8h; OR ceftriaxone 50 mg/kg q24h AND metronidazole 40 mg/kg/day IV div q8h. Data support IV outpatient therapy or oral step-down therapy^{279,280} when clinically improved, particularly when oral therapy can be focused on the most prominent, invasive cultured pathogens.</p>
<ul style="list-style-type: none"> Tuberculosis, abdominal (<i>Mycobacterium bovis</i>, from unpasteurized dairy products)^{14,15,284,285} 	<p>INH 10–15 mg/kg/day (max 300 mg) PO qd for 6–9 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd for 6–9 mo (AII).</p> <p>Some experts recommend routine use of ethambutol in the empiric regimen.</p> <p><i>M bovis</i> is resistant to PZA.</p> <p>If risk factors are present for multidrug resistance (eg, poor adherence to previous therapy), add ethambutol 20 mg/kg/day PO qd OR a fluoroquinolone (moxifloxacin or levofloxacin).</p>	<p>Corticosteroids are routinely used as adjunctive therapy to decrease morbidity from inflammation.²⁸⁶</p> <p>Directly observed therapy preferred; after 2+ wk of daily therapy, can change to twice-weekly dosing double dosage of INH (max 900 mg); rifampin remains same dosage (10–20 mg/kg/day, max 600 mg) (AII).</p> <p>LP ± CT of head for children ≤2 y with active disease to rule out occult, concurrent CNS infection (AIII).</p> <p>No published prospective comparative data on a 6 mo vs 9 mo treatment course in children.</p>

Perirectal abscess (<i>Bacteroides</i> spp, other anaerobes, enteric bacilli, and <i>S aureus</i> predominate) ²⁸⁷	Clindamycin 30–40 mg/kg/day IV div q8h AND cefotaxime or ceftriaxone or gentamicin (BIII)	Surgical drainage alone may be curative. Obtaining cultures and susceptibilities is increasingly important with rising resistance to cephalosporins in community <i>E coli</i> isolates. May represent inflammatory bowel disease.
Peritonitis		
– Peritoneal dialysis indwelling catheter infection (staphylococcal; enteric Gram-negatives; yeast) ^{288,289}	Antibiotic added to dialysate in concentrations approximating those attained in serum for systemic disease (eg, 4 mcg/mL for gentamicin, 25 mcg/mL for vancomycin, 125 mcg/mL for cefazolin, 25 mcg/mL for ciprofloxacin) after a larger loading dose (AII) ²⁸⁹	Selection of antibiotic based on organism isolated from peritoneal fluid; systemic antibiotics if there is accompanying bacteremia/fungemia
– Primary (pneumococcus or group A streptococcus) ²⁹⁰	Ceftriaxone 50 mg/kg/day q24h, or cefotaxime 150 mg/kg/day div q8h; if pen-S, then penicillin G 150,000 U/kg/day IV div q6h; for 7–10 days (AII)	Other antibiotics according to culture and susceptibility tests. Spontaneous pneumococcal peritonitis now infrequent in immunized children.

I. GENITAL AND SEXUALLY TRANSMITTED INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Consider testing for HIV and other STIs in a child with one documented STI; consider sexual abuse in prepubertal children. The most recent CDC STI treatment guidelines are posted online at www.cdc.gov/std/treatment (accessed October 4, 2018).		
Chancroid (<i>Haemophilus ducreyi</i>) ⁵⁶	Azithromycin 1 g PO as single dose OR ceftriaxone 250 mg IM as single dose	Alternative: erythromycin 1.5 g/day PO div tid for 7 days OR ciprofloxacin 1,000 mg PO qd, div bid for 3 days
Chlamydia trachomatis (cervicitis, urethritis) ^{56,291}	Azithromycin 20 mg/kg (max 1 g) PO for 1 dose; OR doxycycline (patients > 7 y) 4.4 mg/kg/day (max 200 mg/day) PO div bid for 7 days	Alternatives: erythromycin 2 g/day PO div qid for 7 days; OR levofloxacin 500 mg PO q24h for 7 days
Epididymitis (associated with positive urine cultures and STIs) ^{56,292,293}	Ceftriaxone 50 mg/kg/day q24h for 7–10 days AND (for older children) doxycycline 200 mg/day div bid for 10 days	Microbiology not well studied in children; in infants, also associated with urogenital tract anomalies. Treat infants for <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> ; may resolve spontaneously; in STI, caused by <i>Chlamydia</i> and gonococcus.
Gonorrhea ^{56,291,294–296}	Antibiotic resistance is an ongoing problem, with new data to suggest the emergence of azithromycin resistance being tracked closely by the CDC. ²⁹⁶	
– Newborns	See Chapter 5.	
– Genital infections (uncomplicated vulvovaginitis, cervicitis, urethritis, or proctitis) ^{56,291,294,295}	Ceftriaxone 250 mg IM for 1 dose (regardless of weight) AND azithromycin 1 g PO for 1 dose or doxycycline 200 mg/day div q12h for 7 days	Cefixime no longer recommended due to increasing cephalosporin resistance. ⁵⁶ Fluoroquinolones are no longer recommended due to resistance. Dual therapy has not been evaluated yet in children but should be effective.
– Pharyngitis ^{56,296}	Ceftriaxone 250 mg IM for 1 dose (regardless of weight) AND azithromycin 1 g PO for 1 dose or doxycycline 200 mg/day div q12h for 7 days	
– Conjunctivitis ⁵⁶	Ceftriaxone 1g IM for 1 dose AND azithromycin 1 g PO for 1 dose	Lavage the eye with saline.

– Disseminated gonococcal infection ^{56,296}	Ceftriaxone 50 mg/kg/day IM, IV q24h (max: 1 g) AND azithromycin 1 g PO for 1 dose; total course for 7 days	No studies in children: increase dosage for meningitis.
Granuloma inguinale (donovanosis, <i>Klebsiella granulomatis</i> , formerly <i>Calymmatobacterium</i>) ⁵⁶	Azithromycin 1 g orally once per week or 500 mg daily for at least 3 weeks and until all lesions have completely healed	Primarily in tropical regions of India, Pacific, and Africa. Options: Doxycycline 4.4 mg/kg/day div bid (max 200 mg/day) PO for at least 3 wk OR ciprofloxacin 750 mg PO bid for at least 3 wk, OR erythromycin base 500 mg PO qid for at least 3 wk OR TMP/SMX 1 double-strength (160 mg/800 mg) tab PO bid for at least 3 wk; all regimens continue until all lesions have completely healed.
Herpes simplex virus, genital infection ^{56,297,298}	Acyclovir 20 mg/kg/dose (max 400 mg) PO tid for 7–10 days (first episode) (AI); OR valacyclovir 20 mg/kg/dose of extemporaneous suspension (directions on package label), max 1 g PO bid for 7–10 days (first episode) (AI); OR famciclovir 250 mg PO tid for 7–10 days (AI); for more severe infection: acyclovir 15 mg/kg/day IV div q8h as 1-h infusion for 7–10 days (AII)	For recurrent episodes: treat with acyclovir PO, valacyclovir PO, or famciclovir PO, immediately when symptoms begin, for 5 days. For suppression: acyclovir 20 mg/kg/dose (max 400 mg) PO bid; OR valacyclovir 20 mg/kg/dose PO qd (little long-term safety data in children; no efficacy data in children). Prophylaxis is recommended by ACOG in pregnant women. ^{299,300}
Lymphogranuloma venereum (<i>C trachomatis</i>) ⁵⁶	Doxycycline 4.4 mg/kg/day (max 200 mg/day) PO (patients >7 y) div bid for 21 days	Alternatives: erythromycin 2 g/day PO div qid for 21 days; OR azithromycin 1 g PO once weekly for 3 wk
Pelvic inflammatory disease (<i>Chlamydia</i> , gonococcus, plus anaerobes) ^{56,301}	Cefoxitin 2 g IV q6h; AND doxycycline 200 mg/day PO or IV div bid; OR cefotetan 2 g IV q12h AND doxycycline 100 mg orally or IV q12h, OR clindamycin 900 mg IV q8h AND gentamicin 1.5 mg/kg IV, IM q8h until clinical improvement for 24 h, followed by doxycycline 200 mg/day PO div bid (AND clindamycin 1,800 mg/day PO div qid for tubo-ovarian abscess) to complete 14 days of therapy	Optional regimen: ceftriaxone 250 mg IM for 1 dose AND doxycycline 200 mg/day PO div bid; WITH/ WITHOUT metronidazole 1 g/day PO div bid; for 14 days

I. GENITAL AND SEXUALLY TRANSMITTED INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Syphilis ^{56,302} (Test for HIV.)		
– Congenital	See Chapter 5.	
– Neurosyphilis (positive CSF VDRL or CSF pleocytosis with serologic diagnosis of syphilis)	Crystalline penicillin G 200–300,000 U/kg/day (max 24,000,000 U/day) div q6h for 10–14 days (AIII)	
– Primary, secondary	Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM as a single dose (AIII); do not use benzathine-procaine penicillin mixtures.	Follow-up serologic tests at 6, 12, and 24 mo; 15% may remain seropositive despite adequate treatment. If allergy to penicillin: doxycycline (patients >7 y) 4.4 mg/kg/day (max 200 mg) PO div bid for 14 days. CSF examination should be obtained for children being treated for primary or secondary syphilis to rule out asymptomatic neurosyphilis. Test for HIV.
– Syphilis of <1 y duration, without clinical symptoms (early latent syphilis)	Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM as a single dose (AIII)	Alternative if allergy to penicillin: doxycycline (patients >7 y) 4.4 mg/kg/day (max 200 mg/day) PO div bid for 14 days
– Syphilis of >1 y duration, without clinical symptoms (late latent syphilis) or syphilis of unknown duration	Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM weekly for 3 doses (AIII)	Alternative if allergy to penicillin: doxycycline (patients >7 y) 4.4 mg/kg/day (max 200 mg/day) PO div bid for 28 days. Look for neurologic, eye, and aortic complications of tertiary syphilis.
Trichomoniasis ⁵⁶	Tinidazole 50 mg/kg (max 2 g) PO for 1 dose (BII) OR metronidazole 2 g PO for 1 dose OR metronidazole 500 mg PO bid for 7 days (BII)	
Urethritis, nongonococcal (See Gonorrhea for gonorrhea therapy.) ^{56,303}	Azithromycin 20 mg/kg (max 1 g) PO for 1 dose, OR doxycycline (patients >7 y) 4.4 mg/kg/day (max 200 mg/day) PO div bid for 7 days (All)	Erythromycin, levofloxacin, or ofloxacin Increasing resistance noted in <i>Mycoplasma genitalium</i> ³⁰³

Vaginitis⁵⁶

– Bacterial vaginosis ^{56,304}	Metronidazole 500 mg PO twice daily for 7 days OR metronidazole vaginal gel (0.75%) qd for 5 days, OR clindamycin vaginal cream for 7 days	Alternative: tinidazole 1 g PO qd for 5 days, OR clindamycin 300 mg PO bid for 7 days Relapse common Caused by synergy of <i>Gardnerella</i> with anaerobes
– Candidiasis, vulvovaginal ^{56,305}	Topical vaginal cream/tabs/suppositories (alphabetic order): butoconazole, clotrimazole, econazole, fenticonazole, miconazole, sertaconazole, terconazole, or tioconazole for 3–7 days (AI); OR fluconazole 10 mg/kg (max 150 mg) as a single dose (AI)	For uncomplicated vulvovaginal candidiasis, no topical agent is clearly superior. Avoid azoles during pregnancy. For recurring disease, consider 10–14 days of induction with topical agent or fluconazole, followed by fluconazole once weekly for 6 mo (AI).
– Prepubertal vaginitis ³⁰⁶	No prospective studies	Cultures from symptomatic prepubertal girls are statistically more likely to yield <i>E coli</i> , enterococcus, coagulase-negative staphylococci, and streptococci (viridans strep and group A strep), but these organisms may also be present in asymptomatic girls.
– <i>Shigella</i> ³⁰⁷	Cefixime 8 mg/kg/day PO qd for 5 days OR ciprofloxacin 30 mg/kg/day PO div bid for 5 days	50% have bloody discharge; usually not associated with diarrhea.
– <i>Streptococcus</i> , group A ³⁰⁸	Penicillin V 50–75 mg/kg/day PO div tid for 10 days	Amoxicillin 50–75 mg/kg/day PO div tid

J. CENTRAL NERVOUS SYSTEM INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Abscess, brain (respiratory tract flora, skin flora, or bowel flora, depending on the pathogenesis of infection based on underlying comorbid disease and origin of bacteremia) ^{309,310}	<p>Until etiology established, use empiric therapy for presumed mixed-flora infection with origins from the respiratory tract, skin, and/or bowel, based on individual patient evaluation and risk for brain abscess (see Comments for MRSA considerations): meropenem 120 mg/kg/day IV div q8h (AIII); OR nafcillin 150–200 mg/kg/day IV div q6h AND cefotaxime 200–300 mg/kg/day IV div q6h or ceftriaxone 100 mg/kg/day IV q24h AND metronidazole 30 mg/kg/day IV div q8h (BIII); for 2–3 wk after successful drainage (depending on pathogen, size of abscess, and response to therapy); longer course if no surgery (3–6 wk) (BIII).</p> <p>For single pathogen abscess, use a single agent in doses that will achieve effective CNS exposure. The blood-brain barrier is not intact in brain abscesses.</p>	<p>Surgery for abscesses ≥ 2 cm diameter.</p> <p>If CA-MRSA suspected, ADD vancomycin 60 mg/kg/day IV div q8h \pm rifampin 20 mg/kg/day IV div q12h, pending culture results. We have successfully treated MRSA intracranial infections with ceftaroline, but no prospective data exist: ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥ 6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII).</p> <p>If secondary to chronic otitis, include meropenem or cefepime in regimen for anti-<i>Pseudomonas</i> activity.</p> <p>For enteric Gram-negative bacilli, consider ESBL-producing <i>Escherichia coli</i> and <i>Klebsiella</i> that require meropenem and are resistant to cefotaxime.</p> <p>Follow resolution of abscess size by CT or MRI for difficult-to-treat pathogens.</p>
Encephalitis ³¹¹ (May be infectious or immune-complex mediated) ³¹²		
– Amebic (<i>Naegleria fowleri</i> , <i>Balamuthia mandrillaris</i> , and <i>Acanthamoeba</i>)	See Chapter 10, Amebiasis.	
– CMV	See Chapter 9, CMV. Not well studied in children. Consider ganciclovir 10 mg/kg/day IV div q12h; for severe immunocompromised, ADD foscarnet 180 mg/kg/day IV div q8h for 3 wk.	Follow quantitative PCR for CMV. Reduce dose for renal insufficiency. Watch for neutropenia.
– Enterovirus	Supportive therapy; no antivirals currently FDA approved.	Pocapavir PO is currently under investigation for enterovirus (poliovirus). As of November 2018, it is not available for compassionate use.

		Pleconaril PO is currently under consideration for submission to FDA for approval for treatment of neonatal enteroviral sepsis syndrome. ³¹³ As of November 2018, it is not available for compassionate use.
– EBV ³¹⁴	Not studied in a controlled comparative trial. Consider ganciclovir 10 mg/kg/day IV div q12h or acyclovir 60 mg/kg/day IV div q8h for 3 wk.	Follow quantitative PCR in CSF for EBV. Efficacy of antiviral therapy not well defined.
– Herpes simplex virus ³¹⁵ (See Chapter 5 for neonatal infection).	Acyclovir 60 mg/kg/day IV as 1–2 h infusion div q8h for 21 days for ≤ 4 mo; for those ≥ 5 mo, 45 mg/kg/day IV for 21 days (AIII)	Perform CSF HSV PCR near end of 21 days of therapy and continue acyclovir until PCR negative. Safety of high-dose acyclovir (60 mg/kg/day) not well defined beyond the neonatal period; can be used, but monitor for neurotoxicity and nephrotoxicity; FDA has approved acyclovir at this dosage for encephalitis for children up to 12 y.
– <i>Toxoplasma</i> (See Chapter 5 for neonatal congenital infection.)	See Chapter 10.	
– Arbovirus (flavivirus—Zika, West Nile, St. Louis encephalitis, tick-borne encephalitis; togavirus—western equine encephalitis, eastern equine encephalitis; bunyavirus—La Crosse encephalitis, California encephalitis) ³¹¹	Supportive therapy	Investigational only (antiviral, interferon, immune globulins). No specific antiviral agents are yet commercially available for any of the arboviruses, including Zika or West Nile.

J. CENTRAL NERVOUS SYSTEM INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Meningitis, bacterial, community-associated		
NOTES		
<ul style="list-style-type: none"> – In areas where pen-R pneumococci exist (>5% of invasive strains), initial empiric therapy for suspect pneumococcal meningitis should be with vancomycin AND cefotaxime or ceftriaxone until susceptibility test results are available. Although ceftaroline is more active than ceftriaxone against pneumococci and, as a beta-lactam, should be expected to achieve therapeutic CSF concentrations, no substantial pediatric data yet exist on CNS infections. – Dexamethasone 0.6 mg/kg/day IV div q6h for 2 days as an adjunct to antibiotic therapy decreases hearing deficits and other neurologic sequelae in adults and children (for <i>Haemophilus</i> and pneumococcus; not prospectively studied in children for meningococcus or <i>E coli</i>). The first dose of dexamethasone is given before or concurrent with the first dose of antibiotic; probably little benefit if given ≥ 1 h after the antibiotic.^{316,317} 		
– Empiric therapy ³¹⁸	Cefotaxime 200–300 mg/kg/day IV div q6h, or ceftriaxone 100 mg/kg/day IV q24h (AI)	If Gram stain or cultures demonstrate a pathogen other than pneumococcus, vancomycin is not needed; vancomycin used empirically for possible pen-R pneumococcus in unimmunized children, or for possible MRSA; high-dose ceftaroline (MRSA dosing) should also prove effective for both pathogens, but no data exist currently for CNS infections.
– <i>Haemophilus influenzae</i> type b ³¹⁸	Cefotaxime 200–300 mg/kg/day IV div q6h, or ceftriaxone 100 mg/kg/day IV q24h; for 10 days (AI)	Alternative: ampicillin 200–400 mg/kg/day IV div q6h (for beta-lactamase–negative strains)
– Meningococcus (<i>Neisseria meningitidis</i>) ³¹⁸	Penicillin G 250,000 U/kg/day IV div q4h; or ceftriaxone 100 mg/kg/day IV q24h, or cefotaxime 200 mg/kg/day IV div q6h; treatment course for 7 days (AI)	Meningococcal prophylaxis: rifampin 10 mg/kg PO q12h for 4 doses OR ceftriaxone 125–250 mg IM once OR ciprofloxacin 500 mg PO once (adolescents and adults)
– Neonatal	See Chapter 5.	
– Pneumococcus (<i>Streptococcus pneumoniae</i>) ³¹⁸	For pen-S and cephalosporin-susceptible strains: penicillin G 250,000 U/kg/day IV div q4–6h, OR ceftriaxone 100 mg/kg/day IV q24h or cefotaxime 200–300 mg/kg/day IV div q6h; for 10 days (AI).	Some pneumococci may be resistant to penicillin but susceptible to cefotaxime and ceftriaxone and may be treated with the cephalosporin alone. For the rare ceftriaxone-resistant strain, add vancomycin to

For pen-R pneumococci (assuming ceftriaxone susceptibility): continue ceftriaxone IV for total course (AIII).

ceftriaxone (once resistance is suspected or documented) to complete a 14-day course. With the efficacy of current pneumococcal conjugate vaccines, primary bacterial meningitis is uncommon, and penicillin resistance has decreased substantially. Test-of-cure LP may be helpful in those with pen-R pneumococci.

Meningitis, TB (*Mycobacterium tuberculosis*; *Mycobacterium bovis*)^{14,15}

For non-immunocompromised children: INH 15 mg/kg/day PO, IV div q12–24h AND rifampin 15 mg/kg/day PO, IV div q12–24h for 12 mo AND PZA 30 mg/kg/day PO div q12–24h for first 2 mo of therapy, AND streptomycin 30 mg/kg/day IV, IM div q12h or ethionamide for first 4–8 wk of therapy; followed by INH and rifampin combination therapy to complete at least 12 mo for the total course.

Hyponatremia from inappropriate ADH secretion is common; ventricular drainage may be necessary for obstructive hydrocephalus. Corticosteroids (can use the same dexamethasone dose as for bacterial meningitis, 0.6 mg/kg/day IV div q6h) for 4 wk until neurologically stable, then taper dose for 1–3 mo to decrease neurologic complications and improve prognosis by decreasing the incidence of infarction.³¹⁹ Watch for rebound inflammation during taper; increase dose to previously effective level, then taper more slowly. For recommendations for drug-resistant strains and treatment of TB in HIV-infected patients, visit the CDC Web site for TB: www.cdc.gov/tb (accessed October 4, 2018).

Shunt infections: The use of antibiotic-impregnated shunts has decreased the frequency of this infection.³²⁰ Shunt removal is usually necessary for cure, with placement of a new external ventricular drain; intraventricular injection of antibiotics should be considered in children who are responding poorly to systemic antibiotic therapy. Duration of therapy varies by pathogen and response to treatment.³²¹

– Empiric therapy pending Gram stain and culture^{318,321}

Vancomycin 60 mg/kg/day IV div q8h, AND ceftriaxone 100 mg/kg/day IV q24h (AII)

If Gram stain shows only Gram-positive cocci, can use vancomycin alone. Cefepime, meropenem, or ceftazidime should be used instead of ceftriaxone if *Pseudomonas* is suspected. For ESBL-containing Gram-negative bacilli, meropenem should be used as the preferred carbapenem for CNS infection.

J. CENTRAL NERVOUS SYSTEM INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
– <i>Staphylococcus epidermidis</i> or <i>Staphylococcus aureus</i> ^{318,321}	Vancomycin (for <i>S epidermidis</i> and CA-MRSA) 60 mg/kg/day IV div q8h; OR nafcillin (if organisms susceptible) 150–200 mg/kg/day AND rifampin; for 10–14 days (AIII)	For children who cannot tolerate vancomycin, ceftaroline has anecdotally been successful: ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BIII). Linezolid, daptomycin, and TMP/SMX are other options.
– Gram-negative bacilli ^{318,321}	Empiric therapy with meropenem 120 mg/kg/day IV div q8h OR cefepime 150 mg/kg/day IV div q8h (AIII). For <i>E coli</i> (without ESBLs): ceftriaxone 100 mg/kg/day IV q12h OR cefotaxime 200–300 mg/kg/day IV div q6h; for at least 10–14 days, preferably 21 days.	Remove shunt. Select appropriate therapy based on in vitro susceptibilities. Meropenem, ceftriaxone, cefotaxime, and cefepime have all been studied in pediatric meningitis. Systemic gentamicin as combination therapy is not routinely recommended. Intrathecal therapy with aminoglycosides not routinely necessary with highly active beta-lactam therapy and shunt removal.

K. URINARY TRACT INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
NOTE: Antibiotic susceptibility profiles of <i>Escherichia coli</i> , the most common cause of UTI, vary considerably. For mild disease, TMP/SMX may be started as initial empiric therapy if local susceptibility $\geq 80\%$ and a 20% failure rate is acceptable. For moderate to severe disease (possible pyelonephritis), obtain cultures and begin an oral 2nd- or 3rd-generation cephalosporin (cefuroxime, cefaclor, cefprozil, cefixime, ceftibuten, cefdinir, cefpodoxime), ciprofloxacin PO, or ceftriaxone IM. Antibiotic susceptibility testing will help direct your therapy to the narrowest spectrum agent.		
Cystitis, acute (<i>E coli</i>) ^{322,323}	<p>For mild disease: TMP/SMX, 8 mg/kg/day of TMP PO div bid for 3 days (See NOTE about resistance to TMP/SMX.)</p> <p>For moderate to severe disease: cefixime 8 mg/kg/day PO qd; OR ceftriaxone 50 mg/kg IM q24h for 3–5 days (with normal anatomy) (BII); follow-up culture after 36–48 h treatment ONLY if still symptomatic</p>	<p>Alternative: amoxicillin 30 mg/kg/day PO div tid OR amoxicillin/clavulanate PO if susceptible (BII); ciprofloxacin 20–30 mg/kg/day PO div bid for suspected or documented resistant organisms³²⁴</p>
Nephronia, lobar <i>E coli</i> and other enteric rods (also called focal bacterial nephritis) ^{325,326}	<p>Ceftriaxone 50 mg/kg/day IV, IM q24h.</p> <p>Duration depends on resolution of cellulitis vs development of abscess (10–21 days) (AIII). For ESBL-positive <i>E coli</i>, carbapenems and fluoroquinolones are often active agents.</p>	<p>Invasive, consolidative parenchymal infection; complication of pyelonephritis, can evolve into renal abscess. Step-down therapy with oral cephalosporins once cellulitis/abscess has initially responded to therapy.</p>

K. URINARY TRACT INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Pyelonephritis, acute (<i>E coli</i>) ^{322,323,327–331}	<p>Ceftriaxone 50 mg/kg/day IV, IM q24h OR gentamicin 5–6 mg/kg/day IV, IM q24h (yes, once daily).</p> <p>For documented or suspected ceftriaxone-resistant ESBL-positive strains, use meropenem IV, imipenem IV, or ertapenem IV³²⁸; OR gentamicin IV, IM, OR pip/tazo.</p> <p>Switch to oral therapy following clinical response (BII). If organism resistant to amoxicillin and TMP/SMX, use an oral 2nd- or 3rd-generation cephalosporin (BII); if cephalosporin-R, can use ciprofloxacin PO 30 mg/kg/day div q12h (BIII); for 7–14 days total (depending on response to therapy).</p>	<p>For mild to moderate infection, oral therapy is likely to be as effective as IV/IM therapy for susceptible strains, down to 3 mo of age.³²⁷</p> <p>If bacteremia documented and infant is <2–3 mo, rule out meningitis and treat 14 days IV + PO (AIII). Aminoglycosides at any dose are more nephrotoxic than beta-lactams but represent effective therapy (AI). Once-daily dosing of gentamicin is preferred to tid.³²⁷</p>
Recurrent urinary tract infection, prophylaxis ^{322,332–335}	<p>Only for those with grade III–V reflux or with recurrent febrile UTI: TMP/SMX 2 mg/kg/dose of TMP PO qd OR nitrofurantoin 1–2 mg/kg PO qd at bedtime; more rapid resistance may develop using beta-lactams (BII).</p>	<p>Prophylaxis not recommended for patients with grade I–II reflux and no evidence of renal damage (although the RIVUR study³³⁴ included these children, and they may also benefit, but early treatment of new infections is recommended for these children). <i>Resistance eventually develops to every antibiotic</i>; follow resistance patterns for each patient. The use of periodic urine cultures is controversial, as there are no comparative data to guide management of asymptomatic bacteriuria in a child at high risk of recurrent UTI.</p>

L. MISCELLANEOUS SYSTEMIC INFECTIONS

Clinical Diagnosis	Therapy (evidence grade)	Comments
Actinomycosis ^{336–338}	Penicillin G 250,000 U/kg/day IV div q6h, OR ampicillin 150 mg/kg/day IV div q8h until improved (often up to 6 wk); then long-term convalescent therapy with penicillin V 100 mg/kg/day (up to 4 g/day) PO for 6–12 mo (AII)	Surgery with debridement as indicated Alternatives: amoxicillin, clindamycin, erythromycin; ceftriaxone IM/IV, doxycycline for children >7 y, or meropenem IV.
Anaplasmosis ^{339,340} (human granulocytotropic anaplasmosis, <i>Anaplasma phagocytophilum</i>)	Doxycycline 4.4 mg/kg/day IV, PO (max 200 mg/day) div bid for 7–10 days (regardless of age) (AIII)	For mild disease, consider rifampin 20 mg/kg/day PO div bid for 7–10 days (BIII).
Anthrax, sepsis/pneumonia, community vs bioterror exposure (inhalation, cutaneous, gastrointestinal, meningoencephalitis) ¹⁶	For community-associated anthrax infection, amoxicillin 75 mg/kg/day div q8h OR doxycycline for children >7 y. For bioterror-associated exposure (regardless of age): ciprofloxacin 20–30 mg/kg/day IV div q12h, OR levofloxacin 16 mg/kg/day IV div q12h not to exceed 250 mg/dose (AIII); OR doxycycline 4.4 mg/kg/day PO (max 200 mg/day) div bid (regardless of age).	For invasive infection after bioterror exposure, 2 or 3 antibiotics may be required. ¹⁶ For oral step-down therapy, can use oral ciprofloxacin or doxycycline; if susceptible, can use penicillin, amoxicillin, or clindamycin. May require long-term postexposure prophylaxis after bioterror event.
Appendicitis (See Table 6H, Gastrointestinal Infections, Intra-abdominal infection, Appendicitis.)		
Brucellosis ^{341–344}	Doxycycline 4.4 mg/kg/day PO (max 200 mg/day) div bid (for children >7 y) AND rifampin (15–20 mg/kg/day div q12h) (BIII); OR for children <8 y: TMP/SMX 10 mg/kg/day TMP IV, PO div q12h AND rifampin 15–20 mg/kg/day div q12h (BIII); for at least 6 wk	Combination therapy with rifampin will decrease the risk of relapse. ADD gentamicin 6–7.5 mg/kg/day IV, IM div q8h for the first 1–2 wk of therapy to further decrease risk of relapse ³⁴⁴ (BIII), particularly for endocarditis, osteomyelitis, or meningitis. Prolonged treatment for 4–6 mo and surgical debridement may be necessary for deep infections (AIII).

L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Cat-scratch disease (<i>Bartonella henselae</i>) ^{345–347}	Supportive care for adenopathy (I&D of infected lymph node); azithromycin 12 mg/kg/day PO qd for 5 days shortens the duration of adenopathy (AIII). No prospective data exist for invasive CSD: gentamicin (for 14 days) AND TMP/SMX AND rifampin for hepatosplenic disease and osteomyelitis (AIII). For CNS infection, use cefotaxime AND gentamicin ± TMP/SMX (AIII). Alternatives: ciprofloxacin, doxycycline.	This dosage of azithromycin has been documented to be safe and effective for streptococcal pharyngitis and may offer greater deep tissue exposure than the dosage studied by Bass et al ⁹ and used for otitis media.
Chickenpox/shingles (varicella-zoster virus)	See Chapter 9, Varicella virus.	
Ehrlichiosis (human monocytic ehrlichiosis, caused by <i>Ehrlichia chaffeensis</i> , and <i>Ehrlichia ewingii</i>) ^{339,348–350}	Doxycycline 4.4 mg/kg/day IV, PO div bid (max 100 mg/dose) for 7–10 days (regardless of age) (AIII)	For mild disease, consider rifampin 20 mg/kg/day PO div bid (max 300 mg/dose) for 7–10 days (BIII).
Febrile neutropenic patient (empiric therapy of invasive infection: <i>Pseudomonas</i> , enteric Gram-negative bacilli, staphylococci, streptococci, yeast, fungi) ^{351,352}	Cefepime 150 mg/kg/day div q8h (AI); or meropenem 60 mg/kg/day div q8h (AII); OR pip/tazo (300-mg pip component/kg/day div q8h for 9 mo; 240 mg/kg/day div q8h for 2–9 mo), OR ceftazidime 150 mg/kg/day IV div q8h AND tobramycin 6 mg/kg/day IV q8h (AI). ADD vancomycin 40 mg/kg/day IV div q8h if MRSA or coagulation-negative staph suspected (eg, central catheter infection) (AIII). ADD metronidazole to ceftazidime or cefepime if colitis or other deep anaerobic infection suspected (AIII).	Alternatives: other anti- <i>Pseudomonas</i> beta-lactams (imipenem) AND antistaphylococcal antibiotics. If no response in 3–4 days and no alternative etiology demonstrated, begin additional empiric therapy with antifungals (BII) ³⁴³ ; dosages and formulations outlined in Chapter 8. Increasingly resistant pathogens (ESBL <i>E coli</i> and KPC <i>Klebsiella</i>) will require alternative empiric therapy if MDR organisms are colonizing or present on the child's hospital unit. For low-risk patients with negative cultures and close follow-up, alternative management strategies are being explored: oral therapy with

		amox/clav and ciprofloxacin may be used, cautious discontinuation of antibiotics (even in those without marrow recovery). ^{351,353}
Human immunodeficiency virus infection	See Chapter 9.	
Infant botulism ³⁵⁴	Botulism immune globulin for infants (BabyBIG) 50 mg/kg IV for 1 dose (AI); BabyBIG can be obtained from the California Department of Public Health at www.infantbotulism.org , through your state health department.	www.infantbotulism.org provides information for physicians and parents. Web site organized by the California Department of Public Health (accessed October 4, 2018). Aminoglycosides should be avoided because they potentiate the neuromuscular effect of botulinum toxin.
Kawasaki syndrome ^{355–358}	No antibiotics; IVIG 2 g/kg as single dose (AI); may need to repeat dose in up to 15% of children for persisting fever that lasts 24 h after completion of the IVIG infusion (AI). For subsequent relapse, many children will respond to a second IVIG infusion, otherwise consult an infectious diseases physician or pediatric cardiologist. Adjunctive therapy with corticosteroids for those at high risk for the development of aneurysms. ³⁵⁶	Aspirin 80–100 mg/kg/day div qid in acute, febrile phase; once afebrile for 24–48 h, initiate low-dosage (3–5 mg/kg/day) aspirin therapy for 6–8 wk (assuming echocardiogram is normal). Role of corticosteroids, infliximab, calcineurin inhibitors, and anti-thrombotic therapy, as well as methotrexate and cyclosporin, for IVIG-resistant Kawasaki syndrome under investigation and may improve outcome in severe cases. ³⁵⁸
Leprosy (Hansen disease) ³⁵⁹	Dapsone 1 mg/kg/day PO qd AND rifampin 10 mg/kg/day PO qd; ADD (for multibacillary disease) clofazimine 1 mg/kg/day PO qd; for 12 mo for paucibacillary disease; for 24 mo for multibacillary disease (AI).	Consult Health Resources and Services Administration National Hansen's Disease (Leprosy) Program, updated May 2018, at www.hrsa.gov/hansens-disease (accessed October 4, 2018) for advice about treatment and free antibiotics: 800/642-2477.

L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Leptospirosis ^{360,361}	Penicillin G 250,000 U/kg/day IV div q6h, or ceftriaxone 50 mg/kg/day IV, IM q24h; for 7 days (BII) For mild disease, doxycycline (>7 y) 4.4 mg/kg/day (max 200 mg/day) PO div bid for 7–10 days and for those ≤7 y or intolerant of doxycycline, azithromycin 20 mg/kg on day 1, 10 mg/kg on days 2 and 3 (BII)	Alternative: amoxicillin for children ≤7 y with mild disease
Lyme disease (<i>Borrelia burgdorferi</i>) ^{350,362–364}	Neurologic evaluation, including LP, if there is clinical suspicion of CNS involvement	
– Early localized disease (Erythema migrans, single or multiple) (any age)	Doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 14 days (AII) OR amoxicillin 50 mg/kg/day (max 1.5 g/day) PO div tid for 14 days (AII)	Alternative: cefuroxime, 30 mg/kg/day (max 1,000 mg/day) PO, in 2 div doses for 14 days OR azithromycin 10 mg/kg/day PO qd for 7 days
– Arthritis (no CNS disease)	Oral therapy as outlined in early localized disease, but for 28 days (AIII).	Persistent or recurrent joint swelling after treatment: repeat a 4-wk course of oral antibiotics or give ceftriaxone 50–75 mg/kg IV q24h for 14–28 days. For persisting arthritis after 2 defined antibiotic treatment courses, use symptomatic therapy.
– Isolated facial (Bell) palsy	Doxycycline as outlined previously, for 14 days (AIII); efficacy of amoxicillin unknown.	LP is not routinely required unless CNS symptoms present. Treatment to prevent late sequelae; will not provide a quick response for palsy.
– Carditis	Oral therapy as outlined in early localized disease, for 14 days (range: 14–21 days) OR ceftriaxone 50–75 mg/kg IV q24h for 14 days (range: 14–21 days) (AIII)	
– Neuroborreliosis	Doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 14 days (AII) OR ceftriaxone 50–75 mg/kg IV q24h OR penicillin G 300,000 U/kg/day IV div q4h; for 14 days (AIII)	

Melioidosis (<i>Burkholderia pseudomallei</i>) ^{365,366}	Acute sepsis: meropenem 75 mg/kg/day div q8h; OR ceftazidime 150 mg/kg/day IV div q8h; followed by TMP/SMX (10 mg/kg/day of TMP) PO div bid for 3–6 mo	Alternative convalescent therapy: amox/clav (90 mg/kg/day amox div tid, not bid) for children ≤7 y, or doxycycline for children >7 y; for 20 wk (All)
Mycobacteria, nontuberculous ^{10,12,13,367}		
– Adenitis in normal host (See Adenitis entries in this table and Table 6A.)	Excision usually curative (BII); azithromycin PO OR clarithromycin PO for 6–12 wk (with or without rifampin) if susceptible (BII)	Antibiotic susceptibility patterns are quite variable; cultures should guide therapy; medical therapy 60%–70% effective. Newer data suggest toxicity of antimicrobials may not be worth the small clinical benefit.
– Pneumonia or disseminated infection in compromised hosts (HIV, gamma-interferon receptor deficiency, cystic fibrosis) ^{12,367–370}	Usually treated with 3 or 4 active drugs (eg, clarithromycin OR azithromycin, AND amikacin, cefoxitin, meropenem). Also test for ciprofloxacin, TMP/SMX, ethambutol, rifampin, linezolid, clofazimine, and doxycycline (BII).	Outcomes particularly poor for <i>Mycobacterium abscessus</i> . ³⁷¹ See Chapter 11 for dosages; cultures are essential, as the susceptibility patterns of nontuberculous mycobacteria are varied.
Nocardiosis (<i>Nocardia asteroides</i> and <i>Nocardia brasiliensis</i>) ^{372,373}	TMP/SMX 8 mg/kg/day TMP div bid or sulfisoxazole 120–150 mg/kg/day PO div qid for 6–12 wk or longer. For severe infection, particularly in immunocompromised hosts, use ceftriaxone or imipenem or meropenem AND amikacin 15–20 mg/kg/day IM, IV div q8h (AIII).	Wide spectrum of disease from skin lesions to brain abscess. Surgery when indicated. Alternatives: doxycycline (for children >7 y), amox/clav, or linezolid. Immunocompromised children may require months of therapy.
Plague (<i>Yersinia pestis</i>) ^{374–376}	Gentamicin 7.5 mg/kg/day IV div q8h (All) OR doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid OR ciprofloxacin 30 mg/kg/day PO div bid. Gentamicin is poorly active in abscesses; consider alternatives for bubonic plague.	A complete listing of options for children is provided on the CDC Web site: https://www.cdc.gov/plague/healthcare/clinicians.html (accessed October 4, 2018).

L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

Clinical Diagnosis	Therapy (evidence grade)	Comments
Q fever (<i>Coxiella burnetii</i>) ^{377,378}	<p>Acute stage: doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 14 days (AII) for children of any age.</p> <p>Endocarditis and chronic disease (ongoing symptoms for 6–12 mo): doxycycline for children >7 y AND hydroxychloroquine for 18–36 mo (AIII).</p> <p>Seek advice from pediatric infectious diseases specialist for children ≤7 y: may require TMP/SMX, 8–10 mg TMP/kg/day div q12h with doxycycline; OR levofloxacin with rifampin for 18 mo.</p>	<p>Follow doxycycline and hydroxychloroquine serum concentrations during endocarditis/chronic disease therapy.</p> <p>CNS: Use fluoroquinolone (no prospective data) (BIII).</p> <p>Clarithromycin may be an alternative based on limited data (CIII).</p>
Rocky Mountain spotted fever (fever, petechial rash with centripetal spread; <i>Rickettsia rickettsii</i>) ^{379,380}	Doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 7–10 days (AI) for children of any age	Start empiric therapy early.
Tetanus (<i>Clostridium tetani</i>) ^{381,382}	Metronidazole 30 mg/kg/day IV, PO div q8h OR penicillin G 100,000 U/kg/day IV div q6h for 10–14 days; AND TIG 3,000–6,000 U IM (AII)	<p>Wound debridement essential; may infiltrate wound with a portion of TIG dose, but not well-studied; IVIG may provide antibody to toxin if TIG not available.</p> <p>Immunize with Td or Tdap.</p> <p>See Chapter 14 for prophylaxis recommendations.</p>
Toxic shock syndrome (toxin-producing strains of <i>S aureus</i> [including MRSA] or group A streptococcus) ^{2,7,8,383,384}	Empiric: vancomycin 45 mg/kg/day IV div q8h AND oxacillin/naftillin 150 mg/kg/day IV div q6h, AND clindamycin 30–40 mg/kg/day div q8h ± gentamicin for 7–10 days (AIII)	<p>Clindamycin added for the initial 48–72 h of therapy to decrease toxin production.</p> <p>Ceftaroline is an option for MRSA treatment, particularly with renal injury from shock and vancomycin (BIII).</p> <p>IVIG may provide additional benefit by binding circulating toxin (CIII).</p> <p>For MSSA: oxacillin/naftillin AND clindamycin ± gentamicin.</p>

		For CA-MRSA: vancomycin AND clindamycin ± gentamicin. For group A streptococcus: penicillin G AND clindamycin.
Tularemia (<i>Francisella tularensis</i>) ^{185,385}	Gentamicin 6–7.5 mg/kg/day IM, IV div q8h; for 10–14 days (All) Additional information from CDC: https://www.cdc.gov/tularemia/clinicians/index.html (accessed October 4, 2018)	Alternatives: ciprofloxacin (for 10 days); doxycycline no longer recommended due to higher relapse rate.

7. Preferred Therapy for Specific Bacterial and Mycobacterial Pathogens

NOTES

- For fungal, viral, and parasitic infections, see chapters 8, 9, and 10, respectively.
- Limitations of space do not permit listing of all possible alternative antimicrobials.
- **Abbreviations:** amox/clav, amoxicillin/clavulanate (Augmentin); amp/sul, ampicillin/sulbactam (Unasyn); CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CAZ/AVI, ceftazidime/avibactam; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; ESBL, extended spectrum beta-lactamase; FDA, US Food and Drug Administration; HRSA, Health Resources and Services Administration; IM, intramuscular; IV, intravenous; IVIG, intravenous immunoglobulin; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*; NARMS, National Antimicrobial Resistance Monitoring System for Enteric Bacteria; NDM, New Delhi metallo-beta-lactamase; PCV13, pneumococcal 13-valent conjugate vaccine; pen-S, penicillin-susceptible; pip/tazo, piperacillin/tazobactam (Zosyn); PO, oral; PZA, pyrazinamide; spp, species; ticar/clav, ticarcillin/clavulanate (Timentin); TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection.

A. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (GRAM POSITIVE)

	Commonly Used Antibiotics (One Agent per Class Listed) (scale 0 to ++ defined in footnote)			
	Penicillin	Ampicillin/ Amoxicillin	Amoxicillin/ Clavulanate	Methicillin/ Oxacillin
<i>Enterococcus faecalis</i> ^a	+	+	+	—
<i>Enterococcus faecium</i> ^a	+	+	+	—
<i>Staphylococcus</i> , coagulase negative	—	—	—	±
<i>Staphylococcus aureus</i> , methicillin-resistant	—	—	—	—
<i>Staphylococcus aureus</i> , methicillin-susceptible	—	—	—	++
<i>Streptococcus pneumoniae</i>	++	++	++	+
<i>Streptococcus pyogenes</i>	++	++	++	++

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); ± = significant resistance (30%–80% in some locations); — = not likely to be effective; 0 = not usually tested for susceptibility for treatment of infections (resistant or has not previously been considered for routine therapy, so little data exist).

^a Need to add gentamicin or other aminoglycoside to ampicillin/penicillin or vancomycin for in vitro bactericidal activity.

Commonly Used Antibiotics (One Agent per Class Listed) (scale 0 to ++ defined in footnote)					
Cefazolin/ Cephalexin	Vancomycin	Clindamycin	Linezolid	Daptomycin	Ceftaroline
—	+	—	+	+	—
—	+	—	+	+	—
±	++	+	++	++	++
—	++	+	++	++	++
++	++	+	++	++	++
++	++	++	++	++	++
++	++	++	++	++	++

B. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (GRAM NEGATIVE)^a

Commonly Used Antibiotics (One Agent per Class Listed)
(scale 0 to ++ defined in footnote)

	Ampicillin/ Amoxicillin	Amoxicillin/ Clavulanate	Cefazolin/ Cephalexin	Cefuroxime	Ceftriaxone/ Cefotaxime
<i>Acinetobacter</i> spp	—	—	—	—	+
<i>Citrobacter</i> spp	—	—	—	+	+
<i>Enterobacter</i> spp ^b	—	—	—	±	+
<i>Escherichia coli</i> ^c	±	+	+	++ ^d	++ ^d
<i>Haemophilus influenzae</i> ^f	++	++	++	++	++
<i>Klebsiella</i> spp ^c	—	—	+	++	++
<i>Neisseria meningitidis</i>	++	++	0	++	++
<i>Pseudomonas aeruginosa</i>	—	—	—	—	—
<i>Salmonella</i> , non-typhoid spp	+	++	0	0	++
<i>Serratia</i> spp ^b	—	—	—	±	+
<i>Shigella</i> spp	+	+	0	+	++
<i>Stenotrophomonas maltophilia</i>	—	—	—	—	—

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); ± = significant resistance (30%–80% in some locations); — = not likely to be effective; 0 = not usually tested for susceptibility for treatment of infections (resistant or has not previously been considered for routine therapy, so little data exist).

^a CDC (NARMS) statistics for each state, by year, are found for many enteric pathogens on the CDC Web site at <https://www.cdc.gov/NARMSNow> and are also provided by the SENTRY surveillance system (JMI Laboratories); we also use current pediatric hospital antibiograms from the editors' hospitals to assess pediatric trends. When sufficient data are available, pediatric community isolate susceptibility data are used. Nosocomial resistance patterns may be quite different, usually with increased resistance, particularly in adults; please check your local/regional hospital antibiogram for your local susceptibility patterns.

^b AmpC will be constitutively produced in low frequency in every population of organisms and will be selected out during therapy with third-generation cephalosporins if used as single agent therapy.

^c Rare carbapenem-resistant isolates in pediatrics (KPC, NDM strains).

^d Will be resistant to virtually all current cephalosporins if ESBL producing.

^e Follow the MIC, and not the report for susceptible (S), intermediate (I), or resistant (R), as some ESBL producers will have low MICs and can be effectively treated with higher dosages.

^f Will be resistant to ampicillin/amoxicillin if beta-lactamase producing.

Commonly Used Antibiotics (One Agent per Class Listed) (scale 0 to ++ defined in footnote)						
Ceftazidime	Cefepime	Meropenem/ Imipenem	Piperacillin/ Tazobactam	TMP/SMX	Ciprofloxacin	Gentamicin
+	+	++	+	+	+	++
+	++	++	+	++	++	++
+	++	++	+	+	++	++
++ ^d	++ ^e	++	++	+	++	++
++	++	++	++	++	++	±
++	++ ^e	++	++	++	++	++
+	++	++	++	0	++	0
+	++	++	++	—	++	+
++	++	++	++	++	++	0
+	++	++	+	++	++	++
++	++	++	++	±	++	0
+	±	±	+	++	++	±

C. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (ANAEROBES)

	Commonly Used Antibiotics (One Agent per Class Listed) (scale 0 to ++ defined in footnote)				
	Penicillin	Ampicillin/ Amoxicillin	Amoxicillin/ Clavulanate	Cefazolin	Cefoxitin
Anaerobic streptococci	++	++	++	++	++
<i>Bacteroides fragilis</i>	±	±	++	—	+
<i>Clostridia</i> (eg, <i>tetani</i> , <i>perfringens</i>)	++	++	++	0	+
<i>Clostridium difficile</i>	—	—	—	0	—

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); ± = significant resistance (30%–80% in some locations); — = not likely to be effective; 0 = not usually tested for susceptibility for treatment of infections (resistant or has not previously been considered for routine therapy, so little data exist).

Commonly Used Antibiotics (One Agent per Class Listed) (scale 0 to ++ defined in footnote)					
Ceftriaxone/ Cefotaxime	Meropenem/ Imipenem	Piperacillin/ Tazobactam	Metronidazole	Clindamycin	Vancomycin
++	++	++	++	++	++
—	++	++	++	+	0
±	++	++	++	+	++
—	++	0	++	—	++

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Acinetobacter baumannii</i> ¹⁻⁴	Sepsis, meningitis, nosocomial pneumonia, wound infection	Meropenem (BIII) or other carbapenem	Use culture results to guide therapy: ceftazidime, amp/sul, pip/tazo, TMP/SMX, ciprofloxacin, tigecycline, colistin/polymyxin B. Watch for emergence of resistance <i>during</i> therapy, including to colistin. Consider combination therapy for life-threatening infection. ⁴ Inhaled colistin for pneumonia caused by MDR strains (BIII).
<i>Actinomyces israelii</i> ⁵	Actinomycosis (cervicofacial, thoracic, abdominal)	Penicillin G; ampicillin (CIII)	Amoxicillin, doxycycline, clindamycin, ceftriaxone, meropenem, pip/tazo, linezolid
<i>Aeromonas hydrophila</i> ⁶	Diarrhea	Ciprofloxacin (CIII)	Azithromycin, cefepime, TMP/SMX
	Sepsis, cellulitis, necrotizing fasciitis	Cefepime (BIII)	Meropenem, ciprofloxacin, TMP/SMX
<i>Aggregatibacter</i> (formerly <i>Actinobacillus actinomycetemcomitans</i>) ⁷	Periodontitis, abscesses (including brain), endocarditis	Ceftriaxone (CIII)	Ampicillin/amoxicillin for beta-lactamase–negative strains, or amox/clav, doxycycline, TMP/SMX, ciprofloxacin
<i>Anaplasma</i> (formerly <i>Ehrlichia phagocytophilum</i>) ^{8,9}	Human granulocytic anaplasmosis	Doxycycline (all ages) (AII)	Rifampin, levofloxacin
<i>Arcanobacterium haemolyticum</i> ¹⁰	Pharyngitis, cellulitis, Lemierre syndrome	Azithromycin; penicillin (BIII)	Erythromycin, amoxicillin, ceftriaxone, clindamycin, doxycycline, vancomycin
<i>Bacillus anthracis</i> ¹¹	Anthrax (cutaneous, gastrointestinal, inhalational, meningoencephalitis)	Ciprofloxacin (regardless of age) (AIII). For invasive, systemic infection, use combination therapy.	Doxycycline, amoxicillin, levofloxacin, clindamycin, penicillin G, vancomycin, meropenem. Bioterror strains may be antibiotic resistant.

<i>Bacillus cereus</i> or <i>subtilis</i> ^{12,13}	Sepsis; toxin-mediated gastroenteritis	Vancomycin (BIII)	Clindamycin, ciprofloxacin, linezolid, daptomycin
<i>Bacteroides fragilis</i> ^{14,15}	Peritonitis, sepsis, abscesses	Metronidazole (AI)	Meropenem or imipenem (AI); pip/tazo (AI); amox/clav (BII). Recent surveillance suggests resistance of up to 25% for clindamycin.
<i>Bacteroides</i> , other spp ^{14,15}	Pneumonia, sepsis, abscesses	Metronidazole (BII)	Meropenem or imipenem; penicillin G or ampicillin if beta-lactamase negative
<i>Bartonella henselae</i> ^{16,17}	Cat-scratch disease	Azithromycin for lymph node disease (BII); gentamicin in combination with TMP/SMX AND rifampin for invasive disease (BIII)	Cefotaxime, ciprofloxacin, doxycycline
<i>Bartonella quintana</i> ^{17,18}	Bacillary angiomatosis, peliosis hepatis	Gentamicin plus doxycycline (BIII); erythromycin; ciprofloxacin (BIII)	Azithromycin, doxycycline
<i>Bordetella pertussis</i> , <i>parapertussis</i> ^{19,20}	Pertussis	Azithromycin (AIII); erythromycin (BII)	Clarithromycin, TMP/SMX, ciprofloxacin (in vitro data)
<i>Borrelia burgdorferi</i> , Lyme disease ^{21–23}	Treatment based on stage of infection (See Lyme disease in Chapter 6.)	Doxycycline if > 7 y (AII); amoxicillin or cefuroxime in children ≤ 7 y (AIII); ceftriaxone IV for CNS/meningitis (AI)	
<i>Borrelia hermsii</i> , <i>turicatae</i> , <i>parkeri</i> , tick-borne relapsing fever ^{24,25}	Relapsing fever	Doxycycline for all ages (AIII)	Penicillin or erythromycin in children intolerant of doxycycline (BIII)
<i>Borrelia recurrentis</i> , louse-borne relapsing fever ^{24,25}	Relapsing fever	Single-dose doxycycline for all ages (AIII)	Penicillin or erythromycin in children intolerant of doxycycline (BIII). Amoxicillin; ceftriaxone.

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Brucella</i> spp ^{26–28}	Brucellosis (See Chapter 6.)	Doxycycline AND rifampin (BIII); OR, for children ≤7 y: TMP/SMX AND rifampin (BIII)	For serious infection: doxycycline AND gentamicin AND rifampin; or TMP/SMX AND gentamicin AND rifampin (AIII). May require extended therapy (months).
<i>Burkholderia cepacia</i> complex ^{29–31}	Pneumonia, sepsis in immunocompromised children; pneumonia in children with cystic fibrosis ³²	Meropenem (BIII); for severe disease, ADD tobramycin (although may be in vitro resistant to aminoglycosides) AND TMP/SMX (AIII).	Imipenem, doxycycline, ceftazidime, pip/tazo, ciprofloxacin, TMP-SMX. Aerosolized antibiotics may provide higher concentrations in lung.
<i>Burkholderia pseudomallei</i> ^{33–35}	Melioidosis	Meropenem (AIII) or ceftazidime (BIII), followed by prolonged TMP/SMX for 12 wk (AII)	TMP/SMX, doxycycline, or amox/clav for chronic disease
<i>Campylobacter fetus</i> ^{36,37}	Sepsis, meningitis in the neonate	Meropenem (BIII)	Cefotaxime, gentamicin, erythromycin, ciprofloxacin
<i>Campylobacter jejuni</i> ^{38,39}	Diarrhea	Azithromycin (BII); erythromycin (BII)	Doxycycline, ciprofloxacin (very high rates of ciprofloxacin-resistant strains in Thailand, Hong Kong, and Spain)
<i>Capnocytophaga canimorsus</i> ^{40,41}	Sepsis after dog bite (increased risk with asplenia)	Pip/tazo OR meropenem; amox/clav (BIII)	Clindamycin, linezolid, penicillin G, ciprofloxacin
<i>Capnocytophaga ochracea</i> ⁴²	Sepsis, abscesses	Clindamycin (BIII); amox/clav (BIII)	Meropenem, pip/tazo, ciprofloxacin
<i>Chlamydia trachomatis</i> ^{43–45}	Lymphogranuloma venereum	Doxycycline (AII)	Azithromycin, erythromycin
	Urethritis, cervicitis	Doxycycline (AII)	Azithromycin, erythromycin, ofloxacin
	Inclusion conjunctivitis of newborn	Azithromycin (AIII)	Erythromycin

	Pneumonia of infancy	Azithromycin (AIII)	Erythromycin, ampicillin
	Trachoma	Azithromycin (AI)	Doxycycline, erythromycin
<i>Chlamydophila</i> (formerly <i>Chlamydia</i>) <i>pneumoniae</i> ^{43,44,46,47}	Pneumonia	Azithromycin (AII); erythromycin (AII)	Doxycycline, ciprofloxacin
<i>Chlamydophila</i> (formerly <i>Chlamydia</i>) <i>psittaci</i> ⁴⁸	Psittacosis	Doxycycline for >7 y; azithromycin (AIII) OR erythromycin (AIII) for ≤7 y	Doxycycline, levofloxacin
<i>Chromobacterium violaceum</i> ^{49,50}	Sepsis, pneumonia, abscesses	Meropenem AND ciprofloxacin (AIII)	Imipenem, TMP/SMX
<i>Citrobacter koseri</i> (formerly <i>diversus</i>) and <i>freundii</i> ^{51,52}	Meningitis, sepsis	Meropenem (AIII) for ampC beta-lactamase resistance	Cefepime, ciprofloxacin, pip/tazo, ceftriaxone AND gentamicin, TMP/SMX Carbapenem-resistant strains now reported

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Clostridium botulinum</i> ^{53–55}	Botulism: foodborne; wound; potentially bioterror related	Botulism antitoxin heptavalent (equine) types A–G FDA approved in 2013 (www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf ; accessed October 3, 2018) No antibiotic treatment except for wound botulism when treatment for vegetative organisms can be provided after antitoxin administered (no controlled data)	For more information, call your state health department or the CDC clinical emergency botulism service, 770/488-7100 (https://www.cdc.gov/botulism/health-professional.html ; accessed October 3, 2018). For bioterror exposure, treatment recommendations per www.cdc.gov .
	Infant botulism	Human botulism immune globulin for infants (BabyBIG) (All) No antibiotic treatment	BabyBIG available nationally from the California Department of Public Health at 510/231-7600 (www.infantbotulism.org ; accessed October 3, 2018)
<i>Clostridium difficile</i> ^{56–58}	Antibiotic-associated colitis (See Chapter 6, Table 6H, Gastrointestinal Infections, <i>Clostridium difficile</i> .)	Metronidazole PO for mild to moderate infection (AI)	Vancomycin PO ± metronidazole PO for severe infection. Vancomycin PO for metronidazole failures. Stop the predisposing antimicrobial therapy, if possible. New pediatric data on fidaxomicin PO. ⁵⁹ No pediatric data on fecal transplantation for recurrent disease.

<i>Clostridium perfringens</i> ^{60,61}	Gas gangrene/necrotizing fasciitis/sepsis (also caused by <i>Clostridium sordellii</i> , <i>Clostridium septicum</i> , <i>Clostridium novyi</i>) Food poisoning	Penicillin G AND clindamycin for invasive infection (BII); no antimicrobials indicated for foodborne illness	Meropenem, metronidazole, clindamycin monotherapy No defined benefit of hyperbaric oxygen over aggressive surgery/antibiotic therapy
<i>Clostridium tetani</i> ^{62,63}	Tetanus	Tetanus immune globulin 3,000–6,000 U IM, with part injected directly into the wound (IVIG at 200–400 mg/kg if TIG not available) Metronidazole (AIII) OR penicillin G (BIII)	Prophylaxis for contaminated wounds: 250 U IM for those with <3 tetanus immunizations. Start/continue immunization for tetanus. Alternative antibiotics: meropenem; doxycycline, clindamycin.
<i>Corynebacterium diphtheriae</i> ⁶⁴	Diphtheria	Diphtheria equine antitoxin (available through CDC under an investigational protocol [www.cdc.gov/diphtheria/dat.html ; accessed October 3, 2018]) AND erythromycin or penicillin G (AIII)	Antitoxin from the CDC Emergency Operations Center, 770/488-7100; protocol: www.cdc.gov/diphtheria/downloads/protocol.pdf (accessed October 3, 2018)
<i>Corynebacterium jeikeium</i> ^{65,66}	Sepsis, endocarditis	Vancomycin (AIII)	Penicillin G AND gentamicin, daptomycin, tigecycline, linezolid
<i>Corynebacterium minutissimum</i> ^{67,68}	Erythrasma; bacteremia in compromised hosts	Erythromycin PO for erythrasma (BIII); vancomycin IV for bacteremia (BIII)	Topical clindamycin for cutaneous infection; meropenem, penicillin/ampicillin, ciprofloxacin
<i>Coxiella burnetii</i> ^{69,70}	Q fever (See Chapter 6, Table 6L, Miscellaneous Systemic Infections, Q fever.)	Acute infection: doxycycline (all ages) (AII) Chronic infection: TMP/SMX AND doxycycline (BII); OR levofloxacin AND rifampin	Alternative for acute infection: TMP/SMX

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Ehrlichia chaffeensis</i> ⁹ <i>Ehrlichia muris</i> ^{71,72}	Human monocytic ehrlichiosis	Doxycycline (all ages) (All)	Rifampin
<i>Ehrlichia ewingii</i> ⁹	<i>E. ewingii</i> ehrlichiosis	Doxycycline (all ages) (All)	Rifampin
<i>Eikenella corrodens</i> ^{73,74}	Human bite wounds; abscesses, meningitis, endocarditis	Amox/clav; meropenem/imipenem; ceftriaxone For beta-lactamase–negative strains: ampicillin; penicillin G (BIII)	Pip/tazo, amp/sul, ciprofloxacin Resistant to clindamycin, cephalixin, erythromycin
<i>Elizabethkingia</i> (formerly <i>Chryseobacterium</i>) <i>meningoseptica</i> ^{75,76}	Sepsis, meningitis (particularly in neonates)	Levofloxacin; TMP/SMX (BIII)	Add rifampin to another active drug; pip/tazo.
<i>Enterobacter</i> spp ^{52,77,78}	Sepsis, pneumonia, wound infection, UTI	Cefepime; meropenem; pip/tazo (BII)	Ertapenem, imipenem, cefotaxime or ceftriaxone AND gentamicin, TMP/SMX, ciprofloxacin Newly emerging carbapenem-resistant strains worldwide ⁷⁹
<i>Enterococcus</i> spp ^{80–82}	Endocarditis, UTI, intra-abdominal abscess	Ampicillin AND gentamicin (AI); bactericidal activity present with combination, not with ampicillin or vancomycin alone	Vancomycin AND gentamicin. For strains that are resistant to gentamicin on synergy testing, use streptomycin or other active aminoglycoside for invasive infections. For vancomycin-resistant strains that are also ampicillin resistant: daptomycin OR linezolid. ^{81,82}
<i>Erysipelothrix rhusiopathiae</i> ⁸³	Cellulitis (erysipeloid), sepsis, abscesses, endocarditis ⁸⁴	Invasive infection: ampicillin (BIII); penicillin G (BIII) Cutaneous infection: penicillin V; amoxicillin; clindamycin	Ceftriaxone, meropenem, ciprofloxacin, erythromycin Resistant to vancomycin, daptomycin, TMP/SMX

<i>Escherichia coli</i> See Chapter 6 for specific infection entities and references. <i>Increasing resistance to 3rd-generation cephalosporins due to ESBLs.</i>	UTI, community acquired, not hospital acquired	A 2nd- or 3rd-generation cephalosporin PO, IM as empiric therapy (BI)	Amoxicillin; TMP/SMX if susceptible. Ciprofloxacin if resistant to other options. For hospital-acquired UTI, review hospital antibiogram for choices.
	Traveler's diarrhea	Azithromycin (AII)	Rifaximin (for nonfebrile, non-bloody diarrhea for children >11 y); cefixime
	Sepsis, pneumonia, hospital-acquired UTI	A 2nd- or 3rd-generation cephalosporin IV (BI)	For ESBL-producing strains: meropenem (AIII) or other carbapenem; pip/tazo and ciprofloxacin if resistant to other antibiotics
	Meningitis	Ceftriaxone; cefotaxime (AIII)	For ESBL-producing strains: meropenem (AIII)
<i>Francisella tularensis</i> ^{85,86}	Tularemia	Gentamicin (AII)	Doxycycline, ciprofloxacin. Resistant to beta-lactam antibiotics.
<i>Fusobacterium</i> spp ^{87,88}	Sepsis, soft tissue infection, Lemierre syndrome	Metronidazole (AIII); clindamycin (BIII)	Penicillin G, meropenem, pip/tazo. Combinations often used for Lemierre syndrome.
<i>Gardnerella vaginalis</i> ^{45,89}	Bacterial vaginosis	Metronidazole (BII)	Tinidazole, clindamycin, metronidazole gel, clindamycin cream
<i>Haemophilus</i> (now <i>Aggregatibacter</i>) <i>aphrophilus</i> ⁹⁰	Sepsis, endocarditis, abscesses (including brain abscess)	Ceftriaxone (AII); OR ampicillin (if beta-lactamase negative) AND gentamicin (BII)	Ciprofloxacin, amox/clav (for strains resistant to ampicillin)
<i>Haemophilus ducreyi</i> ⁴⁵	Chancroid	Azithromycin (AIII); ceftriaxone (BIII)	Erythromycin, ciprofloxacin

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Haemophilus influenzae</i> ⁹¹	Nonencapsulated strains: upper respiratory tract infections	Beta-lactamase negative: ampicillin IV (AI); amoxicillin PO (AI) Beta-lactamase positive: ceftriaxone IV, IM (AI) or cefotaxime IV (AI); amox/clav (AI) OR 2nd- or 3rd-generation cephalosporins PO (AI)	Levofloxacin, azithromycin, TMP/SMX
	Type b strains: meningitis, arthritis, cellulitis, epiglottitis, pneumonia	Beta-lactamase negative: ampicillin IV (AI); amoxicillin PO (AI) Beta-lactamase positive: ceftriaxone IV, IM (AI) or cefotaxime IV (AI); amox/clav (AI) OR 2nd- or 3rd-generation cephalosporins PO (AI)	Other regimens: meropenem IV, levofloxacin IV Full IV course (10 days) for meningitis, but oral step-down therapy well documented after response to treatment for non-CNS infections Levofloxacin PO for step-down therapy
<i>Helicobacter pylori</i> ^{92,93}	Gastritis, peptic ulcer	Triple agent therapy: clarithromycin (susceptible strains) AND amoxicillin AND omeprazole (All); ADD metronidazole for suspected resistance to clarithromycin.	Other regimens include bismuth ^{93,94} in addition to other proton-pump inhibitors.
<i>Kingella kingae</i> ^{95,96}	Osteomyelitis, arthritis	Ampicillin; penicillin G (All)	Ceftriaxone, TMP/SMX, cefuroxime, ciprofloxacin. Resistant to clindamycin.
<i>Klebsiella</i> spp (<i>K pneumoniae</i> , <i>K oxytoca</i>) ^{97–100} Increasing resistance to 3rd-generation cephalosporins (ESBLs) and carbapenems (KPC), as well as to colistin	UTI	A 2nd- or 3rd-generation cephalosporin (All)	Use most narrow spectrum agent active against pathogen: TMP/SMX, ciprofloxacin, gentamicin. ESBL producers should be treated with a carbapenem (meropenem, ertapenem, imipenem), but KPC (carbapenemase)-containing bacteria may require ciprofloxacin, colistin, CAZ/AVI. ⁹⁹

	Sepsis, pneumonia, meningitis	Ceftriaxone; cefotaxime, cefepime (AIII) CAZ/AVI or meropenem/ vaborbactam for carbapenem-R strains	Carbapenem or ciprofloxacin if resistant to other routine antibiotics. Meningitis caused by ESBL producer: meropenem if susceptible. KPC (carbapenemase) producers: ciprofloxacin, colistin, OR CAZ/AVI; approved by FDA for adults in 2015 and should be active against current strains of KPC. ¹⁰¹
<i>Klebsiella granulomatis</i> ⁴⁵	Granuloma inguinale	Azithromycin (AII)	Doxycycline, TMP/SMX, ciprofloxacin
<i>Legionella</i> spp ¹⁰²	Legionnaires disease	Azithromycin (AI) OR levofloxacin (AII)	Erythromycin, clarithromycin, TMP/SMX, doxycycline
<i>Leptospira</i> spp ¹⁰³	Leptospirosis	Penicillin G IV (AII); ceftriaxone IV (AII)	Amoxicillin, doxycycline, azithromycin
<i>Leuconostoc</i> ¹⁰⁴	Bacteremia	Penicillin G (AIII); ampicillin (BIII)	Clindamycin, erythromycin, doxycycline (resistant to vancomycin)
<i>Listeria monocytogenes</i> ¹⁰⁵	Sepsis, meningitis in compromised host; neonatal sepsis	Ampicillin (ADD gentamicin for severe infection, compromised hosts.) (AII)	Ampicillin AND TMP/SMX; ampicillin AND linezolid; levofloxacin
<i>Moraxella catarrhalis</i> ¹⁰⁶	Otitis, sinusitis, bronchitis	Amox/clav (AI)	TMP/SMX; a 2nd- or 3rd-generation cephalosporin
<i>Morganella morganii</i> ^{52,77,107,108}	UTI, neonatal sepsis, wound infection	Cefepime (AIII); meropenem (AIII). Has intrinsic inducible ampC 3rd-generation cephalosporin resistance.	Pip/tazo, ceftriaxone AND gentamicin, ciprofloxacin

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Mycobacterium abscessus</i> ^{109–112}	Skin and soft tissue infections; pneumonia in cystic fibrosis	Clarithromycin or azithromycin (AIII); ADD ceftiofur or imipenem AND amikacin for invasive disease (AIII).	Also test for susceptibility to meropenem, tigecycline, linezolid. May need pulmonary resection. Initial intensive phase of therapy followed by months of “maintenance” therapy.
<i>Mycobacterium avium</i> complex ^{109,113,114}	Cervical adenitis	Clarithromycin (AII); azithromycin (AII)	Surgical excision is more likely to lead to cure than sole medical therapy. May increase cure rate with addition of rifampin or ethambutol.
	Pneumonia	Clarithromycin (AII) or azithromycin (AII) AND ethambutol ± rifampin	Depending on susceptibilities and the severity of illness, ADD amikacin ± ciprofloxacin.
	Disseminated disease in competent host, or disease in immuno-compromised host	Clarithromycin or azithromycin AND ethambutol AND rifampin (AIII)	Depending on susceptibilities and the severity of illness, ADD amikacin ± ciprofloxacin.
<i>Mycobacterium bovis</i> ^{115,116}	Tuberculosis (historically not differentiated from <i>M tuberculosis</i> infection; causes adenitis, abdominal tuberculosis, meningitis)	Isoniazid AND rifampin (AII); ADD ethambutol for suspected resistance (AIII).	ADD streptomycin for severe infection. <i>M bovis</i> is always resistant to PZA.
<i>Mycobacterium chelonae</i> ^{109,113,117,118}	Abscesses; catheter infection	Clarithromycin or azithromycin (AIII); ADD amikacin ± ceftiofur for invasive disease (AIII).	Also test for susceptibility to ceftiofur, TMP/SMX, doxycycline, tobramycin, imipenem, moxifloxacin, linezolid.

<i>Mycobacterium fortuitum</i> complex ^{109,113,118}	Skin and soft tissue infections; catheter infection	Amikacin AND cefoxitin or meropenem (AIII) ± ciprofloxacin (AIII)	Also test for susceptibility to clarithromycin, sulfonamides, doxycycline, linezolid.
<i>Mycobacterium leprae</i> ¹¹⁹	Leprosy	Dapsone AND rifampin for paucibacillary (1–5 patches) (AII). ADD clofazimine for lepromatous, multibacillary (>5 patches) disease (AII).	Consult HRSA (National Hansen's Disease [Leprosy] Program) at www.hrsa.gov/hansens-disease for advice about treatment and free antibiotics: 800/642-2477 (accessed October 3, 2018).
<i>Mycobacterium marinum/balnei</i> ^{109,120}	Papules, pustules, abscesses (swimming pool granuloma)	Clarithromycin ± ethambutol (AIII)	TMP/SMX AND rifampin, ethambutol AND rifampin, doxycycline ± 1 or 2 additional antibiotics Surgical debridement
<i>Mycobacterium tuberculosis</i> ^{115,121} See Tuberculosis in Chapter 6, Table 6F, Lower Respiratory Tract Infections, for detailed recommendations for active infection, latent infection, and exposures in high-risk children.	Tuberculosis (pneumonia; meningitis; cervical adenitis; mesenteric adenitis; osteomyelitis)	For active infection: isoniazid AND rifampin AND PZA (AI); ADD ethambutol for suspect resistance. For latent infection: isoniazid daily, biweekly, or in combination with rifampentine once weekly (AII).	Add streptomycin for severe infection. For MDR tuberculosis, bedaquiline is now FDA approved for adults and available for children. Corticosteroids should be added to regimens for meningitis, mesenteric adenitis, and endobronchial infection (AIII).
<i>Mycoplasma hominis</i> ^{122,123}	Nongonococcal urethritis; neonatal infection including meningitis	Clindamycin (AIII); fluoroquinolones	Doxycycline Usually erythromycin resistant
<i>Mycoplasma pneumoniae</i> ^{124,125}	Pneumonia	Azithromycin (AI); erythromycin (BI); macrolide resistance emerging worldwide ¹²⁶	Doxycycline and fluoroquinolones are active against macrolide-susceptible and macrolide-resistant strains.

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Neisseria gonorrhoeae</i> ⁴⁵	Gonorrhea; arthritis	Ceftriaxone AND azithromycin or doxycycline (AIII)	Oral cefixime as single drug therapy no longer recommended due to increasing resistance ¹²⁷ Spectinomycin IM
<i>Neisseria meningitidis</i> ^{128,129}	Sepsis, meningitis	Ceftriaxone (AI); cefotaxime (AI)	Penicillin G or ampicillin if susceptible with amoxicillin step-down therapy for non-CNS infection. For prophylaxis following exposure: rifampin or ciprofloxacin (ciprofloxacin-resistant strains have now been reported). Azithromycin may be less effective.
<i>Nocardia asteroides</i> or <i>brasiliensis</i> ^{130,131}	Nocardiosis	TMP/SMX (AII); sulfisoxazole (BII); imipenem or meropenem AND amikacin for severe infection (AII)	Linezolid, ceftriaxone, clarithromycin, minocycline, levofloxacin, tigecycline, amox/clav
<i>Oerskovia</i> (now known as <i>Cellulosimicrobium cellulans</i>) ¹³²	Wound infection; catheter infection	Vancomycin ± rifampin (AIII)	Linezolid; resistant to beta-lactams, macrolides, clindamycin, aminoglycosides
<i>Pasteurella multocida</i> ^{133–135}	Sepsis, abscesses, animal bite wound	Penicillin G (AIII); ampicillin (AIII); amoxicillin (AIII)	Amox/clav, ticar/clav, pip/tazo, doxycycline, ceftriaxone, cefpodoxime, cefuroxime, TMP/SMX. Cephalexin may not demonstrate adequate activity. Not usually susceptible to clindamycin.
<i>Peptostreptococcus</i> ¹³⁶	Sepsis, deep head/neck space and intra-abdominal infection	Penicillin G (AII); ampicillin (AII)	Clindamycin, vancomycin, meropenem, imipenem, metronidazole

<i>Plesiomonas shigelloides</i> ^{137,138}	Diarrhea, neonatal sepsis, meningitis	Antibiotics may not be necessary to treat diarrhea: 2nd- and 3rd-generation cephalosporins (AIII); azithromycin (BIII); ciprofloxacin (CIII). For meningitis/sepsis: ceftriaxone.	Meropenem, TMP/SMX, amox/clav
<i>Prevotella</i> (formerly <i>Bacteroides</i>) spp, ¹³⁹ <i>melaninogenica</i>	Deep head/neck space abscess; dental abscess	Metronidazole (AII); meropenem or imipenem (AII)	Pip/tazo, ceftiofloxacin, clindamycin
<i>Propionibacterium acnes</i> ^{140,141}	In addition to acne, invasive infection: sepsis, post-op wound infection	Penicillin G (AIII); vancomycin (AIII)	Cefotaxime, ceftriaxone, doxycycline, clindamycin, linezolid, daptomycin Resistant to metronidazole
<i>Proteus mirabilis</i> ¹⁴²	UTI, sepsis, meningitis	Ceftriaxone (AII) or cefotaxime (AII); cefepime; ciprofloxacin; gentamicin Oral therapy: amox/clav; TMP/SMX, ciprofloxacin	Carbapenem; pip/tazo; increasing resistance to ampicillin, TMP/SMX, and fluoroquinolones, particularly in nosocomial isolates Colistin resistant
<i>Proteus vulgaris</i> , other spp (indole-positive strains) ⁵²	UTI, sepsis, meningitis	Cefepime; ciprofloxacin; gentamicin (BIII) AmpC producer (and some strains with ESBLs), so at risk of 3rd-generation cephalosporin resistance	Meropenem or other carbapenem; pip/tazo; TMP/SMX Colistin resistant
<i>Providencia</i> spp ^{52,143}	Sepsis	Cefepime; ciprofloxacin, gentamicin (BIII)	Meropenem or other carbapenem; pip/tazo; TMP/SMX Colistin resistant

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Pseudomonas aeruginosa</i> ^{144–148}	UTI	Cefepime (AII); other antipseudomonal beta-lactams; tobramycin	Amikacin, ciprofloxacin
	Nosocomial sepsis, pneumonia	Cefepime (AI) or meropenem (AI); OR pip/tazo AND tobramycin (BI); ceftazidime AND tobramycin (BII)	Ciprofloxacin AND tobramycin. Controversy regarding additional clinical benefit in outcomes using newer, more potent beta-lactams over aminoglycoside combinations, but combinations may decrease emergence of resistance. ^{149,150} Ceftolozane/tazobactam was approved by FDA for adults in 2015 and may be active against otherwise resistant strains. Colistin. ¹⁴⁸
	Pneumonia in cystic fibrosis ^{151–154} See Cystic Fibrosis in Chapter 6, Table 6F, Lower Respiratory Tract Infections.	Cefepime (AII) or meropenem (AI); OR ceftazidime AND tobramycin (BII); ADD aerosol tobramycin (AI). Azithromycin provides benefit in prolonging interval between exacerbations.	Inhalational antibiotics for prevention of acute exacerbations: tobramycin; aztreonam; colistin. Many organisms are MDR; consider ciprofloxacin or colistin parenterally; in vitro synergy testing may suggest effective combinations. For MDR organism treatment for acute deterioration, little prospective data on aerosolized antibiotics exists.
<i>Pseudomonas cepacia</i> , <i>mallei</i> , or <i>pseudomallei</i> (See <i>Burkholderia</i> .)			
<i>Rhodococcus equi</i> ¹⁵⁵	Necrotizing pneumonia	Imipenem AND vancomycin (AIII)	Combination therapy with ciprofloxacin or levofloxacin AND azithromycin or rifampin
<i>Rickettsia</i> ^{156,157}	Rocky Mountain spotted fever, Q fever, typhus, rickettsialpox	Doxycycline (all ages) (AII)	Chloramphenicol is less effective than doxycycline.

<i>Salmonella</i> , non-typhi ^{158–160}	Gastroenteritis (may not require therapy if clinically improving and not immunocompromised). Consider treatment for those at higher risk of invasion (<1 y [or, at highest risk, those <3 mo], immunocompromised, and with focal infections or bacteremia).	Ceftriaxone (All); cefixime (All); azithromycin (All)	For susceptible strains: ciprofloxacin; TMP/SMX; ampicillin; resistance to fluoroquinolones detected by nalidixic acid testing
<i>Salmonella typhi</i> ^{158,161}	Typhoid fever	Azithromycin (All); ceftriaxone (All); TMP/SMX (All)	Prefer antibiotics with high intracellular concentrations (eg, TMP/SMX, fluoroquinolones).
<i>Serratia marcescens</i> ^{52,78}	Nosocomial sepsis, pneumonia	Cefepime; meropenem; pipo/tazo (BII)	Ertapenem, imipenem, cefotaxime or ceftriaxone AND gentamicin, TMP/SMX, ciprofloxacin Resistant to colistin
<i>Shewanella</i> spp ^{162,163}	Wound infection, nosocomial pneumonia, peritoneal-dialysis peritonitis, ventricular shunt infection, neonatal sepsis	Ceftazidime (AIII); gentamicin (AIII)	Ampicillin, meropenem, pipo/tazo, ciprofloxacin Resistant to TMP/SMX and colistin
<i>Shigella</i> spp ^{164,165}	Enteritis, UTI, prepubertal vaginitis	Ceftriaxone (All); azithromycin ¹⁶⁶ (All); cefixime (All); ciprofloxacin ¹⁶⁷ (All)	Resistance to azithromycin now reported. Use most narrow spectrum agent active against pathogen: PO ampicillin (not amoxicillin for enteritis); TMP/SMX.

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Spirillum minus</i> ^{168,169}	Rat-bite fever (sodoku)	Penicillin G IV (AII); for endocarditis, ADD gentamicin or streptomycin (AIII).	Ampicillin, doxycycline, cefotaxime, vancomycin, streptomycin
<i>Staphylococcus aureus</i> (See chapters 4 and 6 for specific infections.) ^{170,171}			
– Mild to moderate infections	Skin infections, mild to moderate	MSSA: a 1st-generation cephalosporin (cefazolin IV, cephalexin PO) (AI); oxacillin/nafcillin IV (AI), dicloxacillin PO (AI) MRSA: clindamycin (if susceptible) IV or PO, ceftaroline IV, ¹⁷² vancomycin IV, or TMP/SMX PO (AII)	For MSSA: amox/clav For CA-MRSA: linezolid IV, PO; daptomycin IV ¹⁷³
– Moderate to severe infections, treat empirically for CA-MRSA.	Pneumonia, sepsis, myositis, osteomyelitis, etc	MSSA: oxacillin/nafcillin IV (AI); a 1st-generation cephalosporin (cefazolin IV) (AI) ± gentamicin (AIII) MRSA: vancomycin (AII) OR clindamycin (if susceptible) (AII) OR ceftaroline (AII) Combination therapy with gentamicin and/or rifampin not prospectively studied	For CA-MRSA: linezolid (AII); OR daptomycin ¹⁷⁴ for non-pulmonary infection (AII) (studies published in children); ceftaroline IV (studies published in children) Approved for adults in 2015: dalbavancin, oritavancin, tedizolid (See Chapter 4.)
<i>Staphylococcus</i> , coagulase negative ^{175,176}	Nosocomial bacteremia (neonatal bacteremia), infected intravascular catheters, CNS shunts, UTI	Vancomycin (AII) OR ceftaroline (AII)	If susceptible: nafcillin (or other anti-staph beta-lactam); rifampin (in combination); clindamycin, linezolid; ceftaroline IV (studies published in children)
<i>Stenotrophomonas maltophilia</i> ^{177,178}	Sepsis	TMP/SMX (AII)	Ceftazidime, doxycycline, minocycline, tigecycline, levofloxacin

<i>Streptobacillus moniliformis</i> ^{168,169}	Rat-bite fever (Haverhill fever)	Penicillin G (AIII); ampicillin (AIII); for endocarditis, ADD gentamicin or streptomycin (AIII).	Doxycycline, ceftriaxone, carbapenems, clindamycin, vancomycin
<i>Streptococcus</i> , group A ¹⁷⁹	Pharyngitis, impetigo, adenitis, cellulitis, necrotizing fasciitis	Penicillin (AI); amoxicillin (AI)	A 1st-generation cephalosporin (cefazolin or cephalexin) (AI), clindamycin (AI), a macrolide (AI), vancomycin (AIII) For recurrent streptococcal pharyngitis, clindamycin or amox/clav, or the addition of rifampin to the last 4 days of therapy (AIII)
<i>Streptococcus</i> , group B ¹⁸⁰	Neonatal sepsis, pneumonia, meningitis	Penicillin (AII) or ampicillin (AII)	Gentamicin is used initially from presumed synergy until group B strep has been identified as the cause of infection and a clinical/microbiologic response has been documented (AIII).
<i>Streptococcus milleri/anginosus</i> group (<i>S intermedius</i> , <i>anginosus</i> , and <i>constellatus</i> ; includes some beta-hemolytic group C and group G streptococci) ^{181–183}	Pneumonia, sepsis, skin and soft tissue infection, ¹⁸⁴ sinusitis, ¹⁸⁵ arthritis, brain abscess, meningitis	Penicillin G (AIII); ampicillin (AIII); ADD gentamicin for serious infection (AIII); ceftriaxone. Many strains show decreased susceptibility to penicillin, requiring higher dosages to achieve adequate antibiotic exposure.	Clindamycin, vancomycin

D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

Organism	Clinical Illness	Drug of Choice (evidence grade)	Alternatives
<i>Streptococcus pneumoniae</i> ^{186–189} With widespread use of conjugate pneumococcal vaccines, antibiotic resistance in pneumococci has decreased. ¹⁸⁹	Sinusitis, otitis ¹⁸⁶	Amoxicillin, high-dose (90 mg/kg/day div bid) (AII); standard dose (40–45 mg/kg/day div tid) may again be effective. ¹⁸⁹	Amox/clav, cefdinir, cefpodoxime, cefuroxime, clindamycin, OR ceftriaxone IM
	Meningitis	Ceftriaxone (AI) or cefotaxime (AI); vancomycin is no longer required; ceftriaxone-resistant strains have not been reported to cause meningitis in the post-PCV13 era (AIII).	Penicillin G alone for pen-S strains; ceftriaxone alone for ceftriaxone-susceptible strains
	Pneumonia, ¹⁶⁹ osteomyelitis/ arthritis, ¹⁸⁷ sepsis	Ampicillin (AII); ceftriaxone (AI); cefotaxime (AI)	Penicillin G alone for pen-S strains; ceftriaxone alone for ceftriaxone-susceptible strains
<i>Streptococcus viridans</i> group (alpha-hemolytic streptococci, most commonly <i>S sanguinis</i> , <i>S oralis</i> [mitis], <i>S salivarius</i> , <i>S mutans</i> , <i>S morbillorum</i>) ¹⁹⁰	Endocarditis	Penicillin G ± gentamicin (AII) OR ceftriaxone ± gentamicin (AII)	Vancomycin
<i>Treponema pallidum</i> ^{45,191}	Syphilis (See chapters 5 and 6.)	Penicillin G (AII)	Desensitize to penicillin preferred to alternate therapies. Doxycycline, ceftriaxone.
<i>Ureaplasma urealyticum</i> ^{45,192}	Genitourinary infections	Azithromycin (AII)	Erythromycin; doxycycline, ofloxacin (for adolescent genital infections)
	Neonatal pneumonia (Therapy may not be effective.)	Azithromycin (AIII)	
<i>Vibrio cholerae</i> ^{193,194}	Cholera	Azithromycin (AII) OR doxycycline (AI)	If susceptible: ciprofloxacin

<i>Vibrio vulnificus</i> ^{195,196}	Sepsis, necrotizing fasciitis	Doxycycline AND ceftazidime (AII)	Ciprofloxacin AND cefotaxime or ceftriaxone
<i>Yersinia enterocolitica</i> ^{197,198}	Diarrhea, mesenteric enteritis, reactive arthritis, sepsis	TMP/SMX for enteritis (AIII); ciprofloxacin or ceftriaxone for invasive infection (AIII)	Gentamicin, doxycycline
<i>Yersinia pestis</i> ^{199–201}	Plague	Gentamicin (AIII)	Levofloxacin, doxycycline, ciprofloxacin
<i>Yersinia pseudo-tuberculosis</i> ^{197,198,202,203}	Mesenteric adenitis; Far East scarlet-like fever; reactive arthritis	TMP/SMX (AIII) or ciprofloxacin (AIII)	Ceftriaxone, gentamicin, doxycycline

8. Preferred Therapy for Specific Fungal Pathogens

NOTES

- See Chapter 2 for discussion of the differences between polyenes, azoles, and echinocandins.
- **Abbreviations:** ABLC, amphotericin B lipid complex (Abelcet); AmB, amphotericin B; AmB-D, amphotericin B deoxycholate, the conventional standard AmB (original trade name Fungizone); bid, twice daily; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; div, divided; ECMO, extracorporeal membrane oxygenation; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IV, intravenous; L-AmB, liposomal amphotericin B (AmBisome); PO, orally; qd, once daily; qid, 4 times daily; spp, species; TMP/SMX, trimethoprim/sulfamethoxazole.

A. OVERVIEW OF MORE COMMON FUNGAL PATHOGENS AND THEIR USUAL PATTERN OF ANTIFUNGAL SUSCEPTIBILITIES

Fungal Species	Amphotericin B Formulations	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Flucytosine	Caspofungin, Micafungin, or Anidulafungin
<i>Aspergillus calidoustus</i>	++	—	—	—	—	—	—	++
<i>Aspergillus fumigatus</i>	+	—	±	++	+	++	—	+
<i>Aspergillus terreus</i>	—	—	+	++	+	++	—	+
<i>Blastomyces dermatitidis</i>	++	+	++	+	+	+	—	—
<i>Candida albicans</i>	+	++	+	+	+	+	+	++
<i>Candida auris</i>	±	—	±	±	+	+	±	++
<i>Candida glabrata</i>	+	—	±	±	±	±	+	±
<i>Candida guilliermondii</i>	+	±	+	+	+	+	+	±
<i>Candida krusei</i>	+	—	—	+	+	+	+	++
<i>Candida lusitanae</i>	—	++	+	+	+	+	+	+
<i>Candida parapsilosis</i>	++	++	+	+	+	+	+	+
<i>Candida tropicalis</i>	+	+	+	+	+	+	+	++

<i>Coccidioides immitis</i>	++	++	+	+	++	+	—	—
<i>Cryptococcus</i> spp	++	+	+	+	+	+	++	—
<i>Fusarium</i> spp	±	—	—	++	+	+	—	—
<i>Histoplasma capsulatum</i>	++	+	++	+	+	+	—	—
<i>Lomentospora</i> (formerly <i>Scedosporium</i>) <i>prolificans</i>	—	—	±	±	±	±	—	±
<i>Mucor</i> spp	++	—	±	—	+	+	—	—
<i>Paracoccidioides</i> spp	+	+	++	+	+	+	—	—
<i>Penicillium</i> spp	±	—	++	+	+	+	—	—
<i>Rhizopus</i> spp	++	—	—	—	+	+	—	—
<i>Scedosporium apiospermum</i>	—	—	±	+	+	+	—	±
<i>Sporothrix</i> spp	+	+	++	+	+	+	—	—
<i>Trichosporon</i> spp	—	+	+	++	+	+	—	—

NOTE: ++ = preferred therapy(ies); + = usually active; ± = variably active; — = usually not active.

B. SYSTEMIC INFECTIONS

Infection	Therapy (evidence grade)	Comments
Prophylaxis		
Prophylaxis of invasive fungal infection in patients with hematologic malignancies ^{1–11}	Fluconazole 6 mg/kg/day for prevention of infection (All). Posaconazole for prevention of infection has been well studied in adults (AI) and offers anti-mold coverage. ⁴	Fluconazole is not effective against molds and some strains of <i>Candida</i> . Posaconazole PO, voriconazole PO, and micafungin IV are effective in adults in preventing yeast and mold infections but are not well studied in children for this indication. ¹²
Prophylaxis of invasive fungal infection in patients with solid organ transplants ^{13–17}	Fluconazole 6 mg/kg/day for prevention of infection (All)	AmB, caspofungin, micafungin, voriconazole, or posaconazole may be effective in preventing infection.
Treatment		
Aspergillosis ^{1,18–29}	Voriconazole (AI) 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y or 12–14 y and weighing <50 kg. In children ≥15 y or 12–14 y and weighing >50 kg, use adult dosing (load 12 mg/kg/day IV div q12h on the first day, then 8 mg/kg/day div q12h as a maintenance dose) (All). When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid for children 2–12 y and at least 400 mg/day div bid for children >12 y (All). Dosing in children <2 y is less clear, but doses are generally higher (All). These are only initial dosing recommendations; continued dosing in all ages is guided by close monitoring of trough serum voriconazole concentrations in individual patients (All). Unlike in adults, voriconazole PO bioavailability	Voriconazole is the preferred primary antifungal therapy for all clinical forms of aspergillosis. Early initiation of therapy in patients with strong suspicion of disease is important while a diagnostic evaluation is conducted. Optimal voriconazole trough serum concentrations (generally thought to be 2–5 mcg/mL) are needed. Check trough level 2–5 days after initiation of therapy, and repeat the following week to verify and 4 days after a change of dose. ²⁹ It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability. ³¹ Low voriconazole concentrations are a leading cause of clinical failure. Younger children (especially <3 y) often have lower trough voriconazole levels and need much higher dosing. Total treatment course is for a minimum of 6–12 wk, largely dependent on the degree and duration of immunosuppression and evidence of disease improvement.

in children is only approximately 50%–60%, so trough levels are crucial when using PO.³⁰ Alternatives for primary therapy when voriconazole cannot be administered: L-AmB 5 mg/kg/day (All) or isavuconazole (AI). Dosing of isavuconazole in children is unknown. ABLC is another possible alternative. Echinocandin primary monotherapy should not be used for treating invasive aspergillosis (CII). AmB deoxycholate should be used only in resource-limited settings in which no alternative agent is available (All).

Salvage antifungal therapy options after failed primary therapy include a change of antifungal class (using L-AmB or an echinocandin), switching to isavuconazole, switching to posaconazole (serum trough concentrations ≥ 1 mcg/mL), or using combination antifungal therapy.

Careful consideration has to be used before beginning azole therapy after a patient has failed azole prophylaxis.

Combination antifungal therapy with voriconazole plus an echinocandin may be considered in select patients. The addition of anidulafungin to voriconazole as combination therapy found some statistical benefit to the combination over voriconazole monotherapy in only certain patients.³² In vitro data suggest some synergy with 2 (but not 3) drug combinations: an azole plus an echinocandin is the most well studied. If combination therapy is employed, this is likely best done initially when voriconazole trough concentrations may not yet be appropriate.

Routine antifungal susceptibility testing is not recommended but is suggested for patients suspected of having an azole-resistant isolate or who are unresponsive to therapy.

Azole-resistant *Aspergillus fumigatus* is increasing. If local epidemiology suggests $>10\%$ azole resistance, empiric initial therapy should be voriconazole + echinocandin OR with L-AmB, and subsequent therapy guided based on antifungal susceptibilities.³³

Micafungin likely has equal efficacy to caspofungin against aspergillosis.³⁴

Return of immune function is paramount to treatment success; for children receiving corticosteroids, decreasing the corticosteroid dosage or changing to steroid-sparing protocols is important.

B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
<i>Bipolaris</i>, <i>Cladophialophora</i>, <i>Curvularia</i>, <i>Exophiala</i>, <i>Alternaria</i>, and other agents of phaeohyphomycosis (dematiaceous, pigmented molds) ^{33–42}	<p>Voriconazole (AI) 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y or 12–14 y and weighing <50 kg. In children ≥15 y or 12–14 y and weighing >50 kg, use adult dosing (load 12 mg/kg/day IV div q12h on the first day, then 8 mg/kg/day div q12h as a maintenance dose) (AI). When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid for children 2–12 y and at least 400 mg/day div bid for children >12 y (AII). Dosing in children <2 y is less clear, but doses are generally higher (AIII). These are only initial dosing recommendations; continued dosing in all ages is guided by close monitoring of trough serum voriconazole concentrations in individual patients (AII). Unlike in adults, voriconazole PO bioavailability in children is only approximately 50%–60%, so trough levels are crucial.³⁰</p> <p>Alternatives could include posaconazole (trough concentrations >1 mcg/mL) or combination therapy with an echinocandin + azole or an echinocandin + L-AmB (BIII).</p>	<p>Aggressive surgical debulking/excision is essential for CNS lesions.</p> <p>These can be highly resistant infections, so strongly recommend antifungal susceptibility testing to guide therapy and consultation with a pediatric infectious diseases expert. Antifungal susceptibilities are often variable, but empiric therapy with voriconazole is the best start.</p> <p>Optimal voriconazole trough serum concentrations (generally thought to be 2–5 mcg/mL) are important for success. Check trough level 2–5 days after initiation of therapy, and repeat the following week to verify and 4 days after a change of dose. It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability.³¹ Low voriconazole concentrations are a leading cause of clinical failure. Younger children (especially <3 y) often have lower voriconazole levels and need much higher dosing.</p>
Blastomycosis (North American) ^{43–49}	<p>For moderate–severe pulmonary disease: ABLC or L-AmB 5 mg/kg IV daily for 1–2 wk or until improvement noted, followed by itraconazole oral solution 10 mg/kg/day div bid (max 400 mg/day) PO for a total of 6–12 mo (AIII). Itraconazole loading dose (double dose for first 2 days) is recommended in adults but has not been studied in children (but likely helpful).</p>	<p>Itraconazole oral solution provides greater and more reliable absorption than capsules and only the oral solution should be used (on an empty stomach); serum concentrations of itraconazole should be determined 5 days after start of therapy to ensure adequate drug exposure. For blastomycosis, maintain trough itraconazole concentrations 1–2 mcg/mL (values for both itraconazole and</p>

For mild to moderate pulmonary disease: itraconazole oral solution 10 mg/kg/day div bid (max 400 mg/day) PO for a total of 6–12 mo (AIII). Itraconazole loading dose (double dose for first 2 days) recommended in adults but has not been studied in children (but likely helpful).	hydroxyl-itraconazole are added together). If only itraconazole capsules are available, use 20 mg/kg/day div q12h and take with cola product to increase gastric acidity and bioavailability.
For CNS blastomycosis: L-AmB or ABLC (preferred over AmB-D) for 4–6 wk, followed by an azole (fluconazole is preferred, at 12 mg/kg/day after a loading dose of 25 mg/kg; alternatives for CNS disease are voriconazole or itraconazole), for a total of at least 12 mo and until resolution of CSF abnormalities (AII). Some experts suggest combination therapy with L-AmB/ABLC plus high-dose fluconazole as induction therapy in CNS blastomycosis until clinical improvement (BIII).	Alternative to itraconazole: 12 mg/kg/day fluconazole (BIII) after a loading dose of 25 mg/kg/day. Patients with extrapulmonary blastomycosis should receive at least 12 mo of total therapy. If induction with L-AmB alone is failing, add itraconazole or high-dose fluconazole until clinical improvement. Lifelong itraconazole if immunosuppression cannot be reversed.

Candidiasis^{50–54} (See Chapter 2.)

– Cutaneous	Topical therapy (alphabetic order): ciclopirox, clotrimazole, econazole, haloprogin, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole	Fluconazole 6 mg/kg/day PO qd for 5–7 days Relapse common in cases of chronic mucocutaneous disease, and antifungal susceptibilities critical to drive appropriate therapy
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B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
<p>– Disseminated, acute (including catheter fungemia) infection</p>	<p>For neutropenic patients: An echinocandin is recommended as initial therapy. Caspofungin 70 mg/m² IV loading dose on day 1 (max dose 70 mg), followed by 50 mg/m² IV (max dose 70 mg) on subsequent days (AII); OR micafungin 2 mg/kg/day q24h (children weighing <40 kg), up to max dose 100 mg/day (AII).⁵⁵ ABLC or L-AmB 5 mg/kg/day IV q24h (BII) is an effective but less attractive alternative due to potential toxicity (AII).</p> <p>Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative for patients who are not critically ill and have had no prior azole exposure (CIII). A fluconazole loading dose is standard of care in adult patients but has only been studied in infants⁵⁶—it is likely that the beneficial effect of a loading dose extends to children. Fluconazole can be used as step-down therapy in stable neutropenic patients with susceptible isolates and documented bloodstream clearance (CIII). For children on ECMO, fluconazole is dosed as 35 mg/kg load on day 1 followed by 12 mg/kg/day (BII).⁵⁷</p> <p>For non-neutropenic patients: An echinocandin is also recommended as initial therapy. Caspofungin 70 mg/m² IV loading dose on day 1 (max dose 70 mg), followed by 50 mg/m² IV (max dose 70 mg) on subsequent days (AII); OR micafungin 2 mg/kg/day q24h (children weighing <40 kg), up to max dose 100 mg/day (AI).⁴³</p> <p>Fluconazole (12 mg/kg/day IV or PO q24h, after a load of 25 mg/kg/day) is an acceptable alternative to an echinocandin as initial therapy in selected patients,</p>	<p>Prompt removal of infected IV catheter or any infected devices is absolutely critical to success (AII).</p> <p>For infections with <i>Candida krusei</i> or <i>Candida glabrata</i>, an echinocandin is preferred; however, there are increasing reports of some <i>C. glabrata</i> resistance to echinocandins (treatment would, therefore, be lipid formulation AmB) (BIII). There are increasing reports of some <i>Candida tropicalis</i> resistance to fluconazole.</p> <p>Lipid formulation AmB (5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents (AI). Transition from lipid AmB to fluconazole is recommended after 5–7 days among patients who have isolates that are susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative (AI).</p> <p>Voriconazole (18 mg/kg/day div q12h load, followed by 16 mg/kg/day div q12h) is effective for candidemia but offers little advantage over fluconazole as initial therapy. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to <i>C. krusei</i> or if mold coverage is needed.</p> <p>Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared (AIII).</p> <p>Duration of therapy is for 2 wk AFTER negative cultures in pediatric patients without obvious metastatic complications and after symptom resolution (AII).</p> <p>In neutropenic patients, ophthalmologic findings of choroidal and vitreal infection are minimal until recovery from neutropenia; therefore, dilated</p>

including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* spp (AI). For children on ECMO, fluconazole is dosed as 35 mg/kg load followed by 12 mg/kg/day (BII).⁵⁷

Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for non-neutropenic patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *Candida albicans*), and have negative repeat blood cultures following initiation of antifungal therapy (AII).

For CNS infections: L-AmB/ABLC (5 mg/kg/day), and AmB-D (1 mg/kg/day) as an alternative, combined with or without flucytosine 100 mg/kg/day PO div q6h (AII) until initial clinical response, followed by step-down therapy with fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day); echinocandins do not achieve therapeutic concentrations in CSF.

– Disseminated, chronic (hepatosplenic) infection

Initial therapy with lipid formulation AmB (5 mg/kg daily) OR an echinocandin (caspofungin 70 mg/m² IV loading dose on day 1 [max dose 70 mg], followed by 50 mg/m² IV [max dose 70 mg] on subsequent days OR micafungin 2 mg/kg/day q24h in children weighing <40 kg [max dose 100 mg]) for several weeks, followed by oral fluconazole in patients unlikely to have a fluconazole-resistant isolate (12 mg/kg/day q24h, after a load of 25 mg/kg/day) (AIII).

Therapy should continue until lesions resolve on repeat imaging, which is usually several months. Premature discontinuation of antifungal therapy can lead to relapse (AIII).

fundusoscopic examinations should be performed within the first week after recovery from neutropenia (AIII).

All non-neutropenic patients with candidemia should have a dilated ophthalmologic examination, preferably performed by an ophthalmologist, within the first week after diagnosis (AIII).

If chemotherapy or hematopoietic cell transplantation is required, it should not be delayed because of the presence of chronic disseminated candidiasis, and antifungal therapy should be continued throughout the period of high risk to prevent relapse (AIII).

B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
– Neonatal ⁵³ (See Chapter 5.)	<p>AmB-D (1 mg/kg/day) is recommended therapy (AII).⁵⁸ Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative if patient has not been on fluconazole prophylaxis (AII).⁵⁹ For treatment of neonates and young infants (<120 days) on ECMO, fluconazole is loaded with 35 mg/kg on day 1, followed by 12 mg/kg/day q24h (BII).</p> <p>Lipid formulation AmB is an alternative but carries a theoretical risk of less urinary tract penetration compared with AmB-D (CIII).</p> <p>Duration of therapy for candidemia without obvious metastatic complications is for 2 wk after documented clearance and resolution of symptoms (therefore, generally 3 wk total).</p> <p>Echinocandins should be used with caution and generally limited to salvage therapy or to situations in which resistance or toxicity preclude the use of AmB-D or fluconazole (CIII).</p> <p>Role of flucytosine in neonates with meningitis is questionable and not routinely recommended due to toxicity concerns. The addition of flucytosine (100 mg/kg/day div q6h) may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent (CIII).</p>	<p>In nurseries with high rates of candidiasis (>10%), IV or oral fluconazole prophylaxis (AI) (3–6 mg/kg twice weekly for 6 wk) in high-risk neonates (birth weight <1,000 g) is recommended. Oral nystatin, 100,000 units 3 times daily for 6 wk, is an alternative to fluconazole in neonates with birth weights <1,500 g in situations in which availability or resistance precludes the use of fluconazole (CII).</p> <p>Lumbar puncture and dilated retinal examination recommended in neonates with cultures positive for <i>Candida</i> spp from blood and/or urine (AIII). Same recommended for all neonates with birth weight <1,500 g with candiduria with or without candidemia (AIII).</p> <p>CT or ultrasound imaging of genitourinary tract, liver, and spleen should be performed if blood cultures are persistently positive (AIII).</p> <p>Meningoencephalitis in the neonate occurs at a higher rate than in older children/adults.</p> <p>Central venous catheter removal is strongly recommended.</p> <p>Infected CNS devices, including ventriculostomy drains and shunts, should be removed if possible.</p>
– Oropharyngeal, esophageal ⁵⁰	Mild oropharyngeal disease: clotrimazole 10 mg troches PO 5 times daily OR nystatin 100,000 U/mL, 4–6 mL qid for 7–14 days.	For fluconazole-refractory oropharyngeal or esophageal disease: itraconazole oral solution OR posaconazole OR AmB IV OR an echinocandin for up to 28 days (AII).

	<p>Alternatives also include miconazole mucoadhesive buccal 50-mg tablet to the mucosal surface over the canine fossa once daily for 7–14 days OR 1–2 nystatin pastilles (200,000 U each) qid for 7–14 days (AII).</p> <p>Moderate–severe oropharyngeal disease: fluconazole 6 mg/kg qd PO for 7–14 days (AII).</p> <p>Esophageal candidiasis: oral fluconazole (6–12 mg/kg/day, after a loading dose of 25 mg/kg/day) for 14–21 days (AI). If cannot tolerate oral therapy, use fluconazole IV OR ABLC/L-AmB/AmB-D OR an echinocandin (AI).</p>	<p>Esophageal disease always requires systemic antifungal therapy. A diagnostic trial of antifungal therapy for esophageal candidiasis is appropriate before performing an endoscopic examination (AI).</p> <p>Chronic suppressive therapy (3 times weekly) with fluconazole is recommended for recurrent infections (AI).</p>
– Urinary tract infection	<p>Cystitis: fluconazole 6 mg/kg qd IV or PO for 2 wk (AII). For fluconazole-resistant <i>C glabrata</i> or <i>C krusei</i>, AmB-D for 1–7 days (AIII).</p> <p>Pyelonephritis: fluconazole 12 mg/kg qd IV or PO for 2 wk (AIII) after a loading dose of 25 mg/kg/day. For fluconazole-resistant <i>C glabrata</i> or <i>C krusei</i>, AmB-D with or without flucytosine for 1–7 days (AIII).</p>	<p>Treatment is NOT recommended in asymptomatic candiduria unless high risk for dissemination; neutropenic, low birth weight neonate (<1,500 g); or patient will undergo urologic manipulation (AIII).</p> <p>Neutropenic and low birth weight neonates should be treated as recommended for candidemia (AIII).</p> <p>Removing Foley catheter, if present, may lead to a spontaneous cure in the normal host; check for additional upper urinary tract disease.</p> <p>AmB-D bladder irrigation is not generally recommended due to high relapse rate (an exception may be in fluconazole-resistant <i>Candida</i>) (CIII). For renal collecting system fungus balls, surgical debridement may be required in non-neonates (BIII).</p> <p>Echinocandins have poor urinary concentrations. AmB-D has greater urinary penetration than L-AmB/ABLC.</p>

B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
– Vulvovaginal ⁵⁹	Topical vaginal cream/tablets/suppositories (alphabetic order): butoconazole, clotrimazole, econazole, fenticonazole, miconazole, sertaconazole, terconazole, or tioconazole for 3–7 days (AI) OR fluconazole 10 mg/kg (max 150 mg) as a single dose (AII)	For uncomplicated vulvovaginal candidiasis, no topical agent is clearly superior. Avoid azoles during pregnancy. For severe disease, fluconazole 150 mg given every 72 h for 2–3 doses (AI). For recurring disease, consider 10–14 days of induction with topical agent or fluconazole, followed by fluconazole once weekly for 6 mo (AI).
Chromoblastomycosis (subcutaneous infection by dematiaceous fungi) ^{60–64}	Itraconazole oral solution 10 mg/kg/day div bid PO for 12–18 mo, in combination with surgical excision or repeated cryotherapy (AII). Itraconazole oral solution provides greater and more reliable absorption than capsules and only the oral solution should be used (on an empty stomach); serum concentrations of itraconazole should be determined 5 days after start of therapy to ensure adequate drug exposure. Maintain trough itraconazole concentrations 1–2 mcg/mL (values for both itraconazole and hydroxyl-itraconazole are added together).	Alternative: terbinafine plus surgery; heat and potassium iodide; posaconazole. Lesions are recalcitrant and difficult to treat.
Coccidioidomycosis ^{65–73}	For moderate infections: fluconazole 12 mg/kg IV PO q24h (AII) after loading dose of 25 mg/kg/day. For severe pulmonary disease: AmB-D 1 mg/kg/day IV q24h OR ABLC/L-AmB 5 mg/kg/day IV q24h (AIII) as initial therapy for several weeks until clear improvement, followed by an oral azole for total therapy of at least 12 mo, depending on genetic or immunocompromised risk factors.	Mild pulmonary disease does not require therapy in the normal host and only requires periodic reassessment. There is experience with posaconazole for disease in adults but little experience in children. Isavuconazole experience in adults is increasing. Treat until serum cocci complement fixation titers drop to 1:8 or 1:4, about 3–6 mo.

For meningitis: fluconazole 12 mg/kg/day IV q24h (All) after loading dose of 25 mg/kg/day (All). Itraconazole has also been effective (BIII). If no response to azole, use intrathecal AmB-D (0.1–1.5 mg/dose) with or without fluconazole (AIII). Lifelong azole suppressive therapy required due to high relapse rate. Adjunctive corticosteroids in meningitis has resulted in less secondary cerebrovascular events.⁷⁴

For extrapulmonary (non-meningeal), particularly for osteomyelitis, an oral azole such as fluconazole or itraconazole solution 10 mg/kg/day div bid for at least 12 mo (AIII), and L-AmB/ABLC as an alternative (less toxic than AmB-D) for severe disease or if worsening. Itraconazole oral solution provides greater and more reliable absorption than capsules and only the oral solution should be used (on an empty stomach); serum concentrations of itraconazole should be determined 5 days after start of therapy to ensure adequate drug exposure. Maintain trough itraconazole concentrations 1–2 mcg/mL (values for both itraconazole and hydroxyl-itraconazole are added together).

Disease in immunocompromised hosts may need to be treated longer, including potentially lifelong azole secondary prophylaxis. Watch for relapse up to 1–2 y after therapy.

B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
Cryptococcosis ^{75–79}	<p>For mild–moderate pulmonary disease: fluconazole 12 mg/kg/day (max 400 mg) IV/PO q24h after loading dose of 25 mg/kg/day for 6–12 mo (AII). Itraconazole is alternative if cannot tolerate fluconazole.</p> <p>For meningitis or severe pulmonary disease: induction therapy with AmB-D 1 mg/kg/day IV q24h OR ABLC/L-AmB 5 mg/kg/day q24h; AND flucytosine 100 mg/kg/day PO div q6h for a minimum of 2 wk and a repeat CSF culture is negative, followed by consolidation therapy with fluconazole (12 mg/kg/day with max dose 400 mg after a loading dose of 25 mg/kg/day) for a minimum of 8 more wk (AI). Then use maintenance therapy with fluconazole (6 mg/kg/day) for 6–12 mo (AI).</p> <p>Alternative induction therapies for meningitis or severe pulmonary disease (listed in order of preference): AmB product for 4–6 wk (AII); AmB product plus fluconazole for 2 wk, followed by fluconazole for 8 wk (BII); fluconazole plus flucytosine for 6 wk (BII).</p>	<p>Serum flucytosine concentrations should be obtained after 3–5 days to achieve a 2-h post-dose peak <100 mcg/mL (ideally 30–80 mcg/mL) to prevent neutropenia.</p> <p>For HIV-positive patients, continue maintenance therapy with fluconazole (6 mg/kg/day) indefinitely. Initiate HAART 2–10 wk after commencement of antifungal therapy to avoid immune reconstitution inflammatory syndrome.</p> <p>In organ transplant recipients, continue maintenance fluconazole (6 mg/kg/day) for 6–12 mo after consolidation therapy with higher dose fluconazole.</p> <p>For cryptococcal relapse, restart induction therapy (this time for 4–10 wk), repeat CSF analysis every 2 wk until sterile, and determine antifungal susceptibility of relapse isolate.</p> <p>Successful use of voriconazole, posaconazole, and isavuconazole for cryptococcosis has been reported in adult patients.</p>
Fusarium, Lomentospora (formerly Scedosporium) prolificans , Pseudallescheria boydii (and its asexual form, Scedosporium apiospermum) ^{35,80–84} and other agents of hyalohyphomycosis	<p>Voriconazole (AII) 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y or 12–14 y and weighing <50 kg. In children ≥15 y or 12–14 y and weighing >50 kg, use adult dosing (load 12 mg/kg/day IV div q12h on the first day, then 8 mg/kg/day div q12h as a maintenance dose) (AII).</p> <p>When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid</p>	<p>These can be highly resistant infections, so strongly recommend antifungal susceptibility testing against a wide range of agents to guide specific therapy and consultation with a pediatric infectious diseases expert.</p> <p>Optimal voriconazole trough serum concentrations (generally thought to be 2–5 mcg/mL) are important for success. Check trough level 2–5 days after initiation of therapy, and repeat the following week to verify and 4 days after a change of dose. It is critical to</p>

for children 2–12 y and at least 400 mg/day div bid for children >12 y (All). Dosing in children <2 y is less clear, but doses are generally higher (AIII). These are only initial dosing recommendations; continued dosing in all ages is guided by close monitoring of trough serum voriconazole concentrations in individual patients (All). Unlike in adults, voriconazole PO bioavailability in children is only approximately 50%–60%, so trough levels are crucial at this stage.³⁰

monitor trough concentrations to guide therapy due to high inter-patient variability.³¹ Low voriconazole concentrations are a leading cause of clinical failure. Younger children (especially <3 y) often have lower voriconazole levels and need much higher dosing.

Often resistant to AmB in vitro.

Alternatives: posaconazole (trough concentrations >1 mcg/mL) can be active; echinocandins have been reportedly successful as salvage therapy in combination with azoles; while there are reports of promising in vitro combinations with terbinafine, terbinafine does not obtain good tissue concentrations for these disseminated infections; miltefosine (for leishmaniasis) use has been reported.

B. SYSTEMIC INFECTIONS (continued)

Infection	Therapy (evidence grade)	Comments
Histoplasmosis ^{85–87}	<p>For severe acute pulmonary disease: ABLC/L-AmB 5 mg/kg/day q24h for 1–2 wk, followed by itraconazole 10 mg/kg/day div bid (max 400 mg daily) to complete a total of 12 wk (AIII). Add methylprednisolone (0.5–1.0 mg/kg/day) for first 1–2 wk in patients with hypoxia or significant respiratory distress.</p> <p>For mild to moderate acute pulmonary disease: if symptoms persist for >1 mo, itraconazole 10 mg/kg/day PO solution div bid for 6–12 wk (AIII).</p> <p>For progressive disseminated histoplasmosis: ABLC/L-AmB 5 mg/kg/day q24h for 4–6 wk; alternative treatment is lipid AmB for 1–2 wk followed by itraconazole 10 mg/kg/day div bid (max 400 mg daily) to complete a total of 12 wk (AIII).</p>	<p>Mild pulmonary disease may not require therapy and, in most cases, resolves in 1 mo.</p> <p>CNS histoplasmosis requires initial L-AmB/ABLC (less toxic than AmB-D) therapy for 4–6 wk, followed by itraconazole for at least 12 mo and until CSF antigen resolution.</p> <p>Itraconazole oral solution provides greater and more reliable absorption than capsules and only the oral solution should be used (on an empty stomach); serum concentrations of itraconazole should be determined 5 days after start of therapy to ensure adequate drug exposure. Maintain trough itraconazole concentrations at >1–2 mcg/mL (values for both itraconazole and hydroxyl-itraconazole are added together). If only itraconazole capsules are available, use 20 mg/kg/day div q12h and take with cola product to increase gastric acidity and bioavailability.</p> <p>Potential lifelong suppressive itraconazole if cannot reverse immunosuppression.</p> <p>Corticosteroids recommended for 2 wk for pericarditis with hemodynamic compromise.</p> <p>Voriconazole and posaconazole use has been reported. Fluconazole is inferior to itraconazole.</p>
Mucormycosis (previously known as zygomycosis) ^{28,88–94}	<p>Aggressive surgical debridement combined with induction antifungal therapy: L-AmB at 5–10 mg/kg/day q24h (AII) for 3 wk. Lipid formulations of AmB are preferred to AmB-D due to increased penetration and decreased toxicity.</p> <p>Some experts advocate induction or salvage combination therapy with L-AmB plus an</p>	<p>Following clinical response with AmB, long-term oral step-down therapy with posaconazole (trough concentrations ideally for mucormycosis at >2 mcg/mL) can be attempted for 2–6 mo.</p> <p>No pediatric dosing exists for isavuconazole.</p> <p>Voriconazole has NO activity against mucormycosis or other <i>Zygomycetes</i>.</p>

	<p>echinocandin (although data are largely in diabetic patients with rhinocerebral disease) (CIII)⁹⁵ or combination of L-AmB plus posaconazole.⁹⁶</p> <p>For salvage therapy, isavuconazole (AII)⁹⁷ or posaconazole (AIII).</p> <p>Following successful induction antifungal therapy (for at least 3 wk), can continue consolidation therapy with posaconazole (or use intermittent L-AmB) (BII).</p>	<p>Return of immune function is paramount to treatment success; for children receiving corticosteroids, decreasing the corticosteroid dosage or changing to steroid-sparing protocols is also important.</p>
Paracoccidioidomycosis ^{98–101}	<p>Itraconazole 10 mg/kg/day (max 400 mg daily) PO solution div bid for 6 mo (AIII) OR voriconazole (dosing listed under Aspergillosis) (BI)</p>	<p>Alternatives: fluconazole; isavuconazole; sulfadiazine or TMP/SMX for 3–5 y.</p> <p>AmB is another alternative and may be combined with sulfa or azole antifungals.</p>
Pneumocystis jirovecii (formerly <i>carinii</i>) pneumonia ^{102–104}	<p>Severe disease: preferred regimen is TMP/SMX 15–20 mg TMP component/kg/day IV div q8h (AI) OR, for TMP/SMX intolerant or TMP/SMX treatment failure, pentamidine isethionate 4 mg base/kg/day IV daily (BII), for 3 wk.</p> <p>Mild to moderate disease: start with IV therapy, then after acute pneumonitis is resolved, TMP/SMX 20 mg TMP component/kg/day PO div qid for 3 wk total treatment course (AII).</p>	<p>Alternatives: TMP AND dapsone; OR primaquine AND clindamycin; OR atovaquone.</p> <p>Prophylaxis: preferred regimen is TMP/SMX (5 mg TMP component/kg/day) PO div bid 3 times/wk on consecutive days; OR same dose, given qd, every day; OR atovaquone: 30 mg/kg/day for infants 1–3 mo; 45 mg/kg/day for infants/children 4–24 mo; and 30 mg/kg/day for children >24 mo; OR dapsone 2 mg/kg (max 100 mg) PO qd, OR dapsone 4 mg/kg (max 200 mg) PO once weekly.</p> <p>Use steroid therapy for more severe disease.</p>
Sporotrichosis ^{105,106}	<p>For cutaneous/lymphocutaneous: itraconazole 10 mg/kg/day div bid PO solution for 2–4 wk after all lesions gone (generally total of 3–6 mo) (AII)</p> <p>For serious pulmonary or disseminated infection or disseminated sporotrichosis: ABLC/L-AmB at 5 mg/kg/day q24h until favorable response, then step-down therapy with itraconazole PO for at least a total of 12 mo (AIII)</p> <p>For less severe disease, itraconazole for 12 mo</p>	<p>If no response for cutaneous disease, treat with higher itraconazole dose, terbinafine, or saturated solution of potassium iodide. Fluconazole is less effective.</p> <p>Obtain serum concentrations of itraconazole after 2 wk of therapy; want serum trough concentration >1 mcg/mL.</p> <p>For meningeal disease, initial L-AmB/ABLC (less toxic than AmB-D) should be 4–6 wk before change to itraconazole for at least 12 mo of therapy.</p> <p>Surgery may be necessary in osteoarticular or pulmonary disease.</p>

C. LOCALIZED MUCOCUTANEOUS INFECTIONS

Infection	Therapy (evidence grade)	Comments
Dermatophytoses		
– Scalp (tinea capitis, including kerion) ^{107–112}	<p>Griseofulvin ultramicrosize 10–15 mg/kg/day or microsize 20–25 mg/kg/day qd PO for 6–12 wk (All) (taken with milk or fatty foods to augment absorption).</p> <p>For kerion, treat concurrently with prednisone (1–2 mg/kg/day for 1–2 wk) (All).</p> <p>Terbinafine can be used for only 2–4 wk. Terbinafine dosing is 62.5 mg/day (<20 kg), 125 mg/day (20–40 kg), or 250 mg/day (>40 kg) (All).</p>	<p>Griseofulvin is superior for <i>Microsporum</i> infections, but terbinafine is superior for <i>Trichophyton</i> infections. <i>Trichophyton tonsurans</i> predominates in United States. No need to routinely follow liver function tests in normal healthy children taking griseofulvin.</p> <p>Alternatives: itraconazole oral solution 5 mg/kg qd or fluconazole.</p> <p>2.5% selenium sulfide shampoo, or 2% ketoconazole shampoo, 2–3 times/wk should be used concurrently to prevent recurrences.</p>
– Tinea corporis (infection of trunk/limbs/face) – Tinea cruris (infection of the groin) – Tinea pedis (infection of the toes/feet)	Alphabetic order of topical agents: butenafine, ciclopirox, clotrimazole, econazole, haloprogin, ketoconazole, miconazole, naftifine, oxiconazole, sertaconazole, sulconazole, terbinafine, and tolnaftate (All); apply daily for 4 wk.	<p>For unresponsive tinea lesions, use griseofulvin PO in dosages provided for scalp (tinea capitis, including kerion); fluconazole PO; itraconazole PO; OR terbinafine PO.</p> <p>For tinea pedis: terbinafine PO or itraconazole PO are preferred over other oral agents.</p> <p>Keep skin as clean and dry as possible, particularly for tinea cruris and tinea pedis.</p>
– Tinea unguium (onychomycosis) ^{109,113,114}	Terbinafine 62.5 mg/day (<20 kg), 125 mg/day (20–40 kg), or 250 mg/day (>40 kg). Use for at least 6 wk (fingernails) or 12–16 wk (toenails) (All).	<p>Recurrence or partial response common.</p> <p>Alternative: itraconazole pulse therapy with 10 mg/kg/day div q12h for 1 wk per mo. Two pulses for fingernails and 3 pulses for toenails.</p> <p>Alternatives: fluconazole, griseofulvin.</p>
– Tinea versicolor (also pityriasis versicolor) ^{109,115,116}	<p>Apply topically: selenium sulfide 2.5% lotion or 1% shampoo daily, leave on 30 min, then rinse; for 7 days, then monthly for 6 mo (All); OR ciclopirox 1% cream for 4 wk (BII); OR terbinafine 1% solution (BII); OR ketoconazole 2% shampoo daily for 5 days (BII)</p> <p>For small lesions, topical clotrimazole, econazole, haloprogin, ketoconazole, miconazole, or naftifine</p>	<p>For lesions that fail to clear with topical therapy or for extensive lesions: fluconazole PO or itraconazole PO are equally effective.</p> <p>Recurrence common.</p>

9. Preferred Therapy for Specific Viral Pathogens

NOTE

- **Abbreviations:** AASLD, American Association for the Study of Liver Diseases; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; bid, twice daily; BSA, body surface area; CDC, Centers for Disease Control and Prevention; CLD, chronic lung disease; CMV, cytomegalovirus; CrCl, creatinine clearance; DAA, direct-acting antiviral; div, divided; EBV, Epstein-Barr virus; FDA, US Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; HAART, highly active antiretroviral therapy; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HHS, US Department of Health and Human Services; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFN, interferon; IG, immune globulin; IM, intramuscular; IV, intravenous; PO, orally; postmenstrual age, weeks of gestation since last menstrual period PLUS weeks of chronologic age since birth; PTLT, posttransplant lymphoproliferative disorder; PREP, preexposure prophylaxis; qd, once daily; qid, 4 times daily; RSV, respiratory syncytial virus; SQ, subcutaneous; tab, tablet; TAF, tenofovir alafenamide; tid, 3 times daily; WHO, World Health Organization.

A. OVERVIEW OF NON-HIV, NON-HEPATITIS B OR C VIRAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIVIRALS

Virus	Acyclovir	Baloxavir	Cidofovir	Famciclovir	Foscarnet	Ganciclovir
Cytomegalovirus			+		+	+
Herpes simplex virus	++			++	+	+
Influenza A and B		+				
Varicella-zoster virus	++			++	+	+

Virus	Letermovir	Oseltamivir	Peramivir	Valacyclovir	Valganciclovir	Zanamivir
Cytomegalovirus	+				++	
Herpes simplex virus				++	+	
Influenza A and B		++	+			+
Varicella-zoster virus				++		

NOTE: ++ = preferred therapy(ies); + = acceptable therapy.

B. OVERVIEW OF HEPATITIS B¹ OR C VIRAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIVIRALS

Virus	Adefovir	Daclatasvir Plus Sofosbuvir	Elbasvir/ Grazoprevir (Zepatier)	Entecavir	Glecaprevir/ Pibrentasvir (Mavyret)	Interferon alfa-2b
Hepatitis B virus	+			++		+
Hepatitis C virus ^a		++ ^{b,c}	++ ^{b,d}		++ ^e	

Virus	Lamivudine	Ombitasvir/ Paritaprevir/ Ritonavir Co-packaged With Dasabuvir (Viekira Pak)	Ombitasvir/ Paritaprevir/ Ritonavir Plus Ribavirin	Pegylated Interferon alfa-2a	Ribavirin	Simeprevir Plus Sofosbuvir
Hepatitis B virus	+			++		
Hepatitis C virus ^a		+++ ^b	++ ^d	++ ^f	++ ^f	++ ^b

Virus	Sofosbuvir/ Ledipasvir (Harvoni)	Sofosbuvir Plus Ribavirin	Sofosbuvir/ Velpatasvir (Epclusa)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (Vosevi)	Telbivudine	Tenofovir
Hepatitis B virus					+	++
Hepatitis C virus ^a	+++ ^{b,d,g}	+++ ^c	+ ^e	+ ^e		

NOTE: ++ = preferred therapy(ies); + = acceptable therapy.

^a HCV treatment guidelines from the Infectious Diseases Society of America and the AASLD available at www.hcvguidelines.org (accessed November 2, 2018).

^b Treatment-naïve patients with HCV genotype 1a and 1b infection who do not have cirrhosis.

^c Treatment-naïve patients with HCV genotype 2 and 3 infection who do not have cirrhosis.

^d Treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.

^e Active against all genotypes of HCV (1 through 6).

^f Likely to be replaced in pediatric patients as studies of newer molecules are performed in children.

^g Treatment-naïve patients with HCV genotype 5 and 6 infection who do not have cirrhosis.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS

Infection	Therapy (evidence grade)	Comments
Adenovirus (pneumonia or disseminated infection in immunocompromised hosts) ²	Cidofovir and ribavirin are active in vitro, but no prospective clinical data exist and both have significant toxicity. Two cidofovir dosing schedules have been employed in clinical settings: (1) 5 mg/kg/dose IV once weekly or (2) 1–1.5 mg/kg/dose IV 3 times/wk. If parenteral cidofovir is utilized, IV hydration and oral probenecid should be used to reduce renal toxicity.	Brincidofovir, the orally bioavailable lipophilic derivative of cidofovir also known as CMX001, is under investigation for the treatment of adenovirus in immunocompromised hosts. It is not yet commercially available.
Cytomegalovirus		
– Neonatal ³	See Chapter 5.	
– Immunocompromised (HIV, chemotherapy, transplant-related) ^{4–16}	For induction: ganciclovir 10 mg/kg/day IV div q12h for 14–21 days (All) (may be increased to 15 mg/kg/day IV div q12h). For maintenance: 5 mg/kg IV q24h for 5–7 days per week. Duration dependent on degree of immunosuppression (All). CMV hyperimmune globulin may decrease morbidity in bone marrow transplant patients with CMV pneumonia (All).	Use foscarnet or cidofovir for ganciclovir-resistant strains; for HIV-positive children on HAART, CMV may resolve without anti-CMV therapy. Also used for prevention of CMV disease posttransplant for 100–120 days. Data on valganciclovir dosing in young children for treatment of retinitis are unavailable, but consideration can be given to transitioning from IV ganciclovir to oral valganciclovir after improvement of retinitis is noted. Limited data on oral valganciclovir in infants ^{17,18} (32 mg/kg/day PO div bid) and children (dosing by BSA [dose (mg) = $7 \times \text{BSA} \times \text{CrCl}$]). ⁶
– Prophylaxis of infection in immunocompromised hosts ^{5,19}	Ganciclovir 5 mg/kg IV daily (or 3 times/wk) (started at engraftment for stem cell transplant patients) (BII) Valganciclovir at total dose in milligrams = $7 \times \text{BSA} \times \text{CrCl}$ (use maximum CrCl 150 mL/min/1.73 m ²) orally once daily with	Neutropenia is a complication with ganciclovir and valganciclovir prophylaxis and may be addressed with G-CSF. Prophylaxis and preemptive strategies are effective; neither has been shown clearly superior to the other. ¹⁰

food for children 4 mo–16 y (max dose 900 mg/day) for primary prophylaxis in HIV patients²⁰ who are CMV antibody positive and have severe immunosuppression (CD4 count <50 cells/mm³ in children ≥6 y; CD4 percentage <5% in children <6 y) (CIII)
 Letermovir (adults ≥18 y, CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant) 480 mg administered PO qd or as IV infusion over 1 h through 100 days posttransplant (BI).²¹

Enterovirus

Supportive therapy; no antivirals currently FDA approved

Pocapavir PO is currently under investigation for enterovirus (poliovirus). As of November 2018, it is not available for compassionate use.
 Pleconaril PO is currently under consideration for submission to FDA for approval for treatment of neonatal enteroviral sepsis syndrome.²² As of November 2018, it is not available for compassionate use.

Epstein-Barr virus

– Mononucleosis, encephalitis^{23–25}

Limited data suggest small clinical benefit of valacyclovir in adolescents for mononucleosis (3 g/day div tid for 14 days) (CIII).
 For EBV encephalitis: ganciclovir IV OR acyclovir IV (AIII).

No prospective data on benefits of acyclovir IV or ganciclovir IV in EBV clinical infections of normal hosts. Patients suspected to have infectious mononucleosis should not be given ampicillin or amoxicillin, which cause nonallergic morbilliform rashes in a high proportion of patients with active EBV infection (AII). Therapy with short-course corticosteroids (prednisone 1 mg/kg per day PO [maximum 20 mg/day] for 7 days with subsequent tapering) may have a beneficial effect on acute symptoms in patients with marked tonsillar inflammation with impending airway obstruction, massive splenomegaly, myocarditis, hemolytic anemia, or hemophagocytic lymphohistiocytosis (BIII).

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
– Posttransplant lymphoproliferative disorder ^{26,27}	Ganciclovir (AIII)	Decrease immune suppression if possible, as this has the most effect on control of EBV; rituximab, methotrexate have been used but without controlled data. Preemptive treatment with ganciclovir may decrease PTLD in solid organ transplants.
Hepatitis B virus (chronic) ^{28–46}	<p>AASLD preferred treatments for children and adolescents⁴⁷:</p> <p>IFN-α-2b for children 1–18 y: 3 million U/m² BSA SQ 3 times/wk for 1 wk, followed by dose escalation to 6 million U/m² BSA (max 10 million U/dose); OR entecavir for children \geq 2 y (optimum duration of therapy unknown [BII])</p> <p>Entecavir dosing IF no prior nucleoside therapy:</p> <p>\geq 16 y: 0.5 mg qd</p> <p>2–15 y:</p> <p>10–11 kg: 0.15 mg oral solution qd</p> <p>> 11–14 kg: 0.2 mg oral solution qd</p> <p>> 14–17 kg: 0.25 mg oral solution qd</p> <p>> 17–20 kg: 0.3 mg oral solution qd</p> <p>> 20–23 kg: 0.35 mg oral solution qd</p> <p>> 23–26 kg: 0.4 mg oral solution qd</p> <p>> 26–30 kg: 0.45 mg oral solution qd</p> <p>> 30 kg: 0.5 mg oral solution or tab qd</p> <p>If prior nucleoside therapy:</p> <p>Double the dosage in each weight bracket for entecavir listed previously; OR tenofovir dipivoxil fumarate for adolescents \geq 12 y and adults 300 mg qd.</p>	<p>AASLD nonpreferred treatments for children and adults: Lamivudine 3 mg/kg/day (max 100 mg) PO q24h for 52 wk for children \geq 2 y (children coinfecting with HIV and HBV should use the approved dose for HIV) (AII). Lamivudine approved for children \geq 2 y, but antiviral resistance develops on therapy in 30%; OR adefovir for children \geq 12 y (10 mg PO q24h for a minimum of 12 mo; optimum duration of therapy unknown) (BII); OR telbivudine (adult dose 600 mg qd). There are not sufficient clinical data to identify the appropriate dose for use in children.</p> <p>Indications for treatment of chronic HBV infection, with or without HIV coinfection, are (1) evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>20,000 without HBeAg positivity or >2,000 IU/mL with HBeAg positivity) for >6 mo and persistent elevation of serum transaminase levels for >6 mo, or (2) evidence of chronic hepatitis on liver biopsy (BII). Antiviral therapy is not warranted in children without necroinflammatory liver disease (BIII). Treatment is not recommended for children with immunotolerant chronic HBV infection (ie, normal serum transaminase levels despite detectable HBV DNA) (BII).</p> <p>All patients with HBV and HIV coinfection should initiate ART, regardless of CD4 count. This should include 2 drugs that have HBV activity as well, specifically tenofovir</p>

NOTE: TAF also is a preferred treatment for adults (25 mg daily) but has not been studied in children.

(dipivoxil fumarate or alafenamide) plus lamivudine or emtricitabine.⁴⁷ Patients who are already receiving effective ART that does not include a drug with HBV activity should have treatment changed to include tenofovir (dipivoxil fumarate or alafenamide) plus lamivudine or emtricitabine; alternatively, entecavir is reasonable if patients are receiving a fully suppressive ART regimen.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
Hepatitis C virus (chronic) ^{48–54}	<p>Genotype 1: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naïve without cirrhosis or with compensated cirrhosis, or treatment-experienced with or without cirrhosis</p> <p>Genotype 2: Daily sofosbuvir (400 mg) plus weight-based ribavirin (see later in table) for patients with genotype 2 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis</p> <p>Genotype 3: Daily sofosbuvir (400 mg) plus weight-based ribavirin (see later in table) for patients with genotype 3 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis</p> <p>Genotypes 4, 5, or 6: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis</p> <p>Dosing for ribavirin in combination therapy with sofosbuvir for adolescents ≥ 12 y or ≥ 35 kg:</p> <p><47 kg: 15 mg/kg/day in 2 div doses</p> <p>47–49 kg: 600 mg/day in 2 div doses</p> <p>50–65 kg: 800 mg/day in 2 div doses</p> <p>66–80 kg: 1,000 mg/day in 2 div doses</p> <p>>80 kg: 1,200 mg/day in 2 div doses</p>	<p>Treatment of HCV infections in adults has been revolutionized in recent years with the licensure of numerous highly effective DAAs for use in adults and adolescents ≥ 12 y. It is anticipated that additional safe and effective DAA regimens will be available for children 3–11 y in the near future. Given the efficacy of these new treatment regimens in adults (AI),^{55–70} treatment of children 3–11 y with chronic hepatitis C should be deferred until IFN-free regimens are available. In adolescents ≥ 12 y or ≥ 35 kg, the following treatment is recommended, based on viral genotype⁷¹:</p> <p>None of the DAA HCV drugs currently have been approved for use in children <12 y. Sofosbuvir (Sovaldi) and sofosbuvir in a fixed dose combination tab with ledipasvir (Harvoni) are now approved for patients ≥ 12 y. Treatment should be considered for all HIV/HCV-coinfected children >3 y who have no contraindications to treatment (BIII). Strong consideration should be given to seeking out studies of DAAs if treatment is desired in children <12 y. An alternative would be to not treat with the approved treatment regimen of IFN + ribavirin pending results of these pediatric studies.</p>

Herpes simplex virus

– Third trimester maternal suppressive therapy ^{72–74}	Acyclovir or valacyclovir maternal suppressive therapy in pregnant women reduces HSV recurrences and viral shedding at the time of delivery but does not fully prevent neonatal HSV ⁷³ (BIII).	
– Neonatal	See Chapter 5.	
– Mucocutaneous (normal host)	Acyclovir 80 mg/kg/day PO div qid (max dose 800 mg) for 5–7 days, or 15 mg/kg/day IV as 1–2 h infusion div q8h (AII) Valacyclovir 20 mg/kg/dose (max dose 1 g) PO bid ⁷⁵ for 5–7 days (BII) Suppressive therapy for frequent recurrence (no pediatric data): acyclovir 20 mg/kg/dose bid or tid (max dose 400 mg) for 6–12 mo, then reevaluate need (AIII)	Foscarnet for acyclovir-resistant strains. Immunocompromised hosts may require 10–14 days of therapy. Topical acyclovir not efficacious and therefore is not recommended.
– Genital	Adult doses: acyclovir 400 mg PO tid for 7–10 days; OR valacyclovir 1 g PO bid for 10 days; OR famciclovir 250 mg PO tid for 7–10 days (AI)	All 3 drugs have been used as prophylaxis to prevent recurrence. Topical acyclovir not efficacious and therefore is not recommended.
– Encephalitis	Acyclovir 60 mg/kg/day IV as 1–2 h infusion div q8h; for 21 days for infants ≤4 mo. For older infants and children, 45 mg/kg/day IV as 1–2 h infusion div q8h (AIII).	Safety of high-dose acyclovir (60 mg/kg/day) not well defined beyond the neonatal period; can be used but monitor for neurotoxicity and nephrotoxicity.
– Keratoconjunctivitis	1% trifluridine or 0.15% ganciclovir ophthalmic gel (AII)	Treat in consultation with an ophthalmologist. Topical steroids may be helpful when used together with antiviral agents.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
Human herpesvirus 6		
– Immunocompromised children ⁷⁶	No prospective comparative data; ganciclovir 10 mg/kg/day IV div q12h used in case report (AIII)	May require high dose to control infection; safety and efficacy not defined at high doses.
Human immunodeficiency virus		
Current information on HIV treatment and opportunistic infections for children ⁷⁷ is posted at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf (accessed October 6, 2018); other information on HIV programs is available at www.cdc.gov/hiv/policies/index.html (accessed October 6, 2018). Consult with an HIV expert, if possible, for current recommendations, as treatment options are complicated and constantly evolving.		
– Therapy of HIV infection		
State-of-the-art therapy is rapidly evolving with introduction of new agents and combinations; currently there are 26 individual ARV agents approved for use by the FDA that have pediatric indications, as well as multiple combinations; guidelines for children and adolescents are continually updated on the AIDSinfo and CDC Web sites given previously.	Effective therapy (HAART) consists of ≥3 agents, including 2 nucleoside reverse transcriptase inhibitors, plus either a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, or an integrase inhibitor; many different combination regimens give similar treatment outcomes; choice of agents depends on the age of the child, viral load, consideration of potential viral resistance, and extent of immune depletion, in addition to judging the child's ability to adhere to the regimen.	Assess drug toxicity (based on the agents used) and virologic/immunologic response to therapy (quantitative plasma HIV and CD4 count) initially monthly and then every 3–6 mo during the maintenance phase.
– Children of any age	Any child with AIDS or significant HIV-related symptoms (clinical category C and most B conditions) should be treated (AI).	Adherence counseling and appropriate ARV formulations are critical for successful implementation.

Recent guidance from the WHO and HHS guidelines committees now recommends treatment for **all children** regardless of age, CD4 count, or clinical status, with situation-specific levels of urgency.

– First 3 y after birth	HAART with ≥ 3 drugs is now recommended for all infants ≤ 36 mo, regardless of clinical status or laboratory values (AI).	Preferred therapy in the first 2 wk after birth is zidovudine and lamivudine PLUS either nevirapine or raltegravir. Preferred therapy from 2 wk–3 y: zidovudine and lamivudine or abacavir and lamivudine (>3 mo) PLUS either lopinavir/ritonavir (toxicity concerns preclude its use until a postmenstrual age of 42 wk and a postnatal age of at least 14 days is reached) or raltegravir.
– HIV-infected children ≥ 3 – <6 y	Treat all with any CD4 count (AI).	Preferred regimens comprise zidovudine and lamivudine (at any age) or abacavir and either lamivudine or emtricitabine PLUS either atazanavir/ritonavir or darunavir/ritonavir or raltegravir.
– HIV-infected children ≥ 6 – <12 y	Treat all regardless of CD4 count (AI).	Preferred regimens include abacavir and lamivudine or TAF and either lamivudine or emtricitabine PLUS either atazanavir/ritonavir OR dolutegravir (≥ 30 kg).
– HIV-infected youth ≥ 12 y	Treat all regardless of CD4 count (AI).	Preferred regimens comprise TAF or tenofovir (adolescents/ Tanner stage 4 or 5) plus emtricitabine OR abacavir plus lamivudine PLUS either atazanavir/ritonavir or darunavir/ritonavir or dolutegravir or elvitegravir. NOTE: A recent report suggests the possibility of neural tube defects developing in offspring of women who become pregnant while on dolutegravir and/or use it during the first trimester. Caution should be exercised, including pregnancy testing and counseling, before initiating dolutegravir (and other integrase inhibitors). Further data and advice are anticipated as more data become available.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
– Antiretroviral-experienced child	Consult with HIV specialist.	Consider treatment history and drug resistance testing and assess adherence.
– HIV exposures, nonoccupational	Therapy recommendations for exposures available on the CDC Web site at www.cdc.gov/hiv/guidelines/preventing.html (accessed October 6, 2018)	Postexposure prophylaxis remains unproven but substantial evidence supports its use; consider individually regarding risk, time from exposure, and likelihood of adherence; prophylactic regimens administered for 4 wk.
– Negligible exposure risk (urine, nasal secretions, saliva, sweat, or tears—no visible blood in secretions) OR >72 h since exposure	Prophylaxis not recommended (BIII)	
– Significant exposure risk (blood, semen, vaginal, or rectal secretions from a known HIV-infected individual) AND <72 h since exposure	Prophylaxis recommended (BIII) Preferred regimens 4 wk—<2 y: zidovudine PLUS lamivudine PLUS either raltegravir or lopinavir/ritonavir 2–12 y: tenofovir PLUS emtricitabine PLUS raltegravir ≥13 y: tenofovir PLUS emtricitabine PLUS either raltegravir or dolutegravir	Consultation with a pediatric HIV specialist is advised.
– Significant exposure risk preexposure prophylaxis	Truvada (tenofovir 300 mg/emtricitabine 200 mg): 1 tab daily	Daily PREP has proven efficacy for prevention of HIV infection in individuals at high risk. It is FDA approved for adolescents/youth (13–24 y; ≥35 kg). Strategies for use include both episodic and continuous administration. Baseline HIV and renal function testing is indicated, and it is recommended to evaluate HIV infection status and renal function approximately every 3 mo while on PREP.
– HIV exposure, occupational ¹⁸	See guidelines on CDC Web site at www.cdc.gov/hiv/guidelines/preventing.html (accessed October 6, 2018).	

Influenza virus

Recommendations for the treatment of influenza can vary from season to season; access the American Academy of Pediatrics Web site (www.aap.org) and the CDC Web site (www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; accessed October 6, 2018) for the most current, accurate information.

Influenza A and B

– Treatment^{79–81}

Oseltamivir
 Preterm, <38 wk postmenstrual age:
 1 mg/kg/dose PO bid⁷⁹
 Preterm, 38–40 wk postmenstrual age:
 1.5 mg/kg/dose PO bid⁷⁹
 Preterm, >40 wk postmenstrual age:
 3.0 mg/kg/dose PO bid
 Term, birth–8 mo: 3.0 mg/kg/dose PO bid
 9–11 mo: 3.5 mg/kg/dose PO bid⁸⁰
 12–23 mo: 30 mg/dose PO bid
 2–12 y: ≤15 kg: 30 mg bid; 16–23 kg: 45 mg bid;
 24–40 kg: 60 mg bid; >40 kg: 75 mg bid
 ≥13 y: 75 mg bid
 OR
 Zanamivir
 ≥7 y: 10 mg by inhalation bid for 5 days
 OR
 Peramivir (BII)
 2–12 y: single IV dose 12 mg/kg, up to 600 mg
 max
 13–17 y: single IV dose 600 mg
 OR
 Baloxavir (BII)
 ≥12 y:
 40–79 kg: single PO dose 40 mg
 ≥80 kg: single PO dose 80 mg

Oseltamivir currently is drug of choice for treatment of influenza infections.

For patients 12–23 mo, the original FDA-approved unit dose of 30 mg/dose may provide inadequate drug exposure; 3.5 mg/kg/dose PO bid has been studied,⁸⁰ but study population sizes were small.

Studies of parenteral zanamivir have been completed in children.⁸² However, this formulation of the drug is not yet approved in the United States and is not available for compassionate use.

The adamantanes, amantadine and rimantadine, currently are not effective for treatment due to near-universal resistance of influenza A.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
– Chemoprophylaxis	<p>Oseltamivir 3 mo–12 y: The mg dose given for prophylaxis is the same as for the treatment dose for all ages, but it is given qd for prophylaxis instead of bid for treatment.</p> <p>Zanamivir ≥5 y: 10 mg by inhalation qd for as long as 28 days (community outbreaks) or 10 days (household setting).</p>	<p>Oseltamivir currently is drug of choice for chemoprophylaxis of influenza infection. Unless the situation is judged critical, oseltamivir chemoprophylaxis is not routinely recommended for patients <3 mo because of limited safety and efficacy data in this age group.</p> <p>The adamantanes, amantadine and rimantadine, currently are not effective for chemoprophylaxis due to near-universal resistance of influenza A.</p>
Measles ⁸³	<p>No prospective data on antiviral therapy. Ribavirin is active against measles virus in vitro.</p> <p>Vitamin A is beneficial in children with measles and is recommended by WHO for all children with measles regardless of their country of residence (qd dosing for 2 days): for children ≥1 y: 200,000 IU; for infants 6–12 mo: 100,000 IU; for infants <6 mo: 50,000 IU (BII). Even in countries where measles is not usually severe, vitamin A should be given to all children with severe measles (eg, requiring hospitalization). Parenteral and oral formulations are available in the United States.</p>	<p>IG prophylaxis for exposed, unimmunized children: 0.5 mL/kg (max 15 mL) IM</p>
Respiratory syncytial virus ^{84,85}	<p>Ribavirin (6-g vial to make 20 mg/mL solution in sterile water), aerosolized over 18–20 h daily for 3–5 days (BII)</p>	<p>Aerosol ribavirin provides only a small benefit and should only be considered for use for life-threatening infection with RSV. Airway reactivity with inhalation precludes routine use.</p>

– Prophylaxis (palivizumab, Synagis for high-risk infants) (BI)^{84,85}

Prophylaxis: palivizumab (a monoclonal antibody) 15 mg/kg IM monthly (max 5 doses) for the following high-risk infants (AI):

In first year after birth, palivizumab prophylaxis is recommended for infants born before 29 wk 0 days' gestation.

Palivizumab prophylaxis is not recommended for otherwise healthy infants born at ≥ 29 wk 0 days' gestation.

In first year after birth, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at < 32 wk 0 days' gestation and a requirement for $> 21\%$ oxygen for at least 28 days after birth.

Clinicians may administer palivizumab prophylaxis in the first year after birth to certain infants with hemodynamically significant heart disease.

Palivizumab does not provide benefit in the treatment of an active RSV infection.

Palivizumab prophylaxis may be considered for children < 24 mo who will be profoundly immunocompromised during the RSV season.

Palivizumab prophylaxis is not recommended in the second year after birth except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical support (supplemental oxygen, chronic corticosteroid therapy, or diuretic therapy) during the 6-mo period before the start of the second RSV season.

Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.

Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year after birth.

Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.

The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native populations and possibly in selected other American Indian populations.

Palivizumab prophylaxis is not recommended for prevention of health care–associated RSV disease.

C. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

Infection	Therapy (evidence grade)	Comments
Varicella-zoster virus⁸⁶		
– Infection in a normal host	Acyclovir 80 mg/kg/day (max single dose 800 mg) PO div qid for 5 days (AI)	The sooner antiviral therapy can be started, the greater the clinical benefit.
– Severe primary chickenpox, disseminated infection (cutaneous, pneumonia, encephalitis, hepatitis); immunocompromised host with primary chickenpox or disseminated zoster	Acyclovir 30 mg/kg/day IV as 1–2 h infusion div q8h for 10 days (acyclovir doses of 45–60 mg/kg/day in 3 div doses IV should be used for disseminated or central nervous system infection). Dosing also can be provided as 1,500 mg/m ² /day IV div q8h. Duration in immunocompromised children: 7–14 days, based on clinical response (AI).	Oral valacyclovir, famciclovir, foscarnet also active

10. Preferred Therapy for Specific Parasitic Pathogens

NOTES

- For some parasitic diseases, therapy may be available only from the Centers for Disease Control and Prevention (CDC), as noted. The CDC provides up-to-date information about parasitic diseases and current treatment recommendations at www.cdc.gov/parasites (accessed October 6, 2018). Consultation is available from the CDC for parasitic disease diagnostic services (www.cdc.gov/dpdx; accessed October 6, 2018); parasitic disease testing and experimental therapy at 404/639-3670; for malaria, 770/488-7788 or 855/856-4713 toll-free, Monday through Friday, 9:00 am to 5:00 pm ET, and the emergency number 770/488-7100 for after hours, weekends, and holidays (correct as of July 21, 2018). Antiparasitic drugs available from the CDC Drug Service can be reviewed and requested at www.cdc.gov/laboratory/drugservice/formulary.html (accessed October 6, 2018).
- Additional information about many of the organisms and diseases mentioned here, along with treatment recommendations, can be found in the appropriate sections in the American Academy of Pediatrics *Red Book* and the CDC Web site for parasitic diseases, <https://www.cdc.gov/parasites> (accessed October 6, 2018)
- **Abbreviations:** AmB, amphotericin B; A-P, atovaquone/proguanil; ASTMH, American Society of Tropical Medicine and Hygiene; bid, twice daily; BP, blood pressure; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CrCl, creatinine clearance; CSF, cerebrospinal fluid; CT, computed tomography; DEC, diethylcarbamazine; div, divided; DS, double strength; ECG, electrocardiogram; EOC, Emergency Operations Center; FDA, US Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; PAIR, puncture, aspiration, injection, re-aspiration; PHMB, polyhexamethylene biguanide; PO, orally; qd, once daily; qid, 4 times daily; qod, every other day; spp, species; tab, tablet; TB, tuberculosis; tid, 3 times daily; TMP/SMX, trimethoprim/sulfamethoxazole.

A. SELECTED COMMON PATHOGENIC PARASITES AND SUGGESTED AGENTS FOR TREATMENT

	Albendazole/ Mebendazole	Metronidazole/ Tinidazole	Praziquantel	Ivermectin	Nitazoxanide	DEC	Pyrantel Pamoate	Paromomycin	TMP/SMX
Ascariasis	++			+	+		+		
<i>Blastocystis</i> spp		+			+			+	+
Cryptosporidiosis					+			+	
Cutaneous larva migrans	++			++					
Cyclosporiasis		—			+				++
<i>Cystoisospora</i> spp					+				++
Dientamoebiasis	—	++			+			+	
Liver fluke (<i>Clonorchis</i> and <i>Opisthorchis</i>)	+		++						
Lung fluke	—		++						
<i>Giardia</i> spp	+	++			++			+	
Hookworm	++			—			+		
Loiasis	+					++			
<i>Mansonella ozzardi</i>	—			+		—			
<i>Mansonella perstans</i>	±		—	—		±			
Onchocerciasis				++					
Pinworm	++						++		

Schistosomiasis		++			
<i>Strongyloides</i> spp	+		++		
Tapeworm		++		+	
Toxocariasis	++				+
Trichinellosis	++				
Trichomoniasis		++			
Trichuriasis	++				
<i>Wuchereria bancrofti</i>	+				++

NOTE: ++ = first-line agent or >90% effective; + = alternative or ≤90% effective; ± = significant resistance; — = not likely to be effective.

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS

Disease/Organism	Treatment (evidence grade)	Comments
<i>Acanthamoeba</i>	See Amebic meningoencephalitis.	
Amebiasis¹⁻⁵		
<i>Entamoeba histolytica</i>		
– Asymptomatic intestinal colonization	Paromomycin 25–35 mg/kg/day PO div tid for 7 days; OR iodoquinol 30–40 mg/kg/day (max 650 mg/dose) PO div tid for 20 days; OR diloxanide furoate (not commercially available in the United States) 20 mg/ kg/day PO div tid (max 500 mg/dose) for 10 days (CII)	Follow-up stool examination to ensure eradication of carriage; screen/treat positive close contacts. <i>Entamoeba dispar</i> infections do not require treatment.
– Colitis	Metronidazole 35–50 mg/kg/day PO div tid for 10 days; OR tinidazole (age >3 y) 50 mg/kg/day PO (max 2 g) qd for 3 days FOLLOWED BY paromomycin or iodoquinol, as above, to eliminate cysts (BII)	Avoid antimotility drugs, steroids. Take tinidazole with food to decrease GI side effects; if unable to take tabs, pharmacists can crush tabs and mix with syrup. Avoid alcohol ingestion with metronidazole and tinidazole. Preliminary data support use of nitazoxanide to treat clinical infection, but it may not prevent parasitological failure: age ≥ 12 y, 500 mg bid for 3 days; ages 4–11 y, 200 mg bid for 3 days; ages 1–3 y, 100 mg bid for 3 days.
– Liver abscess, extraintestinal disease	Metronidazole 35–50 mg/kg/day IV q8h, switch to PO when tolerated, for 10 days; OR tinidazole (age >3 y) 50 mg/kg/day PO (max 2 g) qd for 5 days FOLLOWED BY paromomycin or iodoquinol, as above, to eliminate cysts (BII). Nitazoxanide 500 mg bid for 10 days (≥ 12 y).	Serologic assays >95% positive in extraintestinal amebiasis. Percutaneous or surgical drainage may be indicated for large liver abscesses or inadequate response to medical therapy. Avoid alcohol ingestion with metronidazole and tinidazole. Take tinidazole with food to decrease GI side effects; if unable to take tabs, pharmacists can crush tabs and mix with syrup.

Amebic meningoencephalitis⁶⁻¹⁰

<i>Naegleria fowleri</i>	AmB 1.5 mg/kg/day IV div 2 doses for 3 days, then 1 mg/kg/day qd for 11 days; PLUS AmB intrathecally 1.5 mg qd for 2 days, then 1 mg/day qod for 8 days; PLUS azithromycin 10 mg/kg/day IV or PO (max 500 mg/day) for 28 days; PLUS fluconazole 10 mg/kg/day IV or PO qd (max 600 mg/day) for 28 days; PLUS rifampin 10 mg/kg/day qd IV or PO (max 600 mg/day) for 28 days; PLUS miltefosine <45 kg 50 mg PO bid; ≥45 kg 50 mg PO tid for 28 days PLUS dexamethasone 0.6 mg/kg/day div qid for 4 days	Treatment recommendations based on regimens used for 5 known survivors; available at https://www.cdc.gov/parasites/naegleria/treatment-hcp.html (accessed October 6, 2018). Conventional amphotericin preferred; liposomal AmB is less effective in animal models. Treatment outcomes usually unsuccessful; early therapy (even before diagnostic confirmation if indicated) may improve survival.
<i>Acanthamoeba</i>	Combination regimens including miltefosine, fluconazole, and pentamidine favored by some experts; TMP/SMX, metronidazole, and a macrolide may be added. Other drugs that have been used alone or in combination include rifampin, other azoles, sulfadiazine, flucytosine, and caspofungin. Keratitis: topical therapies include PHMB (0.02%) or biguanide chlorhexidine, combined with propamidine isethionate (0.1%) or hexamidine (0.1%) (topical therapies not approved in United States but available at compounding pharmacies).	Optimal treatment regimens uncertain; combination therapy favored. Miltefosine is commercially available; CDC EOC available for consultation about use of this drug (770/488-7100) (accurate as of July 21, 2018). Keratitis should be evaluated by an ophthalmologist. Prolonged treatment often needed.
<i>Balamuthia mandrillaris</i>	Combination regimens preferred. Drugs that have been used alone or in combination include pentamidine, 5-flucytosine, fluconazole, macrolides, sulfadiazine, miltefosine, thioridazine, AmB, itraconazole, and albendazole.	Optimal treatment regimen uncertain; regimens based on case reports; prolonged treatment often needed. Surgical resection of CNS lesions may be beneficial.
<i>Ancylostoma braziliense</i>	See Cutaneous larva migrans.	
<i>Ancylostoma caninum</i>	See Cutaneous larva migrans.	

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
<i>Ancylostoma duodenale</i>	See Hookworm.	
Angiostrongyliasis ^{11–14}		
<i>Angiostrongylus cantonensis</i> (cerebral disease)	Supportive care	Most patients recover without antiparasitic therapy; treatment may provoke severe neurologic symptoms. Corticosteroids, analgesics, and repeat lumbar puncture may be of benefit. Prednisolone (1–2 mg/kg/day, up to 60 mg qd, in 2 div doses, for 2 wk) may shorten duration of headache and reduce need for repeat lumbar puncture. Ocular disease may require surgery or laser treatment.
<i>Angiostrongylus costaricensis</i> (eosinophilic enterocolitis)	Supportive care	Surgery may be pursued to exclude another diagnosis such as appendicitis or to remove inflamed intestine.
Ascariasis (<i>Ascaris lumbricoides</i>) ¹⁵	First line: albendazole 400 mg PO once OR mebendazole 500 mg once or 100 mg bid for 3 days (BII) Pregnant women: pyrantel pamoate 11 mg/kg max 1 g once Alternatives: ivermectin 150–200 mcg/kg PO once (CII); nitazoxanide 7.5 mg/kg once	Follow-up stool ova and parasite examination after therapy not essential. Take albendazole with food (bioavailability increases with food, especially fatty meals). Albendazole has theoretical risk of causing seizures in patients coinfecting with cysticercosis.
Babesiosis (<i>Babesia</i> spp) ^{16–20}	Mild to moderate disease: azithromycin 10 mg/kg/day (max 500 mg/dose) PO on day 1; 5 mg/kg/day from day 2 on (max 250 mg/dose) for 7–10 days PLUS atovaquone 40 mg/kg/day (max 750 mg/dose) PO div bid (preferred due to more favorable adverse event profile) OR clindamycin 30 mg/kg/day IV div tid (max 600 mg per dose), PLUS quinine 25 mg/kg/day PO (max 650 mg/dose) div tid for 7–10 days	Most asymptomatic infections with <i>Babesia microti</i> in immunocompetent individuals do not require treatment. Daily monitoring of hematocrit and percentage of parasitized red blood cells (until <5%) is helpful in guiding management. Exchange blood transfusion may be of benefit for severe disease and <i>Babesia divergens</i> infection.

	Severe disease: azithromycin 10 mg/kg/day (max 500 mg/dose) IV for 7–10 days PLUS atovaquone 40 mg/kg/day (max 750 mg/dose) PO div bid; OR clindamycin 30 mg/kg/day IV div tid (max 600 mg per dose), PLUS quinine 25 mg/kg/day PO (max 650 mg/dose) div tid for 7–10 days	Higher doses of medications and prolonged therapy may be needed for asplenic or immunocompromised individuals. Clindamycin and quinine remains the regimen of choice for <i>Babesia divergens</i> .
<i>Balantidium coli</i> ²¹	Tetracycline (patients >7 y) 40 mg/kg/day PO div qid for 10 days (max 2 g/day) (CII); OR metronidazole 35–50 mg/kg/day PO div tid for 5 days; OR iodoquinol 30–40 mg/kg/day PO (max 2 g/day) div tid for 20 days	Optimal treatment regimen uncertain. Prompt stool examination may increase detection of rapidly degenerating trophozoites. None of these medications are approved for this indication. Nitazoxanide may also be effective.
<i>Baylisascaris procyonis</i> (raccoon roundworm) ^{22,23}	Albendazole 25–50 mg/kg/day PO div q12h for 10–20 days given as soon as possible (<3 days) after exposure (eg, ingestion of raccoon feces or contaminated soil) might prevent clinical disease (CIII).	Therapy generally unsuccessful to prevent fatal outcome or severe neurologic sequelae once CNS disease present. Steroids may be of value in decreasing inflammation in CNS or ocular infection. Albendazole bioavailability increased with food, especially fatty meals.
<i>Blastocystis</i> spp ^{24,25}	Metronidazole 30 mg/kg/day (max 750 mg per dose) PO div tid for 5–10 days (BII); OR tinidazole 50 mg/kg (max 2 g) once (age >3 y) (BII)	Pathogenesis debated. Asymptomatic individuals do not need treatment; diligent search for other pathogenic parasites recommended for symptomatic individuals with <i>B hominis</i> . Paromomycin, nitazoxanide (200 mg PO bid for 3 days for age 4–11 y; 100 mg PO bid for 3 days for age 1–3 y), and TMP/SMX also may be effective. Metronidazole resistance may occur. Take tinidazole with food; tabs may be crushed and mixed with flavored syrup.
<i>Brugia malayi</i> , <i>Brugia timori</i>	See Filariasis.	
Chagas disease (<i>Trypanosoma cruzi</i>) ^{26–28}	See Trypanosomiasis.	

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
<i>Clonorchis sinensis</i>	See Flukes.	
Cryptosporidiosis (<i>Cryptosporidium parvum</i>) ^{29–32}	Nitazoxanide, age 12–47 mo, 5 mL (100 mg) bid for 3 days; age 4–11 y, 10 mL (200 mg) bid for 3 days; age ≥12 y, 500 mg (tab or suspension) PO bid for 3 days (BII). Paromomycin 30 mg/kg/day div bid–qid (CII); OR azithromycin 10 mg/kg/day for 5 days (CII); OR paromomycin AND azithromycin given as combination therapy may yield initial response but may not result in sustained cure in immunocompromised individuals.	Recovery depends largely on the immune status of the host; treatment not required in all immunocompetent individuals. Medical therapy may have limited efficacy in HIV-infected patients not receiving effective antiretroviral therapy. Longer courses (>2 wk) may be needed in solid organ transplant patients.
Cutaneous larva migrans or creeping eruption ^{33,34} (dog and cat hookworm) (<i>Ancylostoma caninum</i> , <i>Ancylostoma braziliense</i> , <i>Uncinaria stenocephala</i>)	Ivermectin 200 mcg/kg PO for 1–2 days (CII); OR albendazole 15 mg/kg/day (max 400 mg) PO qd for 3 days (CII)	Albendazole bioavailability increased with food, especially fatty meals
<i>Cyclospora</i> spp. ^{35,36} (cyanobacterium-like agent)	TMP/SMX 10 mg TMP/kg/day (max 1 DS tab bid) PO div bid for 7–10 days (BIII); nitazoxanide may be an alternative for TMP/SMX-allergic patients 500 mg bid for 7 days (adult dose).	HIV-infected patients may require higher doses/longer therapy. Ciprofloxacin 30 mg/kg/day div bid for 7 days may be an alternative; treatment failures have been reported.
Cysticercosis ^{37–40} (<i>Cysticercus cellulosae</i> ; larva of <i>Taenia solium</i>)	Neurocysticercosis. Patients with 1–2 viable parenchymal cysticerci: albendazole 15 mg/kg/day PO div bid (max 1,200 mg/day) for 10–14 days (CII) plus steroids (prednisone 1.0 mg/kg/day or dexamethasone 0.1 mg/kg/day) begun at least 1 day before antiparasitic therapy, continued during antiparasitic	Collaboration with a specialist with experience treating this condition is recommended. See IDSA/ASTMH guidelines. ⁴⁰ For infection caused by only 1–2 cysts, some do not use steroid therapy routinely with active treatment. Management of seizures, cerebral edema, intracranial hypertension, or hydrocephalus, when present, is the focus of initial therapy and may require antiepileptic

	<p>treatment followed by rapid taper (to reduce inflammation associated with dying organisms)</p> <p>Patients with >2 viable parenchymal cysticerci: albendazole 15 mg/kg/day PO div bid (max 1,200 mg/day) PLUS praziquantel 50 mg/kg/day PO div tid (CII) plus steroids (prednisone 1.0 mg/kg/day or dexamethasone 0.1 mg/kg/day) begun at least 1 day before antiparasitic therapy, continued during antiparasitic treatment followed by rapid taper (to reduce inflammation associated with dying organisms).</p>	<p>drugs, neuroendoscopy, or surgical approaches before considering antiparasitic therapy.</p> <p>Imaging with both CT and MRI is recommended for classifying disease in patients newly diagnosed with neurocysticercosis.</p> <p>Optimal dose and duration of steroid therapy is uncertain. Screening for TB infection and <i>Strongyloides</i> is recommended for patients likely to require prolonged steroid therapy.</p> <p>Take albendazole with food (bioavailability increases with food, especially fatty meals).</p>
<i>Cystoisospora belli</i> (formerly <i>Isospora belli</i>) ²¹	TMP/SMX 8–10 mg TMP/kg/day PO (or IV) div bid for 7–10 days (max 160 mg TMP/800 mg SMX bid); OR ciprofloxacin 500 mg PO div bid for 7 days	<p>Infection often self-limited in immunocompetent hosts; consider treatment if symptoms do not resolve by 5–7 days or are severe.</p> <p>Pyrimethamine plus leucovorin and nitazoxanide are alternatives. Ciprofloxacin is an alternative for adults. Immunocompromised patients should be treated; longer courses or suppressive therapy may be needed for severely immunocompromised patients.</p>
Dientamoebiasis ^{41,42} (<i>Dientamoeba fragilis</i>)	Metronidazole 35–50 mg/kg/day PO div tid for 10 days (max 500–750 mg/dose); OR paromomycin 25–35 mg/kg/day PO div tid for 7 days; OR iodoquinol 30–40 mg/kg/day (max 650 mg/dose) PO div tid for 20 days (BII)	<p>Treatment indicated when no other cause except <i>Dientamoeba</i> found for abdominal pain or diarrhea lasting more than a week.</p> <p>Take paromomycin with meals and iodoquinol after meals.</p> <p>Tinidazole, nitazoxanide, tetracycline, and doxycycline also may be effective.</p> <p>Albendazole and mebendazole have no activity against <i>Dientamoeba</i>.</p>
<i>Diphyllobothrium latum</i>	See Tapeworms.	
<i>Dipylidium caninum</i>	See Tapeworms.	

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
Echinococcosis ^{43,44}		
<i>Echinococcus granulosus</i>	Albendazole 15 mg/kg/day PO div bid (max 800 mg/day) for 1–6 mo alone (CIII) or as adjunctive therapy with surgery or percutaneous treatment; initiate 4–30 days before and continue for at least 1 mo after surgery.	Involvement with specialist with experience treating this condition recommended. Surgery is the treatment of choice for management of complicated cysts. PAIR technique effective for appropriate cysts. Mebendazole is an alternative if albendazole is unavailable; if used, continue for 3 mo after PAIR. Take albendazole with food (bioavailability increases with food, especially fatty meals).
<i>Echinococcus multilocularis</i>	Surgical treatment generally the treatment of choice; postoperative albendazole 15 mg/kg/day PO div bid (max 800 mg/day) should be administered to reduce relapse; duration uncertain (at least 2 y with long-term monitoring for relapse). Benefit of preoperative albendazole unknown.	Involvement with specialist with experience treating this condition recommended. Take albendazole with food (bioavailability increases with food, especially fatty meals).
<i>Entamoeba histolytica</i>	See Amebiasis.	
<i>Enterobius vermicularis</i>	See Pinworms.	
<i>Fasciola hepatica</i>	See Flukes.	
Eosinophilic meningitis		
Filariasis ^{45–47}		
– River blindness (<i>Onchocerca volvulus</i>)	Ivermectin 150 mcg/kg PO once (All); repeat q3–6mo until asymptomatic and no ongoing exposure; OR if no ongoing exposure, doxycycline 4 mg/kg/day PO (max 200 mg/day div bid) for 6 wk followed by a single dose of ivermectin; provide 1 dose of	Doxycycline targets <i>Wolbachia</i> , the endosymbiotic bacteria associated with <i>O. volvulus</i> . Assess for <i>Loa loa</i> coinfection before using ivermectin if exposure occurred in settings where both <i>Onchocerca</i> and <i>L. loa</i> are endemic. Treatment of onchocerciasis in

	ivermectin for symptomatic relief 1 wk before beginning doxycycline.	the setting of <i>Loa loa</i> infection is uncertain and consultation with a specialist familiar with these diseases is recommended.
– Tropical pulmonary eosinophilia ⁴⁸	DEC (from CDC) 6 mg/kg/day PO div tid for 12–21 days; antihistamines/corticosteroids for allergic reactions (CII)	DEC is available from the CDC Parasitic Diseases Inquiry desk at 404/718-4745; https://www.cdc.gov/parasites/lymphaticfilariasis/health_professionals/dtxt.html (accessed October 6, 2018); the CDC Drug Service number is 404/639-3670.
<i>Loa loa</i>	When no evidence of microfilaremia: DEC (from CDC) 8–10 mg/kg/day PO div tid for 21 days When microfilaremia present: day 1: 1 mg/kg (max 50 mg); day 2: 1 mg/kg (max 50 mg) div tid; day 3: 1–2 mg/kg (max 100 mg) div tid; days 4–21: 9 mg/kg/day PO div tid	Involvement with specialist with experience treating this condition recommended. Quantification of microfilarial levels is essential before treatment. Do not use DEC if onchocerciasis is present. Apheresis or albendazole may be used to reduce microfilarial levels before treatment with DEC.
<i>Mansonella ozzardi</i>	Ivermectin 200 mcg/kg PO once	DEC and albendazole not effective
<i>Mansonella perstans</i>	Combination therapy with DEC and albendazole 400 mg PO bid for 21 days may be effective.	Relatively resistant to DEC, ivermectin, albendazole, and mebendazole; doxycycline 4 mg/kg/day PO (max 200 mg/day div bid) for 6 wk beneficial for clearing microfilaria in Mali
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> , <i>Brugia timori</i> , <i>Mansonella streptocerca</i>	DEC (from CDC) 6 mg/kg/day div tid for 12 days OR 6 mg/kg/day PO as a single dose (All). Consider adding doxycycline 4 mg/kg/day PO (max 200 mg/day div bid) for 4–6 wk.	Avoid DEC with <i>Onchocerca</i> and <i>L loa</i> coinfection; doxycycline (4 mg/kg/day PO, max 200 mg/day div bid, for 4–6 wk) may be used; albendazole has activity against adult worms. Effectiveness of doxycycline in <i>Mansonella streptocerca</i> unknown. DEC is available from CDC (404/639-3670) (accessed October 6, 2018).

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
Flukes		
Liver flukes ⁴⁹ (<i>Clonorchis sinensis</i> , <i>Opisthorchis</i> spp)	Praziquantel 75 mg/kg PO div tid for 2 days (BII); OR albendazole 10 mg/kg/day PO for 7 days (CIII) OR mebendazole 30 mg/kg for 20–30 days. Single 40 mg/kg dose praziquantel may be effective for <i>Opisthorchis viverrini</i> . ⁵⁰	Take praziquantel with liquids and food. Take albendazole with food (bioavailability increases with food, especially fatty meals).
Lung fluke ^{51,52} (<i>Paragonimus westermani</i> and other <i>Paragonimus</i> lung flukes)	Praziquantel 75 mg/kg PO div tid for 3 days (BII)	Triclabendazole (available from CDC) (10 mg/kg PO once or twice) may also be effective; triclabendazole should be taken with food to facilitate absorption.
Sheep liver fluke ⁵³ (<i>Fasciola hepatica</i> , <i>Fasciola gigantica</i>)	Triclabendazole (from CDC) 10 mg/kg PO for 1–2 days (BII) OR nitazoxanide PO (take with food), age 12–47 mo, 100 mg/dose bid for 7 days; age 4–11 y, 200 mg/dose bid for 7 days; age ≥12 y, 1 tab (500 mg)/dose bid for 7 days (CII)	Responds poorly to praziquantel; albendazole and mebendazole ineffective
Giardiasis (<i>Giardia intestinalis</i> [formerly <i>lamblia</i>]) ^{54–56}	Tinidazole 50 mg/kg/day (max 2 g) PO for 1 day (approved for age >3 years) (BII); OR nitazoxanide PO (take with food), age 1–3 y, 100 mg/dose bid for 3 days; age 4–11 y, 200 mg/dose bid for 3 days; age ≥12 y, 500 mg/dose bid for 3 days (BII)	Alternatives: metronidazole 15 mg/kg/day (max 250 mg/dose) PO div tid for 5–7 days (BII); albendazole 10–15 mg/kg/day (max 400 mg/dose) PO for 5 days (CII) OR mebendazole 200 mg PO tid for 5 days; OR paromomycin 30 mg/kg/day div tid for 5–10 days; furazolidone 8 mg/kg/day (max 100 mg/dose) in 4 doses for 7–10 days (not available in United States); quinacrine (refractory cases) 6 mg/kg/day PO div tid (max 100 mg/dose) for 5 days. If therapy ineffective, may try a higher dose or longer course of the same agent, or an agent in a different class; combination therapy may be considered for refractory cases.

Prolonged courses may be needed for immunocompromised patients (eg, hypogammaglobulinemia).
Treatment of asymptomatic carriers not usually indicated.

Hookworm ^{57–59} <i>Necator americanus</i> , <i>Ancylostoma duodenale</i>	Albendazole 400 mg once (repeat dose may be necessary) (BII); OR mebendazole 100 mg PO for 3 days OR 500 mg PO once; OR pyrantel pamoate 11 mg/kg (max 1 g/day) (BII) PO qd for 3 days
<i>Hymenolepis nana</i>	See Tapeworms.
<i>Isospora belli</i>	See <i>Cytospora belli</i> .

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
Leishmaniasis ^{60–67} (including kala-azar) <i>Leishmania</i> spp	<p>Visceral: liposomal AmB 3 mg/kg/day on days 1–5, day 14, and day 21 (AI); OR sodium stibogluconate (from CDC) 20 mg/kg/day IM or IV for 28 days (or longer) (BIII); OR miltefosine 2.5 mg/kg/day PO (max 150 mg/day) for 28 days (BII) (FDA-approved regimen: 50 mg PO bid for 28 days for weight 30–44 kg; 50 mg PO tid for 28 days for weight ≥ 45 kg); other AmB products available but not approved for this indication.</p> <p>Cutaneous and mucosal disease: There is no generally accepted treatment of choice; treatment decisions should be individualized.</p> <p>Uncomplicated cutaneous: combination of debridement of eschars, cryotherapy, thermotherapy, intralesional pentavalent antimony, and topical paromomycin (not available in United States).</p> <p>Complicated cutaneous: oral or parenteral systemic therapy with miltefosine 2.5 mg/kg/day PO (max 150 mg/day) for 28 days (FDA-approved regimen: 50 mg PO bid for 28 days for weight 30–44 kg; 50 mg PO tid for 28 days for weight ≥ 45 kg) (BII); OR sodium stibogluconate 20 mg/kg/day IM or IV for 20 days (BIII); OR pentamidine isethionate 2–4 mg/kg/day IV or IM qod for 4–7 doses; OR amphotericin (various regimens); OR azoles (fluconazole 200–600 mg PO qd for 6 wk; or ketoconazole or itraconazole); also intralesional and topical alternatives.</p> <p>Mucosal: sodium stibogluconate 20 mg/kg/day IM or IV for 28 days; OR AmB (Fungizone) 0.5–1 mg/kg/day IV qd or qod for cumulative total of approximately 20–45 mg/kg; OR liposomal AmB approximately</p>	<p>Consultation with a specialist familiar with management of leishmaniasis is advised strongly, especially when treating patients with HIV coinfection.</p> <p>See IDSA/ASTMH guidelines.⁶⁰</p> <p>Region where infection acquired, spp of <i>Leishmania</i>, skill of practitioner with some local therapies, and drugs available in the United States affect therapeutic choices.</p> <p>For immunocompromised patients with visceral disease, FDA-approved dosing of liposomal amphotericin is 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38, with further therapy on an individual basis.</p>

3 mg/kg/day IV qd for cumulative total of approximately 20–60 mg/kg; OR miltefosine 2.5 mg/kg/day PO (max 150 mg/day) for 28 days (FDA-approved regimen: 50 mg PO bid for 28 days for weight 30–44 kg; 50 mg PO tid for 28 days for weight ≥ 45 kg); OR pentamidine isethionate 2–4 mg/kg/day IV or IM qod or 3 times per week for ≥ 15 doses (considered a lesser alternative).

Lice

Pediculus capitis or *humanus*,
Phthirus pubis^{68,69}

Follow manufacturer's instructions for topical use: permethrin 1% (≥ 2 mo) OR pyrethrin (children aged ≥ 2 y) (BII); OR 0.5% ivermectin lotion (≥ 6 mo) (BII); OR spinosad 0.9% topical suspension (≥ 6 mo) (BII); OR benzyl alcohol lotion 5% (≥ 6 mo) (BIII); OR malathion 0.5% (children aged ≥ 2 y) (BIII); OR topical or oral ivermectin 200 mcg/kg PO once (400 mcg/kg for ≥ 15 kg); repeat 7–10 days later.

Launder bedding and clothing; for eyelash infestation, use petrolatum; for head lice, remove nits with comb designed for that purpose.
Benzyl alcohol can be irritating to skin; parasite resistance unlikely to develop.
Consult health care professional before re-treatment with ivermectin lotion; re-treatment with spinosad topical suspension usually not needed unless live lice seen 1 wk after treatment.
Administration of 3 doses of ivermectin (1 dose/wk separately by weekly intervals) may be needed to eradicate heavy infection.

Malaria^{70–74}

Plasmodium falciparum,
Plasmodium vivax,
Plasmodium ovale,
Plasmodium malariae

CDC Malaria Hotline 770/488-7788 or 855/856-4713 toll-free (Monday–Friday, 9:00 am–5:00 pm ET) or emergency consultation after hours 770/488-7100; online information at www.cdc.gov/malaria (accessed October 6, 2018). Consult infectious diseases or tropical medicine specialist if unfamiliar with malaria.

Consultation with a specialist familiar with management of malaria is advised, especially for severe malaria.
No antimalarial drug provides absolute protection against malaria; fever after return from an endemic area should prompt an immediate evaluation.
Emphasize personal protective measures (insecticides, bed nets, clothing, and avoidance of dusk–dawn mosquito exposures).

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
Prophylaxis		See https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria#5217 (accessed October 6, 2018).
For areas with chloroquine-resistant <i>P falciparum</i> or <i>P vivax</i>	A-P: 5–8 kg, ½ pediatric tab/day; ≥9–10 kg, ¾ pediatric tab/day; ≥11–20 kg, 1 pediatric tab (62.5 mg atovaquone/25 mg proguanil); ≥21–30 kg, 2 pediatric tabs; ≥31–40 kg, 3 pediatric tabs; ≥40 kg, 1 adult tab (250 mg atovaquone/100 mg proguanil) PO qd starting 1–2 days before travel and continuing 7 days after last exposure; for children <5 kg, data on A-P limited (BII); OR mefloquine: for children <5 kg, 5 mg/kg; ≥5–9 kg, 1/8 tab; ≥10–19 kg, ¼ tab; ≥20–30 kg, ½ tab; ≥31–45 kg, ¾ tab; ≥45 kg (adult dose), 1 tab PO once weekly starting the wk before arrival in area and continuing for 4 wk after leaving area (BII); OR doxycycline (patients >7 y): 2 mg/kg (max 100 mg) PO qd starting 1–2 days before arrival in area and continuing for 4 wk after leaving area (BIII); OR primaquine (check for G6PD deficiency before administering): 0.5 mg/kg base qd starting 1 day before travel and continuing for 5 days after last exposure (BII)	Avoid mefloquine for persons with a history of seizures or psychosis, active depression, or cardiac conduction abnormalities; see black box warning. Avoid A-P in severe renal impairment (CrCl <30). <i>P falciparum</i> resistance to mefloquine exists along the borders between Thailand and Myanmar and Thailand and Cambodia, Myanmar and China, and Myanmar and Laos; isolated resistance has been reported in southern Vietnam. Take doxycycline with adequate fluids to avoid esophageal irritation and food to avoid GI side effects; use sunscreen and avoid excessive sun exposure. Tafenoquine approved August 2018 for use in those ≥18 y; must test for G6PD deficiency before use; pregnancy testing recommended before use. Loading dose 200 mg daily for 3 days before travel; 200 mg weekly during travel; after return, 200 mg once 7 days after last maintenance dose; tabs must be swallowed whole. May also be used to prevent malaria in areas with chloroquine-resistant malaria.
For areas without chloroquine-resistant <i>P falciparum</i> or <i>P vivax</i>	Chloroquine phosphate 5 mg base/kg (max 300 mg base) PO once weekly, beginning the wk before arrival in area and continuing for 4 wk after leaving area (available in suspension outside the United States and Canada and at compounding pharmacies) (All). After return from heavy or prolonged (months) exposure to infected mosquitoes: consider treatment with	

primaquine (check for G6PD deficiency before administering) 0.5 mg base/kg PO qd with final 2 wk of chloroquine for prevention of relapse with *P ovale* or *P vivax*.

Treatment of disease

– Chloroquine-resistant
P falciparum or *P vivax*

Oral therapy: artemether/lumefantrine 6 doses over 3 days at 0, 8, 24, 36, 48, and 60 h; <15 kg, 1 tab/dose; ≥15–25 kg, 2 tabs/dose; ≥25–35 kg, 3 tabs/dose; >35 kg, 4 tabs/dose (BII); A-P: for children <5 kg, data limited; ≥5–8 kg, 2 pediatric tabs (62.5 mg atovaquone/25 mg proguanil) PO qd for 3 days; ≥9–10 kg, 3 pediatric tabs qd for 3 days; ≥11–20 kg, 1 adult tab (250 mg atovaquone/100 mg proguanil) qd for 3 days; >20–30 kg, 2 adult tabs qd for 3 days; >30–40 kg, 3 adult tabs qd for 3 days; >40 kg, 4 adult tabs qd for 3 days (BII); OR quinine 30 mg/kg/day (max 2 g/day) PO div tid for 3–7 days AND doxycycline 4 mg/kg/day div bid for 7 days OR clindamycin 30 mg/kg/day div tid (max 900 mg tid) for 7 days.

Parenteral therapy (check with CDC): quinidine gluconate salt 10 mg/kg (max 600 mg) IV (1 h infusion in physiologic [normal] saline solution) followed by continuous infusion of 0.02 mg/kg/min until oral therapy can be given (BII); alternative: artesunate 2.4 mg/kg/dose IV for 3 days at 0, 12, 24, 48, and 72 h (from CDC) (BI) AND a second oral agent (A-P, clindamycin, or doxycycline for aged ≥7 y).

For prevention of relapse with *P vivax*, *P ovale*: primaquine (check for G6PD deficiency before administering) 0.5 mg base/kg/day PO for 14 days.

See <https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf> (accessed October 6, 2018).

Mild disease may be treated with oral antimalarial drugs; severe disease (impaired level of consciousness, convulsion, hypotension, or parasitemia >5%) should be treated parenterally. Avoid mefloquine for treatment of malaria, if possible, given higher dose and increased incidence of adverse events.

Take clindamycin and doxycycline with plenty of liquids. Do not use primaquine or tafenoquine during pregnancy. Continuously monitor ECG, BP, and glucose in patients receiving quinidine.

Avoid artemether/lumefantrine and mefloquine in patients with cardiac arrhythmias, and avoid concomitant use of drugs that prolong QT interval. Take A-P and artemether/lumefantrine with food or milk. Use artesunate for quinidine intolerance, lack of quinidine availability, or treatment failure; www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf (accessed October 6, 2018); artemisinin should be used in combination with other drugs to avoid resistance.

For relapses of primaquine-resistant *P vivax* or *P ovale*, consider retreatment with primaquine 30 mg (base) for 28 days.

Tafenoquine approved July 2018 for prevention of relapse with *P vivax* malaria in those ≥16 y. 300 mg on the first or second day of appropriate therapy for acute malaria. Must test for G6PD deficiency before use; pregnancy testing recommended before use; tabs must be swallowed whole.

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
– Chloroquine-susceptible <i>P falciparum</i> , chloroquine-susceptible <i>P vivax</i> , <i>P ovale</i> , <i>P malariae</i>	Oral therapy: chloroquine 10 mg/kg base (max 600 mg base) PO then 5 mg/kg 6, 24, and 48 h after initial dose. Parenteral therapy: quinidine, as above. After return from heavy or prolonged (months) exposure to infected mosquitoes: consider treatment with primaquine (check for G6PD deficiency before administering) 0.5 mg base/kg PO qd with final 2 wk of chloroquine for prevention of relapse with <i>P ovale</i> or <i>P vivax</i> .	Alternative if chloroquine not available: hydroxychloroquine 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 h. For relapses of primaquine-resistant <i>P vivax</i> or <i>P ovale</i> , consider retreating with primaquine 30 mg (base) for 28 days.
<i>Mansonella ozzardi</i> , <i>Mansonella perstans</i> , <i>Mansonella streptocerca</i>	See Filariasis.	
<i>Naegleria</i>	See Amebic meningoencephalitis.	
<i>Necator americanus</i>	See Hookworm.	
<i>Onchocerca volvulus</i>	See Filariasis.	
<i>Opisthorchis</i> spp	See Flukes.	
<i>Paragonimus westermani</i>	See Flukes.	
Pinworms (<i>Enterobius vermicularis</i>)	Mebendazole 100 mg once, repeat in 2 wk; OR albendazole <20 kg, 200 mg PO once; ≥20 kg, 400 mg PO once; repeat in 2 wk (BII); OR pyrantel pamoate 11 mg/kg (max 1 g) PO once (BII); repeat in 2 wk.	Treat entire household (and if this fails, consider treating close child care/school contacts); re-treatment of contacts after 2 wk may be needed to prevent reinfection.
<i>Plasmodium</i> spp	See Malaria.	
Pneumocystis	See Chapter 8, Table 8B, <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia.	

Scabies (<i>Sarcoptes scabiei</i>) ⁷⁵	Permethrin 5% cream applied to entire body (including scalp in infants), left on for 8–14 h then bathe, repeat in 1 wk (BII); OR ivermectin 200 mcg/kg PO once weekly for 2 doses (BII); OR crotamiton 10% applied topically overnight on days 1, 2, 3, and 8, bathe in am (BII).	Launder bedding and clothing. Crotamiton treatment failure has been observed. Ivermectin safety not well established in children <15 kg and pregnant women. Reserve lindane for patients >10 y who do not respond to other therapy; concern for toxicity. Itching may continue for weeks after successful treatment; can be managed with antihistamines.
Schistosomiasis (<i>Schistosoma haematobium</i> , <i>Schistosoma japonicum</i> , <i>Schistosoma mansoni</i> , <i>Schistosoma mekongi</i> , <i>Schistosoma intercalatum</i>) ^{76–78}	Praziquantel 40 (for <i>S haematobium</i> , <i>S mansoni</i> , and <i>S intercalatum</i>) or 60 (for <i>S japonicum</i> and <i>S mekongi</i>) mg/kg/day PO div bid (if 40 mg/day) or tid (if 60 mg/day) for 1 day (AI)	Take praziquantel with food and liquids. Oxamniquine (not available in United States) 20 mg/kg PO div bid for 1 day (Brazil) or 40–60 mg/kg/day for 2–3 days (most of Africa) (BII). Re-treat with the same dose if eggs still present 6–12 wk after initial treatment.
Strongyloidiasis (<i>Strongyloides stercoralis</i>) ^{79,80}	Ivermectin 200 mcg/kg PO qd for 1–2 days (BI); OR albendazole 400 mg PO bid for 7 days (or longer for disseminated disease) (BII)	Albendazole is less effective but may be adequate if longer courses used. For immunocompromised patients (especially with hyperinfection syndrome), parenteral veterinary formulations may be lifesaving. Ivermectin safety not well established in children <15 kg and pregnant women.
Tapeworms – <i>Taenia saginata</i> , <i>Taenia solium</i> , <i>Hymenolepis nana</i> , <i>Diphyllobothrium latum</i> , <i>Dipylidium caninum</i>	Praziquantel 5–10 mg/kg PO once (25 mg/kg once; may repeat 10 days later; for <i>H nana</i>) (BII); OR niclosamide 50 mg/kg (max 2 g) PO once, chewed thoroughly (not available in United States)	Nitazoxanide may be effective (published clinical data limited) 500 mg PO bid for 3 days for age >11 y; 200 mg PO bid for 3 days for age 4–11 y; 100 mg PO bid for 3 days for age 1–3 y.

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
Toxocariasis ⁸¹ (<i>Toxocara canis</i> [dog roundworm] and <i>Toxocara cati</i> [cat roundworm])	Visceral larval migrans: albendazole 400 mg PO bid for 5 days (BII) Ocular larva migrans: albendazole 400 mg PO, 15 mg/kg/day div bid, max 800 mg/day (800 mg div bid for adults) for 2–4 wk with prednisone (0.5–1 mg/kg/day with slow taper)	Mild disease often resolves without treatment. Corticosteroids may be used for severe symptoms in visceral larval migrans. Mebendazole (100–200 mg/day PO bid for 5 days) and DEC (available only from CDC) are alternatives.
Toxoplasmosis (<i>Toxoplasma gondii</i>) ^{82–84}	Pyrimethamine 2 mg/kg/day PO div bid for 2 days (max 100 mg) then 1 mg/kg/day (max 25 mg/day) PO qd AND sulfadiazine 120 mg/kg/day PO div qid (max 6 g/day); with supplemental folinic acid and leucovorin 10–25 mg with each dose of pyrimethamine (AI) for 3–6 wk. See Chapter 5 for congenital infection. For treatment in pregnancy, spiramycin 50–100 mg/kg/day PO div qid (available as investigational therapy through the FDA at 301/796-0563) (CII).	Experienced ophthalmologic consultation encouraged for treatment of ocular disease. Treatment continued for 2 wk after resolution of illness (approximately 3–6 wk); concurrent corticosteroids given for ocular or CNS infection. Prolonged therapy if HIV positive. Take pyrimethamine with food to decrease GI adverse effects; sulfadiazine should be taken on an empty stomach with water. Clindamycin, azithromycin, or atovaquone plus pyrimethamine may be effective for patients intolerant of sulfa-containing drugs. Consult expert advice for treatment during pregnancy and management of congenital infection.
Traveler's diarrhea ^{85–88}	Azithromycin 10 mg/kg qd for 1–3 days (AII); OR rifaximin 200 mg PO tid for 3 days (ages ≥ 12 y) (BIII); OR ciprofloxacin (BII)	Azithromycin preferable to ciprofloxacin for travelers to Southeast Asia and India given high prevalence of fluoroquinolone-resistant <i>Campylobacter</i> . Do not use rifaximin for <i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> and other causes of invasive diarrhea. Antibiotic regimens may be combined with loperamide (≥ 2 y).
Trichinellosis (<i>Trichinella spiralis</i>) ⁸⁹	Albendazole 400 mg PO bid for 8–14 days (BII) OR mebendazole 200–400 mg PO tid for 3 days, then 400–500 mg PO tid for 10 days	Therapy ineffective for larvae already in muscles. Anti-inflammatory drugs, steroids for CNS or cardiac involvement or severe symptoms.

Trichomoniasis (<i>Trichomonas vaginalis</i>) ⁹⁰	Tinidazole 50 mg/kg (max 2 g) PO for 1 dose (BII) OR metronidazole 2 gm PO for 1 dose OR metronidazole 500 mg PO bid for 7 days (BII)	Treat sex partners simultaneously. Metronidazole resistance occurs and may be treated with higher-dose metronidazole or tinidazole.
<i>Trichuris trichiura</i>	See Whipworm (Trichuriasis).	
Trypanosomiasis		
– Chagas disease ^{26–28} (<i>Trypanosoma cruzi</i>)	Benznidazole PO: age <12 y, 5–7.5 mg/kg/day div bid for 60 days; ≥12 y, 5–7 mg/kg/day div bid for 60 days (BIII); OR nifurtimox PO (from CDC): age 1–10 y, 15–20 mg/kg/day div tid or qid for 90 days; 11–16 y, 12.5–15 mg/kg/day div tid or qid for 90 days; ≥17 y, 8–10 mg/kg/day div tid–qid for 90–120 days (BIII)	Therapy recommended for acute and congenital infection, reactivated infection, and chronic infection in children aged <18 y; consider in those up to age 50 with chronic infection without advanced cardiomyopathy. Benznidazole has been approved by the FDA for use in children ages 2–12 y; https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8983d6a0-f63f-4f8e-bba4-38223f39e29b (accessed October 6, 2018). Side effects are common but occur less often in younger patients. Both drugs contraindicated in pregnancy.
Sleeping sickness ^{91–94} – Acute (hemolympathic) stage (<i>Trypanosoma brucei gambiense</i> [West African]; <i>T. brucei rhodesiense</i> [East African])	<i>Tb gambiense</i> : pentamidine isethionate 4 mg/kg/day (max 300 mg) IM or IV for 7–10 days (BII) <i>Tb rhodesiense</i> : suramin (from CDC) 100–200 mg test dose IV, then 20 mg/kg (max 1 g) IV on days 1, 3, 7, 14, and 21 (BII)	CSF examination required for all patients to assess CNS involvement. Consult with infectious diseases or tropical medicine specialist if unfamiliar with trypanosomiasis. Examination of the buffy coat of peripheral blood may be helpful. <i>Tb gambiense</i> may be found in lymph node aspirates.

B. PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

Disease/Organism	Treatment (evidence grade)	Comments
– Late (CNS) stage (<i>Trypanosoma brucei gambiense</i> [West African]; <i>T brucei rhodesiense</i> [East African])	<i>Tb gambiense</i> : eflornithine (from CDC) 400 mg/kg/day IV div bid for 7 days PLUS nifurtimox 5 mg/kg PO tid for 10 days (BIII); OR eflornithine 400 mg/kg/day IV div qid for 14 days; OR melarsoprol (from CDC) 2.2 mg/day (max 180 mg) in 10 daily injections (BIII). <i>Tb rhodesiense</i> : melarsoprol, 2–3.6 mg/kg/day IV for 3 days; after 7 days, 3.6 mg/kg/day for 3 days; after 7 days, 3.6 mg/kg/day for 3 days; corticosteroids often given with melarsoprol to decrease risk of CNS toxicity.	CSF examination needed for management (double-centrifuge technique recommended); perform repeat CSF examinations every 6 mo for 2 y to detect relapse.
<i>Uncinaria stenocephala</i>	See Cutaneous larva migrans.	
Whipworm (Trichuriasis) <i>Trichuris trichiura</i>	Mebendazole 100 mg PO bid for 3 days OR 500 mg PO qd for 3 days; OR albendazole 400 mg PO for 3 days; OR ivermectin 200 mcg/kg/day PO qd for 3 days (BII)	Treatment can be given for 5–7 days for heavy infestation.
<i>Wuchereria bancrofti</i>	See Filariasis.	
Yaws	Azithromycin 30 mg/kg max 2 g once (also treats bejel and pinta)	Alternative regimens include IM benzathine penicillin and second-line agents doxycycline, tetracycline, and erythromycin.

11. Alphabetic Listing of Antimicrobials

NOTES

- Higher dosages in a dose range are generally indicated for more serious infections. For pathogens with higher minimal inhibitory concentrations against beta-lactam antibiotics, a more prolonged infusion of the antibiotic will allow increased antibacterial effect (see Chapter 3).
- Maximum dosages for adult-sized children (eg, ≥ 40 kg) are based on US Food and Drug Administration (FDA)-approved product labeling or post-marketing data.
- Antiretroviral medications are not listed in this chapter. See Chapter 9.
- Drugs with FDA-approved dosage, or dosages based on randomized clinical trials, are given a Level of Evidence I. Dosages for which data are collected from noncomparative trials or small comparative trials are given a Level of Evidence II. Dosages based on expert or consensus opinion or case reports are given a Level of Evidence III.
- If no oral liquid form is available, round the child's dose to a combination of available solid dosage forms. Consult a pediatric pharmacist for recommendations on mixing with food (eg, crushing tablets, emptying capsule contents) and the availability of extemporaneously compounded liquid formulations.
- Cost estimates are in US dollars per course, or per month for maintenance regimens. Estimates are based on wholesale acquisition costs at the editor's institution. These may differ from that of the reader. Legend: \$ = <\$100, \$\$ = \$100–\$400, \$\$\$ = \$401–\$1,000, \$\$\$\$ = >\$1,000, \$\$\$\$\$ = >\$10,000.
- There are some agents that we do not recommend even though they may be available. We believe they are significantly inferior to those we do recommend (see chapters 5–10) and could possibly lead to poor outcomes if used. Such agents are not listed.
- Abbreviations:** AOM, acute otitis media; AUC:MIC, area under the curve–minimum inhibitory concentration; bid, twice daily; BSA, body surface area; CABP, community-acquired bacterial pneumonia; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; cap, capsule or caplet; CDC, Centers for Disease Control and Prevention; CF, cystic fibrosis; CMV, cytomegalovirus; CNS, central nervous system; CrCl, creatinine clearance; div, divided; DR, delayed release; EC, enteric coated; ER, extended release; FDA, US Food and Drug Administration; GI, gastrointestinal; hs, bedtime; HSV, herpes simplex virus; IBW, ideal body weight; IM, intramuscular; IV, intravenous; IVesic, intravesical; IVPB, intravenous piggyback (premixed bag); LD, loading dose; MAC, *Mycobacterium avium* complex; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S aureus*; NS, normal saline (physiologic saline solution); oint, ointment; OPC, oropharyngeal candidiasis; ophth, ophthalmic; PCP, *Pneumocystis* pneumonia; PEG, pegylated; PIP, piperacillin; PMA, post-menstrual age; PO, oral; pwd, powder; qd, once daily; qhs, every bedtime; qid, 4 times daily; RSV,

respiratory syncytial virus; RTI, respiratory tract infection; SIADH, syndrome of inappropriate antidiuretic hormone; SMX, sulfamethoxazole; soln, solution; SPAG-2, small particle aerosol generator model-2; SQ, subcutaneous; SSSI, skin and skin structure infection; STI, sexually transmitted infection; susp, suspension; tab, tablet; TB, tuberculosis; TBW, total body weight; tid, 3 times daily; TMP, trimethoprim; top, topical; UTI, urinary tract infection; vag, vaginal; VZV, varicella-zoster virus.

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Acyclovir, ^a Zovirax (See Valacyclovir as another oral formulation to achieve therapeutic acyclovir serum concentrations.)	500-, 1,000-mg vials (\$)	IV	15–45 mg/kg/day (I) (See chapters 5 and 9.) Max 1,500 mg/m ² /day (II) (See Chapter 12.)	q8h
	200-mg/5-mL susp (\$\$)	PO	900 mg/m ² /day (I)	q8h
	200-mg cap (\$)		60–80 mg/kg/day, max 3,200 mg/day (I)	q6–8h
	400-, 800-mg tab (\$)		Adult max 4 g/day for VZV (I) (See chapters 5 and 9.)	
Albendazole, Albenza	200-mg tab (\$\$\$\$-\$\$\$\$\$)	PO	15 mg/kg/day, max 800 mg/day (I) (See Chapter 10 for other dosages.)	q12h
Amikacin, ^a Amikin	500-, 1,000-mg vials (\$)	IV, IM	15–22.5 mg/kg/day ^b (I) (See Chapter 1.) 30–35 mg/kg/day ^b for CF (II)	q8–24h q24h
		IVesic	50–100 mL of 0.5 mg/mL in NS (III)	q12h
Amoxicillin, ^a Amoxil	125-, 200-, 250-, 400-mg/5-mL susp (\$)	PO	Standard dose: 40–45 mg/kg/day (I) High dose: 80–90 mg/kg/day (I)	q8–12h q12h
	125-, 250-mg chew tab (\$)		150 mg/kg/day for penicillin-resistant	q8h
	250-, 500-mg cap (\$)		<i>Streptococcus pneumoniae</i> otitis media (III)	
	500-, 875-mg tab (\$)		Max 4,000 mg/day (III)	
Amoxicillin ER, Moxatag	775-mg tab (\$\$)	PO	≥ 12 y and adults 775 mg/day (I)	q24h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Amoxicillin/clavulanate, ^a Augmentin	16:1 Augmentin XR: 1,000/62.5-mg tab (\$\$)	PO	16:1 formulation: ≥ 40 kg and adults 4,000-mg amoxicillin/day (not per kg) (I)	q12h
	14:1 Augmentin ES: 600/42.9-mg/5-mL susp (\$)	PO	14:1 formulation: 90-mg amoxicillin/kg/day (I), max 4,000 mg/day (III)	q12h
	7:1 Augmentin (\$): 875/125-mg tab 200/28.5-, 400/57-mg chew tab 200/28.5-, 400/57-mg/5-mL susp	PO	7:1 formulation: 25- or 45-mg amoxicillin/kg/day, max 1,750 mg/day (I)	q12h
	4:1 Augmentin: 500/125-mg tab (\$) 125/31.25-mg/5-mL susp (\$\$\$) 250/62.5-mg/5-mL susp (\$)	PO	20- or 40-mg amoxicillin component/kg/day (max 1,500 mg/day) (I)	q8h
	2:1 Augmentin: 250 mg/125-mg tab (\$)	PO	2:1 formulation: ≥ 40 kg: 750-mg amoxicillin/day (not per kg) (I)	q8h
Amphotericin B deoxycholate, ^a Fungizone	50-mg vial (\$\$)	IV	1–1.5 mg/kg pediatric and adults (I), no max 0.5 mg/kg for <i>Candida</i> esophagitis or cystitis (II)	q24h
		IVesic	50–100 mcg/mL in sterile water \times 50–100 mL (III)	q8h
Amphotericin B, lipid complex, Abelcet	100-mg/20-mL vial (\$\$\$\$)	IV	5 mg/kg pediatric and adult dose (I) No max	q24h
Amphotericin B, liposomal, AmBisome	50-mg vial (\$\$\$\$)	IV	5 mg/kg pediatric and adult dose (I) No max	q24h
Ampicillin sodium ^a	125-, 250-, 500-mg vial (\$) 1-, 2-, 10-g vial (\$)	IV, IM	50–200 mg/kg/day, max 8 g/day (I) 300–400 mg/kg/day, max 12 g/day endocarditis/meningitis (III)	q6h q4–6h

Ampicillin trihydrate ^a	500-mg cap (\$)	PO	50–100 mg/kg/day if <20 kg (I) ≥20 kg and adults 1–2 g/day (I)	q6h
Ampicillin/sulbactam, ^a Unasyn	1/0.5-, 2/1-, 10/5-g vial (\$)	IV, IM	200-mg ampicillin component/kg/day (I) ≥40 kg and adults 4–max 8 g/day (I)	q6h
Anidulafungin, Eraxis	50-, 100-mg vial (\$\$)	IV	1.5–3 mg/kg LD, then 0.75–1.5 mg/kg (II) Max 200-mg LD, then 100 mg (I)	q24h
Atovaquone, ^a Mepron	750-mg/5-mL susp (\$\$\$)	PO	30 mg/kg/day if 1–3 mo or >24 mo (I) 45 mg/kg/day if >3–24 mo (I) Max 1,500 mg/day (I)	q12h q24h for prophylaxis
Atovaquone and proguanil, ^a Malarone	62.5/25-mg pediatric tab (\$-\$\$) 250/100-mg adult tab (\$\$)	PO	Prophylaxis for malaria: 11–20 kg: 1 pediatric tab, 21–30 kg: 2 pediatric tabs, 31–40 kg: 3 pediatric tabs, >40 kg: 1 adult tab (I) Treatment: 5–8 kg: 2 pediatric tabs, 9–10 kg: 3 pediatric tabs, 11–20 kg: 1 adult tab, 21–30 kg: 2 adult tabs, 31–40 kg: 3 adult tabs, >40 kg: 4 adult tabs (I)	q24h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Azithromycin, ^a Zithromax	250-, 500-, 600-mg tab (\$) 100-, 200-mg/5-mL susp (\$) 1-g packet for susp (\$)	PO	Otitis: 10 mg/kg/day for 1 day, then 5 mg/kg for 4 days; or 10 mg/kg/day for 3 days; or 30 mg/kg once (I). Pharyngitis: 12 mg/kg/day for 5 days, max 2,500-mg total dose (I). Sinusitis: 10 mg/kg/day for 3 days, max 1.5-g total dose (I). CABP: 10 mg/kg for 1 day, then 5 mg/kg/day for 4 days (max 1.5-g total dose), or 60 mg/kg once of ER (Zmax) susp, max 2 g (I). MAC prophylaxis: 5 mg/kg/day, max 250 mg (I), or 20 mg/kg, max 1.2 g weekly. Adult dosing for RTI: 500 mg day 1, then 250 mg daily for 4 days or 500 mg for 3 days. Adult dosing for STI: Non-gonorrhea: 1 g once. Gonorrhea: 2 g once. See other indications in Chapter 6.	q24h
	500-mg vial (\$)	IV	10 mg/kg, max 500 mg (II)	q24h
Aztreonam, ^a Azactam	1-, 2-g vial (\$-\$-\$-\$)	IV, IM	90–120 mg/kg/day, max 8 g/day (I)	q6–8h
Baloxavir (Xofluza)	20-, 40-mg tab (\$-\$)	PO	≥ 12 y: 40–<80 kg: 40 mg (not per kg), ≥ 80 kg: 80 mg (not per kg)	One time
Benznidazole	12.5-, 100-mg tab	PO	2–12 y: 5–8 mg/kg/day (I)	q12h
Bezlotoxumab, Zinplava	1-g vial (\$\$\$\$)	IV	Adults: 10 mg/kg	One time
Capreomycin, Capastat	1-g vial (\$\$\$\$)	IV, IM	15–30 mg/kg (III), max 1 g (I)	q24h

Caspofungin, ^a Cancidas	50-, 70-mg vial (\$\$\$)	IV	Load with 70 mg/m ² once, then 50 mg/m ² , max 70 mg (I)	q24h
Cefaclor, ^a Ceclor	250-mg/5-mL susp (\$\$) 250-, 500-mg cap (\$) 500-mg ER tab (\$\$)	PO	20–40 mg/kg/day, max 1 g/day (I)	q12h
Cefadroxil, ^a Duricef	250-, 500-mg/5-mL susp (\$) 500-mg cap (\$) 1-g tab (\$)	PO	30 mg/kg/day, max 2 g/day (I)	q12–24h
Cefazolin, ^a Ancef	0.5-, 1-, 10-g vial (\$)	IV, IM	25–100 mg/kg/day (I)	q8h
			100–150 mg/kg/day for serious infections (III), max 12 g/day	q6h
Cefdinir, ^a Omnicef	125-, 250-mg/5-mL susp (\$) 300-mg cap (\$)	PO	14 mg/kg/day, max 600 mg/day (I)	q12–24h
Cefepime, ^a Maxipime	1-, 2-g vial (\$) 1-, 2-g IVPB (\$\$)	IV, IM	100 mg/kg/day, max 4 g/day (I)	q12h
			150 mg/kg/day empiric therapy of fever with neutropenia, max 6 g/day (I)	q8h
Cefixime, Suprax	100-, 200-mg/5-mL susp ^a (\$\$) 100-, 200-mg chew tab (\$\$) 400-mg cap (\$\$)	PO	8 mg/kg/day, max 400 mg/day (I)	q24h
			For convalescent oral therapy of serious infections, up to 20 mg/kg/day (III)	q12h
Cefotaxime, ^a Claforan	0.5-, 1-, 2-, 10-g vial (\$)	IV, IM	150–180 mg/kg/day, max 8 g/day (I)	q8h
			200–225 mg/kg/day for meningitis, max 12 g/day (I)	q6h
Cefotetan, ^a Cefotan	1-, 2-g vial (\$\$) 1-, 2-g IVPB (\$\$)	IV, IM	60–100 mg/kg/day (II), max 6 g/day (I)	q12h
Cefoxitin, ^a Mefoxin	1-, 2-, 10-g vial (\$)	IV, IM	80–160 mg/kg/day, max 12 g/day (I)	q6–8h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Cefpodoxime, ^a Vantin	100-mg/5-mL susp (\$) 100-, 200-mg tab (\$)	PO	10 mg/kg/day, max 400 mg/day (I)	q12h
Cefprozil, ^a Cefzil	125-, 250-mg/5-mL susp (\$) 250-, 500-mg tab (\$)	PO	15–30 mg/kg/day, max 1 g/d (I)	q12h
Ceftaroline, Teflaro	400-, 600-mg vial (\$\$\$)	IV	≥ 2 mo– < 2 y: 24 mg/kg/day (I) ≥ 2 y: 36 mg/kg/day (I) > 33 kg: 1.2 g/day (I) Adults: 1.2 g/day (I) 45–60 mg/kg/day, max 3 g/day \pm prolonged infusion for CF (II)	q8h q8–12h q12h q8h
Ceftazidime, ^a Tazicef, Fortaz	0.5-, 1-, 2-, 6-g vial (\$) 1-, 2-g IVPB (\$\$)	IV, IM	90–150 mg/kg/day, max 6 g/day (I)	q8h
		IV	200–300 mg/kg/day for serious <i>Pseudomonas</i> infection, max 12 g/day (II)	q8h
Ceftazidime/avibactam, Avycaz	2-g/0.5-g vial (\$\$\$\$)	IV	Adults 7.5 g (6 g/1.5 g)/day (I) Investigational in children	q8h
Ceftolozane/tazobactam, Zerbaxa	1.5-g (1-g/0.5-g) vial (\$\$\$\$)	IV	Adults 4.5 g (3 g/1.5 g)/day (I) Investigational in children	q8h
Ceftriaxone, ^a Rocephin	0.25-, 0.5-, 1-, 2-, 10-g vial (\$)	IV, IM	50–75 mg/kg/day, max 2 g/day (I) Meningitis: 100 mg/kg/day, max 4 g/day (I) 50 mg/kg, max 1 g, 1–3 doses q24h for AOM (II)	q24h q12h
Cefuroxime, ^a Ceftin	250-, 500-mg tab (\$)	PO	20–30 mg/kg/day, max 1 g/day (I) For bone and joint infections, up to 100 mg/kg/day, max 3 g/day (III)	q12h q8h
Cefuroxime, ^a Zinacef	0.75-, 1.5-g vial (\$)	IV, IM	100–150 mg/kg/day, max 6 g/day (I)	q8h

Cephalexin, ^a Keflex	125-, 250-mg/5-mL susp (\$)	PO	25–50 mg/kg/day (I)	q12h
	250-, 500-mg cap, tab (\$) 750-mg cap (\$\$)		75–100 mg/kg/day for bone and joint, or severe infections (II), max 4 g/day (I)	q6–8h
Chloroquine phosphate, ^a Aralen	250-, 500-mg (150-, 300-mg base) tabs (\$-\$\$)	PO	See Chapter 10.	
Cidofovir, ^a Vistide	375-mg vial (\$\$\$)	IV	5 mg/kg (III); see Chapter 9.	Weekly
Ciprofloxacin, ^a Cipro	250-, 500-mg/5-mL susp (\$) 250-, 500-, 750-mg tab (\$)	PO	20–40 mg/kg/day, max 1.5 g/day (I)	q12h
	100-mg tab (\$)		Adult females 200 mg/day for 3 days (I)	
	200-, 400-mg IVPB (\$)	IV	20–30 mg/kg/day, max 1.2 g/day (I)	q12h
Ciprofloxacin extended release, ^a Cipro XR	500-, 1,000-mg ER tab (\$)	PO	Adults 500–1,000 mg (I)	q24h
Clarithromycin, ^a Biaxin	125-, 250-mg/5-mL susp (\$-\$\$) 250-, 500-mg tab (\$)	PO	15 mg/kg/day, max 1 g/day (I)	q12h
	500-mg ER tab (\$)		Adults 1 g (I)	q24h
Clindamycin, ^a Cleocin	75 mg/5-mL soln (\$) 75-, 150-, 300-mg cap (\$)	PO	10–25 mg/kg/day, max 1.8 g/day (I) 30–40 mg/kg/day for CA-MRSA, intra-abdominal infection, or AOM (III)	q8h
	0.3-, 0.6-, 0.9-, 9-g vial (\$) 0.3-, 0.6-, 0.9-g IVPB (\$)	IV, IM	20–40 mg/kg/day, max 2.7 g/day (I)	q8h
Clotrimazole, ^a Mycelex	10-mg lozenge (\$)	PO	≥3 y and adults: dissolve lozenge in mouth (I).	5 times daily
Colistimethate, ^a Coly-Mycin M	150-mg (colistin base) vial (\$-\$\$) 1-mg base = 2.7-mg colistimethate	IV, IM	2.5- to 5-mg base/kg/day based on IBW (I) Up to 5- to 7-mg base/kg/day (III)	q8h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Cycloserine, Seromycin	250-mg cap (\$\$\$\$)	PO	10–20 mg/kg/day (III) Adults max 1 g/day (I)	q12h
Daclatasvir, Daklinza	30-, 60-, 90-mg tab (\$\$\$\$\$)	PO	Adults: 30–90 mg + sofosbuvir ± ritonavir (I). See Chapter 9, Hepatitis C virus.	q24h
Dalbavancin, Dalvance	500-mg vial (\$\$\$\$)	IV	Adults 1,500 mg (I) 6–<18 y: 18 mg/kg (max 1,500 mg) (II) 3 mo–< 6 y: 22.5 mg/kg (II)	One time
Dapsone ^a	25-, 100-mg tab (\$)	PO	2 mg/kg, max 100 mg (I)	q24h
			4 mg/kg, max 200 mg (I)	Once weekly
Daptomycin, ^a Cubicin	500-mg vial (\$\$\$)	IV	For SSSI (I): 1–2 y: 10 mg/kg. 2–6 y: 9 mg/kg. 7–11 y: 7 mg/kg. 12–17 y: 5 mg/kg. For <i>Staphylococcus aureus</i> bacteremia (I): 1–6 y: 12 mg/kg. 7–11 y: 9 mg/kg. 12–17 y: 7 mg/kg. For other indications, see Chapter 6. Adults: 4–6 mg/kg TBW (I).	q24h
Dasabuvir/ombitasvir/ paritaprevir/ritonavir, Viekira XR	200-/8.33-/50-/33.33-mg ER tab (\$\$\$\$\$)	PO	Adults 3 tabs ± ribavirin (I). See Chapter 9, Hepatitis C virus.	q24h
Delaflaxacin, Baxdela	450-mg tab (\$\$\$\$)	PO	Adults 450 mg (I)	q12h
	300-mg vial (\$\$\$\$)	IV	Adults 300 mg (I)	

Demeclocycline, ^a Declomycin	150-, 300-mg tab (\$\$)	PO	≥8 y: 7–13 mg/kg/day, max 600 mg/day (I). Dosage differs for SIADH.	q6–12h
Dicloxacinil, ^a Dynapen	250-, 500-mg cap (\$)	PO	12–25 mg/kg/day (adults 0.5–1 g/day) (I) For bone and joint infections, up to 100 mg/kg/ day, max 2 g/day (III)	q6h
Doxycycline, Vibramycin	25-mg/5-mL susp ^a (\$) 50-mg/5-mL syrup (\$\$) 20-, 50-, 75-, 100-mg tab/cap ^a (\$) 150-mg tab ^a (\$\$) 200-mg tab ^a (\$\$\$)	PO	≥8 y: 4.4 mg/kg/day LD on day 1, then 2.2–4.4 mg/kg/day, max 200 mg/day (I)	q12–24h
	100-mg vial ^a (\$\$)	IV		
Elbasvir/Grazoprevir, Zepatier	50-mg/100-mg tab (\$\$\$\$)	PO	Adults 1 tab	q24h
Entecavir, Baraclude See Chapter 9, Hepatitis B virus.	0.05-mg/mL soln (\$\$\$) 0.5-, 1-mg tab (\$\$\$\$)	PO	2–<16 y (I) (Double the following doses if previous lamivudine exposure.): 10–11 kg: 0.15 mg >11–14 kg: 0.2 mg >14–17 kg: 0.25 mg >17–20 kg: 0.3 mg >20–23 kg: 0.35 mg >23–26 kg: 0.4 mg >26–30 kg: 0.45 mg >30 kg: 0.5 mg ≥16 y: 0.5 mg (I)	q24h
Ertapenem, Invez	1-g vial (\$\$\$)	IV, IM	30 mg/kg/day, max 1 g/day (I) ≥13 y and adults: 1 g/day (I)	q12h q24h
Erythromycin base	250-, 500-mg tab ^a (\$\$\$) 250-mg EC cap ^a (\$) 250-, 333-, 500-mg DR tab (Ery-Tab) (\$\$)	PO	50 mg/kg/day, max 4 g/day (I). Dose differs for GI prokinesis.	q6–8h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Erythromycin ethylsuccinate, ^a EES, EryPed	200-, 400-mg/5-mL susp (\$\$-\$\$\$) 400-mg tab (\$\$\$)	PO	50 mg/kg/day, max 4 g/day (I). Dose differs for GI prokinesis.	q6–8h
Erythromycin lactobionate, Erythrocin	0.5-g vial (\$\$\$)	IV	20 mg/kg/day, max 4 g/day (I)	q6h
Erythromycin stearate	250-mg tab (\$\$-\$\$\$)	PO	50 mg/kg/day, max 4 g/day (I)	q6–8h
Ethambutol, ^a Myambutol	100-, 400-mg tab (\$)	PO	15–25 mg/kg, max 2.5 g (I)	q24h
Ethionamide, Trecator	250-mg tab (\$\$)	PO	15–20 mg/kg/day, max 1 g/day (I)	q12–24h
Famciclovir, ^a Famvir	125-, 250-, 500-mg tab (\$)	PO	Adults 0.5–2 g/day (I)	q8–12h
Fluconazole, ^a Diflucan	50-, 100-, 150-, 200-mg tab (\$) 50-, 200-mg/5-mL susp (\$)	PO	6–12 mg/kg/day, max 800 mg/day (I). 800–1,000 mg/day may be used for some CNS fungal infections. See Chapter 8.	q24h
	200-, 400-mg IVPB (\$)	IV		
Flucytosine, ^a Ancobon	250-, 500-mg cap (\$\$\$\$)	PO	100 mg/kg/day (I) ^c	q6h
Foscarnet, Foscavir	6-g vial (\$\$\$\$)	IV	CMV/VZV: 180 mg/kg/day (I)	q8–12h
			CMV suppression: 90–120 mg/kg (I)	q24h
			HSV: 120 mg/kg/day (I)	q8–12h
Ganciclovir, ^a Cytovene	500-mg vial (\$\$)	IV	CMV treatment: 10 mg/kg/day (I)	q12h
			CMV suppression: 5 mg/kg (I)	q24h
			VZV: 10 mg/kg/day (III)	q12h

Gentamicin ^{a,c}	10-mg/mL vial (\$) 40-mg/mL vial (\$)	IV, IM	3–7.5 mg/kg/day, CF 7–10 mg/kg/day. See Chapter 1 for q24h dosing.	q8–24h
		I/Vesic	0.5 mg/mL in NS x 50–100 mL (III)	q12h
Glecaprevir/Pibrentasvir, Mavyret	100-mg/40-mg tab (\$\$\$\$\$)	PO	Adults 300 mg/120 mg (I)	q24h
Griseofulvin microsize, ^a Grifulvin V	125-mg/5-mL susp (\$)	PO	20–25 mg/kg (II), max 1 g (I)	q24h
	500-mg tab (\$\$)			
Griseofulvin ultramicrosize, ^a Gris-PEG	125-, 250-mg tab (\$)	PO	10–15 mg/kg (II), max 750 mg (I)	q24h
Imipenem/cilastatin, ^a Primaxin	250/250-, 500/500-mg vial (\$\$)	IV, IM	60–100 mg/kg/day, max 4 g/day (I) IM form not approved for <12 y	q6h
Interferon-PEG Alfa-2a, Pegasys Alfa-2b, PegIntron	All (\$\$\$\$) 180-mcg vials, prefilled syringes 50-mcg vial	SQ	See Chapter 9, Hepatitis B and C virus.	Weekly
Isavuconazonium (isavuconazole), Cresemba	186-mg cap (100-mg base) (\$\$\$\$)	PO	Adults 200 mg base per <i>dose</i> PO/IV (base = isavuconazole)	q8h x 6 doses, then q24h
	372-mg vial (200-mg base) (\$\$\$\$)	IV		
Isoniazid, ^a Nydrazid	50-mg/5-mL soln (\$\$)	PO	10–15 mg/kg/day, max 300 mg/day (I)	q12–24h
	100-, 300-mg tab (\$) 1,000-mg vial (\$\$)	IV, IM	With directly observed biweekly therapy, dosage is 20–30 mg/kg, max 900 mg/dose (I).	Twice weekly
Itraconazole, Sporanox	50-mg/5-mL soln (\$\$) (Preferred over capsules; see Chapter 8.) 100-mg cap ^a (\$)	PO	10 mg/kg/day (II), max 200 mg/day	q12h
			5 mg/kg/day for chronic mucocutaneous <i>Candida</i> (II)	q24h
Ivermectin, ^a Stromectol	3-mg tab (\$)	PO	0.15–0.2 mg/kg, no max (I)	1 dose
Ketoconazole, ^a Nizoral	200-mg tab (\$)	PO	≥ 2 y: 3.3–6.6 mg/kg, max 400 mg (I)	q24h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Letemovir, Prevymis	240-, 480-mg tab (\$\$\$\$) 240-, 480-mg vial (\$\$\$\$)	PO IV	Adults 480 mg (I). Adults 240 mg if concomitant cyclosporine therapy (I). See Chapter 9, Cytomegalovirus.	q24h
Levofloxacin, ^a Levaquin	125-mg/5-mL soln (\$) 250-, 500-, 750-mg tab (\$) 500-, 750-mg vial (\$) 250-, 500-, 750-mg IVPB (\$)	PO, IV	For postexposure anthrax prophylaxis (I): <50 kg: 16 mg/kg/day, max 500 mg/day ≥50 kg: 500 mg For respiratory infections: <5 y: 20 mg/kg/day (II) ≥5 y: 10 mg/kg/day, max 500 mg/day (II)	q12h q24h q12h q24h
Linezolid, ^a Zyvox	100-mg/5-mL susp (\$\$) 600-mg tab (\$) 200-, 600-mg IVPB (\$\$)	PO, IV	Pneumonia, complicated SSSI: (I) Birth–11 y: 30 mg/kg/day >11 y: 1.2 g/day Uncomplicated SSSI: (I) Birth–<5 y: 30 mg/kg/day 5–11 y: 20 mg/kg/day >11–18 y: 1.2 g/day	q8h q12h q8h q12h q12h
Mebendazole See Chapter 10.	100-mg chew tab, Emverm (\$\$\$–\$\$\$\$)	PO	≥2y: 100 mg (not per kg) (I) 1 dose for pinworm	q12h for 3 days
Mefloquine, ^a Lariam	250-mg tab (\$)	PO	See Chapter 10, Malaria.	
Meropenem, ^a Merrem	0.5-, 1-g vial (\$)	IV	60 mg/kg/day, max 3 g/day (I) 120 mg/kg/day meningitis, max 6 g/day (I)	q8h q8h
Meropenem/Vaborbactam, Vabomere	2-g vial (contains 1-g each meropenem + vaborbactam) (\$\$\$\$)	IV	Adults 6 g meropenem/day (I) Investigational in children	q8h

Methenamine hippurate, ^a Hiprex	1-g tab (\$)	PO	6–12 y: 1–2 g/day (I) > 12 y: 2 g/day (I)	q12h
Methenamine mandelate ^a	0.5-, 1-g tab (\$)		< 6 y: 75 mg/kg/day (I) 6–12 y: 2 g/day (I) > 12 y: 4 g/day (I)	q6h
Metronidazole, ^a Flagyl	250-, 500-mg tab (\$) 250-mg/5-mL susp (\$) 375-mg cap (\$\$)	PO	30–50 mg/kg/day, max 2,250 mg/day (I)	q8h
	500-mg IVPB (\$)	IV	22.5–40 mg/kg/day (II), max 4 g/day (I)	q6–8h
Micafungin, Mycamine	50-, 100-mg vial (\$\$\$)	IV	2–4 mg/kg, max 150 mg (I)	q24h
Miltefosine, Impavido	50-mg cap. Available from CDC. See Chapter 10.	PO	2.5 mg/kg/day (II) ≥ 12 y (I): 30–44 kg: 100 mg/day ≥ 45 kg: 150 mg/day	bid bid tid
Minocycline, Minocin	50-, 75-, 100-mg cap ^a (\$) 50-, 75-, 100-mg tab ^a (\$) 100-mg vial (\$\$\$)	PO, IV	≥ 8 y: 4 mg/kg/day, max 200 mg/day (I)	q12h
Minocycline, Solodyn ^a	55-, 65-, 80-, 105-, 115-mg ER tab (\$\$\$)	PO	≥ 12 y: 1 mg/kg/day for acne (I).	q24h
Ximino ^a	45-, 90-, 135-mg ER cap (\$\$\$)		Round dose to nearest strength tab or cap.	
Moxidectin	2-mg tab	PO	≥ 12 y: 8 mg (I)	Once
Moxifloxacin, ^a Avelox	400-mg tab (\$) 400-mg IVPB (\$\$)	PO, IV	Adults 400 mg/day (I)	q24h
Nafcillin, ^a Nallpen	1-, 2-, 10-g vial (\$\$)	IV, IM	150–200 mg/kg/day (II) Max 12 g/day div q4h (I)	q6h
Neomycin sulfate ^a	500-mg tab (\$)	PO	50–100 mg/kg/day (II), max 12 g/day (I)	q6–8h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Nitazoxanide, Alinia	100-mg/5-mL susp (\$\$\$) 500-mg tab (\$\$\$)	PO	1–3 y: 200 mg/day (I) 4–11 y: 400 mg/day (I) ≥12 y: 1 g/day (I)	q12h
Nitrofurantoin, ^a Furadantin	25-mg/5-mL susp (\$\$)	PO	5–7 mg/kg/day, max 400 mg/day (I) 1–2 mg/kg for UTI prophylaxis (I)	q6h q24h
Nitrofurantoin macrocrystals, ^a Macrodan	25-, 50-, 100-mg cap (\$)	PO	Same as susp	
Nitrofurantoin monohydrate and macro-crystalline, ^a Macrobid	100-mg cap (\$)	PO	>12 y: 200 mg/day (I)	q12h
Nystatin, ^a Mycostatin	500,000-U/5-mL susp (\$) 500,000-U tabs (\$)	PO	Infants 2 mL/dose, children 4–6 mL/dose, to coat oral mucosa Tabs: 3–6 tabs/day	q6h tid–qid
Obiltoximab, Anthim	600-mg/6-mL vial	IV	≤15 kg: 32 mg/kg (I) >15–40 kg: 24 mg/kg (I) >40 kg and adults: 16 mg/kg (I)	One time
Oritavancin, Orbactiv	400-mg vial (\$\$\$)	IV	Adults 1.2 g/day (I) Investigational in children	One time
Oseltamivir, ^a Tamiflu (See chapters 5 and 9, Influenza.)	30-mg/5-mL susp (\$) 30-, 45-, 75-mg cap ^a (\$)	PO	Preterm <38 wk PMA (II): 2 mg/kg/day Preterm 38–40 wk PMA (II): 3 mg/kg/day Preterm >40 wk PMA (II), and term, birth–8 mo (I): 6 mg/kg/day 9–11 mo (II): 7 mg/kg/day	q12h

			≥ 12 mo (I): (not per kg) ≤ 15 kg: 60 mg/day > 15 –23 kg: 90 mg/day > 23 –40 kg: 120 mg/day > 40 kg: 150 mg/day	
			Prophylaxis: Give half the daily dose q24h. Not recommended for infants < 3 mo.	q24h
Oxacillin, ^a Bactocill	1-, 2-, 10-g vial (\$\$)	IV, IM	100 mg/kg/day, max 12 g/day (I) 150–200 mg/kg/day for meningitis (III)	q4–6h
Palivizumab, Synagis	50-, 100-mg vial (\$\$\$\$)	IM	15 mg/kg (I). See Chapter 9 for indications.	Monthly during RSV season, max 5 doses
Paromomycin, ^a Humatin	250-mg cap (\$)	PO	25–35 mg/kg/day, max 4 g/day (I)	q8h
Penicillin G intramuscular				
– Penicillin G benzathine, Bicillin L-A	600,000 U/mL in 1-, 2-, 4-mL prefilled syringes (\$\$)	IM	Newborns and infants: 50,000 U/kg; children < 60 lb: 300,000–600,000 U, children ≥ 60 lb: 900,000 U (I) (FDA approved in 1952 for dosing by pounds) Adults 1.2–2.4 million U	1 dose
– Penicillin G benzathine/procaine, Bicillin C-R	1,200,000 IU per 2 mL prefilled syringe as 600,000 IU benzathine + 600,000 IU procaine per mL (\$\$)	IM	< 30 lb: 600,000 U 30–60 lb: 900,000–1,200,000 U > 60 lb: 2,400,000 U (I)	1 dose (may need repeat injections q2–3d)
Penicillin G intravenous				
– Penicillin G K, ^a Pfizerpen	5-, 20-million U vial (\$)	IV, IM	100,000–300,000 U/kg/day (I). Max daily dose is 24 million U.	q4–6h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
– Penicillin G sodium ^a	5-million U vial (\$\$)	IV, IM	100,000–300,000 U/kg/day (I). Max daily dose is 24 million U.	q4–6h
Penicillin V oral				
– Penicillin V K ^a	125-, 250-mg/5-mL soln (\$) 250-, 500-mg tab (\$)	PO	25–50 mg/kg/day, max 2 g/day (I)	q6h
Pentamidine, Pentam, Nebupent	300-mg vial (\$\$\$) 300-mg vial (\$\$)	IV, IM Inhaled	4 mg/kg/day (I), max 300 mg 300 mg for prophylaxis (I)	q24h Monthly
Peramivir, Rapivab	200-mg vial (\$\$-\$\$\$\$)	IV	12 mg/kg, max 600 mg (I)	One time
Piperacillin/tazobactam, ^a Zosyn	2/0.25-, 3/0.375-, 4/0.5-, 12/1.5-, 36/4.5-g vial (\$)	IV	≤40 kg: 240–300 mg PIP/kg/day, max 16 g PIP/day (I)	q8h
Plazomicin, Zemdri	500-mg vial	IV	Adults 15 mg/kg (I)	q24h
Polymyxin B ^a	500,000 U vial (\$) 1 mg = 10,000 U	IV	2.5 mg/kg/day (I) Adults 2 mg/kg LD, then 2.5–3 mg/kg/day, dose based on TBW, no max (II)	q12h
Posaconazole, Noxafil	200-mg/5-mL susp (\$\$\$\$)	PO	<13 y: under investigation, 18 mg/kg/day with serum trough monitoring. See Chapter 8.	q8h
			≥13 y and adults (I):	
			<i>Candida</i> or <i>Aspergillus</i> prophylaxis: 600 mg/day	q8h
			OPC treatment: 100 mg q12h for 1 day, then 100 mg/day	q24h
			Refractory OPC: 800 mg/day	q12h

	100-mg DR tab (\$\$\$-\$\$\$\$) 300-mg/16.7-mL vial (\$\$\$\$)	PO, IV	≥13 y and adults (I): <i>Candida</i> or <i>Aspergillus</i> prophylaxis: 300 mg q12h for 1 day, then 300 mg/day	q24h
Praziquantel, ^a Biltricide	600-mg tri-scored tab (\$-\$\$)	PO	20–25 mg/kg, no max (I)	q4–6h for 3 doses
Primaquine phosphate ^a	15-mg base tab (\$) (26.3-mg primaquine phosphate)	PO	0.3 mg base/kg, max 30 mg (III) (See Chapter 10.)	q24h
Pyrantel pamoate ^a	250-mg base/5-mL susp (\$) (720-mg pyrantel pamoate/5-mL)	PO	11 mg (base)/kg, max 1 g (I)	Once
Pyrazinamide ^a	500-mg tab (\$)	PO	30 mg/kg/day, max 2 g/day (I) Directly observed biweekly therapy, 50 mg/kg (I) use IBW, no max.	q24h Twice weekly
Quinupristin/dalfopristin, Synercid	150/350-mg vial (500-mg total) (\$\$\$\$)	IV	22.5 mg/kg/day (II) Adults 15–22.5 mg/kg/day, no max (I)	q8h q8–12h
Raxibacumab	1,700-mg/35-mL vial Available from CDC	IV	≤15 kg: 80 mg/kg >15–50 kg: 60 mg/kg >50 kg: 40 mg/kg (I)	Once
Ribavirin, Rebetol, Ribasphere	200-mg/5-mL soln (\$) (200-mg cap/tab ^a (\$) (400-, 600-mg tab (\$\$\$\$) 600-, 800-, 1,000-, 1,200-mg dose paks (\$\$\$\$)	PO	15 mg/kg/day (I). 12–17 y able to take caps/tabs: 40–49 kg: 600 mg/day 50–65 kg: 800 mg/day 66–80 kg: 1,000 mg/day 81–105 kg: 1,200 mg/day >105 kg: 1,400 mg/day Given as combination therapy with other agents; see Chapter 9, Hepatitis C virus.	q12h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Ribavirin, Virazole	6-g vial (\$\$\$\$)	Inhaled	1 vial by SPAG-2; see Chapter 9, Respiratory syncytial virus.	q24h
Rifabutin, ^a Mycobutin	150-mg cap (\$\$)	PO	5 mg/kg for MAC prophylaxis (II) 10–20 mg/kg for MAC or TB treatment (I) Max 300 mg/day	q24h
Rifampin, ^a Rifadin	150-, 300-mg cap (\$) 600-mg vial (\$-\$\$\$)	PO, IV	10–20 mg/kg, max 600 mg for TB (I)	q24h
			With directly observed biweekly therapy, dosage is still 10–20 mg/kg/dose (max 600 mg).	Twice weekly
			20 mg/kg/day for 2 days for meningococcus prophylaxis, max 1.2 g/day (I)	q12h
Rifampin/isoniazid/ pyrazinamide, Rifater	120-/50-/300-mg tab (\$\$)	PO	≥ 15 y and adults (I): ≤ 44 kg: 4 tab 45–54 kg: 5 tab ≥ 55 kg: 6 tab	q24h
Rifapentine, Priftin	150-mg tab (\$\$)	PO	≥ 12 y and adults: 600 mg/dose (I)	Twice weekly
Rifaximin, Xifaxan	200-mg tab (\$\$\$)	PO	≥ 12 y and adults: 600 mg/day (I) 20–30 mg/kg/day, max 1.6 g/day (III)	q8h
Secnidazole, Solosec	2-g granules (\$\$)	PO	Adults 2 g (I)	Once
Sofosbuvir, Sovaldi	400-mg tab (\$\$\$\$\$)	PO	≥ 12 y and adults: 400 mg (I). See Chapter 9, Hepatitis C virus.	q24h
Sofosbuvir/Ledipasvir, Harvoni	400-/90-mg tab (\$\$\$\$\$)	PO	≥ 12 y and adults: 1 tab (I). See Chapter 9, Hepatitis C virus.	q24h
Sofosbuvir/Velpatasvir, Epclusa	400-/100-mg tab (\$\$\$\$\$)	PO	Adults 1 tab (I). See Chapter 9, Hepatitis C virus.	q24h

Sofosbuvir/Velpatasvir/ Voxilaprevir, Vosevi	400-/100-/100-mg tab	PO	Adults 1 tab (I). See Chapter 9, Hepatitis C virus.	q24h
Streptomycin ^a	1-g vial (\$\$)	IM, IV	20–40 mg/kg/day, max 1 g/day ^c (I)	q12–24h
Sulfadiazine ^a	500-mg tab (\$\$)	PO	120–150 mg/kg/day, max 4–6 g/day (I). See Chapter 10.	q6h
			Rheumatic fever secondary prophylaxis 500 mg qd if ≤27 kg, 1,000 mg qd if >27 kg (II)	q24h
Tedizolid, Sivextro	200-mg tab (\$\$\$\$) 200-mg vial (\$\$\$\$)	PO, IV	Adults 200 mg (I) 12–17 y: 200 mg (II) Investigational in younger children	q24h
Telavancin, Vibativ	250-, 750-mg vial (\$\$\$\$)	IV	Adults 10 mg/kg (I)	q24h
Terbinafine, Lamisil	250-mg tab ^a (\$)	PO	Adults 250 mg (I)	q24h
Tetracycline ^a	250-, 500-mg cap (\$\$)	PO	≥8 y: 25–50 mg/kg/day (I)	q6h
Tinidazole, ^a Tindamax	250-, 500-mg tab (\$)	PO	50 mg/kg, max 2 g (I). See Chapter 10.	q24h
Tobramycin, ^a Nebcin	10-mg/mL vial (\$) 40-mg/mL vial (\$)	IV, IM	3–7.5 mg/kg/day (CF 7–10) ^c ; see Chapter 1 regarding q24h dosing.	q8–24h
Tobramycin inhalation, Tobi, ^a Bethkis	300-mg ampule (\$\$\$\$)	Inhaled	≥6 y: 600 mg/day (I)	q12h
Tobi Podhaler	28-mg cap for inhalation (\$\$\$\$\$)	Inhaled	≥6 y: 224 mg/day via Podhaler device (I)	q12h

A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

Generic and Trade Names	Dosage Form (cost estimate)	Route	Dose (evidence level)	Interval
Trimethoprim/ sulfamethoxazole, ^a Bactrim, Septra	80-mg TMP/400-mg SMX tab (single strength) (\$)	PO, IV	8–10 mg TMP/kg/day (I) Higher dosing for MIC 1 (II) 0–<6 y: 15 mg/kg/day 6–21 y: 12 mg/kg/day	q12h
	160-mg TMP/800-mg SMX tab (double strength) (\$)			
	40-mg TMP/200-mg SMX per 5-mL oral susp (\$)		2 mg TMP/kg/day for UTI prophylaxis (I)	q24h
	16-mg TMP/80-mg SMX per mL injection soln in 5-, 10-, 30-mL vial (\$\$)		15–20 mg TMP/kg/day for PCP treatment (I), no max	q6–8h
Valacyclovir, ^a Valtrex	500-mg, 1-g tab (\$)	PO	150 mg TMP/m ² /day, OR 5 mg TMP/kg/day for PCP prophylaxis (I), max 160 mg TMP/day	q12h 3 times a wk OR q24h
Valganciclovir, ^a Valcyte	250-mg/5-mL soln (\$\$\$) 450-mg tab (\$\$)	PO	VZV: ≥3 mo: 60 mg/kg/day (I, II) HSV: ≥3 mo: 40 mg/kg/day (II) Max single dose 1 g (I)	q8h q12h
			Congenital CMV treatment: 32 mg/kg/day (II). See Chapter 5. CMV prophylaxis (mg): $7 \times \text{BSA} \times \text{CrCl}$ (using the modified Schwartz formula for CrCl), max 900 mg (I). See Chapter 9.	q12h q24h
Vancomycin, Vancocin	125-, 250-mg/5-mL susp (\$-\$\$) 125-, 250-mg cap ^a (\$\$)	PO	40 mg/kg/day (I), max 500 mg/day (III)	q6h
	0.5-, 0.75-, 1-, 5-, 10-g vial ^a (\$)	IV	30–40 mg/kg/day ^c (I) For invasive MRSA infection, 60–70 mg/kg/day adjusted to achieve an AUC:MIC of >400 mg/L x h (II)	q6–8h

Voriconazole, ^{a,c} Vfend See Chapter 8, Aspergillosis.	200-mg/5-mL susp (\$\$\$) 50-, 200-mg tab (\$\$)	PO	≥ 2 y and < 50 kg: 18 mg/kg/day, max 700 mg/day (I) ≥ 50 kg: 400–600 mg/day (I)	q12h
	200-mg vial (\$\$)	IV	≥ 2 y and < 50 kg: 18 mg/kg/day LD for 1 day, then 16 mg/kg/day (I) ≥ 50 kg: 12 mg/kg/day LD for 1 day, then 8 mg/kg/day (I)	q12h
Zanamivir, Relenza	5-mg blister cap for inhalation (\$)	Inhaled	Prophylaxis: ≥ 5 y: 10 mg/day (I)	q24h
			Treatment: ≥ 7 y: 20 mg/day (I)	q12h

^a Available in a generic formulation.

^b Given as a cocktail with ribavirin ± interferon-PEG.

^c Monitor serum concentrations.

B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR, MUCOSA)

Generic and Trade Names	Dosage Form	Route	Dose	Interval
Acyclovir, Sitavig	50-mg tab	Buccal	Adults 50 mg, for herpes labialis	One time
Azithromycin, AzaSite	1% ophth soln	Ophth	1 drop	bid for 2 days then qd for 5 days
Bacitracin ^a	Ophth oint	Ophth	Apply to affected eye.	q3–4h
	Oint ^b	Top	Apply to affected area.	bid–qid
Benzyl alcohol, Ulesfia	5% lotion	Top	Apply to scalp and hair.	Once; repeat in 7 days.
Besifloxacin, Besivance	0.6% ophth susp	Ophth	≥1 y: 1 drop to affected eye	tid
Butenafine, Mentax, Lotrimin-Ultra	1% cream	Top	≥12 y: apply to affected area.	qd
Butoconazole, Gynazole-1	2% prefilled cream	Vag	Adults 1 applicatorful	One time
Ciclopirox, ^a Loprox, Penlac	0.77% cream, gel, lotion	Top	≥10 y: apply to affected area.	bid
	1% shampoo		≥16 y: apply to scalp.	Twice weekly
	8% nail lacquer		≥12 y: apply to infected nail.	qd
Ciprofloxacin, ^a Cetraxal	0.2% otic soln	Otic	≥1 y: apply 3 drops to affected ear.	bid for 7 days
Ciprofloxacin, Ciloxan	0.3% ophth soln ^a	Ophth	Apply to affected eye.	q2h for 2 days then q4h for 5 days
	0.3% ophth oint			q8h for 2 days then q12h for 5 days
Ciprofloxacin, Otiprio	6% otic susp	Otic	≥6 mo: 0.1 mL each ear intratympanic, 0.2 mL to external ear canal for otitis externa	One time

Ciprofloxacin + dexamethasone, Ciprodex	0.3% + 0.1% otic soln	Otic	≥6 mo: apply 4 drops to affected ear.	bid for 7 days
Ciprofloxacin + fluocinolone, Otovel	0.3% + 0.025% otic soln	Otic	≥6 mo: instill 0.25 mL to affected ear.	bid for 7 days
Ciprofloxacin + hydrocortisone, Cipro HC	0.2% + 1% otic soln	Otic	≥1 y: apply 3 drops to affected ear.	bid for 7 days
Clindamycin				
Cleocin	100-mg ovule	Vag	1 ovule	qhs for 3 days
	2% vaginal cream ^a		1 applicatorful	qhs for 3–7 days
Cleocin-T ^a	1% soln, gel, lotion	Top	Apply to affected area.	qd–bid
Clindesse	2% cream	Vag	Adolescents and adults 1 applicatorful	One time
Evoclin ^a	1% foam			qd
Clindamycin + benzoyl peroxide, BenzaClin	1% gel ^a	Top	≥12 y: apply to affected area.	bid
Acanya	1.2% gel	Top	Apply small amount to face.	q24h
Clindamycin + tretinoin, Ziana, Veltin	1.2% gel	Top	Apply small amount to face.	hs
Clotrimazole, ^{a,b} Lotrimin	1% cream, lotion, soln	Top	Apply to affected area.	bid
Gyne-Lotrimin-3 ^{a,b}	2% cream	Vag	≥12 y: 1 applicatorful	qhs for 7–14 days
Gyne-Lotrimin-7 ^{a,b}	1% cream			qhs for 3 days
Clotrimazole + betamethasone, ^a Lotrisone	1% + 0.05% cream, lotion	Top	≥12 y: apply to affected area.	bid
Colistin + neomycin + hydrocortisone, Coly-Mycin S, Cortisporin TC otic	0.3% otic susp	Otic	Apply 3–4 drops to affected ear canal; may use with wick.	q6–8h

B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR, MUCOSA) (continued)

Generic and Trade Names	Dosage Form	Route	Dose	Interval
Cortisporin; bacitracin + neomycin + polymyxin B + hydrocortisone	Oint	Top	Apply to affected area.	bid–qid
Cortisporin; neomycin + polymyxin B + hydrocortisone	Otic soln ^a	Otic	3 drops to affected ear	bid–qid
	Cream	Top	Apply to affected area.	bid–qid
Dapsone, Aczone	5% gel 7.5% gel	Top	≥ 12 y: Apply to affected area.	bid qd
Econazole, ^a Spectazole	1% cream	Top	Apply to affected area.	qd–bid
Efinaconazole, Jublia	10% soln	Top	Apply to toenail.	qd for 48 wk
Erythromycin ^a	0.5% ophth oint	Ophth	Apply to affected eye.	q4h
Akne-Mycin	2% oint	Top	Apply to affected area.	bid
Ery Pads	2% pledgets ^a			
Eryderm, ^a Erygel ^a	2% soln, gel			
Erythromycin + benzoyl peroxide, ^a Benzamycin	3% gel	Top	≥ 12 y: apply to affected area.	qd–bid
Ganciclovir, Zirgan	0.15% ophth gel	Ophth	≥ 2 y: 1 drop in affected eye	q3h while awake (5 times/day) until healed then tid for 7 days
Gatifloxacin, Zymar	0.3% ophth soln	Ophth	1 drop in affected eye	q2h for 2 days then q6h
Gatifloxacin, ^a Zymaxid	0.5% ophth soln	Ophth	≥ 1 y: 1 drop in affected eye	q2h for 1 day then q6h

Gentamicin, ^a Garamycin	0.1% cream, oint	Top	Apply to affected area.	tid–qid
	0.3% ophth soln, oint	Ophth	Apply to affected eye.	q1–4h (soln) q4–8h (oint)
Gentamicin + prednisolone, Pred-G	0.3% ophth soln, oint	Ophth	Adults: apply to affected eye.	q1–4h (soln)
				qd–tid (oint)
Imiquimod, ^a Aldara	5% cream	Top	≥12y: to perianal or external genital warts	3 times per wk
Ivermectin, Sklice	0.5% lotion	Top	≥6 mo: thoroughly coat hair and scalp, rinse after 10 minutes.	Once
Ivermectin, Soolantra	1% cream	Top	Adults: apply to face.	qd
Ketoconazole, ^a Nizoral	2% shampoo	Top	≥12 y: apply to affected area.	qd
	2% cream			qd–bid
Extina, Xolegel	2% foam, gel			bid
Nizoral A-D	1% shampoo			bid
Levofloxacin, ^a Quixin	0.5% ophth soln	Ophth	Apply to affected eye.	q1–4h
Luliconazole, Luzu	1% cream	Top	≥12 y: apply to affected area.	q24h for 1–2 wk
Mafenide, Sulfamylon	8.5% cream	Top	Apply to burn.	qd–bid
	5-g pwd for reconstitution		To keep burn dressing wet	q4–8h as needed
Malathion, ^a Ovide	0.5% soln	Top	≥6 y: apply to hair and scalp.	Once
Maxitrol ^b ; neomycin + polymyxin + dexamethasone	Susp, oint	Ophth	Apply to affected eye.	q4h (oint) q1–4h (susp)

B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR, MUCOSA) (continued)

Generic and Trade Names	Dosage Form	Route	Dose	Interval
Metronidazole ^a	0.75% cream, gel, lotion	Top	Adults: apply to affected area.	bid
	0.75% vag gel	Vag	Adults 1 applicatorful	qd–bid
	1% gel	Top	Adults: apply to affected area.	qd
Noritate	1% cream	Top	Adults: apply to affected area.	qd
Miconazole				
Fungoid ^{a,b}	2% tincture	Top	Apply to affected area.	bid
Micatin ^{a,b} and others	2% cream, pwd, oint, spray, lotion, gel	Top	Apply to affected area.	qd–bid
Monistat-1 ^{a,b}	1.2-g ovule + 2% cream	Vag	≥ 12 y: insert one ovule (plus cream to external vulva bid as needed).	Once
Monistat-3 ^{a,b}	200-mg ovule, 4% cream			qhs for 3 days
Monistat-7 ^{a,b}	100-mg ovule, 2% cream			qhs for 7 days
Vusion	0.25% oint	Top	To diaper dermatitis	Each diaper change for 7 days
Moxifloxacin, Vigamox	0.5% ophth soln	Ophth	Apply to affected eye.	tid
Mupirocin, Bactroban	2% oint, ^a cream ^a	Top	Apply to infected skin.	tid
Naftifine, Naftin	1%, 2% cream ^a 2% gel	Top	Apply to affected area.	qd
Natamycin, Natacyn	5% ophth soln	Ophth	Adults: apply to affected eye.	q1–4h
Neosporin ^a				
bacitracin + neomycin + polymyxin B	Ophth oint	Ophth	Apply to affected eye.	q4h
	Oint ^{a,b}	Top	Apply to affected area.	bid–qid

gramicidin + neomycin + polymyxin B	Ophth soln	Ophth	Apply to affected eye.	q4h
Nystatin, ^a Mycostatin	100,000 U/g cream, oint, pwd	Top	Apply to affected area.	bid–qid
Nystatin + triamcinolone, ^a Mycolog II	100,000 U/g + 0.1% cream, oint	Top	Apply to affected area.	bid
Ofloxacin, ^a Floxin Otic, Ocuflox	0.3% otic soln	Otic	5–10 drops to affected ear	qd–bid
	0.3% ophth soln	Ophth	Apply to affected eye.	q1–6h
Oxiconazole, Oxistat	1% cream, ^a lotion	Top	Apply to affected area.	qd–bid
Ozenoxacin, Xepi	1% cream		Apply to affected area.	bid for 5 days
Permethrin, Nix ^{a,b}	1% cream	Top	Apply to hair/scalp.	Once for 10 min
Elimite ^a	5% cream		Apply to all skin surfaces.	Once for 8–14 h
Piperonyl butoxide + pyrethrins, ^{a,b} Rid	4% + 0.3% shampoo, gel	Top	Apply to affected area.	Once for 10 min
Polysporin, ^a polymyxin B + bacitracin	Ophth oint	Ophth	Apply to affected eye.	qd–tid
	Oint ^b	Top	Apply to affected area.	qd–tid
Polytrim, ^a polymyxin B + trimethoprim	Ophth soln	Ophth	Apply to affected eye.	q3–4h
Retapamulin, Altabax	1% oint	Top	Apply thin layer to affected area.	bid for 5 days
Selenium sulfide, ^a Selsun	2.5% lotion	Top	Lather into scalp or affected area.	Twice weekly then every 1–2 wk
	2.25% shampoo			
Selsun Blue ^{a,b}	1% shampoo			qd
Sertaconazole, Ertaczo	2% cream	Top	≥12 y: apply to affected area.	bid
Silver sulfadiazine, ^a Silvadene	1% cream	Top	Apply to affected area.	qd–bid

B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR, MUCOSA) (continued)

Generic and Trade Names	Dosage Form	Route	Dose	Interval
Spinosad, ^a Natroba	0.9% susp	Top	Apply to scalp and hair.	Once; may repeat in 7 days.
Sulconazole, Exelderm	1% soln, cream	Top	Adults: apply to affected area.	qd–bid
Sulfacetamide sodium ^a	10% soln	Ophth	Apply to affected eye.	q1–3h
	10% ophth oint			q4–6h
	10% lotion, wash, cream	Top	≥12 y: apply to affected area.	bid–qid
Sulfacetamide sodium + prednisolone, ^a Blephamide	10% ophth oint, soln	Ophth	Apply to affected eye.	tid–qid
Tavaborole, Kerydin	5% soln	Top	Adults: apply to toenail.	qd for 48 wk
Terbinafine, ^b Lamisil-AT	1% cream, ^a spray, gel	Top	Apply to affected area.	qd–bid
Terconazole, ^a Terazol	0.4% cream	Vag	Adults 1 applicatorful or 1 suppository	qhs for 7 days
	0.8% cream 80-mg suppository			qhs for 3 days
Tioconazole ^{a,b}	6.5% ointment	Vag	≥12 y: 1 applicatorful	One time
Tobramycin, Tobrex	0.3% soln, ^a oint	Ophth	Apply to affected eye.	q1–4h (soln) q4–8h (oint)
Tobramycin + dexamethasone, Tobradex	0.3% soln, ^a oint	Ophth	Apply to affected eye.	q2–6h (soln) q6–8h (oint)
Tobramycin + loteprednol, Zylet	0.3% + 0.5% ophth susp	Ophth	Adults: apply to affected eye.	q4–6h
Tolnaftate, ^{a,b} Tinactin	1% cream, soln, pwd, spray	Top	Apply to affected area.	bid
Trifluridine, ^a Viroptic	1% ophth soln	Ophth	1 drop (max 9 drops/day)	q2h

^a Generic available.^b Over the counter.

12. Antibiotic Therapy for Children Who Are Obese

When prescribing an antimicrobial for a child who is obese or overweight, selecting a dose based on milligrams per kilograms of total body weight (TBW) may overexpose the child if the drug doesn't freely distribute into fat tissue. Conversely, underexposure can occur when a dosage is reduced for obesity for drugs without distribution limitations.

The Table lists major antimicrobials classes and our suggestion on how to calculate an appropriate dose. The evidence to support these recommendations are Level II–III (pharmacokinetic studies in children, extrapolations from adult studies, and expert opinion). Whenever a dose is used that is greater than one prospectively investigated for efficacy and safety, the clinician must weigh the benefits with potential risks. Data are not available on all agents.

For **gentamicin**, using the child's fat-free mass, an approximate 30% reduction in dosing weight, has been recommended. When performing this empiric dosing strategy with aminoglycosides in children who are obese, we recommend closely following serum concentrations.

Vancomycin is traditionally dosed based on TBW in obese adults due to increases in kidney size and glomerular filtration rate. In obese children, weight-adjusted distribution volume and clearance are slightly lower than in their nonobese counterparts. An empiric maximum dose of 60 mg/kg/day based on TBW, or dosing using body surface area, may be more appropriate. We recommend closely following serum concentrations.

In the setting of **cephalosporins** for surgical prophylaxis (see Chapter 14), adult studies of obese patients have generally found that distribution to the subcutaneous fat tissue target is subtherapeutic when standard doses are used. Given the wide safety margin of these agents in the short-term setting of surgical prophylaxis, maximum single doses are recommended in obese adults (eg, cefazolin 2–3 g instead of the standard 1 g) with re-dosing at 4-hour intervals for longer cases. In obese children, we recommend dosing cephalosporins for surgical prophylaxis based on TBW up to the adult maximum.

In critically ill obese adults, extended infusion times have been shown to increase the likelihood of achieving therapeutic serum concentrations with **carbapenems** and **piperacillin/tazobactam**.

Daptomycin dosing can be performed using TBW, but the maximum dose should be 500 mg for skin infections and 750 mg for bloodstream infections. Bolus administration over 2 minutes can improve the likelihood of achieving target concentrations in cases where the maximum dose is less than the calculated dose in an obese adolescent.

DOSING RECOMMENDATIONS

DRUG CLASS	BY EBW ^a	BY ADJUSTED BW	BY TBW ^b
ANTIBACTERIALS			
Beta-lactams			
Piperacillin			X (up to adult max)
Cephalosporins			X (up to adult max)
Carbapenems			X (up to adult max)
Clindamycin			X (no max)
Vancomycin		1,500–2,000 mg/m ² /d	20 mg/kg LD then 60 mg/kg/day div q6–8h
Aminoglycosides		0.7 x TBW	
Fluoroquinolones		EBW + 0.45 (TBW-EBW)	
Rifampin	X		
Miscellaneous			
TMP/SMX			X
Metronidazole	X		
Linezolid	X		
Daptomycin			X (see max doses in comments above)
ANTIFUNGALS			
Amphotericin B (all formulations)			X
Fluconazole			X (max 1,200 mg/day)
Flucytosine	X		
Anidulafungin			X (max 250 mg LD, max 125 mg/day)
Caspofungin			X (max 150 mg/day)
Micafungin			X (max 300 mg/day)
Voriconazole	X		

DOSING RECOMMENDATIONS

DRUG CLASS	BY EBW ^a	BY ADJUSTED BW	BY TBW ^b
ANTIVIRALS (NON-HIV)			
Nucleoside analogues (acyclovir, ganciclovir)	X		
Oseltamivir	X		
ANTIMYCOBACTERIALS			
Isoniazid	X		
Rifampin			X (max 1,200 mg/day)
Pyrazinamide			X (max 2,000 mg/day)
Ethambutol			X (max 1,600 mg/day)

Abbreviations: BMI, body mass index; BW, body weight; EBW, expected body weight; HIV, human immunodeficiency virus; LD, loading dose; TBW, total body weight; TMP/SMX, trimethoprim/sulfamethoxazole.

^a EBW (kg) = BMI 50th percentile for age \times actual height (m)²; from Le Grange D, et al. *Pediatrics*. 2012;129(2): e438–e446 PMID: 22218841.

^b Actual measured body weight.

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13. Sequential Parenteral-Oral Antibiotic Therapy (Oral Step-down Therapy) for Serious Infections

The concept of oral step-down therapy is not new; evidence-based recommendations from Nelson and colleagues appeared 40 years ago in the *Journal of Pediatrics*.^{1,2} Bone and joint infections,^{3–5} complicated bacterial pneumonia with empyema,⁶ deep-tissue abscesses, and appendicitis,^{7,8} as well as cellulitis or pyelonephritis,⁹ may require initial parenteral therapy to control the growth and spread of pathogens and minimize injury to tissues. For abscesses in soft tissues, joints, bones, and empyema, most organisms are removed by surgical drainage and, presumably, killed by the initial parenteral therapy. When the signs and symptoms of infection begin to resolve, often within 2 to 4 days, continuing intravenous (IV) therapy may not be required, as a normal host neutrophil response begins to assist in clearing the infection.¹⁰ In addition to following the clinical response prior to oral switch, following objective laboratory markers, such as C-reactive protein (CRP) or procalcitonin (PCT), during the hospitalization may also help the clinician better assess the response to antibacterial therapy, particularly in the infant or child who is difficult to examine.^{11,12} For many children who are documented to have successful treatment with step-down oral therapy following drainage of abscesses, it is likely that a proportion may actually no longer require any additional antibiotic therapy.¹³ However, defining those children who may benefit from oral step-down therapy is difficult, as the extent of a deep infection, the adequacy of source control (drainage), and the susceptibility of pathogen(s) involved are not always known.

For the beta-lactam class of antibiotics, absorption of orally administered antibiotics in *standard* dosages provides peak serum concentrations that are routinely only 5% to 20% of those achieved with IV or intramuscular administration. However, *high-dose* oral beta-lactam therapy provides the tissue antibiotic exposure thought to be required to eradicate the remaining pathogens at the infection site as the tissue perfusion improves. For beta-lactams, begin with a dosage 2 to 3 times the normal dosage (eg, 75–100 mg/kg/day of amoxicillin or 100 mg/kg/day of cephalexin). High-dose oral beta-lactam antibiotic therapy of osteoarticular infections has been associated with treatment success since 1978.³ It is reassuring that high-quality retrospective cohort data have recently confirmed similar outcomes achieved in those treated with oral step-down therapy compared with those treated with IV.¹⁴ High-dose prolonged oral beta-lactam therapy may be associated with reversible neutropenia; checking for hematologic toxicity every few weeks during therapy is recommended.¹⁵

Clindamycin and many antibiotics of the fluoroquinolone class (ciprofloxacin, levofloxacin) and oxazolidinone class (linezolid, tedizolid) have excellent absorption of their oral formulations and provide virtually the same tissue antibiotic exposure at a particular mg/kg dose, compared with that dose given intravenously. Trimethoprim/sulfamethoxazole and metronidazole are also very well absorbed.

One must also assume that the parent and child are compliant with the administration of each antibiotic dose, that the oral antibiotic will be absorbed from the gastrointestinal tract into the systemic circulation (no vomiting or diarrhea), and that the parents will seek medical care if the clinical course does not continue to improve for their child.

Monitor the child clinically for a continued response on oral therapy; follow CRP or PCT after the switch to oral therapy and if there are concerns about continued response, make sure the antibiotic and dosage you selected are appropriate and the family is compliant. In one of the first published series of oral step-down therapy for osteoarticular infection, failures caused by presumed noncompliance were reported.¹⁶

14. Antimicrobial Prophylaxis/Prevention of Symptomatic Infection

This chapter provides a summary of recommendations for prophylaxis of infections, defined as providing therapy prior to the onset of clinical signs or symptoms of infection. Prophylaxis can be considered in several clinical scenarios.

A. Postexposure Antimicrobial Prophylaxis to Prevent Infection

Given for a relatively short, specified period after exposure to specific pathogens/organisms, where the risks of acquiring the infection are felt to justify antimicrobial treatment to eradicate the pathogen or prevent symptomatic infection in situations in which the child (healthy or with increased susceptibility to infection) is likely to have been inoculated/exposed (eg, asymptomatic child closely exposed to meningococcus; a neonate born to a mother with active genital herpes simplex virus).

B. Long-term Antimicrobial Prophylaxis to Prevent Symptomatic New Infection

Given to a particular, defined population of children who are of relatively high risk of acquiring a severe infection from a single or multiple exposures (eg, a child postsplenectomy; a child with documented rheumatic heart disease to prevent subsequent streptococcal infection), with prophylaxis provided during the period of risk, potentially months or years.

C. Prophylaxis of Symptomatic Disease in Children Who Have Asymptomatic Infection/Latent Infection

Where a child has a documented but asymptomatic infection and targeted antimicrobials are given to prevent the development of symptomatic disease (eg, latent tuberculosis infection or therapy of a stem cell transplant patient with documented cytomegalovirus viremia but no symptoms of infection or rejection; to prevent reactivation of herpes simplex virus). Treatment period is usually defined, particularly in situations in which the latent infection can be cured (tuberculosis), but other circumstances, such as reactivation of a latent virus, may require months or years of prophylaxis.

D. Surgical/Procedure Prophylaxis

A child receives a surgical/invasive catheter procedure, planned or unplanned, in which the risk of infection postoperatively or post-procedure may justify prophylaxis to prevent an infection from occurring (eg, prophylaxis to prevent infection following spinal rod placement). Treatment is usually short-term, beginning just prior to the procedure and ending at the conclusion of the procedure, or within 24 to 48 hours.

E. Travel-Related Exposure Prophylaxis

Not discussed in this chapter; please refer to information on specific disease entities (eg, traveler's diarrhea, chapters 6 and 10) or specific pathogens (eg, malaria, Chapter 10). Constantly updated, current information for travelers about prophylaxis and current worldwide infection risks can be found on the Centers for Disease Control and Prevention Web site at www.cdc.gov/travel (accessed October 6, 2018).

NOTE

- Abbreviations: AHA, American Heart Association; ALT, alanine aminotransferase; amox/clav, amoxicillin/clavulanate; ARF, acute rheumatic fever; bid, twice daily; CDC, Centers for Disease Control and Prevention; CPB, cardiopulmonary bypass; CSF, cerebrospinal fluid; div, divided; DOT, directly observed therapy; GI, gastrointestinal; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IGRA, interferon-gamma release assay; IM, intramuscular; INH, isoniazid; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not applicable; PCR, polymerase chain reaction; PO, orally; PPD, purified protein derivative; qd, once daily; qid, 4 times daily; spp, species; TB, tuberculosis; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection.

A. POSTEXPOSURE ANTIMICROBIAL PROPHYLAXIS TO PREVENT INFECTION

Prophylaxis Category	Therapy (evidence grade)	Comments
Bacterial		
Bites, animal and human ¹⁻⁵ (<i>Pasteurella multocida</i> [animal], <i>Eikenella corrodens</i> [human], <i>Staphylococcus</i> spp, and <i>Streptococcus</i> spp)	Amox/clav 45 mg/kg/day PO div tid (amox/clav 7:1; see Chapter 1 for amox/clav description) for 3–5 days (All) OR ampicillin and clindamycin (BII). For penicillin allergy, consider ciprofloxacin (for <i>Pasteurella</i>) plus clindamycin (BIII).	Recommended for children who (1) are immunocompromised; (2) are asplenic; (3) have moderate to severe injuries, especially to the hand or face; or (4) have injuries that may have penetrated the periosteum or joint capsule (All). ³ Consider rabies prophylaxis for at-risk animal bites (All) ⁶ ; consider tetanus prophylaxis. ⁷ Human bites have a very high rate of infection (do not close open wounds routinely). Cat bites have a higher rate of infection than dog bites. <i>Staphylococcus aureus</i> coverage is only fair with amox/clav and provides no coverage for MRSA.

Endocarditis prophylaxis^{8,9}: Given that (1) endocarditis is rarely caused by dental/GI procedures and (2) prophylaxis for procedures prevents an exceedingly small number of cases, the risks of antibiotics most often outweigh benefits. However, some “highest risk” conditions are currently recommended for prophylaxis: (1) prosthetic heart valve (or prosthetic material used to repair a valve); (2) previous endocarditis; (3) cyanotic congenital heart disease that is unrepaired (or palliatively repaired with shunts and conduits); (4) congenital heart disease that is repaired but with defects at the site of repair adjacent to prosthetic material; (5) completely repaired congenital heart disease using prosthetic material, for the first 6 months after repair; or (6) cardiac transplant patients with valvulopathy. Routine prophylaxis no longer is required for children with native valve abnormalities. Follow-up data in children suggest that following these new guidelines, no increase in endocarditis has been detected,¹⁰ but in adults in the United States¹¹ and in the United Kingdom,¹² some concern for increase in the number of cases of endocarditis has been documented since widespread prophylaxis was stopped. More recent data from California and New York do not support an increase in infective endocarditis with the current approach to prophylaxis.¹³

A. POSTEXPOSURE ANTIMICROBIAL PROPHYLAXIS TO PREVENT INFECTION (continued)

Prophylaxis Category	Therapy (evidence grade)	Comments
Bacterial (continued)		
– In highest-risk patients: dental procedures that involve manipulation of the gingival or periodontal region of teeth	Amoxicillin 50 mg/kg PO 1 h before procedure OR ampicillin or ceftriaxone or cefazolin, all at 50 mg/kg IM/IV 30–60 min before procedure	If penicillin allergy: clindamycin 20 mg/kg PO (1 h before) or IV (30 min before) OR azithromycin 15 mg/kg or clarithromycin 15 mg/kg (1 h before)
– Genitourinary and gastrointestinal procedures	None	No longer recommended
Lyme disease (<i>Borrelia burgdorferi</i>) ¹⁴	Doxycycline 4.4 mg/kg (up to 200 mg max), once. Dental staining should not occur with a single course of doxycycline. Amoxicillin prophylaxis is not well studied, and experts recommend a full 14-day course if amoxicillin is used.	ONLY (1) for those in highly Lyme-endemic areas AND (2) the tick has been attached for >36 h (and is engorged) AND (3) prophylaxis started within 72 h of tick removal.
Meningococcus (<i>Neisseria meningitidis</i>) ^{15,16}	For prophylaxis of close contacts, including household members, child care center contacts, and anyone directly exposed to the patient's oral secretions (eg, through kissing, mouth-to-mouth resuscitation, endotracheal intubation, endotracheal tube management) in the 7 days before symptom onset Rifampin Infants <1 mo: 5 mg/kg PO q12h for 4 doses Children ≥1 mo: 10 mg/kg PO q12h for 4 doses (max 600 mg/dose) OR Ceftriaxone Children <15 y: 125 mg IM once Children ≥16 y: 250 mg IM once OR Ciprofloxacin 500 mg PO once (adolescents and adults)	A single dose of ciprofloxacin should not present a significant risk of cartilage damage, but no prospective data exist in children for prophylaxis of meningococcal disease. For a child, an equivalent exposure to ciprofloxacin to that in adults would be 15–20 mg/kg as a single dose (max 500 mg). A few ciprofloxacin-resistant strains have now been reported. Insufficient data to recommend azithromycin at this time. Meningococcal vaccines may also be recommended in case of an outbreak.

Pertussis^{17,18}

Same regimen as for treatment of pertussis:
 azithromycin 10 mg/kg/day qd for 5 days OR
 clarithromycin (for infants > 1 mo) 15 mg/kg/day
 div bid for 7 days OR erythromycin (estolate pref-
 erable) 40 mg/kg/day PO div qid for 14 days (All)
 Alternative: TMP/SMX 8 mg/kg/day div bid for
 14 days (BIII)

Prophylaxis to family members; contacts defined by CDC:
 persons within 21 days of exposure to an infectious per-
 tussis case, who are at high risk of severe illness or who
 will have close contact with a person at high risk of
 severe illness (including infants, pregnant women in their
 third trimester, immunocompromised persons, contacts
 who have close contact with infants <12 mo). Close con-
 tact can be considered as face-to-face exposure within
 3 feet of a symptomatic person; direct contact with respi-
 ratory, nasal, or oral secretions; or sharing the same con-
 fined space in close proximity to an infected person for
 ≥1 h.

Community-wide prophylaxis is not currently
 recommended.

Azithromycin and clarithromycin are better tolerated than
 erythromycin (see Chapter 5); azithromycin is preferred in
 exposed very young infants to reduce pyloric stenosis
 risk.

Tetanus (*Clostridium tetani*)^{7,19}**Need for Tetanus Vaccine or TIG^a**

Clean Wound		Contaminated Wound		
Number of past tetanus vaccine doses	Need for tetanus vaccine	Need for TIG 500 U IM ^a	Need for tetanus vaccine	Need for TIG 500 U IM ^a
<3 doses	Yes	No	Yes	Yes
≥3 doses	No (if <10 y ^b) Yes (if ≥10 y ^b)	No	No (if <5 y ^b) Yes (if ≥5 y ^b)	No

^a IV immune globulin should be used when TIG is not available.

^b Years since last tetanus-containing vaccine dose.

For deep, contaminated wounds, wound debridement is essential. For wounds that cannot be fully debrided, consider metronidazole 30 mg/kg/day PO div q8h until wound healing is underway and anaerobic conditions no longer exist, as short as 3–5 days (BIII).

A. POSTEXPOSURE ANTIMICROBIAL PROPHYLAXIS TO PREVENT INFECTION (continued)

Prophylaxis Category	Therapy (evidence grade)	Comments
Bacterial (continued)		
Tuberculosis (<i>Mycobacterium tuberculosis</i>) Exposed children <4 y, or immunocompromised patient (high risk of dissemination) ^{20,21} For treatment of latent TB infection, see recommendations in Section C of this chapter (Table 14C).	Scenario 1: Previously uninfected child becomes exposed to a person with active disease. Exposed children <4 y, or immunocompromised patient (high risk of dissemination): INH 10–15 mg/kg PO qd for at least 2–3 mo (AIII) at which time the PPD/IGRA may be assessed. Older children may also begin prophylaxis postexposure, but if exposure is questionable, can wait 2–3 mo after exposure to assess for infection; if PPD/IGRA at 2–3 mo is positive and child remains asymptomatic at that time, start INH for 9–12 mo.	If PPD or IGRA remains negative at 2–3 mo and child remains well, consider stopping empiric therapy. However, tests at 2–3 mo may not be reliable in immunocompromised patients. This regimen is to prevent infection in a compromised host after exposure, rather than to treat latent asymptomatic infection.
	Scenario 2: Asymptomatic child is found to have a positive skin test/IGRA test for TB, documenting latent TB infection. INH 10–15 mg/kg PO qd for 9 mo (≥ 12 mo for an immunocompromised child) OR INH 20–30 mg/kg PO directly observed therapy twice weekly for 9 mo	Other options For INH intolerance or INH resistance if a direct contact can be tested: rifampin 10 mg/kg PO qd for 4 mo For children ≥ 2 y, can use once-weekly DOT with INH AND rifapentine for 12 wk (much less data for children 2–12 y) ²²
Viral		
Herpes simplex virus		
During pregnancy	For women with recurrent genital herpes: acyclovir 400 mg PO tid; valacyclovir 500 mg PO bid from 36-wk gestation until delivery (CII) ²³	Neonatal HSV disease after maternal suppression has been documented ²⁴

Neonatal: Primary or nonprimary first clinical episode of maternal infection, neonate exposed at delivery ²⁵	<p>Asymptomatic, exposed neonate: at 24 h after birth, culture mucosal sites (see Comments), obtain CSF and whole-blood PCR for HSV DNA, obtain ALT, and start preemptive therapeutic acyclovir IV (60 mg/kg/day div q8h) for 10 days (AII).</p> <p>Some experts would evaluate at birth for exposure following presumed maternal primary infection and start preemptive therapy rather than wait 24 h.</p>	<p>Reference 25 provides a management algorithm that determines the type of maternal infection and, thus, the appropriate evaluation and preemptive therapy of the neonate.</p> <p>Mucosal sites for culture: conjunctivae, mouth, nasopharynx, rectum.</p> <p>Any symptomatic baby, at any time, requires a full evaluation for invasive infection and IV acyclovir therapy for 14–21 days, depending on extent of disease.</p>
Neonatal: Recurrent maternal infection, neonate exposed at delivery ²⁵	<p>Asymptomatic, exposed neonate: at 24 h after birth, culture mucosal sites (see Comments) and obtain whole-blood PCR for HSV DNA. Hold on therapy unless cultures or PCR are positive, at which time the diagnostic evaluation should be completed (CSF PCR for HSV DNA, serum ALT) and preemptive therapeutic IV acyclovir (60 mg/kg/day div q8h) should be administered for 10 days (AIII).</p>	<p>Reference 25 provides a management algorithm that determines the type of maternal infection and, thus, the appropriate evaluation and preemptive therapy of the neonate.</p> <p>Mucosal sites for culture: conjunctivae, mouth, nasopharynx, rectum.</p> <p>Any symptomatic baby, at any time, requires a full evaluation for invasive infection and IV acyclovir therapy for 14–21 days, depending on extent of disease.</p>
Neonatal: Following symptomatic disease, to prevent recurrence during first year after birth ²⁵	See recommendations in Section C of this chapter (Table 14C).	
Keratitis (ocular) in otherwise healthy children	See recommendations in Section C of this chapter (Table 14C).	

A. POSTEXPOSURE ANTIMICROBIAL PROPHYLAXIS TO PREVENT INFECTION (continued)

Prophylaxis Category	Therapy (evidence grade)	Comments
Viral (continued)		
Influenza virus (A or B) ²⁶	<p>Oseltamivir prophylaxis (AI)</p> <p>3–≤8 mo: 3 mg/kg/dose qd for 10 days</p> <p>9–11 mo: 3.5 mg/kg/dose PO qd for 10 days²⁷</p> <p>Based on body weight for children ≥12 mo</p> <p>≤15 kg: 30 mg qd for 10 days</p> <p>>15–23 kg: 45 mg qd for 10 days</p> <p>>23–40 kg: 60 mg qd for 10 days</p> <p>>40 kg: 75 mg qd for 10 days</p>	Not routinely recommended for infants 0 to ≤3 mo unless situation judged critical because of limited data on use and variability of drug exposure in this age group.
	<p>Zanamivir prophylaxis (AI)</p> <p>Children ≥5 y: 10 mg (two 5-mg inhalations) qd for as long as 28 days (community outbreaks) or 10 days (household settings)</p>	
Rabies virus ²⁸	<p>Rabies immune globulin, 20 IU/kg, infiltrate around wound, with remaining volume injected IM (All)</p> <p>PLUS</p> <p>Rabies immunization (All)</p>	<p>For dog, cat, or ferret bite from symptomatic animal, immediate rabies immune globulin and immunization; otherwise, can wait 10 days for observation of animal, if possible, prior to rabies immune globulin or vaccine.</p> <p>Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require anti-rabies prophylaxis.</p> <p>For bites of bats, skunks, raccoons, foxes, most other carnivores, and woodchucks, immediate rabies immune globulin and immunization (regard as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests).</p>

Fungal

Pneumocystis jiroveci (previously *Pneumocystis carinii*)^{29,30}

Non-HIV infection regimens
 TMP/SMX as 5–10 mg TMP/kg/day PO, div 2 doses, q12h, either qd or 3 times/wk on consecutive days (AI); OR TMP/SMX 5–10 mg TMP/kg/day PO as a *single dose*, qd, given 3 times/wk on consecutive days (AI) (once-weekly regimens have also been successful); OR dapsone 2 mg/kg (max 100 mg) PO qd, or 4 mg/kg (max 200 mg) once weekly; OR atovaquone 30 mg/kg/day for infants 1–3 mo; 45 mg/kg/day for infants/children 4–24 mo; and 30 mg/kg/day for children >24 mo until no longer immunocompromised, based on oncology or transplant treatment regimen

Prophylaxis in specific populations based on degree of immunosuppression. For children with HIV, please see the Aidsinfo.gov Web site: https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed October 6, 2018).

B. LONG-TERM ANTIMICROBIAL PROPHYLAXIS TO PREVENT SYMPTOMATIC NEW INFECTION

Prophylaxis Category	Therapy (evidence grade)	Comments
Bacterial otitis media ^{31,32}	Amoxicillin or other antibiotics can be used in half the therapeutic dose qd or bid to prevent infections if the benefits outweigh the risks of (1) development of resistant organisms for that child and (2) antibiotic side effects.	True, recurrent bacterial otitis is far less common in the era of conjugate pneumococcal immunization. To prevent recurrent infections, as alternative to antibiotic prophylaxis, also consider the risks and benefits of placing tympanostomy tubes to improve middle ear ventilation. Studies have demonstrated that amoxicillin, sulfisoxazole, and TMP/SMX are effective. However, antimicrobial prophylaxis may alter the nasopharyngeal flora and foster colonization with resistant organisms, compromising long-term efficacy of the prophylactic drug. Continuous PO-administered antimicrobial prophylaxis should be reserved for control of recurrent acute otitis media, only when defined as ≥ 3 distinct and well-documented episodes during a period of 6 mo or ≥ 4 episodes during a period of 12 mo. Although prophylactic administration of an antimicrobial agent limited to a period when a person is at high risk of otitis media has been suggested (eg, during acute viral respiratory tract infection), this method has not been evaluated critically.
Rheumatic fever	For >27.3 kg (>60 lb): 1.2 million U penicillin G benzathine, q4wk (q3wk for high-risk children) For <27.3 kg: 600,000 U penicillin G benzathine, q4wk (q3wk for high-risk children) OR Penicillin V (phenoxymethyl) oral, 250 mg PO bid	AHA policy statement at http://circ.ahajournals.org/content/119/11/1541.full.pdf (accessed October 6, 2018). Doses studied many years ago, with no new data; ARF is an uncommon disease currently in the United States. Alternatives to penicillin include sulfisoxazole or macrolides, including erythromycin, azithromycin, and clarithromycin.
Urinary tract infection, recurrent ^{33–36}	TMP/SMX 3 mg/kg/dose TMP PO qd OR nitrofurantoin 1–2 mg/kg PO qd at bedtime; more rapid resistance may develop using beta-lactams (BII).	Only for those with grade III–V reflux or with recurrent febrile UTI: prophylaxis no longer recommended for patients with grade I–II (some also exclude grade III) reflux. Prophylaxis prevents infection but may not prevent scarring. Early treatment of new infections is recommended for children not given prophylaxis. Resistance eventually develops to every antibiotic; follow resistance patterns for each patient.

C. PROPHYLAXIS OF SYMPTOMATIC DISEASE IN CHILDREN WHO HAVE ASYMPTOMATIC INFECTION/LATENT INFECTION

Prophylaxis Category	Therapy (evidence grade)	Comments
Herpes simplex virus		
Neonatal: Following symptomatic disease, to prevent recurrence during first year after birth ²⁵	Acyclovir 300 mg/m ² /dose PO tid for 6 mo, following cessation of IV acyclovir treatment of acute disease (AI)	Follow absolute neutrophil counts at 2 and 4 wk, then monthly during prophylactic/suppressive therapy.
Keratitis (ocular) in otherwise healthy children	Suppressive acyclovir therapy for frequent recurrence (no pediatric data): 20 mg/kg/dose bid (up to 400 mg) for ≥1 y (AIII)	Based on data from adults. Anecdotally, some children may require tid dosing to prevent recurrences. Check for acyclovir resistance for those who relapse while on appropriate therapy. Suppression oftentimes required for many years. Watch for severe recurrence at conclusion of suppression.
Tuberculosis ^{20,21} (latent TB infection [asymptomatic infection], defined by a positive skin test or IGRA, with no clinical or radiographic evidence of active disease)	INH 10–15 mg/kg/day (max 300 mg) PO qd for 9 mo (12 mo for immunocompromised patients) (AI); treatment with INH at 20–30 mg twice weekly for 9 mo is also effective (AIII).	Single drug therapy if no clinical or radiographic evidence of active disease. For exposure to known INH-resistant but rifampin-susceptible strains, use rifampin 10 mg/kg PO qd for 6 mo (AIII). For children ≥2 y, can use once weekly DOT with INH AND rifapentine for 12 wk (much less data for children 2–12 y). ²² For exposure to drug-resistant strains, consult with TB specialist.

D. SURGICAL/PROCEDURE PROPHYLAXIS^{37–47}

The CDC National Healthcare Safety Network uses a classification of surgical procedure-related wound infections based on an estimation of the load of bacterial contamination: Class I, clean; Class II, clean-contaminated; Class III, contaminated; and Class IV, dirty/infected.^{38,43,44} Other major factors creating risk for postoperative surgical site infection include the duration of surgery (a longer-duration operation, defined as one that exceeded the 75th percentile for a given procedure) and the medical comorbidities of the patient, as determined by an American Society of Anesthesiologists score of III, IV, or V (presence of severe systemic disease that results in functional limitations, is life-threatening, or is expected to preclude survival from the operation). The virulence/pathogenicity of bacteria inoculated and the presence of foreign debris/devitalized tissue/surgical material in the wound are also considered risk factors for infection.

For all categories of surgical prophylaxis, dosing recommendations are derived from (1) choosing agents based on the organisms likely to be responsible for inoculation of the surgical site; (2) giving the agents at an optimal time (<60 min for cefazolin, or <60 to 120 min for vancomycin and ciprofloxacin) before starting the operation to achieve appropriate serum and tissue exposures at the time of incision; (3) providing additional doses during the procedure at times based on the standard dosing guideline for that agent; and (4) stopping the agents at the end of the procedure or for no longer than 24–48 h after the end of the procedure.^{39–42,45–47} Optimal duration of prophylaxis after delayed sternal or abdominal closure is not well defined in adults or children.

Bathing with soaps or an antiseptic agent the night before surgery is recommended, with alcohol-based presurgical skin preparation.⁴⁴

Procedure/Operation	Recommended Agents	Preoperative Dose	Intraoperative Re-dosing Interval (h) for Prolonged Surgery
Cardiovascular			
Cardiac ⁴⁸ <i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , <i>Corynebacterium</i> spp	Cefazolin	30 mg/kg	4
	Vancomycin, if MRSA likely ⁴²	15 mg/kg	8
	Ampicillin/sulbactam if enteric Gram-negative bacilli a concern	50 mg/kg of ampicillin	3
Cardiac with cardiopulmonary bypass ⁴⁹	Cefazolin	30 mg/kg	15 mg/kg at CPB start and also at rewarming. Begin postoperative prophylaxis 30 mg/kg at 8 h after intraoperative rewarming dose.

Vascular <i>S epidermidis</i> , <i>S aureus</i> , <i>Corynebacterium</i> spp, Gram- negative enteric bacilli, particularly for procedures in the groin	Cefazolin, OR	30 mg/kg	4
	Vancomycin, if MRSA likely ⁴²	15 mg/kg	8
Thoracic (noncardiac)			
Lobectomy, video-assisted thoraco- scopic surgery, thoracotomy (but no prophylaxis needed for simple chest tube placement for pneumothorax)	Cefazolin, OR	30 mg/kg	4
	Ampicillin/sulbactam if enteric Gram-negative bacilli a concern	50 mg/kg of ampicillin	3
	Vancomycin or clindamycin if drug allergy or MRSA likely ⁴²	15 mg/kg vancomycin 10 mg/kg clindamycin	8 6
Gastrointestinal			
Gastroduodenal Enteric Gram-negative bacilli, respira- tory tract Gram-positive cocci	Cefazolin	30 mg/kg	4
Biliary procedure, open Enteric Gram-negative bacilli, entero- cocci, <i>Clostridia</i>	Cefazolin, OR	30 mg/kg	4
	Cefoxitin	40 mg/kg	2
Appendectomy, non-perforated	Cefoxitin, OR	40 mg/kg	2
	Cefazolin and metronidazole	30 mg/kg cefazolin, 10 mg/kg metronidazole	4 for cefazolin 8 for metronidazole

D. SURGICAL/PROCEDURE PROPHYLAXIS^{37–47} (continued)

Procedure/Operation	Recommended Agents	Preoperative Dose	Intraoperative Re-dosing Interval (h) for Prolonged Surgery
Gastrointestinal (continued)			
Complicated appendicitis or other ruptured colorectal viscus⁵⁰ Enteric Gram-negative bacilli, enterococci, anaerobes. For complicated appendicitis, antibiotics provided to treat ongoing infection, rather than prophylaxis.	Cefazolin and metronidazole, OR	30 mg/kg cefazolin and 10 mg/kg metronidazole	4 for cefazolin 8 for metronidazole
	Cefoxitin, OR	40 mg/kg	2
	Ceftriaxone and metronidazole, OR	50 mg/kg ceftriaxone and 10 mg/kg metronidazole	12 for ceftriaxone 8 for metronidazole
	Ertapenem, OR	15 mg/kg (max 500 mg) for children 3 mo–12 y; 1 g for children ≥13 y	8
	Meropenem, OR	20 mg/kg	4
	Imipenem	20 mg/kg	4
Genitourinary			
Cystoscopy (only requires prophylaxis for children with suspected active UTI or those having foreign material placed) Enteric Gram-negative bacilli, enterococci	Cefazolin, OR	30 mg/kg	4
	TMP/SMX (if low local resistance), OR Select a 3rd-generation cephalosporin (cefotaxime) or fluoroquinolone (ciprofloxacin) if the child is colonized with cefazolin-resistant, TMP/SMX-resistant strains.	4–5 mg/kg	N/A
Open or laparoscopic surgery Enteric Gram-negative bacilli, enterococci	Cefazolin	30 mg/kg	4

Head and Neck Surgery

Assuming incision through respiratory tract mucosa Anaerobes, enteric Gram-negative bacilli, <i>S aureus</i>	Clindamycin, OR	10 mg/kg	6
	Cefazolin and metronidazole	30 mg/kg cefazolin and 10 mg/kg metronidazole	4 for cefazolin 8 for metronidazole
	Ampicillin/sulbactam if enteric Gram-negative bacilli a concern	50 mg/kg of ampicillin	3

Neurosurgery

Craniotomy, ventricular shunt placement <i>S epidermidis</i> , <i>S aureus</i>	Cefazolin, OR	30 mg/kg	4
	Vancomycin, if MRSA likely	15 mg/kg	8

Orthopedic

Internal fixation of fractures, spinal rod placement, ⁴³ prosthetic joints <i>S epidermidis</i> , <i>S aureus</i>	Cefazolin, OR	30 mg/kg	4
	Vancomycin, if MRSA likely ⁴²	15 mg/kg	8

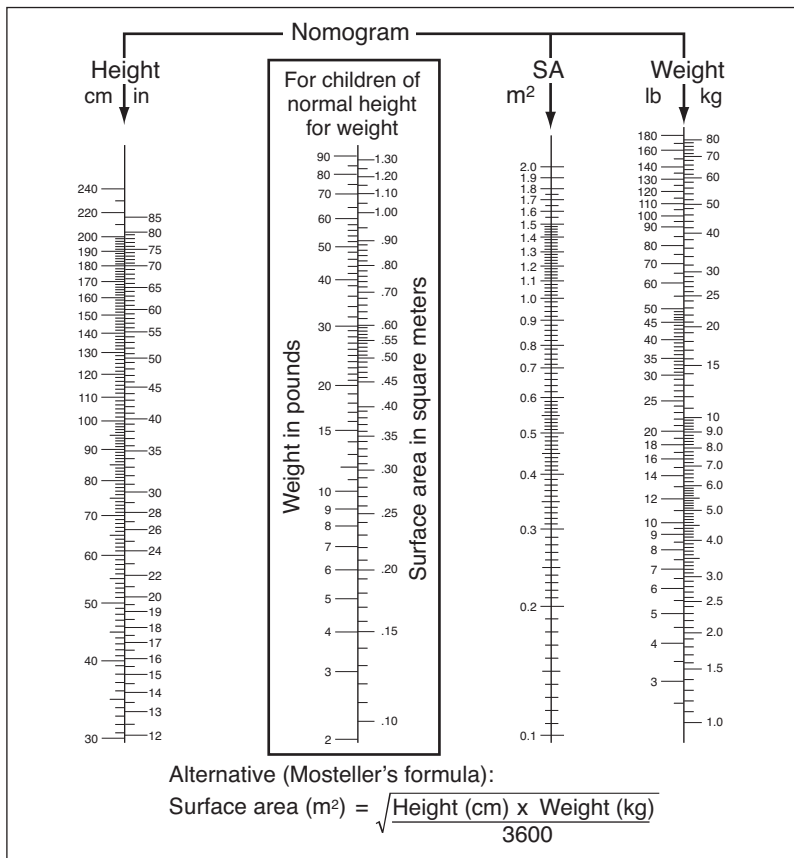
Trauma

Exceptionally varied; no prospective, comparative data in children; agents should focus on skin flora (<i>S epidermidis</i> , <i>S aureus</i>) as well as the flora inoculated into the wound, based on the trauma exposure, that may include enteric Gram-negative bacilli, anaerobes (including <i>Clostridia</i> spp), and fungi. Cultures at time of wound exploration are critical to focus therapy for potential pathogens inoculated into the wound.	Cefazolin (for skin), OR	30 mg/kg	4
	Vancomycin (for skin), if MRSA likely, OR	15 mg/kg	8
	Meropenem OR imipenem (for anaerobes, including <i>Clostridia</i> spp, and non-fermenting Gram-negative bacilli), OR	20 mg/kg for either	4
	Gentamicin and metronidazole (for anaerobes, including <i>Clostridia</i> spp, and non-fermenting Gram-negative bacilli), OR	2.5 mg/kg gentamicin and 10 mg/kg metronidazole	6 for gentamicin 8 for metronidazole
	Piperacillin/tazobactam	100 mg/kg piperacillin component	2

Appendix

Nomogram for Determining Body Surface Area

Based on the nomogram shown below, a straight line joining the patient's height and weight will intersect the center column at the calculated body surface area (BSA). For children of normal height and weight, the child's weight in pounds is used, and then the examiner reads across to the corresponding BSA in meters. Alternatively, Mosteller's formula can be used.



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