292 Antimicrobial Agents

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Antimicrobial agents are essential in the therapy of bacterial infections. The approach to antimicrobial therapy is outlined in Chapter 289 (Principles of Anti-Infective Therapy), providing the clinician with an overview of the selection of agents based on the characteristics of infected children with respect to their pathogens and antibiotic susceptibilities, sites of infection, drug absorption, distribution and elimination, comorbidities, and a consideration of the benefits versus the risks of antimicrobial therapy. In this chapter, the agents themselves are discussed, providing a background on mechanism of action, spectrum of antibacterial activity, antibiotic resistance, and current clinical use. A more detailed discussion for specific infections is found in each chapter describing that infection. An in-depth discussion of antibiotic resistance and the ways to detect resistance is presented in Chapter 291. Pharmacokinetic-pharmacodynamic basis of optimal antibiotic therapy is discussed in Chapter 292. Table 292-1 provides a summary of the pharmacokinetics, tissue distribution, metabolism, and excretion of commonly used antimicrobial agents within each of the antibiotic classes. Table 292-2 provides the spectrum of activity of each antibiotic. Appendices 292-1 and 292-2 provide dosages of antibiotics.

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
AMINOGLYCOSIDES						
Gentamicin, amikacin, kanamycin, tobramycin	Poorly absorbed	<25%	Primarily to extracellular fluids and vascularized tissues, fetus, ascitic, synovial, and amniotic fluid; minimally into CSF	None	Renal	Neonates <1 week, 5–14 hours (varies inversely with birthweight) Neonates >1 week and infants, 3–5 hours Children/adults, ~2 hours
Streptomycin	Poorly absorbed	35%	Same as gentamicin	10–30% at unknown site	Renal	Neonates, 4–10 hours Adults, 2–3 hours
β-LACTAMS						
Penicillin G	Erratic, 15–80% Not available in oral formulation	60–65%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic <30%	Renal	Neonates, 1–3 hours varies inversely with (postnatal age) Infants/children, 0.5–1.2 hours
Penicillin V	60%	80%	Penetrates most tissues; poorly into CSF, not used to treat meningitis	Same as penicillin G with additional gut inactivation (metabolized) of 35–70% of an oral dose	Same as penicillin G	Adults, 0.5 hour
PENICILLINASE-RESISTANT PENICILLINS						
Dicloxacillin	35–76% Give on empty stomach	98%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF	Hepatic 10%	Renal	Adults, 30–40 minutes
Oxacillin	No oral form available	94%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic ~50%	Renal	Neonates and infants, 1–2 hours Adults, 30–60 minutes
Nafcillin	Not administered orally	90%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 60%	Biliary (with enterohepatic recirculation); renal 10–30%	Neonates, 2.2–5.5 hours Infants, 1–2 hours Children and adults, 30–90 minutes

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents—cont'd

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
AMINOPENICILLINS						
Amoxicillin	85%	20%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal	Neonates, 3.7 hours Children, 1–2 hours Adults, 1–1.5 hours
Clavulanate (amoxicillin pharmacokinetics not affected by clavulanate)	Well absorbed	25%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF	Hepatic extensive	Renal 25–40%	Adults, 1 hour
Ampicillin	50%	22% 10% in neonates	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal	Neonates, <1 week, 3–6 hours Neonates, >1 week, 2–4 hours Children, 1–2 hours Adults, 1–1.5 hours
Sulbactam	Not administered orally	38%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal	Adults 1–1.5 hours
EXTENDED-SPECTRUM PENICILLINS						
Carbenicillin (as indanyl sodium)	30–40%	50%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic minimal	Renal	Neonates, ~3 hours Children/adults, ~1 hour
Ticarcillin	Not administered orally	45%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic 10%	Renal	Neonates <1 week, 4–5 hours Neonates >1 week, ~2 hours Infants/children, ~1 hour
Piperacillin	Not administered orally	15–20%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic minimal	Renal; biliary <20%	Neonates, 2–3 hours Infants/children, 0.5–1 hour Adults, 0.5 hour (increases to 1–1.5 hours for high dose due to saturation of hepatobiliary excretion (dose-dependent $t_{1/2}$))
Tazobactam (piperacillin kinetics are unaffected by tazobactam)	Not administered orally	20–23%	Penetrates most tissues, fetus, and amniotic fluid; poorly into CSF[b]	Hepatic minimal	Renal	Infants, 1.6 hours Children/adults, 45 minutes–1 hour
CEPHALOSPORINS **FIRST-GENERATION**						
Cefadroxil	Well absorbed	20%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal (slower excretion rate than cephalexin)	Adult, 1–2 hours
Cefazolin	Not administered orally	80%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal	Neonates, 3–5 hours Adult, 1.5–2.5 hours
Cephalexin	Well absorbed; ↓ with food	6%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal; some biliary	Neonates, 5 hours Infants, 2.5 hours Children/adults, 1 hour
Cephradine	Well absorbed; ↓ with food	10%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal; some biliary	Children/adults, ~1 hour

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents—cont'd

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
SECOND-GENERATION						
Cefaclor	Well absorbed	25%	Penetrates most tissues; unknown fetal, amniotic, and CSF distribution	Unknown	Renal (nonrenal: elimination at unknown site in renal failure)	Adults, 0.5–1 hour
Cefprozil	95%	36%	Penetrates middle-ear fluids and tonsillar, adenoidal, skin, and soft tissues well; unknown fetal, amniotic and CSF distribution	Unknown	Renal; nonrenal 30%	Infants/children, 1.5–2 hours Adults, 1–1.5 hours
Cefuroxime	37% (as axetil); ↑ to 52% when given with food	50%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF	None	Renal	Neonates, 3–6 hours Infants/children, 1.5–2 hours Adults, 1.2 hours
Cefoxitin	Not administered orally	75%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[a]	Hepatic minimal	Renal	Neonates, 1.4 hours Infants/children/adults, ~45 minutes
Loracarbef	90% but can with food	25%	Penetrates most tissues, unknown fetal, amniotic and CSF distribution	None	Renal	Children/adults, ~1 hour
THIRD-GENERATION						
Cefdinir	16–21% cap; 25% suspension	60–70%	Penetrates most tissues; unknown fetal, amniotic and CSF distribution	None	Renal	Adults, 1.7 hours
Cefixime	40–50%	65–70%	Not well studied	Unknown	Renal, biliary	Adults, 3–4 hours
Cefoperazone	Not administered orally	90%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[a]	Hepatic <20%	Biliary, renal 20–30%	Neonates, 6–10 hours (varies inversely with postnatal age) Infants/children, 2.2–2.3 hours Adults, ~2 hours
Cefotaxime	Not administered orally	35–40%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	Hepatic	Renal	Neonates, 2–6 hours (varies inversely with gestational and postnatal age) Infants/children, 1–1.5 hours Older children/adults, 45 minutes–1 hour
Cefpodoxime	50%	20–30%	Penetrates most tissues, unknown fetal, amniotic, and CSF distribution	None	Renal	Adults, 2–3 hours
Ceftazidime	Not administered orally	<10%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	None	Renal	Neonates, 4–7 hours (varies inversely with gestational age) Adults, 1.4–2 hours
Ceftibuten	>90%	65–77%	Penetrates most tissues, unknown fetal, amniotic, and CSF distribution	Hepatic minimal	Renal	Children/adults, 1.5–2.5 hours
Ceftizoxime	Not administered orally	31%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[b]	None	Renal	Neonates, 2–4 hours Adults, 1–2 hours

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents—cont'd

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
Ceftriaxone	Not administered orally	95%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	None	Renal; biliary	Neonates, 9–19 hours Children, 4–7 hours Adults, 6–9 hours
Fourth-generation						
Cefepime	Not administered orally	20%	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	Hepatic minimal	Renal	Neonates, 3–7 hours Children/adults, ~2 hours
Other β-lactams, monobactams						
Aztreonam	Not administered orally	50–70%	Penetrates most tissues, fetus, and amniotic fluid; minimally into CSF[b]	Minimal hydrolysis at unknown site	Renal; biliary minor	Neonates <1 week, 6–10 hours (varies inversely with birthweight) Neonates >1 week, ~3 hours Children/adults, 1.5–2 hours
Carbapenems						
Meropenem	Not administered orally	Minimal	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b]	Renal, serum, hepatic 20–25%	Renal; biliary minor	Neonates, 2–3 hours Infants, 1.5 hours Adults, 1 hour
Imipenem (I) + cilastatin (C)	Not administered orally	20% (I) 40% (C)	Penetrates most tissues, fetus, and amniotic fluid; adequately into CSF[b] but relatively contraindicated for meningitis	Renal, serum, hepatic 20–25%	Renal; biliary minor	Neonates, 1.5–2.5 hours (cilastatin 3–8 hours) Infants/children, 1–1.4 hours Adults, ~1 hour
Ertapenem	Not administered orally	95%	Penetrates interstitial fluids; unknown fetal, amniotic, and CSF distribution	Renal 20%, hepatic minor	Renal; biliary minor	Infants/children, 2.5 hours Adolescents/adults, 4 hours
Chloramphenicol succinate (injection)	PO forms (base and palmitate salt) not available	~50%	Widely distributed including fetal, amniotic, and CSF	Hepatic	Renal (as succinate salt and glucuronide metabolite) biliary minimal	Highly variable; see text
Fluoroquinolones and quinolones						
Ciprofloxacin	60–80%; >90% in adolescents with CF	20–40%	Penetrates most tissues, fetus, amniotic fluid; minimally into CSF[b]	Hepatic <20%	Renal, feces	Neonates/infants/children/adults, ~3–5 hours
Gatifloxacin	96%	20%	Penetrates most tissues including CSF; fetal, amniotic unknown	Minimal	Renal	Infants/children, 4–7 hours Adults, 7–8 hours
Levofloxacin	99%	24–38%	Penetrates most tissues, fetus, amniotic fluid, CSF	Minimal	Renal	Infants/children, 4–7 hours Adults, 6–8 hours
Norfloxacin	30–40%	10–15%	Penetrates GU and GI, fetus and amniotic fluid; CSF unknown	Hepatic extensive	Renal, biliary	Adults, 3–4 hours
Nalidixic acid	>90%	90–95%	Not widely distributed; penetrates renal tissue well; crosses placenta	Hepatic, renal	Renal (85% as inactive form)	Adults, 1.5 hours

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents—cont'd

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
KETOLIDES						
Telithromycin	57%	60–70%	Widely distributed; fetal, amniotic fluid and CSF unknown	Hepatic	Renal, biliary	Adults, 9–10 hours
LINCOSAMIDES						
Clindamycin	90%	94%	Penetrates most tissues, fetus, amniotic fluid; minimally into uninflamed CSF, but adequately into inflamed CSF or brain abscess	Hepatic	Biliary; renal minor	Neonates, 3.6–8.7 hours (inversely related to gestational age and birthweight) Infants/children/adults, ~2–3.5 hours
LIPOPEPTIDES						
Daptomycin	Not administered orally	~90%	Limited distribution; fetal, amniotic, and CSF penetration unknown	Renal	Renal	Adults, 7–10 hours
MACROLIDES AND AZALIDES						
Azithromycin	37%	20–50%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary; renal, minimal	Infants/children, >50 hours Adults, 35–40 hours
Clarithromycin	50–55%	60–70%	Penetrates most tissues, fetus; CSF penetration unknown	Hepatic	Renal 40–50% (as drug and active metabolite)	Infants/children/adults, 3–7 hours (dose-dependent)
Erythromycin	Poor, 25–65% depending on salt and form	80–90%	Penetrates most tissues, fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary, renal minimal	Adult, 1–2 hours (estolate 3–8 hours)
METRONIDAZOLE	100%	<20%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic	Renal (60–80% with 10–20% as unchanged drug); biliary minor	Neonates, 22.5 to 109 hours (varies inversely with gestational age) Children/adults, 6–14 hours
NITROFURANTOIN	Well absorbed	90%	Mainly urinary tract, prostate, and placenta	Tissues	Renal, biliary	Adults, 20 minutes
OXAZOLIDINONES						
Linezolid	100%	31%	Penetrates most tissues, including CSF; fetus, amniotic fluid unknown	Hepatic	Renal	Neonates, 1.5–10 hours (varies inversely with gestational age) Infants/children, 2–3 hours Adults, 3–6 hours
POLYMYXINS						
Colistimethate (injection)	Not administered orally	Minimal	Penetrates most tissues, fetus and amniotic fluid; minimal to pleural or joint cavities or to CSF	Tissue minor and slow	Renal	Children, 2–3 hours Adults, 1.5–3 hours
RIFAMYCINS						
Rifampin	90–95%	60–90%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Biliary, renal	Infants/children/adults, ~2–4 hours

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TABLE 292-1. Pharmacokinetics, Tissue Distribution, Metabolism, and Excretion of Antimicrobial Agents—cont'd

Agent	Oral Bioavailability	Protein Binding	Body Distribution and CSF Penetration	Metabolism	Excretion	$t_{1/2}$[a] (Elimination)
Rifaximin	Poorly absorbed	N/A	Minimal systemic distribution due to poor oral bioavailability, but high intraluminal GI concentrations	Hepatic minimal	Feces absorption	Minimal systemic
STREPTOGRAMINS						
Quinupristin-dalfopristin	Not administered orally	55–78% (Q) 11–26% (D)	Penetrates most tissues; minimally into CSF; fetus, amniotic fluid unknown	Hepatic, conversion to several active metabolites	Biliary; renal ~15%	Adults, 0.85 hours (Q) 0.75 hours (D) 2.5–3.5 hours (Q + m) ~1 hour (D + m): m = metabolites
SULFONAMIDES AND TRIMETHOPRIM						
Sulfadiazine	100%	20%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugated forms)	Adults, 7–17 hours
Sulfamethoxazole	100%	65%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugated forms)	Adults, 9–12 hours
Sulfisoxazole	100%	85%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic wide individual variation	Renal (free and conjugated forms)	Adults, 5–8 hours
Trimethoprim	100%	~45%	Widely distributed, including fetus, amniotic fluid, CSF	Hepatic <20%	Renal	Infants/children, 3–5.5 hours Adults, 8–10 hours
TETRACYCLINES AND GLYCYLCYCLINES						
Doxycycline	90–100%	82%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic	Renal, biliary	Adults, ~20 hours
Minocycline	90–100%	76%	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic minimal	Biliary, renal	Adults, 11–22 hours
Tetracycline (T), Demeclocycine (D)	75–80%; decreases significantly with food	65% (T) 41–91% (D)	Widely distributed including fetus, amniotic fluid; minimally into CSF[b]	Hepatic minimal	Renal, biliary	Adults, 7–10 hours (T) Adults, 10–17 hours (D)
Tigecycline	Not administered orally	70–90%	Widely distributed; fetal, amniotic fluid and CSF unknown	Hepatic 5–20%	Biliary, renal	Adults, 40 hours
GLYCOPEPTIDES						
Vancomycin	Negligible	30%	Penetrates most tissues, fetus, amniotic fluid; adequately but erratically into CSF[b]	None	Renal; biliary minimal	Neonates, 4–11 hours (varies inversely with gestational age) Infants, 2–4 hours Children, 2–2.5 hours Adults, 4–6 hours

CF, cystic fibrosis; CSF, cerebrospinal fluid; GI, gastrointestinal; GU, genitourinary; IV, intravenous; PO, orally.

[a]*Agents with both minimal metabolism and urinary excretion will have a prolonged* $t_{1/2}$ *in a patient with renal impairment.*

[b]*Concentration of drug in CSF significantly increased with inflamed meninges.*

TABLE 292-2. Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class

I. Cell Wall-Active Agents		
A. Antibiotic Class: Transpeptidase Inhibitors		
	β-Lactam Antibiotics	**Spectrum of Activity[a]**
PENICILLINS		
Natural penicillins	Penicillin G Penicillin V Benzathine penicillin G Procaine penicillin G Benzathine/procaine penicillin G combinations	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis*[b] *Enterococcus faecium*[b] *Actinomyces* *Bacillus anthracis* *Listeria monocytogenes* **Gram-negative** *Eikenella corrodens* *Neisseria meningitidis* *Neisseria gonorrhoeae* *Pasteurella multocida* *Borrelia burgdorferi* *Spirillum minus* *Streptobacillus moniliformis* *Treponema pallidum* *Leptospira* species **Anaerobes** *Bacteroides* and *Prevotella* species (non-β-lactamase-producing strains) *Fusobacterium* species *Veillonella* species *Clostridium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species *Propionibacterium* species
Penicillinase-stable penicillins	Methicillin Oxacillin Nafcillin Cloxacillin Dicloxacillin	**Gram-positive** Streptococci (as above for penicillins) *Staphylococcus aureus* (except MRSA)
Aminopenicillins	Ampicillin Amoxicillin	**Gram-positive** Streptococci (as above for penicillins) *Enterococcus faecalis*[b] *Enterococcus faecium*[b] *Listeria monocytogenes* **Gram-negative** *Escherichia coli* *Haemophilus influenzae* *Neisseria meningitidis* **Anaerobes** For ampicillin: as above for penicillins
	Amoxicillin/clavulanate	Adds activity to amoxicillin: *Staphylococcus aureus* (except MRSA) *Haemophilus influenzae,* β-lactamase-producing strains **Anaerobes** As above for penicillins, but now includes: *Bacteroides* and *Prevotella* species, β-lactamase-producing strains
	Ampicillin/sulbactam	Adds activity to ampicillin: *Staphylococcus aureus* (except MRSA) *Escherichia coli*, β-lactamase-producing strains *Klebsiella* species *Proteus mirabilis* *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Morganella morganii* **Anaerobes** As above for penicillins, but now includes: *Bacteroides* and *Prevotella* species (β-lactamase-producing strains)
Extended-spectrum pencillins	Carbenicillin Ticarcillin Piperacillin	**Gram-positive** Streptococci (as above for penicillins) **Gram-negative** *Escherichia coli* *Haemophilus influenzae* *Proteus mirabilis* *Proteus vulgaris* *Morganella morganii* *Pseudomonas aeruginosa* *Providencia rettgeri* *Enterobacter* species **Anaerobes** *Bacteroides* and *Prevotella* species (non-β-lactamase-producing strains) *Fusobacterium* species *Veillonella* species *Clostridium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species
	Ticarcillin/clavulanate Piperacillin/tazobactam	Adds β-lactamase-producing strains of: *Staphylococcus aureus* (except MRSA) *Escherichia coli* *Haemophilus influenzae* *Klebsiella* species *Serratia marcescens* *Citrobacter* species *Enterobacter* species **Anaerobes** *Bacteroides* and *Prevotella* species (including β-lactamase-producing strains) *Fusobacterium* species *Veillonella* species *Clostridium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species

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TABLE 292-2. Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class—cont'd

I. Cell Wall-Active Agents

A. Antibiotic Class: Transpeptidase Inhibitors

	β-Lactam Antibiotics	Spectrum of Activity[a]
CEPHALOSPORINS		
First-generation	Cephalothin Cephapirin Cefazolin Cephalexin Cephradine Cefadroxil	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA) **Gram-negative** *Escherichia coli* *Proteus mirabilis*
Second-generation	Cefamandole Cefuroxime Cefonicid Ceforanide Cefaclor Cefoxitin Cefotetan	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA) **Gram-negative** *Escherichia coli* *Haemophilus influenzae* (including β-lactamase-producing strains) *Klebsiella* species *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Neisseria meningitidis* *Proteus mirabilis* *Providencia rettgeri* *Salmonella* species *Shigella* species **Anaerobes** *Bacteroides* and *Prevotella* species (non-β-lactamase-producing strains, except for cefoxitin and, to a lesser extent, cefotetan) *Fusobacterium* species *Veillonella* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species
Third-generation	Cefotaxime Ceftriaxone Ceftazidime Cefoperazone Ceftizoxime Cefixime Cefpodoxime Ceftibuten Cefdinir	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA) **Gram-negative** *Citrobacter* species *Enterobacter* species *Escherichia coli* *Haemophilus influenzae* (including β-lactamase-producing strains) *Klebsiella* species *Morganella morganii* *Neisseria gonorrhoeae* (including β-lactamase-producing strains) *Neisseria meningitidis*

I. Cell Wall-Active Agents

A. Antibiotic Class: Transpeptidase Inhibitors

	β-Lactam Antibiotics	Spectrum of Activity[a]
		Proteus mirabilis *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Serratia marcescens* For ceftazidime and cefoperazone: *Pseudomonas aeruginosa* **Anaerobes** *Bacteroides* and *Prevotella* species (non-β-lactamase-producing strains) *Fusobacterium* species *Eubacterium* species *Peptococcus* species
Fourth-generation	Cefepime	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* (except MRSA) **Gram-negative** As above for third-generation cephalosporins, but including *Pseudomonas aeruginosa*) **Anaerobes** *Bacteroides* and *Prevotella* species (non-β-lactamase-producing strains) *Fusobacterium* species *Veillonella* species *Eubacterium* species *Peptococcus* species
Fifth-generation	Ceftaroline	As above for third-generation cephalosporins, but also includes MRSA strains of *Staphylococcus aureus*
CARBAPENEMS	Imipenem (with cilastatin) Meropenem Ertapenem Doripenem	**Gram-positive** Streptococci Groups A, B, C, D, G, F Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis* *Staphylococcus aureus* (except MRSA) **Gram-negative** *Acinetobacter* species *Citrobacter* species *Enterobacter* species *Escherichia coli* (including ESBL-producing strains) *Gardnerella vaginalis* *Haemophilus influenzae* *Klebsiella* species (including ESBL-producing strains) *Morganella morganii* *Proteus vulgaris* *Providencia rettgeri* *Pseudomonas aeruginosa* (except ertapenem) *Serratia* species

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TABLE 292-2. Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class—cont'd

I. Cell Wall-Active Agents		
A. Antibiotic Class: Transpeptidase Inhibitors		
	β-Lactam Antibiotics	**Spectrum of Activity[a]**
CARBAPENEMS (cont'd)		**Anaerobes** *Bifidobacterium* species *Clostridium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species *Propionibacterium* species *Bacteroides* and *Prevotella* species (including β-lactamase-producing strains) *Fusobacterium* species
MONOBACTANS	Aztreonam	**Gram-negative** *Citrobacter* species *Enterobacter* species *Escherichia coli* *Haemophilus influenzae* (including β-lactamase-producing strains) *Klebsiella* species *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia* species
B. Antibiotic Class: Transglycosylase Inhibitors		
		Spectrum of Activity[a]
GLYCOPEPTIDES	Vancomycin Teicoplanin (not available in the United States)	**Gram-positive** Streptococci Groups A, B, C, G, F Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis*[b] *Enterococcus faecium*[b] *Staphylococcus aureus* (including MRSA, but not vancomycin-intermediate or vancomycin-resistant strains) *Staphylococcus epidermidis* *Actinomyces* species *Lactobacillus* species *Listeria monocytogenes* **Anaerobes** *Clostridium difficile*
II. Cell Membrane Active Agents		
A. Antibiotic Class: Lipopeptides		
		Spectrum of Activity[a]
	Daptomycin	*Staphylococcus aureus* (including methicillin-resistant and vancomycin-resistant strains) *Enterococcus faecalis* (vancomycin-susceptible and -resistant strains) *Enterococcus faecium* (vancomycin-susceptible and -resistant strains) Streptococci Groups A, B Viridans group streptococci
B. Antibiotic Class: Polymyxins		
	Colistin	*Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Actinobacter* species *Citrobacter* species
II. Cell Membrane Active Agents		
B. Antibiotic Class: Polymyxins		
		Haemophilus species *Salmonella* species *Shigella* species
III. Ribosome-Active Agents		
A. Antibiotic Class: Macrolides		
MACROLIDES	Erythromycin	**Gram-positive** *Corynebacterium diphtheriae* *Corynebacterium minutissimum* *Listeria monocytogenes* *Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* **Gram-negative** *Bordetella pertussis* *Legionella pneumophila* *Neisseria gonorrhoeae* **Other pathogens** *Chlamydia trachomatis* *Entamoeba histolytica* *Mycoplasma pneumoniae* *Treponema pallidum* *Ureaplasma urealyticum*
	Clarithromycin	**Gram-positive** *Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* **Gram-negative** *Haemophilus influenzae* *Moraxella catarrhalis* *Helicobacter pylori* **Other pathogens** *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Mycobacterium avium* complex
AZALIDES	Azithromycin	**Gram-positive** *Staphylococcus aureus* Streptococci Groups A, B C, F, G Viridans group streptococci *Streptococcus pneumoniae* *Bordetella pertussis* **Gram-negative** *Haemophilus influenzae* *Haemophilus ducreyi* *Moraxella catarrhalis* *Neisseria gonorrhoeae* **Other pathogens** *Chlamydophila pneumoniae* *Chlamydia trachomatis* *Legionella pneumophila* *Mycoplasma hominis* *Mycoplasma pneumoniae* *Ureaplasma urealyticum*
KETOLIDES	Telithromycin	**Gram-positive** *Staphylococcus aureus* Streptococci Groups A, C and G Viridans group streptococci **Gram-negative** *Haemophilus influenzae* *Moraxella catarrhalis* **Other pathogens** *Bordetella pertussis* *Mycoplasma pneumoniae* *Legionella pneumophila* *Chlamydophila pneumoniae*

Continued

TABLE 292-2. Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class—cont'd

III. Ribosome-Active Agents		
B. Antibiotic Class: Tetracyclines		
TETRACYCLINES	Tetracycline Minocycline Doxycycline	**Gram-positive** *Actinomyces* species **Gram-negative** *Vibrio cholerae* *Brucella* species *Campylobacter* species *Francisella tularensis* *Listeria monocytogenes* *Yersinia pestis* *Neisseria meningitidis* *Neisseria gonorrhoeae* **Other pathogens** *Borrelia recurrentis* *Chlamydophila psittaci* *Chlamydia trachomatis* *Mycoplasma pneumoniae* *Ureaplasma* *Treponema pallidum* *Entamoeba* species
GLYCYLCYCLINES	Tigecycline	**Gram-positive** Streptococci Groups A, B Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis* *Enterococcus faecium* *Staphylococcus aureus* *Listeria monocytogenes* *Clostridium perfringens* *Peptostreptococcus* species **Gram-negative** *Acinetobacter baumannii* *Aeromonas hydrophila* *Citrobacter freundii* *Citrobacter koseri* *Enterobacter cloacae* *Enterobacter aerogenes* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Pasteurella multocida* *Serratia marcescens* *Stenotrophomonas maltophilia* *Bacteroides* species **Other pathogens** *Chlamydia trachomatis* *Mycoplasma pneumoniae* *Ureaplasma* *Mycobacterium abscessus* *Mycobacterium chelonae* *Mycobacterium fortuitum*
C. Antibiotic Class: Lincosamides		
LINCOSAMIDES	Clindamycin	**Gram-positive** Streptococci Groups A, B *Streptococcus pneumoniae* *Staphylococcus aureus*
III. Ribosome-Active Agents		
C. Antibiotic Class: Lincosamides		
		Anaerobes *Bacteroides fragilis* *Prevotella melaninogenica* *Fusobacterium* species *Peptococcus* species *Peptostreptococcus* species *Actinomyces* species *Clostridium perfringens* *Propionibacterium* species
D. Antibiotic Class: Aminoglycosides		
AMINOGLYCOSIDES	Streptomycin	**Gram-negative** *Brucella* species *Francisella* species *Mycobacterium tuberculosis*
	Gentamicin Netilmicin Tobramycin Amikacin	**Gram-positive** *Staphylococcus aureus* **Gram-negative** *Escherichia coli* *Klebsiella* species *Enterobacter* species *Serratia* species *Citrobacter* species *Morganella morganii* *Acinetobacter* species *Providencia* species *Proteus mirabilis* *Proteus vulgaris* *Pseudomonas aeruginosa*
	Paromomycin	*Entamoeba histolytica* *Dientamoeba fragilis* *Cryptosporidium* species
E. Antibiotic Class: Oxazolidinones		
OXAZOLIDINONES	Linezolid	**Gram-positive** Streptococci Groups A, B Viridans group streptococci *Streptococcus pneumoniae* *Staphylococcus aureus* *Enterococcus faecium* *Enterococcus faecalis*
F. Antibiotic Class: Streptogramins		
STREPTOGRAMINS	Quinupristin/dalfopristin	**Gram-positive** Streptococci Groups A, B *Staphylococcus aureus* *Enterococcus faecium*
IV. Nucleic Acid-Active Antibiotics		
A. Antibiotic Class: Rifamycins		
RIFAMYCINS	Rifampin	**Gram-positive** *Staphylococcus aureus* **Gram-negative** *Neisseria meningitidis* *Haemophilus influenzae* **Other** *Mycobacterium tuberculosis* *Mycobacterium avium* complex

Continued

TABLE 292-2. Spectrum of Activity of Antimicrobial Agents by Microbial Site of Activity and Antimicrobial Drug Class—cont'd

IV. Nucleic Acid-Active Antibiotics		
A. Antibiotic Class: Rifamycins		
	Rifabutin	*Mycobacterium tuberculosis*
	Rifapentine	*Mycobacterium avium* complex
	Rifaximin	Susceptible at concentrations achieved within the gastrointestinal lumen: *Campylobacter* *Escherichia coli* *Salmonella* species *Shigella* species *Vibrio* species *Yersinia* species
B. Antibiotic Class: Quinolones		
Quinolones	Nalidixic acid	**Gram-negative** *Escherichia coli* *Enterobacter* species *Morganella morganii* *Proteus mirabilis* *Proteus vulgaris* *Providencia rettgeri*
Fluoroquinolones	Ciprofloxacin	**Gram-positive** *Streptococcus pyogenes* *Streptococcus pneumoniae* *Staphylococcus aureus* *Enterococcus faecalis* *Bacillus anthracis* **Gram-negative** *Aeromonas* species *Acinetobacter* species *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter cloacae* *Citrobacter diversus* *Citrobacter freundii* *Campylobacter jejuni* *Proteus mirabilis* *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Serratia marcescens* *Pseudomonas aeruginosa* *Morganella morganii* *Salmonella* species *Shigella* species *Haemophilus influenzae* *Haemophilus parainfluenzae* *Moraxella catarrhalis* *Neisseria gonorrhoeae*[b] *Pasteurella multocida* *Vibrio* species *Yersinia enterocolitica* **Other pathogens** *Legionella pneumophila*
IV. Nucleic Acid-Active Antibiotics		
B. Antibiotic Class: Quinolones		
	Levofloxacin Gemifloxacin Moxifloxacin	**Gram-positive** Streptococci Group A Viridans group streptococci *Streptococcus pneumoniae* *Enterococcus faecalis* *Staphylococcus aureus* *Actinomyces* species *Bacillus anthracis* *Listeria monocytogenes* **Gram-negative** *Acinetobacter* species *Escherichia coli* *Enterobacter* species *Klebsiella* species *Proteus* species *Providencia* species *Serratia marcescens* *Citrobacter* species *Morganella morganii* *Pseudomonas aeruginosa* *Haemophilus influenzae* *Moraxella catarrhalis* **Anaerobes** *Clostridium perfringens* **Other pathogens** *Legionella pneumophila* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae*
C. Antibiotic Class: Nitroimadazoles		
Nitroimadazoles	Metronidazole	**Anaerobes** *Clostridium* species *Eubacterium* species *Peptococcus* species *Peptostreptococcus* species *Bacteroides fragilis* *Fusobacterium* species
D. Antibiotic Class: Sulfonamides		
Sulfonamides	Sulfisoxazole Sulfamethoxazole	
Sulfa in combination with another antimicrobial agent	Sulfamethoxazole plus trimethoprim	**Gram-positive** *Streptococcus pneumoniae*[b] **Gram-negative** *Escherichia coli* *Klebsiella* species *Enterobacter* species *Morganella morganii* *Proteus mirabilis* *Proteus vulgaris* *Shigella* species *Haemophilus influenze* **Other pathogens** *Pneumocystis jirovecii*
	Sulfadiazine plus pyramethamine	*Toxoplasma gondii* *Plasmodium* species

ESBL, extended-spectrum β-lactamases; MRSA, methicillin-resistant Staphylococcus aureus.

[a]*A majority of strains of the listed bacteria are susceptible; however, some organisms within the group may be less susceptible or resistant to one or more agents listed. Susceptibility pattern for each pathogen and antibiotic may be available to physicians through local health care institutions.*

[b]*Important exceptions exist.*

CELL WALL-ACTIVE AGENTS

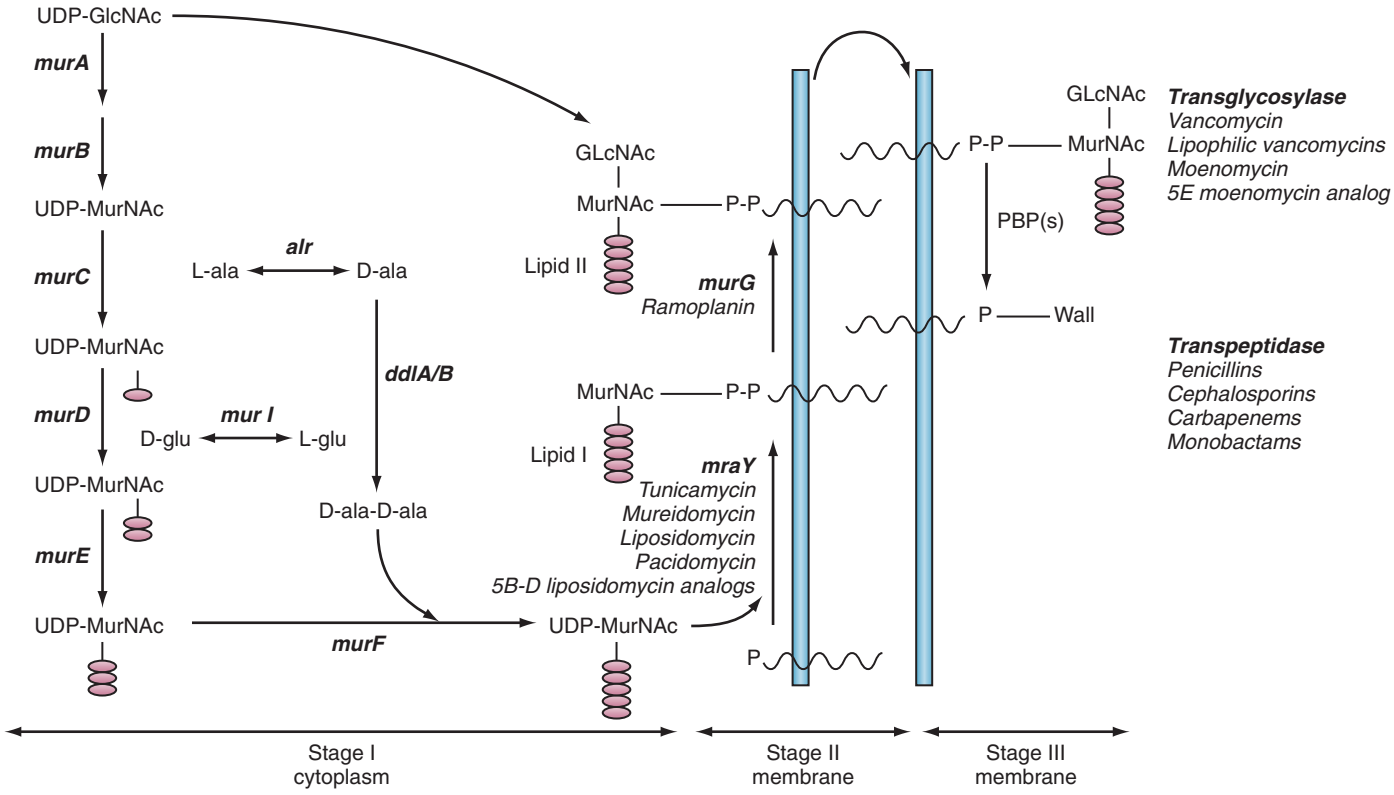
The synthesis of the bacterial cell wall is remarkably complicated and still is not understood fully.[1–3] Several steps are involved in cell wall creation, from the synthesis of precursors within the bacterial cytoplasm to the intricate construction of a lattice-like structure around the organism that maintains cell shape and osmotic integrity. Gram-negative cell walls consist of inner (plasma) and outer membranes, and are more complicated than those of gram-positive organisms that contain a single membrane. Many steps in cell wall synthesis have been exploited as targets of currently available antimicrobial agents and others provide potential targets for ongoing anti-infective research (Figure 292-1). Our understanding of mechanisms of cell death following interruption of cell wall synthesis has increased to include both direct mechanisms from cell wall damage, as well as initiation of metabolic pathways for programmed cell death.[3]

The saccharide precursors of cell walls, *N*-acetylmuramic acid (MurNAc), and *N*-acetylglucosamine (GlcNAc) are modified enzymatically by a series of steps, with MurNAc acquiring a side chain consisting of five peptides, incorporating D-alanine, D-alanine as the terminal two amino acids in this chain. This MurNAc-pentapeptide is subsequently attached to a GlcNAc saccharide unit, completing the disaccharide pentapeptide building block required for cell wall peptidoglycan formation (see Figure 292-1). Agents that inhibit these initial steps have been identified in a research setting and many are currently under investigation as clinically important targets.[4,5] The disaccharide pentapeptide building block subsequently is transferred through the cell membrane to undergo further modification ultimately to create the peptidoglycan structure either outside the cell membrane (in gram-positive organisms), or between the inner plasma membrane and outer membrane within the cell wall (in gram-negative organisms). Linking of the disaccharide pentapeptide building blocks occurs by transglycosylation, and creates repeating disaccharide subunits (Glc NAc-MurNAc-pentapeptide) to produce long glycan chains.[6] Vancomycin and related glycopeptide antibiotics inhibit this step in cell wall synthesis by binding to the terminal D-ala, D-ala of the pentapeptide attached to MurNAc, and interfering sterically with the enzymatic function of the transglycosylase.[7]

The mature glycan chains containing the repeating disaccharide units are subsequently linked by connecting the pentapeptides located on the MurNAc units from adjacent glycan chains. In this transpeptidation step, a stable bridge is created between glycan chains to form the two-dimensional peptidoglycan structure.[6] The β-lactam class of antibiotics inhibits the transpeptidase function by binding covalently to the active serine site of the enzyme responsible for linking the two pentapeptide arms from MurNAc units on adjacent glycan strands.[8] The structure of enzymes that are responsible for transglycosylation and transpeptidation varies somewhat between bacteria. Fortunately, the active sites of these enzymes tend to be quite conserved. An organism often contains several transpeptidases, each responsible for a different cell wall function, including repair, elongation, septation, and cell wall thickening, among others. Some of these enzymes contain both transglycosylation and transpeptidation functions. Historically, these enzymes were identified by penicillin attachment to them, and are also known as penicillin-binding proteins, or PBPs.

β-Lactam Antibiotics

The β-lactam antibiotics all share the capacity to inhibit the transpeptidase cross-linking of peptidoglycan in the final steps of



UDP, uridine diphosphate; MurNAc, N-Acetylmuramic acid; GLcNAc, N-Acetylglucosamine; PBP(s), penicillin binding proteins (transpeptidase); L-ala, L-alanine; D-ala, D-alanine.

Figure 292-1. The peptidoglycan synthesis pathway in cell wall formation. (Redrawn with modification from Wong VK, Pompliano DL Peptidoglycan biosynthesis: unexploited targets within a familiar pathway. In: Rosen BP, Mobashery S (eds) Resolving the Antibiotic Paradox. New York, Kluwer Academic/Plenum Publishers, 1998, pp 197–217.)

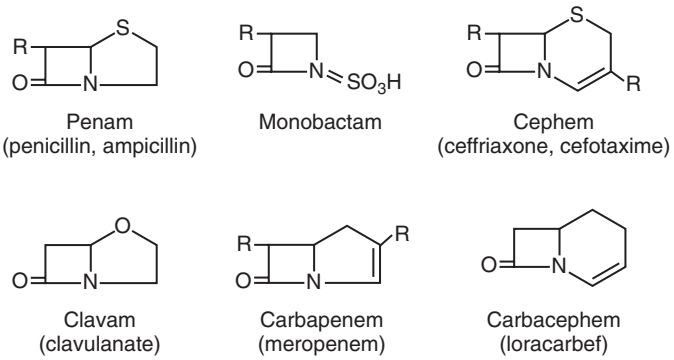


Figure 292-2. β-Lactam antibiotic structures.

formation of the cell wall. Whereas the β-lactam structure itself is consistent across all antibiotics in this class, the ring to which the lactam moiety is fused is variable, with relatively small differences in the composition of the ring allowing for variable activity against the PBPs of both gram-positive and gram-negative bacteria (Figure 292-2). The addition of chemical "chains" to the ring structures enhances activity against certain organisms, but simultaneously can decrease activity against others. Differences in the charges of the antibiotic molecule affect the ability of the compound to reach and to bind to its target, particularly for gram-negative pathogens.

In general, the β-lactam antibiotics are bactericidal with the concentrations required for killing being very close to those required for inhibition of growth. The maximal bactericidal effect occurs on rapidly growing bacteria; in stationary phase, this class of antibiotics has substantially less impact on the viability of organisms.[9]

Resistance to β-Lactam Antibiotics

Probably just as ancient as the natural antibiotics are natural mechanisms of resistance to them (Figure 292-3). Resistance to the β-lactam antibiotics occurs primarily in four ways: (1) enzymatic hydrolysis of the β-lactam ring by bacterial β-lactamases, rendering the antibiotic harmless; (2) alterations in the structure of the transpeptidase, so that binding of the antibiotic to the active serine site of the transpeptidase does not occur; (3) efflux pumps that, in gram-negative organisms, quickly and efficiently remove the antibiotics from the periplasmic space before they can bind to the transpeptidases; and (4) alterations in the gram-negative outer membrane proteins that prevent the antibiotic from entering the periplasmic space. Each of these resistance mechanisms is variably effective and can lead either to profound resistance or merely to slightly increased resistance that has no clinical impact. Unfortunately, some pathogens combine several resistance mechanisms, each creating incremental increases in β-lactam resistance, ultimately leading to the development of an organism that is no longer susceptible to these antibiotics.

Chemical modifications of the β-lactam ring and associated drug structure can enhance the intrinsic activity of a drug against bacterial pathogens. Modifications that alter ionic charges on the molecule can allow the new agent (e.g., ampicillin) to enter the gram-negative bacterial periplasmic space, in contrast to an older agent (e.g., penicillin G) that could not. Side chains can create enhanced stability of the antibiotic against one or more of the hundreds of β-lactamases that have been identified, or can enhance binding to bactericidal targets within the organism.[4] Unfortunately, new, more active and broader-spectrum β-lactamases are reported with disturbing regularity.[10] Although many different efflux pump systems exist, changes in the structure and charge of the antibiotic can decrease the affinity of the antibiotic for the pump, while hopefully not decreasing its affinity for the target transpeptidase.

Penicillins

The penicillins are the most commonly used antibiotics in pediatrics, and can be divided broadly into four different groups: (1) natural penicillins; (2) penicillinase-stable penicillins; (3) aminopenicillins; and (4) extended-spectrum penicillins.

Natural Penicillins

Natural penicillins are the natural products of *Penicillium chrysogenum*. It is likely that both penicillins and penicillin-resistance mechanisms evolved millions of years ago as result of competition for survival between single-cell organisms.[11] Fleming's observations in the 1920s led to the identification of penicillin, and the discovery of the mechanism by which *Penicillium* killed other bacteria, paving the way for the modern era of antibacterial therapy. The basic structure of penicillin, 6-aminopenicillanic acid, is characteristic of the lactam ring fused to a larger ring structure to create a penam nucleus that is the basic structure of all penicillins (see Figure 292-2). Of the natural penicillins, only penicillin G (crystalline penicillin G, benzyl penicillin G) and penicillin V (phenoxymethyl-penicillin) currently are available commercially. Penicillin G is available in both oral and parenteral formulations. For intramuscular injection, penicillin G is also available in repository forms of the drug. Procaine penicillin G and benzathine penicillin G both have much longer serum elimination half-lives as a result of prolonged absorption from the muscle injection site, compared with crystalline penicillin G. However, the peak serum concentrations of the repository forms of penicillin G are considerably lower than those achieved with intravenous administration of crystalline penicillin G. Therefore, the only situations in which the repository forms of penicillin are effective are those in which the targeted organisms are exquisitely susceptible to penicillin, in tissues with good perfusion. Intramuscular procaine penicillin has a half-life of approximately 12 hours and achieves peak serum concentrations of about 2 μg/mL, compared with a half-life of 30 to 50 minutes for crystalline penicillin G, and achieved peak serum concentrations of approximately 20 μg/mL. Benzathine penicillin G yields even lower serum concentrations (only about 1.5 μg/mL), but can remain above 0.2 μg/mL for 3 weeks or longer. Combinations of procaine and benzathine penicillin, either in equal amounts or as a 3:1 (benzathine:procaine) mixture, also are available. As these repository forms of penicillin are used infrequently, extreme caution must be taken never to administer them intravenously, which can be lethal.

In clinical practice, although active against a wide range of bacteria (see Table 292-2), the natural penicillins are used most widely for treatment and prevention of infections caused by streptococci. Pharyngitis, lower respiratory tract infection, skin and skin structure infections, and bloodstream infection (BSI) caused by group A streptococcus (*Streptococcus pyogenes*) are effectively treated with penicillin. The in vitro susceptibility of these organisms has remained unchanged over the past several decades,[12] although the efficacy in the treatment of streptococcal pharyngitis in more recent studies is less than expected, for reasons that are not well understood.[13] Intramuscular injections of benzathine penicillin every 3 to 4 weeks are effective in the prevention of rheumatic fever due to the prolonged tonsillar tissue concentrations of penicillin G.

Empiric penicillin therapy of infections suspected to be caused by *Streptococcus pneumoniae* has not been appropriate during the past decade as a result of widespread decreased susceptibility of pneumococci to penicillin. By mutation, stable alterations in the structure of several pneumococcal PBPs yield penicillin-nonsusceptible organisms, treatment of which requires use of higher dosages of penicillins or agents from other antibiotic classes. However, if culture results document susceptibility, penicillin still represents highly effective therapy.

Most anaerobes, with the exception of β-lactamase-producing strains of *Bacteroides* sp. and *Prevotella* sp. are highly susceptible to penicillin G. However, due to the common presence of *Bacteroides fragilis* among the anaerobes present in intra-abdominal infections

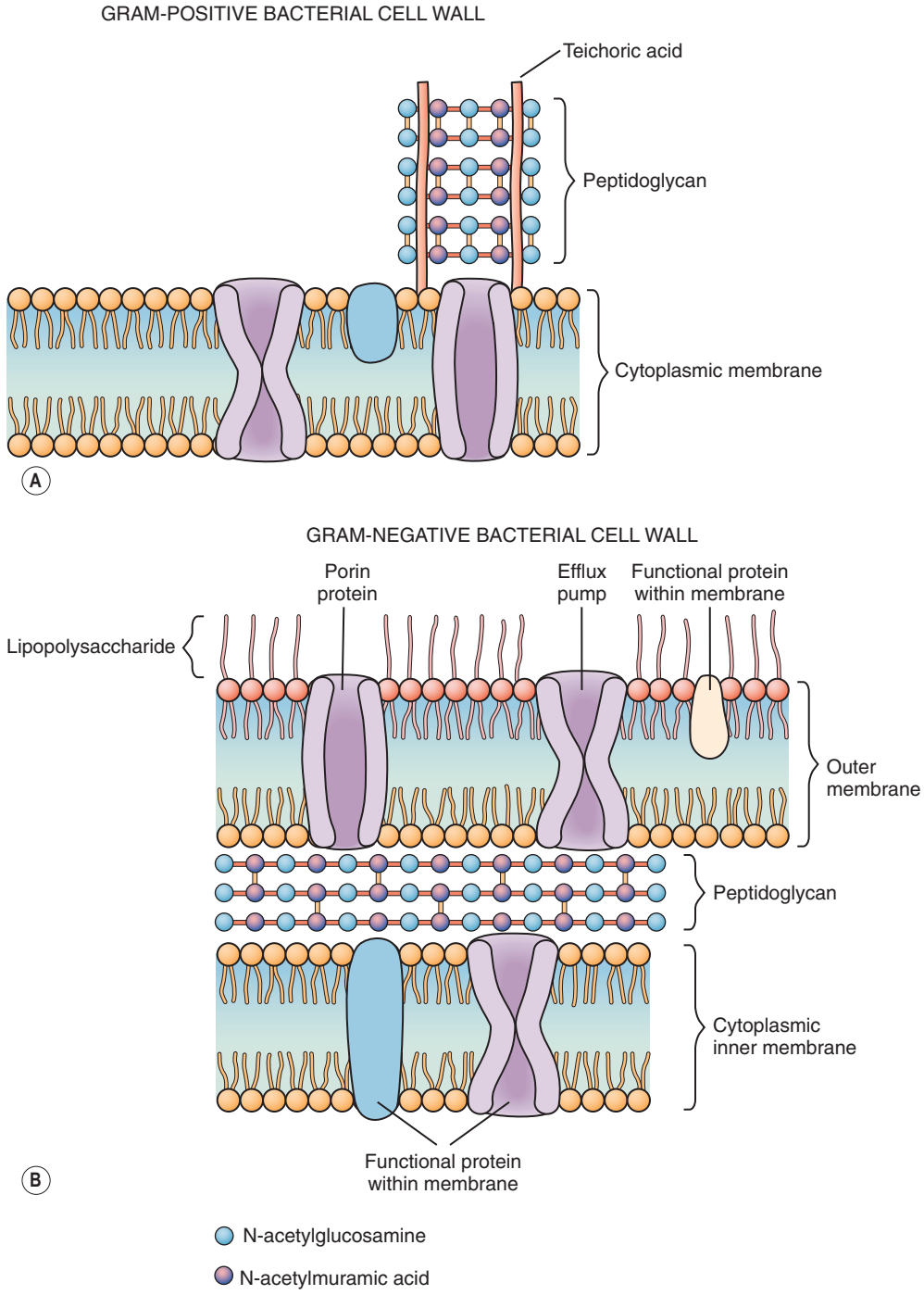


Figure 292-3. Structure of bacterial cell walls of gram-positive and gram-negative bacteria.

and *Prevotella melaninogenica* among the organisms causing sinus-related and deep head and neck space infections, including brain abscesses, agents active against β-lactamase-producing anaerobes are preferred to treat infections at these sites.

Penicillin G continues to play a role in the treatment of infections caused by other α- and β-hemolytic streptococci, most of which remain susceptible. For life-threatening infections such as bacterial endocarditis, susceptibility testing should be performed to ensure that the organisms do not exhibit penicillin tolerance, which may decrease treatment success using single drug therapy at standard dosages.

Penicillin G is effective therapy of less common infections, including diphtheria, naturally occurring anthrax, actinomycosis, leptospirosis, and syphilis.

Penicillinase-Resistant Penicillins

This class of semisynthetic penicillins was created to meet the challenge of the development of penicillin-resistant *Staphylococcus aureus.* The bulky side chains prevent the staphylococcal β-lactamases from binding to and hydrolyzing the lactam ring of the molecule. However, these antibiotics are resistant only to

staphylococcal penicillinases, and not to the β-lactamases of gram-negative organisms, to which they remain vulnerable. These antibiotics are not active against methicillin-resistant strains of *S. aureus* (MRSA) due to the presence of a transpeptidase (PBP 2a) which had not been capable of being bound and inactivated by any β-lactam antibiotic until the advent of ceftaroline (approved by the Food and Drug Administration (FDA) in 2010).

In clinical practice, these antibiotics are used to treat infections caused by susceptible strains of *S. aureus.* They are available in both parenteral and oral formulations. With the emergence of community-associated (CA)-MRSA, their long-standing role in the empiric therapy of presumed staphylococcal infections is now compromised. For susceptible strains of *S. aureus,* however, they remain among the safest and most effective therapeutic agents available.

Aminopenicillins

This class of semisynthetic penicillins (as represented by ampicillin and amoxicillin) contains an amino substitution in the phenyl acetamido side chain of the penam nucleus, providing a polar charge on the molecule that allows activity against gram-negative pathogens, including *Escherichia coli* and *Haemophilus influenzae* (see Table 292-2). However, aminopenicillins are not stable to staphylococcal penicillinases, or to the hundreds of different β-lactamases provided by gram-negative pathogens. Their activity against other gram-positive organisms, such as group A and group B streptococci still is excellent, and activity against most enterococci is equivalent to or better than penicillin G.

As a means of enhancing the activity of the aminopenicillins against β-lactamase-producing pathogens, the concurrent use of a second agent that binds irreversibly to a pathogen's β-lactamase has led to a useful group of drugs. These concurrently used agents, called β-lactamase inhibitors, have little antibiotic activity on their own as they have been selected for avid binding characteristics to specific β-lactamases, rather than to PBPs. However, just as diversity exists in the affinity of binding of penicillin to the target PBPs of various pathogens, diversity also exists in the binding affinity of each β-lactamase inhibitor to the β-lactamases of different organisms. Currently, clavulanate is paired with amoxicillin in an oral formulation in the United States (and a parenteral formulation in other parts of the world), and ampicillin is paired with sulbactam in a parenteral preparation (see Table 292-2).

The clinical uses of ampicillin and amoxicillin are extensive. The enhanced activity against *E. coli* and other gram-negative enteric bacilli compared with penicillin G permits ampicillin and amoxicillin to be used for the treatment of some urinary tract infections (UTIs) and gastrointestinal infections. The excellent activity against β-lactamase-negative strains of *Haemophilus influenzae* allows ampicillin and amoxicillin to be used in the treatment of upper and lower respiratory tract infections. Ampicillin is one of the most bactericidal agents (when used together with gentamicin) for susceptible strains of *Enterococcus.* Unfortunately, the development of resistance in *E. coli, Shigella, Salmonella,* and *H. influenzae* has limited the usefulness of aminopenicillins against these pathogens.

However, the addition of clavulanate to amoxicillin allows activity against β-lactamase-producing strains of *H. influenzae* and *Moraxella catarrhalis* as well as *S. aureus.* This combination increases the clinical usefulness of amoxicillin in the treatment of community-associated upper and lower respiratory tract infections (e.g., acute otitis media, sinusitis, and pneumonia), in addition to skin and skin structure infections. The addition of sulbactam to ampicillin allows activity against an array of β-lactamase-producing organisms, including staphylococci, many enteric gram-negative bacilli, and *Bacteroides fragilis.* This allows for the treatment of skin and skin structure infections as well as some intra-abdominal infections, not possible with ampicillin alone.

Extended-Spectrum Penicillins

These semisynthetic penicillins are designed to increase activity against gram-negative pathogens, including *Klebsiella, Enterobacter,* and, for some agents, *Pseudomonas* (see Table 292-2). The two major classes are the carboxypenicillins, represented by ticarcillin and carbenicillin, and the acylureidopenicillins, represented by piperacillin. Although the spectrum of activity of these antibiotics has been enhanced beyond the aminopenicillins, they remain susceptible to hydrolysis by many β-lactamases, including those of staphylococcus. Similar to the aminopenicillins, activity of these drugs has been enhanced by pairing them with β-lactamase inhibitors, such as ticarcillin-clavulanate and piperacillin-tazobactam.

The clinical uses of these antibiotics reflect their broad activity against gram-negative enteric bacilli and *Pseudomonas aeruginosa.* While originally available as a single-antibiotic agent, ticarcillin now is only available in combination with clavulanate, while piperacillin still is available and may be used as a single agent for therapy for a variety of gram-negative infections. However, an enhanced antibacterial spectrum when paired with a β-lactamase inhibitor increases the activity against many organisms, including *S. aureus, B. fragilis, P. melaninogenica,* and many gram-negative enteric bacilli (*E. coli* and *Klebsiella* sp.) (see Table 292-2). This allows for successful therapy for skin and skin structure infections, intra-abdominal infections, and, gram-positive and gram-negative hospital-associated infections, such as wound infections, UTIs, and pneumonia. The extended-spectrum penicillins also retain good activity against ampicillin-susceptible strains of *Enterococcus.*

Cephalosporins

Cephalosporins, like the penicillins, are β-lactam antibiotics found in nature. Cephalosporin C, the precursor molecule for antibiotics used in humans, was originally isolated from *Cephalosporium acremonium.* Successive modifications of the cephem ring structure have resulted in "generations" of cephalosporin antibiotics. There is no official scientific designation of generations; rather, the description of enhanced activity of the second generation over the first was created as a marketing tool.[14] However, the ability to distinguish the relative activity of the large number of cephalosporin antibiotics by generation is quite useful (see Table 292-2).

In general, the first-generation cephalosporins (represented by cefazolin intramuscularly (IM)/intravenously (IV) and cephalexin orally (PO)) are active against gram-positive pathogens, group A streptococcus, and penicillinase-producing *S. aureus* (methicillin-susceptible strains) (MSSA), which has led to their use for skin and skin structure infections and surgical prophylaxis, as well as for invasive infections caused by these organisms. Although they are better tolerated than the penicillinase-stable penicillins (e.g., methicillin), they are somewhat less active in vitro against *S. aureus,* and may not be as effective in the treatment of serious infections such as endocarditis. Cephalosporins uniformly lack activity against all enterococci.

The cephalosporins are active against many strains of *Escherichia coli,* allowing treatment of urinary tract and intestinal infections. However, increasing resistance to first-generation cephalosporins during the past few decades has limited the usefulness of these agents in the treatment of both community-associated and hospital-associated infections.

The second-generation cephalosporins have enhanced activity against gram-negative pathogens as well as demonstrating enhanced stability against β-lactamases compared with first-generation agents (see Table 292-2). This increases the spectrum of activity of these agents to include many enteric gram-negative bacilli, and β-lactamase-positive strains of *Haemophilus influenzae.* The activity of second-generation agents against staphylococci is decreased, although not sufficiently to lead to clinical failures in treatment of mild to moderate staphylococcal infections. This broad spectrum of activity allows for single-drug therapy of staphylococcal, streptococcal, and *Haemophilus influenzae* infections in children. However, due to poor penetration of the first- and second-generation cephalosporins into cerebrospinal fluid (CSF), use is limited for the treatment of invasive BSIs caused by *S. pneumoniae* and *H. influenzae*. Within the second generation of agents, all of which share the cephem ring structure (see Figure 292-2), are both true cephalosporins and the cephamycins. The

cephamycins were originally isolated from *Streptomyces* sp., and contain an additional side chain that enhances stability to β-lactamases, providing these agents (cefoxitin and cefotetan) with improved activity against β-lactamase-containing strains of *B. fragilis.* Given reasonable activity against gram-positive organisms (except enterococci), gram-negative enteric bacilli, and anaerobes, these antibiotics are effective in the treatment of intra-abdominal infections.

Oral second-generation agents were used widely for the treatment of upper and lower respiratory tract infections in children. However, with increasing β-lactam resistance in *S. pneumoniae* caused by changes in the PBP structures of these pathogens, treatment failures of pneumococcal infections using the oral second-generation cephalosporins occur more commonly than previously.

The third-generation cephalosporins have further enhanced gram-negative activity, which extends to *P. aeruginosa* for ceftazidime, but at the expense of a further decrease in activity against staphylococci. They lack activity against enterococci. Enhanced activity against enteric gram-negative bacilli has led to successful therapy of UTIs and many nosocomial infections. Therapy of infections caused by *Enterobacter, Serratia,* and *Citrobacter* species, which have the ability to produce chromosomally mediated (inducible) β-lactamases, may fail. Failure is likely to be due to the selection of organisms at the site of infection, which based on alterations in β-lactamase gene regulation, constitutively hyperproduce these enzymes, conferring resistance to third-generation agents.[15] The third-generation cephalosporins are, in general, also hydrolyzed by the extended-spectrum β-lactamases (ESBLs) produced most commonly by *E. coli* and *Klebsiella* sp.[10,16] The activity of the third-generation agents is superb against virtually all strains of *H. influenzae.* These agents, in general, achieve CSF concentrations that are effective for treatment of bacterial meningitis caused by all three major pediatric pathogens: *H. influenzae, S. pneumoniae,* and *Neisseria meningitidis.* Of note, certain penicillin-resistant strains of *S. pneumoniae* have decreased susceptibility to these cephalosporins and have been associated with clinical and microbiologic failure at tissue sites with decreased antibiotic penetration, such as the central nervous system (CNS).[17,18] However, the most active of the third-generation cephalosporins against *S. pneumoniae,* ceftriaxone and cefotaxime, have not been associated with treatment failure of respiratory tract infections caused by penicillin-resistant strains when appropriate dosing regimens are used. None of the third-generation agents should be considered optimal for the treatment of infections caused by MSSA as other cephalosporins and penicillinase-stable penicillins are more active against this pathogen.

Of the third-generation agents, ceftriaxone has a prolonged serum half-life compared with the other agents, allowing for its once-daily use for treatment of exquisitely susceptible organisms. The infrequent dosing and the ability to use either intramuscular or intravenous routes of administration have allowed for outpatient therapy of serious, invasive infections at a point when the child's clinical condition is stable.[19]

The fourth-generation cephalosporin, cefepime, maintains activity against *P. aeruginosa,* displays enhanced stability to the ampC chromosomal β-lactamases of *Enterobacter, Serratia,* and *Citrobacter* species, while retaining significant (but not optimal) activity against *S. aureus* (see Table 292-2).[20] This broad activity allows for empiric therapy of neutropenic children with fever, and allows for treatment of a wide variety of nosocomial gram-negative infections.[20–24] However, lack of activity against β-lactamase-positive strains of *B. fragilis* and against *Enterococcus* limits the ability to treat intra-abdominal infections with cefepime alone.

The fifth generation of cephalosporins, represented currently by only one available product, ceftaroline, combines the gram-negative and gram-positive activity of the third- and fourth-generation cephalosporins with in vitro and clinically demonstrable activity against CA-MRSA. These agents have been designed to bind to and inactivate PBP2a, which confers resistance of MRSA to all other currently available β-lactam agents.[25] However, ceftaroline is not active against *Pseudomonas,* and is not stable to ESBLs.

Carbapenems

Carbapenems, also naturally occurring, were initially isolated from a species of *Streptomyces*, with the β-lactam moiety contained within a carbapenem nucleus (see Figure 292-2). Carbapenems demonstrate the broadest spectrum of activity of all of the β-lactam antibiotics and currently include imipenem, meropenem, doripenem, and ertapenem.[26] Carbapenems are active against both gram-positive pathogens, including MSSA but not MRSA and streptococci (with moderate activity against ampicillin-susceptible enterococci) and gram-negative pathogens, including *P. aeruginosa* for imipenem and meropenem, with enhanced stability against both the chromosomal ampC β-lactamases of *Enterobacter, Serratia,* and *Citrobacter* species and the ESBLs of *E. coli* and *Klebsiella* (see Table 292-2). They are highly active against anaerobic organisms, including β-lactamase-producing strains of *Bacteroides* and *Prevotella.* Of these agents, the antibacterial spectrum of activity of imipenem, meropenem, and doripenem is similar, whereas ertapenem matches the activity of the other carbapenems against enteric bacilli, but is not as potent against *P. aeruginosa.* Imipenem is paired with cilastatin, a renal dehydropeptidase inhibitor that inhibits the destruction of imipenem by renal tubular enzymes providing both an increase in the serum half-life of imipenem and a decrease in the renal toxicity of the compound. Imipenem use was associated with unexpected seizures in an open, noncomparative clinical trial in children with meningitis,[27] probably attributable to competitive inhibition of the inhibitory CNS neural pathways. Therefore, meropenem, which does not produce clinically detectable CNS side effects, is the preferred carbapenem agent for treatment of CNS infections, including meningitis, brain abscess, epidural abscess, and subdural empyema. Ertapenem has the most prolonged serum half-life of the carbapenems, and requires only once-daily dosing in older children (≥13 years of age) and once- or twice-a-day dosing in younger children. Carbapenems are used primarily for nosocomial infections or infections in immunocompromised hosts when exceptionally broad spectrum of activity is essential. Data support clinical and microbiologic efficacy in pneumonia, UTIs, wound infections, bone and joint infections, and skin and skin structure infections.[28] Imipenem and meropenem have been used as single-drug empiric therapy of fever and neutropenia in immunocompromised children.[21] Carbapenems provide good, but not optimal, activity against *S. aureus.* They provide the best activity of all β-lactam agents against pathogens harboring either chromosomally mediated ampC β-lactamases or ESBLs. Recent emergence of carbapenemase-producing *Klebsiella* and other gram-negative pathogens may limit the usefulness of these broad-spectrum agents in the near future.[29] Use of such broad-spectrum agents must be weighed against the risk of promoting resistance and profoundly altering normal flora.

Monobactams

This unique β-lactam structure is a naturally occurring antibiotic isolated from *Chromobacterium* sp.; it is not fused to an adjacent ring, in contrast to penicillins, cephalosporins, and carbapenems. Aztreonam, the only available agent in this class, has been modified chemically with side chains,[30] and demonstrates gram-negative activity comparable with the third-generation cephalosporins but without significant gram-positive or anaerobic activity. Clinical use in pediatrics is limited primarily to treatment of community-acquired infections in which enteric gram-negative organisms are suspected or proven pathogens and aminoglycosides are not adequate or appropriate therapy. Aztreonam was recently FDA-approved as an inhalational antibiotic for children with cystic fibrosis who are 7 years of age and older, for the treatment of *P. aeruginosa* lower respiratory tract infection, with doses given three times daily for 28 days.

Glycopeptide Antibiotics

Glycopeptides interfere with cell wall formation in the steps that create the glycan chains prior to cross-linking the chains in the

formation of peptidoglycan (see Figure 292-1). These antibiotics have a large, complex structure that consists of multiple peptides linked together into three rings, with various side-chain substitutions, including large saccharide moieties attached to the central polycyclic structure. Strong hydrogen bonds occur between a glycopeptide antibiotic and the terminal D-alanine, D-alanine dipeptide of the pentapeptide side chains of the MurNAc subunits of the glycan chain. Once bound, the glycopeptides sterically prevent the transglycosylation steps required for lengthening the glycan chain.[5] Glycopeptide antibiotics are primarily active against gram-positive organisms, in which the cell wall construction occurs outside the cell membrane (see Figure 292-3). Little activity is demonstrated against gram-negative organisms, as the large structure does not cross the gram-negative outer membrane easily, preventing contact with enzymes responsible for transglycosylation in the periplasmic space. Recent documented resistance in gram-positive pathogens to vancomycin has led to intense investigation of derivatives of vancomycin and teicoplanin, another parenteral glycopeptide antibiotic that has been available outside the U.S. for several years.

Vancomycin

Vancomycin is a natural product, originally isolated from *Streptomyces* sp. in 1956. Vancomycin is the only glycopeptide currently available in the U.S. Originally developed to treat staphylococcal infections, vancomycin was rarely used following the availability of the penicillinase-stable penicillins, which were tolerated better. However, since the first appearance of healthcare-associated (HA)-MRSA four decades ago, vancomycin has played a continuing role in the treatment of nosocomial *S. aureus* infections. Recently, with the increasing prevalence of CA-MRSA, vancomycin is now routinely used in the empiric therapy of serious suspected staphylococcal infections.[31,32] Concern for decreased bactericidal activity and clinical efficacy of vancomycin compared with the penicillinase-stable penicillins for treatment of MSSA, as well as greater toxicity, make vancomycin non-preferred therapy for infections caused by MSSA.

Resistance to vancomycin has developed in several ways. In *Enterococcus* sp., *vanA*-mediated resistance, the most common resistance seen in clinical isolates, leads to complete resistance to vancomycin. A transmissible set of 7 genes, which encode a series of biologic functions that allows *Enterococcus* to sense the presence of vancomycin, to cleave the D-alanine, D-alanine dipeptide from the pentapeptide chain, and to substitute D-alanine, D-lactate at the terminus of the pentapeptide, results in a 1000-fold decrease in binding of vancomycin.[33,34] The new pentapeptide appears to be as viable a precursor for peptidoglycan formation as the original pentapeptide. The *vanA* resistance mechanism has now been detected in *S. aureus* infecting adult patients, creating vancomycin-resistant *S. aureus* (VRSA). A more common resistance mechanism of *S. aureus* to vancomycin, producing a heterogeneous population of intermediately susceptible strains or hVISA, is proliferation of the D-alanine, D-alanine glycan structures, creating a disorganized, thickened cell wall, leading to increases in the binding and trapping of vancomycin to nonfunctional dipeptides.[35–38] Under vancomycin pressure, these strains, which are present in every large population of staphylococci, are selected. However, as these strains are not fully resistant to vancomycin, retrospective data suggest that higher dosages of vancomycin (if tolerated by the patient) can remain effective therapy for hVISA.[39,40]

Three new glycopeptide antibiotics, dalbavancin, telavancin, and oritavancin, have demonstrated clinical efficacy in small clinical trials, but none is yet approved for use.[41] Modifications of the glycopeptide to enhance binding to targets, to increase stability of antibiotic binding by creating glycopeptide dimers, and to anchor the glycopeptide to the cell membrane have all been successful strategies for enhancing the activity of this class of agents. Although these newer agents have shown increased in vitro activity against *S. aureus* compared with vancomycin, prospective, controlled clinical data to document improved outcomes in adults are not available, and no data exist currently for children.

Clinical uses of vancomycin include therapy for gram-positive infections in children who are penicillin-allergic, therapy of infections caused by *S. pneumoniae* that are resistant to penicillin,[42] and therapy of infections caused by MRSA. Treatment of *Clostridium difficile* infections with orally administered vancomycin is highly effective, but is not first-line therapy because of the emergence of vancomycin-resistant enterococci (VRE) following oral vancomycin therapy. In selected cases of metronidazole failure, vancomycin represents effective alternative therapy.[43]

A common reaction can occur with the rapid infusion of vancomycin, the red-man or red-neck syndrome, characterized by flushing and hypotension. This reaction is histamine-mediated and not immunoglobulin E-mediated and is distinct from anaphylaxis. The risk of this reaction varies directly with the rapidity of the vancomycin infusion; therefore, each dose of vancomycin usually is infused over 1 hour. For children who develop red-man syndrome, prolonging the infusion time or pretreating with an antihistamine may permit continuation of therapy with vancomycin.

Cell Membrane Active Antibiotics

Daptomycin

Daptomycin, a natural product derived from *Streptomyces* sp., is a novel lipopeptide antibiotic that is rapidly bactericidal based on effects on the gram-positive cell membrane. Daptomycin has a unique structure that consists of 13 amino acids, including a cyclic peptide containing 9 amino acids, attached to a lipophilic fatty acid tail that inserts into the cell membrane. The mechanism of action of daptomycin is not well understood, but it appears that depolarization of the membrane occurs as the antibiotic polymerizes within the bacterial cell membrane, producing channels in the membrane that result in leakage of cell contents, inhibition of protein, DNA and RNA synthesis, and cell death. Based on in vitro assays, daptomycin is one of the most rapidly bactericidal antibiotics against *S. aureus* and is active against a wide variety of gram-positive organisms, including MSSA, MRSA, VRSA, streptococci, and enterococci (including VRE) (see Table 292-2).[44]

Clinical use of daptomycin has focused on MRSA infections that are unresponsive to vancomycin. Efficacy has been demonstrated in adults for skin and skin structure infections, and for BSI. Surprisingly, daptomycin is not effective for the treatment of pneumonia, based on clinical trials in which response rates were not equivalent to comparator agents. Daptomycin is inactivated by surfactant, yielding relatively low concentrations in bronchial-alveolar epithelial lining fluid and lung parenchyma.[45] Limited pharmacokinetic and clinical data have been reported in children.[46–48] The prolonged half-life in adults of 8 to 9 hours allows for once-daily dosing.

In the first human clinical trials five decades ago, daptomycin was associated with a high incidence of myalgias and muscle weakness accompanied by elevations in serum creatine kinase. This adverse effect appears to depend on the frequency of dosing, with less adverse effect noted with a decreased frequency of dosing. While toxicity was prohibitive when daptomycin was administered every 6 to 8 hours, the drug demonstrated no greater toxicity than comparator agents when administered to adults in a dose of 4 mg/kg once daily.[37] As the approved dosage of daptomycin was increased to 6 mg/kg daily in adults for the treatment of BSI and endocarditis, no significant muscle toxicity was noted.[49]

Colistin

Colistin is a polymyxin antibiotic that is a natural product isolated from *Bacillus polymyxa,* and consists of 10 linked amino acids, with 6 forming a peptide ring structure attached to a fatty-acid side chain. Colistin is also known as polymyxin E, structurally similar to polymyxin B, which is used extensively as a topical agent. The polymyxin antibiotics were first discovered in 1947, with the first clinical use of colistin in the U.S. in 1959.[50] Colistin is available in the U.S. as a sodium methanesulfonate salt, known as colistimethate. The dosage is calculated as the colistin base, at 2.5 to

5.0 mg/kg per day given in 2 to 4 divided doses. Colistimethate is hydrolyzed to colistin, but the rate and extent of hydrolysis and the contributions of biologic activity of the parent compound and products of metabolism are not well known. The mechanism of bactericidal activity against the cytoplasmic membrane is based on cationic detergent activity, binding to lipopolysaccharides in the outer cell membrane, displacing calcium and magnesium and disrupting the lipid component of the cell membrane. Permeability changes subsequently occur in the membrane, disrupting the osmotic gradient of the cell and impacting cellular metabolism and nucleic acid synthesis.[51]

Colistin has been used as both intravenous and inhalational treatment for multidrug resistant gram-negative pathogens in children with cystic fibrosis (CF),[52] and more recently, in non-CF patients with gram-negative pneumonia.[53] For treatment of gram-negative CNS infections, colistin has been injected intrathecally.[54,55] Only limited, retrospective clinical data are available to guide therapy with this agent.[54,55]

Colistin has significant toxicity, primarily renal and neurologic. Renal side effects include decreased urine output with elevated blood urea nitrogen and serum creatinine, proteinuria, hematuria, and acute tubular necrosis. Because colistin is eliminated by renal excretion, it is imperative to assess renal function closely during therapy, decreasing the dosage if any degree of renal insufficiency is noted. Drug accumulation and additional renal toxicity occur if dosing is not altered when renal insufficiency first occurs. Renal toxicity usually is reversible if detected early. Neuromuscular side effects had been noted in adults and children treated with colistin in case series reported up to 50 years ago, most often manifest as oral and perioral paresthesias, weakness, lethargy, confusion, ataxia, and respiratory muscle paralysis. However, more recent experience with colistin, particularly in children, has not described this neuromuscular toxicity.[54,55] Colistin also crosses the placenta and has been shown to be teratogenic in certain laboratory animals following drug exposures in pregnant animals.

Due to the toxicity, clinical use of parenteral colistimethate is limited to therapy of infections caused by multidrug-resistant gram-negative pathogens for which no other option is available. Other clinical uses include inhaled therapy in ventilated patients with nosocomial multidrug-resistant gram-negative pulmonary infections[56] and aerosolized colistimethate in children with CF as adjunctive antimicrobial therapy.[57,58]

RIBOSOME-ACTIVE ANTIBIOTICS

The bacterial ribosome, highly conserved over millions of years, has long been a target of antibiotics. As our ability to understand the function of the ribosome has increased, and with recent advances in our ability to visualize ribosomal structures with crystallography, our knowledge of the mechanism of activity of both older and newer agents and our ability to design more effective antibiotics has improved substantially. The ribosome contains a 30S and a 50S subunit, each comprising rRNA and ribosomal proteins. Several sites have been documented to be antibiotic targets on each of the subunits and at the junction of the subunits. Targets include: the entry site of mRNA, the initial recognition and binding site of tRNAs, the site of attachment of the tRNA-peptide chain where peptide bonds are formed (the peptidyl transferase center), and the exit channel of the growing polypeptide.[59–61] The critical chemical and structural relationships between the ribosomal rRNA and the peptidyl transferase center, which promote the chemical reactions to create a new peptide, as well as movement of mRNA and the newly formed peptide through the ribosome, provide opportunities for interference in bacterial protein synthesis.

Macrolides

The currently available macrolides consist of the erythromycins, azithromycin, and clarithromycin. All share structural similarities with either a 14-member lactone ring (erythromycin, clarithromycin) or a 15-member ring (azithromycin). All bind to at least one site in common within the peptide exit tunnel of the ribosome: domain V of the 23S RNA within the 50S subunit. To achieve activity in most bacteria, binding to a specific adenine residue of the rRNA, A2058, within this channel prevents the orderly movement of protein out of the ribosome.[62]

Clarithromycin is similar structurally to erythromycin, with only the addition of a single methyl group to the erythromycin ring, primarily conferring improved stability to gastric acid. While erythromycin, clarithromycin, and azithromycin contain a cladinose carbohydrate attached to the lactone ring, a new class of ketolides, represented by telithromycin, substitutes a ketone in this position while adding highly charged side chains to the C11 and C12 positions. These changes improve the binding characteristics to both the peptide tunnel binding site within domain V, and create an additional unique binding site at adjacent domain II within the ribosome, improving activity against many macrolide-resistant gram-positive organisms. Azithromycin is structurally similar to erythromycin, but contains a 15-member ring with the addition of a nitrogen atom within the ring itself, structurally changing the drug from a macrolide to an azalide, but containing the same side chain-attached carbohydrate moieties as erythromycin. This change improves gram-negative activity as well as increasing gastric acid stability. The degradation products of azithromycin provide far less stimulation of gastric motility, improving the tolerability of azithromycin over erythromycin.

In general, the macrolides are inhibitory, not bactericidal, to bacteria and therefore are not used for the treatment of serious and life-threatening infections when other bactericidal agents can be used. The various macrolide agents have different binding affinities for their ribosomal targets in different organisms. Binding generally is reversible, with a prolonged rate of dissociation off the ribosome potentially adding to a more prolonged postantibiotic effect seen with some macrolides (see Table 290-1).[63]

The macrolides are most active against gram-positive cocci and bacilli, and, to a lesser extent, gram-negative bacilli (see Table 292-2). Some of these agents also are active against spirochetes and certain mycobacteria. Pathogens that lack a formal cell wall (e.g., *Mycoplasma* and *Ureaplasma*) and are not susceptible to β-lactam antibiotics often remain susceptible to macrolides.

All of the macrolides achieve high antibiotic concentrations within phagocytic cells. These concentrations often are much higher than those measured in serum, providing access of these antibiotics to infected tissue spaces by means of neutrophils and establishing a higher tissue concentration than antibiotics that enter primarily by diffusion alone. However, presence in the intracellular location leads to less free drug available to expose extracellular pathogens. Macrolides are particularly effective therapy against susceptible intracellular pathogens.

In general, macrolides are well tolerated. Clarithromycin and azithromycin are better tolerated than erythromycin, which has problematic gastrointestinal side effects in some children. With the exception of azithromycin, this class of antibiotics is metabolized by hepatic cytochrome P450 system, and drug–antibiotic interactions should be considered as they may increase or decrease the macrolide and concurrent drug concentrations.[64] Azithromycin has demonstrated minimal drug–drug interactions, and may represent the preferred macrolide in certain situations, particularly for immunocompromised children receiving multiple medications concurrently.

Resistance to the macrolides occurs when molecular changes occur at the critical ribosomal attachment site, most commonly a mono- or dimethylation of the A2058 adenine binding site. A rapidly increasing number of recognized methyltransferase enzymes have now been reported. Most of these are encoded by gram-positive organisms, are most often inducible, but may be constitutively produced and lead to high-level resistance to erythromycin, clarithromycin, and azithromycin.[65] Less frequent alterations at this site also impact binding, with either substitution of guanine for adenine or structural changes in the L4 ribosomal protein.[66] Efflux pumps represent another common mechanism of resistance in gram-positive pathogens, including pneumococcus, group A streptococcus, and *S. aureus.* The most common pumps

are active against all the macrolides – erythromycin, clarithromycin, and azithromycin.[65,67]

Erythromycin

Erythromycin, a natural product isolated from *Saccharopolyspora erythraea* (formerly *Streptomyces*) in 1949, was first approved for clinical use in 1952. Erythromycin is degraded by gastric acid, and has long been associated with stimulation of motilin receptors in the stomach and possibly in the colon, leading to adverse gastrointestinal side effects, including cramping and diarrhea.[68,69] Many preparations have attempted to bypass exposure of erythromycin to gastric acid, thereby avoiding products of macrolide hydrolysis. These preparations include enteric coating of orally administered tablets, delayed-release formulations, polymer coating of beads, and various formulations of salts and esters.[70] The lactobionate salt used for intravenous administration of erythromycin can cause phlebitis at the site of injection.

Erythromycin is used for the treatment of group A streptococcal infections in children who are penicillin-allergic. Erythromycin is an alternative treatment for both streptococcal pharyngitis and streptococcal or staphylococcal impetigo. The usefulness of erythromycin for respiratory tract infections caused by *S. pneumoniae* has been greatly diminished by the development of widespread resistance to the macrolides.[42] Macrolide therapy of upper respiratory tract infections (otitis media and sinusitis) or lower respiratory tract infections (pneumonia) potentially caused by *S. pneumoniae* has a relatively high likelihood of failure, particularly in younger children who are at highest risk of infections caused by antibiotic-resistant strains. For upper respiratory tract infections, erythromycin has inadequate activity against *H. influenzae,* and must be paired with another agent such as a sulfonamide for empiric therapy. Macrolides are effective therapy for pneumonia caused by *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* or *Legionella pneumophila*.

Erythromycin and azithromycin are the preferred antibiotics for treatment of *Campylobacter* gastroenteritis. Erythromycin also remains the most appropriate therapy for diphtheria (*Corynebacterium diphtheriae*). Erythromycin, clarithromycin, or azithromycin is recommended for treatment or prophylaxis of pertussis (*Bordetella pertussis*).[71] Azithromycin is preferred for treatment or prophylaxis for pertussis in neonates, based on concerns for the development of pyloric stenosis.[71] Efficacy of erythromycin also has been demonstrated in infections caused by *Chlamydophila pneumoniae* and *Chlamydia trachomatis,* including neonatal conjunctivitis and pneumonia, as well as urogenital infections during pregnancy. Erythromycin is active in vitro against *Ureaplasma urealyticum*, but its role in the treatment of neonatal infections associated with this organism is not well defined.[72]

Clarithromycin

With the improved activity demonstrated against *H. influenzae* and improved tolerability compared with erythromycin, treatment of respiratory tract infections is the most common clinical use for clarithromycin. FDA-approved indications include pharyngitis/tonsillitis, acute otitis media, acute maxillary sinusitis, and community-acquired pneumonia caused by susceptible strains of *S. pneumoniae, H. influenzae, M. catarrhalis, M. pneumoniae, C. pneumoniae,* and *L. pneumophila*. For *S. pneumoniae*, strains that are resistant to erythromycin from either methyltransferase or efflux mechanisms also are resistant to clarithromycin. The activity of clarithromycin against *H. influenzae* is only moderate, but in noninferiority-designed clinical trials of clarithromycin for the treatment of respiratory tract infections, the microbiologic and clinical efficacy was not significantly less than that of other approved agents.

Clarithromycin is one of the most effective macrolides for treatment and prevention of disseminated mycobacterial infections due to *Mycobacterium avium* complex (MAC) in human immunodeficiency virus (HIV)-infected persons. Although not well studied in immunocompetent children, clarithromycin may play a role in the treatment of cervical adenitis and pneumonia caused by MAC (or other nontuberculous mycobacteria proved to be susceptible in vitro), in conjunction with other antibiotics and/or surgery.[73]

Clarithromycin plays a role in the treatment of *Helicobacter pylori* infections in combination with amoxicillin and lansoprazole, or omeprazole, or in combination with ranitidine.[74,75] Clarithromycin has demonstrated efficacy similar to erythromycin in pertussis infections in small clinical trials, and is considered as one of three first-line drugs. Although approved for treatment of skin and skin structure infections, clarithromycin is not often used for this indication as other more cost-effective or more active agents are available in the treatment of infections caused by *S. aureus.* Similarly, other β-lactam and macrolide antibiotics are preferred for the treatment of streptococcal pharyngitis.

Azithromycin

Azithromycin has among the highest intracellular concentrations of the macrolides and provides the most prolonged tissue concentrations at the site of infection, allowing the antibiotic to be administered for very short courses for respiratory tract infections without compromising prolonged tissue site activity. Erythromycin-resistant strains of *S. pneumoniae* also are resistant to azithromycin. Group A streptococcus has variable resistance to macrolides. Activity against *H. influenzae* is moderate, with in vitro activity increased compared with erythromycin, but decreased compared with clarithromycin. However, the relatively small differences in susceptibility may be offset by higher concentrations of antibiotic if there is an intracellular site of infection. Azithromycin also is active against the pathogens causing atypical pneumonia (see Table 292-2).

Azithromycin is far better tolerated than erythromycin, can be given once daily, and is available in both oral and intravenous formulations. Based on noninferiority-designed clinical trials, azithromycin is approved for treatment of streptococcal pharyngitis, acute otitis media, sinusitis, and community-acquired pneumonia in children. Because of prolonged tissue concentrations, particularly using larger azithromycin dosages, 5-day, 3-day, and 1-day treatment courses, all providing a total treatment dosage of 30 mg/kg, have been shown to be comparable for clinical and microbiologic outcomes with 10-day treatment courses of comparator β-lactam antibiotics in acute, uncomplicated otitis media. However, as the dose increases, the gastrointestinal tolerability of the antibiotic decreases, with vomiting and diarrhea occurring in about 10% of children receiving 30 mg/kg as a single dose.[76] Although clinical data on single-dose treatment courses for otitis media are available, data exist only for treatment courses of 3 and 5 days for sinusitis, and for 5 days for treatment of community-acquired pneumonia and streptococcal pharyngitis. The dosage for treatment of streptococcal pharyngitis is 12 mg/kg per day once daily for 5 days, which is larger than that for otitis and provides a total dosage of 60 mg/kg.

Azithromycin has the widest use in children for the treatment of upper and lower respiratory tract infections.[77] However, other uses have been documented in clinical trials, although FDA approval for many of these infections has not been requested. Treatment of pertussis has been shown to be effective in small trials.[78] Azithromycin is the recommended macrolide for prophylaxis or treatment of infants under 1 month of age and is considered equal to erythromycin and clarithromycin in older individuals.[71]

Azithromycin also is used in the treatment of sexually transmitted infections, including *Chlamydia trachomatis*-caused infections (urethritis, cervicitis, and lymphogranuloma venereum), chancroid, granuloma inguinale, and gonorrhea.[79]

Similar to clarithromycin, azithromycin has been shown to play a role in the prophylaxis and therapy of MAC infections in HIV-infected children.[80] Azithromycin also may have a role in therapy of cutaneous and lymph node infection caused by these pathogens in healthy children.

Azithromycin has enhanced activity compared with the other macrolides against many gastrointestinal pathogens, including *E. coli, Salmonella, Shigella,* and *Campylobacter*.[81] In vitro activity demonstrated against *Salmonella* is particularly advantageous given the

intracellular location of this pathogen.[82] With widespread resistance among gastrointestinal pathogens to β-lactam antibiotics, fluoroquinolones, and trimethoprim-sulfamethoxazole in certain parts of the world, the utility of empiric azithromycin therapy for traveler's diarrhea has increased.[83]

Azithromycin is the only antibiotic that has been prospectively evaluated for the treatment of cat-scratch lymphadenitis.[84] However, the clinical response to treatment of lymph node disease is not dramatic, and azithromycin has not been evaluated prospectively for the treatment in other tissue sites of infection, such as liver, bone, or CNS.

Tetracyclines

The tetracyclines were derived as natural products from *Streptomyces* spp., with discovery in the 1940s and subsequent availability of two agents by 1948, chlortetracycline and oxytetracycline.[85] Tetracyclines bind reversibly to the ribosome at the aminoacyl acceptor site (A site) where the amino acid-charged tRNA binds to the ribosome immediately adjacent to the site on the ribosome holding the mRNA strand.

The aminoacyl tRNA binds to the A site together with an elongation factor (EF-Tu) and guanosine triphosphate (GTP), which supplies the energy required to drive protein synthesis. The protein synthesis step includes the chemical reaction to attach the amino acid to the growing peptide chain, together with changes in the conformation of the ribosome that are associated with movement of the protein chain and the mRNA through the ribosome, followed by the subsequent release of the "empty" tRNA.[86] It appears that the flat, four-ring structure characteristic of the tetracyclines binds to at least two locations within the ribosome. Binding at the classically recognized A site appears to prevent movement of the tRNA/mRNA/EF-Tu complex into the "P site" (peptidyl site) by steric hindrance, which prevents elongation of the growing peptide. Binding to a second site in the 30S ribosome may stabilize the ribosome in an inappropriate conformation at the crucial site of recognition of the aminoacyl tRNA's anticodon with the corresponding codon within the mRNA, thereby preventing placement of the correct amino acid in the elongating chain.[87] Inhibition of peptide formation by tetracyclines occurs after the binding of the tRNA to the complex and after expenditure of GTP-mediated energy, presenting the bacteria with an energy cost in addition to blocking the synthesis of a new protein.

The tetracyclines are effective against many gram-positive and gram-negative bacteria as well as against cell wall-deficient pathogens (*Mycoplasma*, *Rickettsia*) and certain single-cell parasites (see Table 292-2). Eukaryotic cells have elongation factors different than bacteria, and are therefore not susceptible to the protein synthesis inhibition activity of this class of antibiotics. The tetracyclines enter the gram-negative cell wall through outer membrane porin proteins and are sufficiently lipophilic to allow passage through the cytoplasmic membrane of both gram-negative and gram-positive bacteria. The tetracyclines are, in general, bacteriostatic.

Resistance to tetracyclines occurred quickly following their availability for clinical use, primarily based on efflux pumps and, to a lesser extent, on the presence of ribosomal protection proteins and tetracycline-inactivating enzymes. Of concern, the number of resistance genes and the number of bacterial species that contain them continues to increase.[85,88] These resistance mechanisms are present on plasmids, conjugative transposons, and integrons, allowing free exchange of resistance determinants between a wide range of bacteria. Over 200 different efflux pumps have been characterized, most of which are active against tetracycline, some of which also are active against minocycline, and fewer of which also are active against the most recently available tetracycline, tigecycline. The ribosomal protection proteins have sequence homologies with bacterial elongation factors present in the tRNA/mRNA/EF-Tu complex. It is believed that, as these protection proteins themselves bind to the ribosome, changes in the conformation at the tetracycline binding site occur, preventing the binding of tetracycline but not interfering with protein synthesis. Resistance at the second 30S ribosomal binding site also has been described, due to base substitutions in the rRNA of the 30S unit.

Advances in the design of the structure of the early tetracyclines led to doxycycline (in 1967) and minocycline (in 1972), both of which provide a greater spectrum of activity and improved solubility, creating improvements in both oral and parenteral preparations (see Table 292-2). Doxycycline and minocycline can be taken with food (with the exceptions noted below). In most cases, doxycycline and minocycline demonstrate increased activity against gram-positive organisms, and decreased activity against gram-negative organisms compared with tetracycline. Activity against *Enterococcus faecium*, but not *E. faecalis*, is achieved with newer agents. Minocycline, however, demonstrates improved activity against gram-negative organisms, including *H. influenzae*, *M. catarrhalis*, *E. coli*, and *Klebsiella* spp. compared with tetracycline, but only fair activity against *Salmonella* and *Shigella* spp. and *Pseudomonas aeruginosa*. Tigecycline, a derivative of minocycline, increases the spectrum of activity against many enteric gram-negative bacilli and anaerobes, including *B. fragilis*, but still lacks a high degree of activity against *P. aeruginosa* (see Table 292-2). Historically, clinical use in pediatrics has been limited by the binding of tetracyclines to teeth and bones in growing children. Permanent staining of the teeth (not affecting the structural integrity of the tooth) and enamel hypoplasia occurs with any tetracycline antibiotic, with the degree of staining directly proportional to the number of tetracycline courses prescribed. A single course of therapy is not associated with clinically detectable changes.[89–91] Stable calcium complexes also can develop in bone, and reversible decreases in long-bone growth rates in juvenile animals have been observed. The clinical impact of these observations for children is not well defined but has been a cause for concern, limiting the use of tetracyclines to children 8 years of age and older.[92] In addition, the tetracyclines cross the placenta to expose the fetus; skeletal embryopathy in experimental animals has been noted. The oral tetracyclines cannot be taken with dairy products due to the insoluble chelation complexes that form with calcium; similar complexes form with magnesium and iron ions. When ingested with foods containing these ions, absorption from the gastrointestinal tract is blocked.

In adults and older children, the tetracyclines have been used for the treatment of mild to moderate respiratory tract infections, skin and skin structure infections (most commonly acne), and sexually transmitted infections. Some agents in this class demonstrate activity against strains of CA-MRSA,[93] penicillin-resistant pneumococci, and VRE, and have been used in the treatment of these infections. However, few prospective, comparative data are available to assess the efficacy of tetracyclines against these pathogens, with the exception of recent studies on tigecycline (see below).

Tetracyclines are first-line therapy for infections caused by *Rickettsia*, *Ehrlichia*, and *Anaplasma* spp. (most notably Rocky Mountain spotted fever), tularemia (oral therapy for less severe infections), brucellosis (with rifampin), cholera, *Chlamydia* genital infections, and Lyme disease (*Borrelia burgdorferi*) in older children.

Tigecycline

Tigecycline is a chemically modified minocycline, with the addition of a *t*-butylglycylamido side chain to the C9 carbon of the "D" tetracycline ring.[94] Tigecycline is not affected by the majority of efflux pumps and ribosomal protection proteins that decrease the activity of other tetracyclines. Tigecycline has a higher binding affinity to the ribosomal binding site than the previous tetracyclines[85] and has a broader spectrum of activity than any other tetracycline agent (see Table 292-2). In rat models, bone discoloration was documented, suggesting that tigecycline forms calcium complexes in bone similar to other tetracyclines.

In adults, tigecycline is approved for treatment of complicated skin and skin structure infections and complicated intra-abdominal infections given its activity against enteric gram-negative bacilli and anaerobes, including *B. fragilis*. Tigecycline retains activity

against the agents of atypical pneumonia that is equivalent to, or better than, earlier tetracyclines.

The ultimate clinical role of tigecycline has yet to be defined in the treatment of nosocomial infections caused by multidrug-resistant gram-negative and gram-positive organisms that remain susceptible to tigecycline. For children, the risks of bone toxicity and tooth staining need to be balanced with the benefits of therapy, particularly for drug-resistant pathogens. For situations in which no alternatives exist, the tetracyclines represent effective therapy.

Lincosamides

The lincosamides are naturally occurring compounds derived from *Streptomyces* spp. Clindamycin, approved in 1966, is the only lincosamide available in the U.S. and is a semisynthetic derivative of lincomycin. The lincosamide antibiotics bind to the 50S subunit at a site which overlaps both the A and P sites on the ribosome, preventing the docking of charged tRNAs and their movement through the peptidyl transferase center, thus inhibiting the formation of protein. The P-site attachment of clindamycin occurs at the same ribosomal-RNA structural bases as the macrolide binding sites (A2058, A2059), explaining the competitive inhibition between binding of the two classes of antibiotics for the ribosome, as well the resistance that occurs to both antibiotics by altering a single base.[95] The lincosamides generally are considered bacteriostatic, although bactericidal activity can be demonstrated against certain organisms at antibiotic concentrations 2 to 4 times the minimum inhibitory concentration (MIC).[96]

Resistance to the lincosamides occurs primarily in bacteria that constitutively produce the methyltransferase that mono- or dimethylates the A2058 adenine present at the outlet of the ribosomal peptidyl transferase center. This inducible enzyme most often is activated only in the presence of the appropriate substrate, usually a macrolide. In contrast, the lincosamides appear to be poor inducers of the methylase enzyme. Therefore, organisms that have inducible resistance may remain susceptible to clindamycin, even following exposure to the antibiotic. However, genetically altered strains that have lost gene regulation and constitutively produce methylase occur at a rate of approximately one in 10^7 *S. aureus;* selection of constitutive mutants can occur during therapy with subsequent treatment failure.[67,97] This situation is most likely to occur in serious, deep, high-density bacterial infections, but not with mild to moderate skin infections or cutaneous and soft-tissue abscesses that can be incised and drained. The commonly encountered efflux pumps that are active against the macrolides are not active against clindamycin.

High intracellular concentrations of clindamycin in phagocytic cells are believed to be beneficial in certain clinical infections.[98] However, no prospectively collected data have confirmed the benefit in clinical or microbiologic cure of infection either as a result of improved intracellular killing of organisms such as staphylococci, or improved delivery of clindamycin to the site of infection through phagocytic cell migration.

Clinical use of clindamycin has changed substantially over the past decade. Commonly used for its activity against anaerobes in the treatment of intra-abdominal infections such as appendicitis, clindamycin resistance of *Bacteroides fragilis* has increased and clindamycin no longer is recommended as the anaerobic agent of choice.[99,100] Clindamycin continues to have a good spectrum of activity for use in deep head and neck space infections, dental abscesses, and aspiration pneumonia (with or without empyema). Less common uses continue for treatment of gram-positive cocci, such as failures of penicillin in group A streptococcal pharyngitis, and for treatment of *S. aureus* infections due to susceptible organisms.

In the early 1990s, the emergence of penicillin- and macrolide-resistant *S. pneumoniae* causing upper and lower respiratory tract infections promoted the use of clindamycin in the treatment of mild to moderate respiratory tract infections in children. Although no formal, randomized prospective comparative studies were performed in acute otitis media, sinusitis, and pneumonia, clindamycin has been recommended for treatment of infection due to penicillin-resistant pneumococci.[101]

Since the mid-1990s, with the dramatic emergence of CA-MRSA, the use of clindamycin for skin and skin structure infections and bone and joint infections has increased substantially. Although most published data on the efficacy of clindamycin in the treatment of MRSA are retrospective, clindamycin appears to be effective for these pathogens.[102,103] While some regions of the U.S. in which MRSA is prevalent have documented decreasing resistance to clindamycin due to spread in the community of certain clindamycin-susceptible clones,[83] other areas may experience increasing clindamycin resistance, particularly with methylase-harboring organisms that confer resistance to both clindamycin and macrolides. Susceptibility of MRSA and MSSA should be assessed locally to determine empiric therapy for serious infections.[104,105]

The ability of clindamycin to target ribosomal protein production has led to use in the treatment of toxin-mediated infections caused by *S. aureus* (toxic shock syndrome) and *S. pyogenes* (toxic shock-like illness), either alone or in combination with a cell wall-active antibiotic agent. In vitro data and retrospectively analyzed human data suggest some benefit of combined therapy.[106]

The principal adverse event associated with clindamycin is a direct function of its activity against normal anaerobic gastrointestinal flora – diarrhea.[85] *Clostridium difficile*-mediated pseudomembranous colitis is a potential complication of virtually any broad-spectrum antibiotic, including clindamycin.[107] Accurate, prospectively collected data on the incidence of *C. difficile* enterocolitis are not available for clindamycin-treated children, but increasing reports of enterocolitis have not occurred with the increased use of clindamycin for pneumococcal and staphylococcal infections.

Aminoglycosides

The aminoglycoside/aminocyclitol class of antibiotics is derived from *Streptomyces* spp. and *Micromonospora* spp. In general, these antibiotics contain a 2-deoxystreptamine ring attached to two or three additional moieties, most often amino sugars, all connected together by glycosidic linkages. Medicinal chemists have created substitutions at up to 10 different positions on the three rings or associated amino groups that have led to the creation of several semisynthetic aminoglycoside antibiotics. However, given the nephrotoxicity and ototoxicity inherent to aminoglycosides, little recent activity has occurred in the development of newer agents for community infections. All aminoglycosides currently available in the U.S. are generic formulations, with gentamicin, tobramycin, and amikacin representing those most often used in children.

All of the aminoglycoside antibiotics share a common binding region within the 30S ribosome, which is located at the peptidyl transferase center where charged tRNAs are first recognized and attach to the A site. With aminoglycoside binding close to the A site, conformational changes occur at the ribosomal tRNA docking site that creates enhanced affinity for tRNA binding, facilitating incorrect binding of noncognate tRNAs that do not match the corresponding codon on the mRNA. With attachment of incorrect tRNAs, misreading occurs and amino acid sequences in the resulting peptide are incorrect, leading to the creation of nonfunctional proteins. With binding of the aminoglycoside, proofreading for the accuracy of the attached tRNA also is compromised, as subsequent conformational changes that should occur in the 30S unit to allow for exact recognition of the attached tRNA cannot take place.[86,108–110] The structures of two of the larger aminoglycosides, streptomycin and spectinomycin, allow for additional binding sites within the 30S ribosome. Streptomycin attaches at four different domains within the 30S rRNA, as well as having a unique attachment to one of the ribosomal proteins. Spectinomycin, a larger structure with fused rings, appears to bind at the A site in a unique manner which also blocks the movement of the aminoacyl tRNA/peptidyl tRNA/EF-Tu complex from the A site to the P site during the peptidyl transferase reaction. With the production of abnormal proteins that may be incorporated into cellular structures such as the cell membrane, increased permeability of the

membrane occurs. With increased permeability, the aminoglycosides demonstrate enhanced entry into the cells, allowing further saturation of aminoglycoside binding sites on the ribosome, thus preventing the formation of new, functional ribosomes, which ultimately results in cell death. The aminoglycosides are bactericidal, and show concentration-dependent killing of bacteria (Table 289-1).

Resistance to aminoglycosides occurs primarily with the acquisition of a variety of aminoglycoside-modifying enzymes, many of which are carried on plasmids and transposons for efficient spread between bacteria. The most common are acetyltransferases, adenyltransferases, and phosphotransferases.[109] Many different efflux pump systems also play a major role in aminoglycoside resistance, particularly in gram-negative bacilli.[109] Ribosomal RNA methylase genes from *Actinomyces* that confer resistance to aminoglycosides recently have been identified in clinical isolates of enteric gram-negative bacilli and *Pseudomonas aeruginosa*.[111] Although this mechanism of resistance currently is uncommon, these genes now have the potential to spread quickly within clinical settings.

The clinical use of aminoglycosides occurs primarily for the treatment of gram-negative facultative bacillary infections – from the premature neonate through the adolescent.[112–114] Aminoglycosides are strongly polar, with high solubility in water but poor solubility in lipids resulting in poor penetration into the CNS, vitreous, bronchial secretions, and saliva. Aminoglycosides are concentrated in the proximal renal tubules and excreted in urine and achieve urinary tract concentrations up to 100 times the serum concentration. Due to the toxicity of the aminoglycosides at serum concentrations that are only 5- to 10-fold above the bacterial MICs, they are not usually used as the sole agents for treatment of serious infections. The aminoglycosides frequently are paired with a β-lactam antibiotic to create synergistic antibacterial activity and potentially to retard the emergence of antibiotic resistance, although the clinical impact of combination therapy has not been well demonstrated beyond the immunocompromised host.[115] Empiric and definitive therapy of early- and late-onset neonatal septicemia with gentamicin-containing combinations for enteric gram-negative infections is still considered appropriate three decades following the first recommendations in this age group, although well-controlled, prospective, comparative studies generally have not been performed.[112,113,116] Therapy of nosocomial infections with aminoglycoside-containing regimens is still acceptable in institutions in which nosocomial gram-negative pathogens remain susceptible.[117]

In gram-positive infections, the aminoglycosides add enhanced bacterial killing to cell wall-active agents, particularly in the treatment of serious infections.[118] Enterococcal infections are treated with ampicillin or vancomycin in combination with gentamicin in order to achieve bactericidal activity. The combination of penicillin plus gentamicin, or nafcillin plus gentamicin, are considered by some experts to be the most effective therapy for infective endocarditis caused by susceptible strains of viridans streptococci and *S. aureus*, respectively, especially for initial therapy.[119] However, controversy exists over the role of aminoglycosides in combination therapy, as clinical benefits have not been documented to be substantial, while renal toxicity is not uncommon.[120]

Empiric therapy of nosocomial infections and infections in immunocompromised hosts has included combination regimens containing aminoglycosides to enhance the spectrum of β-lactam agents, to provide potential synergy, and to minimize the emergence of resistant pathogens.[21] Aminoglycosides are also used in combination with other agents in the treatment of intra-abdominal infections. However, the cationic charges on the aminoglycoside molecule change as the pH changes in infected tissues, with the acidic environment of an abscess decreasing the ability of these antibiotics to enter bacterial cells (as documented by MICs that can be higher than those safely achievable in serum).[121] In addition, the active transport of aminoglycosides through the inner cell membrane into the cytoplasm of the bacteria requires an oxygen-dependent transport system not present in anaerobes, explaining the lack of activity of this class of agent in the treatment of anaerobic infections.

Given the high level of activity against certain gram-negative pathogens and lack of current prospective treatment trials using newer agents, the aminoglycosides still represent preferred therapy for tularemia and plague.

Streptomycin remains highly active against most strains of *Mycobacterium tuberculosis* requiring parenteral therapy, which leads to use in treatment of multidrug-resistant tuberculosis. Streptomycin may be particularly useful in the treatment of serious, life-threatening tuberculosis, including tuberculous meningitis. Although originally approved for use in 1952 and previously important for the treatment of infections caused by *Brucella* and *Francisella* spp., streptomycin has been replaced by gentamicin because of concerns for streptomycin-induced vestibular, auditory, and renal toxicity.

Paromomycin is an oral, nonabsorbable aminoglycoside. This agent is effective in the treatment of intestinal protozoal infections, including amebiasis and cryptosporidiosis.

Inhaled aminoglycosides, most commonly tobramycin, are used clinically to treat cystic fibrosis. Achieving high enough antibiotic concentrations in respiratory tract secretions and at the bronchial mucosa to be effective against *P. aeruginosa* is not usually possible with parenterally administered aminoglycosides, but high concentrations can be achieved with inhaled tobramycin, without concern for nephro- or ototoxicity.[122] The use of aerosolized aminoglycosides in patients with pneumonia caused by other multidrug-resistant gram-negative pathogens has not been prospectively investigated in controlled studies, but case series in adults suggest their potential role.[123]

Nephrotoxicity of aminoglycosides is dose-dependent and primarily is tubular. Monitoring renal function or aminoglycoside serum concentrations during therapy permits early detection of decreased renal function attributable to the aminoglycoside. Aminoglycoside ototoxicity can be either cochlear (with hearing loss) or vestibular (with vertigo), and correlates with increasing serum trough concentration as a function of overall drug exposure, rather than the peak serum concentration.[124]

Providing children with a single daily dose of aminoglycosides to decrease nephrotoxicity while maintaining or increasing efficacy has not been widely accepted due to the lack of well-controlled studies in children. However, limited data that exist in children, taken together with convincing data in adults, suggest that once-daily dosing could become routine for children, except possibly for certain severe infections, such as meningitis or persistent BSI.[125,126]

While streptomycin was the first aminoglycoside available for use, the toxicity and rapid development of resistance in bacteria limited its long-term viability. Kanamycin was approved for use in 1957 but was replaced by the less nephrotoxic gentamicin in 1963 as a more broadly active antibiotic against resistant gram-negative pathogens. Tobramycin was approved in 1968 and provided a small but predictable increase in in vitro activity against *P. aeruginosa* with a concomitant small but clinically insignificant decrease in activity against enteric gram-negative bacilli, allowing its use as the anti-pseudomonal aminoglycoside of choice. Amikacin, a semisynthetic derivative of kanamycin, was approved in 1972, and offered enhanced activity against many gentamicin- and tobramycin-resistant pathogens, in addition to providing serum antibiotic concentrations approximately 3- to 4-fold greater than those achievable with gentamicin or tobramycin. Amikacin also is useful in the treatment of infections caused by some strains of nontuberculous mycobacteria.

Streptogramins A and B

The streptogramins are two of a series of naturally occurring antibiotics isolated from *Streptomyces pristinaespiralis*. Two antibiotics have been modified from the naturally occurring pristinomycins I and IIA to create the semisynthetic antibiotics quinupristin (streptogramin B) and dalfopristin (streptogramin A), respectively. These two antibiotics are present in the FDA-approved combination Synercid in a 70:30 ratio.[127] Quinupristin and dalfopristin have completely different chemical structures, each with

a distinct but overlapping binding region within the P site of the peptidyl transferase center in the ribosome. Binding of dalfopristin to this region produces a conformational change that significantly increases the affinity of binding of quinupristin, in part explaining the synergy observed when the combination is used. Dalfopristin inhibits protein synthesis by interfering with substrate attachment to both A and P sites of the 50S subunit, while quinupristin blocks peptide bond synthesis during elongation by causing incorrect positioning of the peptidyl tRNA at the P site.[128] Once elongation has been initiated, quinupristin triggers the premature release of the elongating peptide chain. Quinupristin binds to the peptidyl transferase site at a similar location as the macrolides and lincosamides; methylation of the A2058 adenine at this important binding site prevents binding of quinupristin as well as the macrolides and clindamycin, and creates the macrolide-lincosamide-streptogramin (MLS) resistance phenotype.

Unfortunately, many mechanisms of bacterial resistance limit the clinical utility of quinupristin/dalfopristin, with resistance developing in some patients soon after starting therapy. Alterations of target binding sites, efflux removal of antibiotics from cytoplasm, and enzymatic alteration of the antibiotic structure all have been reported.[65,129] Although each of the streptogramins independently produces inhibitory effects on protein synthesis, the combination is bactericidal for a number of gram-positive pathogens, including *S. aureus.*

The agents have been available in Europe for several years as topical therapy, but with the development and spread of enterococci that are resistant to vancomycin, β-lactams, and aminoglycosides, an urgent need for quinupristin/dalfopristin was well documented. Clinical use is largely limited to serious infections caused by vancomycin-resistant strains of *Enterococcus faecium* (VRE). The combination is not active against the more common enterococcal pathogen, *Enterococcus faecalis.* Although quinupristin/dalfopristin also is FDA-approved for treatment of skin and skin structure infections caused by *S. aureus,* there are better evaluated and tolerated agents for therapy in children.

Quinupristin/dalfopristin significantly inhibits cytochrome P450 CYP3A function and may impact serum concentrations of concomitant drugs which are eliminated by this pathway. Phlebitis was a major side effect in quinupristin/dalfopristin-treated patients, occurring in almost half of adults receiving therapy. This combination agent has not been systematically studied for children under 16 years of age.

Oxazolidinones

Linezolid is the first antibiotic in the oxazolidinone class to be approved and used in children. This class of antibiotics is unique in that members are not natural products, but were discovered as one of a number of compounds created as potential monoamine oxidase-inhibiting agents.[130] However, some of these compounds also demonstrated antibacterial activity, although initially, many were associated with significant toxicity. Subsequent chemical modifications led to the development of linezolid, which demonstrated a reasonable balance between antimicrobial activity, clinical efficacy, and acceptable clinical toxicity. The oxazolidinones have a unique mechanism of action on the ribosome, distinct from all other classes of antimicrobial agents. The antibiotic binds to an area close to the ribosomal peptidyl transferase center and inhibits the initiation of protein synthesis by preventing the formation of the initiation complex of fMet-tRNA/elongation factors/mRNA/GTP at the peptidyl transferase center. The movement of the complex from the ribosome's "A site" of tRNA attachment to the peptidyl "P site" is blocked and coupling of amino acids and lengthening of the peptide chain cannot occur.[131]

Linezolid demonstrates bactericidal activity against *S. pneumoniae,* but bacteriostatic activity against *S. aureus* and *Enterococcus* species. However, limited studies comparing vancomycin, a bactericidal agent (with limitations in activity in infected lung), with linezolid in the treatment of nosocomial pneumonia caused by MRSA suggest equivalent clinical outcomes.[132,133] Activity of linezolid is primarily limited to gram-positive bacteria, due to the presence of an efflux pump (AcrAB) present in many gram-negative organisms. Linezolid is not active against *Mycoplasma* or *Ureaplasma*.[134]

Resistance to linezolid has been described and consists of structural changes at the linezolid binding site that prevent attachment.[65,135] These relatively infrequent changes, which tend to occur more frequently with more prolonged therapy, are primarily single-base changes in the rRNA occurring around the peptidyl transferase site. Transferable resistance to the oxazolidinones through conjugative transposons has been documented.[65]

Linezolid has been studied clinically for nosocomial and community-acquired pneumonia, and for complicated and uncomplicated skin and skin structure infections.[136,137] The clinical and microbiologic response rates for each of these tissue-specific infections in children were equivalent to comparator agents, usually vancomycin. The in vitro activity and clinical efficacy of linezolid in the treatment of infections caused by penicillin- and macrolide-resistant pneumococci, VRE, MRSA, and VRSA support a role for linezolid when other, better-studied agents are not available or are not tolerated. The most common current clinical use of linezolid in children is for the treatment of MRSA-associated skin or respiratory tract infections.[138] Little data other than case reports are available for the use of linezolid in treatment of bone and joint infections[139] and CNS infections.[140]

Data on pharmacokinetics for both parenterally and orally administered linezolid are available in children, including premature neonates.[141] Linezolid is virtually 100% absorbed by the oral route, allowing equivalent mg/kg dosing for both intravenous and oral formulations. Linezolid is not metabolized by the cytochrome P450 system, and does not induce this enzyme or compete with other drugs in P450-mediated metabolism. Some concerns have been raised regarding hematologic toxicity, including neutropenia and thrombocytopenia, which was found to be dependent on dose and duration of therapy.[130] However, prospective, comparative data in the pediatric FDA registration studies failed to demonstrate a significant difference in toxicity compared with other agents. Also of concern in the early pediatric clinical trials of linezolid was the possibility of hypertension due to effects of the antibiotic's mild monoamine oxidase (MAO) inhibitor activity. However, no MAO inhibitor side effects were noted in any phase I to III pediatric trial, permitting children to remain on usual diets while receiving treatment.[142]

NUCLEIC ACID-ACTIVE ANTIBIOTICS

RNA Polymerase

Rifamycins

The rifamycins, rifampin (also called rifampicin), rifabutin, rifapentine, and the oral nonabsorbed rifaximin, are all semisynthetic derivatives of natural products of *Streptomyces* spp. The intracellular target for the rifamycins is DNA-dependent RNA polymerase and has been well defined on a molecular level.[143] During the creation of an RNA strand from the bacterial DNA strand, the polymerase requires functional channels within the enzyme for both the DNA template strand and complementary strand, as well as for the elongating RNA strand. As the RNA bases dock sequentially at the active site within the polymerase, the newly created RNA strand moves forward, one base at a time. The rifamycins bind in the channel occupied by the newly created RNA strand, approximately 2 to 3 bases downstream from the active site, blocking the RNA strand from moving out of the polymerase and terminating the further elongation of that RNA segment as it also uncouples the RNA strand from the active site.[143,144] Although the actual active site of the polymerase is highly conserved between bacterial species, there is some diversity between bacteria around the active site with respect to the RNA polymerase structure. This diversity alters the binding affinity for rifampin across bacterial and mycobacterial species and provides one basis for the variable susceptibility to this class of agents. Rifampin demonstrates bactericidal activity against susceptible organisms.

Given the large size of the rifamycin molecule, multiple binding sites within the polymerase, and the restricted target binding pocket in the polymerase, it is not surprising that many different single amino acid substitutions from mutational events within the polymerase will lead to decreased rifamycin binding and stable resistance with little impact on the viability of the organism. In *S. aureus,* at least 18 genotypes resistant to rifampin have been characterized, some of which contain multiple base substitutions.[145] Each of these mutations is likely to affect either the binding affinity or the access of rifampin to the binding pocket to a different degree. Most mutations causing rifampin resistance also produce resistance to rifabutin and rifapentine.[146]

The rifamycins have a remarkably broad spectrum of activity that includes *Staphylococcus* spp., *S. pyogenes, Neisseria* spp., *H. influenzae, Campylobacter jejuni, H. pylori, C. trachomatis,* both tuberculous and nontuberculous *Mycobacterium* spp., *Aspergillus* spp., *Naegleria fowleri,* and *Toxoplasma gondii* (see Table 292-2). Rifabutin has increased in vitro activity against *M. tuberculosis* compared with rifampin, but has not been documented to result in improved microbiologic outcomes in treated patients.[147] Rifabutin also has increased activity against MAC compared with rifampin, most likely due to binding to additional sites within the polymerase.[143,148,149] Rifapentine has both increased in vitro activity against *M. tuberculosis* in addition to an extended serum elimination half-life (16 hours) compared with rifampin (2 to 3 hours).

Rifamycins achieve high intracellular concentrations, between 5- and 20-fold greater than extracellular concentrations.[148] This likely explains the effectiveness of this class in the therapy for mycobacterial infections, in which pathogens are sequestered intracellularly.

Of the rifamycins, rifampin is the agent most commonly used in pediatrics. Rifabutin and rifapentine were developed for treatment of mycobacterial infections, and neither is currently FDA-approved for use in children. Rifampin is used in children as part of combination therapy for tuberculosis. Rifampin also can be used in combination therapy for treatment of nontuberculous mycobacterial infections such as adenitis, cellulitis, or pneumonia. For treatment of bacterial infections, rapid emergence of resistance in virtually every pathogen dictates a need for combination antibiotic therapy. Combination therapy may allow for eradication of rifampin-resistant strains before they become clinically important. Rifampin has been used in combination therapy of *Bartonella henselae* infections (cat-scratch disease), multidrug-resistant *S. aureus* infections (particularly MRSA), and multidrug-resistant pneumococcal infections, including meningitis.[150] Although not well studied in prospective comparative clinical trials, the excellent tissue penetration of rifampin may provide improved clinical outcomes compared with β-lactam antibiotic therapy alone in deep bone and joint infections and in foreign-body or device infections associated with intravascular catheters or implanted devices. As single-drug therapy, rifampin is only used for the eradication of colonization of *N. meningitidis* and in the prophylaxis when indicated for *N. meningitidis* and *H. influenzae* type b.

Rifabutin has documented efficacy in both prophylaxis and therapy of MAC (in combination with other agents) in HIV-infected adults, but clarithromycin and azithromycin are recommended as preferred therapy for HIV-infected children.[80] Only limited data are available in children with MAC infections.[73,151,152] The extended half-life of rifapentine provides a rationale for once-weekly therapy, although the failure rate in those with more serious tuberculosis, and the bacteriologic relapse rate was slightly higher in those treated with rifapentine compared with rifampin.[147,153] Rifapentine has not been evaluated in children.

Rifaximin is an oral agent that is not absorbed from the gastrointestinal tract and produces high intraluminal antibiotic concentrations with little systemic toxicity. Microbiologic activity has been demonstrated in vitro at achievable intraluminal antibiotic concentrations against *E. coli, Salmonella, Shigella, Vibrio, Yersinia,* and *Campylobacter* species. Although the susceptibility of these enteric pathogens is about 32 to 64 μg/mL, a concentration not achievable in tissues, the concentrations achieved in the gastrointestinal tract are as high as 8000 μg/mL, providing an antibiotic exposure that is well above that required for an antibacterial effect.[154] Although this antibiotic is currently only approved for traveler's diarrhea in adults,[155] an oral nonabsorbable, broad-spectrum agent for other gastrointestinal pathogens could have considerable value for children.

The most common clinical side effect of treatment with rifampin is nausea, which appears to decrease as the treatment course progresses. The most common adverse effect of treatment is hepatotoxicity, as assessed by elevation of hepatic transaminase levels; however, most children receiving rifampin for tuberculosis therapy also receive other hepatotoxic agents, preventing an accurate assessment of the role of rifampin as a single agent causing liver injury.[156] Children receiving multiple hepatotoxic agents should be assessed at regular intervals for evidence of hepatic injury.

The drug–drug interaction profile of the rifamycins frequently complicates clinical management. The P450 CYP3A system is activated by the rifamycins. If the child is receiving other drug(s) metabolized by this system, decreased, potentially ineffective serum concentrations of that drug may be present. In addition, if the concurrent drug represents a competitive substrate for P450 metabolism, increased and potentially toxic serum concentrations of that drug may result from decreased metabolism.[148] The potency of CYP3A induction is greatest with rifampin and least with rifabutin. Rifabutin is also a CYP3A substrate itself, resulting in higher rifabutin serum concentrations when given concomitantly with CYP3A inhibitors.

DNA-Dependent DNA Polymerase

Quinolones and Fluoroquinolones

The quinolones are a diverse group of antibiotics that target DNA synthesis and are active against a wide range of bacteria, *Mycoplasma, Chlamydia,* and *Chlamydophila* spp., and, for some agents, mycobacteria.[157,158] The first of the quinolone antibiotics was discovered during the commercial preparation of the antimalarial agent chloroquine, and was subsequently modified for antibacterial use in humans.[157] The first approved quinolone agent, nalidixic acid, has a limited gram-negative spectrum of activity and a poor pharmacokinetic profile for treatment of invasive infections. With chemical modifications to the basic quinolone (and the closely related naphthyridone) ring structure, the spectrum of activity and pharmacokinetics have been greatly enhanced, allowing for once-daily dosing for infections in many different tissue sites. The 6-fluoroquinolones (beginning with norfloxacin and ciprofloxacin) demonstrated a significant improvement in antibacterial activity, and virtually all subsequently approved compounds are fluoroquinolones.

The quinolones all interfere with DNA synthesis by interfering with two closely related type II topoisomerase enzymes involved in DNA synthesis: DNA gyrase and topoisomerase IV.[158,159] Each of these enzymes comprised 4 subunits: DNA gyrase contains 2 subunits of GyrA and 2 of GyrB, whereas topoisomerase IV consists of 2 subunits of ParC and 2 of ParE (in *Staphylococcus aureus,* these topoisomerase IV subunits are termed GrlA and GrlB). The DNA gyrase is responsible for uncoiling DNA ahead of the replication fork to allow for DNA strand replication by DNA polymerase, or for the creation of RNA strands by RNA polymerase. In the process of uncoiling and coiling, strands of DNA are cut and then religated by these enzymes in order to maintain a stable double-helix structure. The topoisomerase IV appears to be primarily responsible for stabilizing the newly created strands of DNA as they separate from template strands following replication. The quinolones bind to these enzymes at specific nucleic acid strand attachment sites, producing conformational changes in the DNA gyrase/DNA or topoisomerase IV/DNA complexes and stabilizing them, thus "freezing" the complex. This leads to an inability to translocate the entire DNA replication complex along the DNA strand, halting the process of nucleic acid replication. Binding of the fluoroquinolones leads to single- and double-strand DNA breaks without religation, and the subsequent release of DNA fragments into the cell, which leads to cell death in ways that are not well understood. The

DNA gyrase/DNA replication complex may also be involved in altering the formation and stability of DNA loops involved in the transcription process, representing another mechanism by which fluoroquinolones impact cell function.

Although quinolones can bind to some extent to both of these enzymes, structural characteristics of each quinolone create unique binding characteristics to each of these two enzymes for every drug in this class. The differences in binding to DNA gyrase and topoisomerase IV lead to differences in the susceptibility of organisms to the various quinolones as well as differences in the development of resistance. In general, the quinolones preferentially bind to DNA gyrase in gram-negative bacteria, and to topoisomerase IV in gram-positive bacteria, although some of the newer quinolones bind to both enzymes equally well. Binding to DNA gyrase, occurring before the replication fork of DNA synthesis, produces a more rapid effect on the formation of DNA, whereas binding to the topoisomerase IV after strand duplication has occurred creates a less immediate effect on cell death. However, as both enzymes function to nick and religate strands of DNA during the coiling/uncoiling process, the quinolone effects after binding to either, or both enzymes, can lead to cell death. These agents display bactericidal activity against bacterial pathogens, with dose-dependent pharmacodynamic activity best described by the ratio of AUC : MIC (the ratio of the area under the serum concentration versus time curve to the MIC of the antibiotic for that organism).[160]

As with many antibiotics, resistance can develop in many different ways, and resistance from multiple different mechanisms can be additive. The most common resistance occurs from alterations in the amino acids present at certain critical and virtually identical sites on the two enzymes, DNA gyrase, and topoisomerase IV, that prevent avid binding of the quinolone. Single gene mutations leading to these amino acid changes are primarily found in the quinolone resistance-determining regions of *gyrA* and *parC*.[161] Additional but less common mutations have been detected in *gyrB* and *parE*. For *E. coli*, accumulating additional amino acid changes leads to increasing resistance. The first-step mutation in *E. coli* most often occurs in the *gyrA* subunit of DNA gyrase, leading to a mild-to-moderate increase in the MIC, depending on the quinolone being assessed. A second-step mutation, usually in *parC*, generally leads to resistance that cannot be overcome at achievable tissue concentrations. For *S. pneumoniae* and *S. aureus*, the first-step mutation most often occurs in the *parC* (or *GrlA*) subunit of topoisomerase IV.[161,162] Depending on both drug and bacteria, mutations in one of the subunit sites can lead to substantial increases in resistance for a particular drug, but for drugs that bind to both gyrase and topoisomerase IV sites, a mutation at one site does not effectively raise the MIC to a level that usually leads to treatment failure. When two or more mutations occur that affect binding to both enzymes, clinical failures become more common.

Efflux pumps also are effective mechanisms to prevent quinolone binding intracellularly to the gyrase and topoisomerase targets. Efflux pumps affect intracellular concentrations of different quinolones to differing degrees.[162] In addition, newly described mutations in aminoglycoside acetyltransferases confer the ability to acetylate ciprofloxacin, decreasing its activity against *E. coli* 2- to 4-fold, with the modified enzyme still retaining activity against the aminoglycosides. This mechanism of resistance is transferable to other bacteria, in contrast to the *gyrA* or *parC* mutations which only spread horizontally from patient to patient. It is not known how problematic these strains will become.[163]

Safety issues for children have been a concern for this entire class of agents. Although nalidixic acid was approved for children by the FDA in 1963, more extensive animal toxicology studies were available for the agents that followed. Preclinical juvenile animal toxicity data for ciprofloxacin in the late 1970s suggested the potential for damage to joints in young children. Therefore, no routine pediatric drug development was undertaken for this compound or any other fluoroquinolone until the need for potential use of these agents for children was demonstrated to the FDA in 1997.[164] No quinolone-associated arthropathy has yet been documented clearly in children for agents available in the U.S. although a suggestion of transient arthralgia exists from an FDA safety database of ciprofloxacin.[165] Long-term toxicity studies currently are in progress, but are not of sufficient size to be able to detect or define rates of rare adverse effects on joints or tendons. It is encouraging, nonetheless, that lack of reported toxicity from current published data and from data presented to the FDA suggests that joint toxicity is not a common problem in children, if it exists at all.[166]

Nalidixic Acid, Norfloxacin

Nalidixic acid was approved in 1963 for use in children down to 3 months of age for the treatment of UTI. Norfloxacin, used for treatment of UTIs in children in other areas of the world, is not FDA-approved for children in the U.S. With the FDA approval of ciprofloxacin for children with UTIs in 2004, ciprofloxacin is the preferred quinolone agent for these infections when a fluoroquinolone is needed for gram-negative pathogens, based on the quality of prospectively collected data regarding both safety and efficacy in children.

Ciprofloxacin

Ciprofloxacin was one of the first of the 6-fluoroquinolones to be FDA-approved for adults, but large clinical trial investigations in children did not begin until the late 1990s, with the exception of studies in children with cystic fibrosis. Ciprofloxacin was recently studied for complicated UTI, and was the first 6-fluoroquinolone to be approved for use in pediatrics. Although all of the fluoroquinolones have a bitter taste, a tolerable suspension formulation of ciprofloxacin is available for children. Current usage of the fluoroquinolones is limited, based on concerns of cartilage toxicity. The antimicrobial activity of ciprofloxacin is provided in Table 292-2, and includes most of the enteric gram-negative bacilli as well as *P. aeruginosa*. Activity against the gram-positive pathogens and anaerobic pathogens generally is only fair.

Current clinical use of ciprofloxacin centers on gram-negative infections for which no other oral antibiotic agent is available.[165,167] In this setting, ciprofloxacin and other fluoroquinolones represent effective therapy in which the risk/benefit assessment favors treatment with an oral quinolone agent rather than parenteral therapy with a nonquinolone agent. These infections may be located in virtually any tissue site except the CNS. Examples of infections, many of which are hospital-associated, include complicated UTI, bone or joint infection (including those caused by *P. aeruginosa*), soft-tissue infection, and lower respiratory tract infection. Many of these children have comorbid conditions that have created a need for previous courses of antibiotics and therefore the selection of multidrug-resistant pathogens. Because these infections are uncommon, no prospective, randomized, controlled clinical trials of use of ciprofloxacin in children are available. In addition, some reluctance may exist on the part of the pharmaceutical industry to perform these studies due to potential toxicity. In addition to complicated UTI, FDA approval has also been given for the treatment of inhalational anthrax in children.

Fluoroquinolones achieve effective concentrations in the gastrointestinal tract and have an advantage over β-lactam antibiotics in that they also achieve high intracellular antibiotic concentrations, particularly effective in the treatment of *Salmonella* infections. Ciprofloxacin has been studied in children for shigellosis and salmonellosis, and provides equivalent or superior rates of eradication compared with standard agents.[168,169]

With the high bioavailability of orally administered fluoroquinolones and activity against most gram-negative pathogens for immunocompromised children, selective use of these agents (with or without additional oral therapy for gram-positive pathogens) in low-risk children with fever and neutropenia is a promising area of clinical investigation.[170]

Levofloxacin

Levofloxacin was the first available agent in a series of newer fluoroquinolone agents with enhanced activity against gram-positive

pathogens, including *S. pneumoniae* and *S. aureus.* Levofloxacin has been clinically effective in treatment of upper and lower respiratory tract infections in adults,[171] with successfully completed clinical trials in children in both acute otitis media and community-acquired pneumonia. No safety issues of significant concern were raised in adult or pediatric clinical programs. No joint-related toxicity was noted in children, with a sufficiently large number of subjects prospectively studied to detect a 1% adverse event rate. The most acknowledged clinical need for levofloxacin in children is for the treatment of unresponsive or recurrent otitis media due to pneumococci resistant to β-lactam and macrolide agents.[172] Use for therapy of serious infections is appropriate in situations for which no other class of active parenteral agent exists, or use as oral therapy of infections in situations for which only nonquinolone parenteral therapies exist.[165] Levofloxacin also is approved for treatment of inhalational anthrax in children.

Moxifloxacin, Gemifloxacin

New generations of fluoroquinolones demonstrate increased activity against *S. pneumoniae* compared with earlier fluoroquinolones.[173] None of these newer agents have been studied adequately or approved for use in children.

Nitroimidazoles

Metronidazole

Metronidazole is a synthetic nitroimidazole antibiotic with a poorly defined mechanism of action despite decades of extensive use. Originally introduced for the treatment of *Trichomonas* infections (hence the original trade name, Flagyl), use in pediatrics has been most extensive for treatment of anaerobic infections, despite the fact that the antibiotic has never been approved by the FDA for use in children for these indications. Metronidazole is taken into cells by passive diffusion and the nitro side chain on the imidazole ring is reduced intracellularly by the pyruvate-ferredoxin reductase complex into a toxic nitro radical that reacts with DNA, leading to DNA strand breaks, helix destabilization, and ultimately cell death in both dividing and nondividing cells.[150,151] Metronidazole demonstrates concentration-dependent bactericidal activity. One of the major metabolites, a hydroxy derivative, retains significant antibiotic activity. Metronidazole is active against anaerobic bacteria and certain protozoa, including *Trichomonas, Entamoeba,* and *Giardia* (see Table 292-2).

In addition to direct bactericidal activity, metronidazole also appears to have direct effects on decreasing neutrophil generation of hydrogen peroxide and hydroxyl radicals, which may lead to decreased inflammation at the site of infection. Some evidence suggests that metronidazole may also inhibit lymphocyte transformation and granuloma formation.[152] The clinical relevance of these observations is not known.

Although resistance to metronidazole is uncommon, a number of bacteria, including some strains of *B. fragilis,* contain *nim* genes which code for an inactivating enzyme that may exist on both plasmids and within chromosomes. This enzyme effectively reduces the nitro group on metronidazole into a stable and inactive amine.[174–176]

Metronidazole is available in intravenous, oral tablet and capsule formulations, and topical formulations. Although metronidazole has a very bitter taste and is not well tolerated when pulverized and placed in suspension, the absorption from the gastrointestinal tract is excellent, with >90% bioavailability. Although rectal administration yields approximately 70% to 80% bioavailability, this route of administration has never gained widespread acceptance for children. Metronidazole provides excellent therapeutic concentrations in a wide range of tissue sites, including CSF, in which concentrations are very close to those achieved in serum.[177–179] Although the serum elimination half-life is approximately 8 hours, early studies performed in adults for FDA approval used 6-hour dosing regimens, which remains the current FDA dosing recommendation in the package label. The observed half-life with oral administration appears to be longer than that found for IV administration, for unknown reasons. For most clinical situations, based on the pharmacodynamics of antibiotic exposure, dosing every 8 hours should be adequate. One of the metabolites of metronidazole that displays significant antibacterial activity has a more extended half-life, averaging 11 to 13 hours, providing another rationale for less frequent dosing.

Clinical use in pediatrics primarily is for the treatment of anaerobic infections.[174,180] Given the excellent tissue penetration characteristics of metronidazole, activity against all susceptible anaerobes is achievable in most tissue sites. However, data from randomized, prospective clinical trials may not be available for many sites of infection. As most infections involving anaerobes also involve facultative or aerobic organisms, additional antibiotics are necessary.

Metronidazole is bactericidal for *Bacteroides* spp. and has been used extensively in the treatment of intra-abdominal infections, including complicated appendicitis, penetrating injury to the bowel, and colitis.[99] These infections often involve multiple susceptible anaerobic species, including *B. fragilis.* Other mixed aerobic/anaerobic infections include deep head and neck space infections (e.g., parapharyngeal abscesses, Ludwig angina) and necrotizing fasciitis/cellulitis (e.g., necrotizing synergistic fasciitis, Fournier gangrene, and omphalitis). *Clostridia* spp. also are susceptible to metronidazole, and can be effectively treated when causing deep-tissue infections. Some penicillin-susceptible anaerobic gram-positive cocci, however, are not susceptible to metronidazole.

Metronidazole, in combination with other antibiotics and proton pump inhibitors, is part of a treatment regimen for *H. pylori*-mediated ulcer disease.[181] In addition, some benefit from metronidazole in the treatment of Crohn disease may occur;[182] antibiotic and anti-inflammatory properties of the agent both may play a role.

Given the excellent penetration into CSF and bactericidal capacity, metronidazole treatment of anaerobic organisms causing meningitis or ventriculitis (traumatic, postsurgical, or nosocomial), or treatment of anaerobic brain abscesses is effective.[178] Prospective, comparative data to document efficacy for these indications are not available.

Metronidazole also can be used for female genital tract infections, including bacterial vaginosis, and as part of antimicrobial therapy of pelvic inflammatory disease.

One of the most common pediatric uses for metronidazole is in the treatment of *Clostridium difficile* enterocolitis.[43] Following the documented increases in vancomycin resistance of gastrointestinal tract flora with the use of oral vancomycin in adults for *C. difficile* colitis, metronidazole became the drug of choice in therapy for children as well as adults. Although clinical response rates comparing oral metronidazole therapy with oral vancomycin therapy for *C. difficile* infection have been equivalent in the past, currently there is concern regarding the efficacy of metronidazole in the treatment of *C. difficile* infection.[183]

Entamoeba histolytica trophozoites (but not cysts) are susceptible to metronidazole, allowing therapy for both intestinal and extraintestinal amebiasis, including amebic liver abscess.[184] Metronidazole is one of the drugs of choice for treatment of *Giardia* intestinal infections and is an alternative treatment for *Dientamoeba* infections.[184] For sexually active adolescent females and males, metronidazole still remains effective therapy for *Trichomonas* infections.[185]

Sulfonamides (Single Agents or in Combination with Trimethoprim or Pyrimethamine)

Sulfisoxazole, Sulfamethoxazole, Sulfadiazine

The sulfonamide class was one of the first available antibiotics for human use, with striking clinical responses documented in 1937 in the treatment of erysipelas by sulfanilamide and its prodrug.[186,187] Unfortunately, due to widespread resistance in common bacterial pathogens after decades of extensive use, sulfonamides now are focused in a few areas of remaining effectiveness. However, for

pathogens that remain susceptible to sulfonamides, either used alone or since 1968 when used in combination with trimethoprim, these agents have a long history of efficacy with reasonable safety. Sulfonamides now are used almost exclusively in combination with trimethoprim for the treatment or prophylaxis of bacterial infections.[188] Sulfadiazine currently is used in combination with pyrimethamine for the treatment of toxoplasmosis.

The sulfonamides are bacteriostatic by means of competitive inhibition of *para*-aminobenzoic acid, utilized by dihydropteroate synthase in the synthesis of dihydrofolic acid, a precursor of purine bases in the formation of nucleic acid. Bacteria that are required to synthesize folic acid are susceptible to this class of compounds.

Sulfa agents are well absorbed from the gastrointestinal tract and are, in general, metabolized by the liver and excreted by the kidney. Both sulfisoxazole and sulfamethoxazole are highly protein-bound (70% to 80%). Due to sulfonamide binding to albumin, bilirubin may be displaced from its albumin binding sites, causing kernicterus in ill, acidotic neonates with hyperbilirubinemia as a result of subsequent bilirubin binding to CNS tissue. However, no cases of kernicterus have been documented in full-term, well-appearing infants. Despite FDA labeling cautions against the use of this class of agents in infants under 2 months of age, they are safe in nonacidotic term infants as early as the second week of life, as physiologic neonatal jaundice is resolving.

Sulfonamides are responsible for one of the most serious drug-related adverse events, an intense immune-mediated separation of skin at the dermal-epidermal junction. This immune reaction also can result in separation of the respiratory and gastrointestinal tract mucosa from supporting connective tissue. Variously called Stevens–Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme major, the spectrum of reactions varies from a cutaneous erythematous, blistering rash to severe, extensive, life-threatening sloughing of skin and mucosa of the respiratory and gastrointestinal tract.[189,190] At the first sign of a skin reaction in a child receiving sulfa therapy, the child should be evaluated, the sulfonamide discontinued, and careful observation begun.

Trimethoprim plus Sulfamethoxazole (TMP-SMX)

Trimethoprim, available as a single agent but used far more commonly in children in combination with sulfamethoxazole, acts at the metabolic step following that inhibited by sulfonamides in the synthesis of purine bases.[188] TMP-SMX prevents the formation of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting dihydrofolate reductase. The combination of sulfamethoxazole and trimethoprim blocks two consecutive steps in the synthesis of thymidine, providing both synergistic activity against most pathogens, and decreasing the risk of development of resistance to either the sulfa agent or the trimethoprim. Trimethoprim displays bactericidal activity against bacteria, as does the combination.

Current clinical uses of TMP-SMX are limited in the treatment of UTI due to increasing resistance of *E. coli*, but TMP-SMX therapy is effective in regions where susceptibility remains substantial. For children with urinary tract anomalies and significant reflux, TMP-SMX prophylaxis has been documented to decrease the number of recurrent UTIs.[191]

In the treatment of respiratory tract infections, the rate of pneumococcal resistance to sulfa in most areas of the U.S. is greater than 40%, precluding it as first-line therapy of acute otitis media, sinusitis, or community-acquired pneumonia. Despite in vitro susceptibility of *S. pyogenes,* TMP-SMX is not recommended for treatment of streptococcal pharyngitis since host immune response to streptococci is not prevented reliably (which is required in order to prevent the development of acute rheumatic fever).

TMP-SMX has been used increasingly for the treatment of CA-MRSA skin and skin structure infections although prospective, controlled studies were never performed for skin and skin structure infections at the time of original antibiotic approval, or since the emergence of CA-MRSA. In vitro susceptibility of CA-MRSA to TMP-SMX is almost universal; data on comparable efficacy with clindamycin are limited and conflicting depending on lesions and outcomes studied.[192,193]

TMP-SMX is used for certain hospital-associated infections caused by multidrug-resistant (MDR) enteric gram-negative bacilli such as *Enterobacter* and *Klebsiella* species and *Stenotrophomonas maltophilia* (which often remains susceptible). TMP-SMX is generally bactericidal, although not consistently for high-density inocula of gram-negative bacilli. TMP-SMX is considered safer than most other options (e.g., colistin, fluoroquinolones) in the treatment of MDR gram-negative infections, and may provide an adequate therapy for infections in most tissue sites, including meningitis, in situations for which no other well-evaluated therapy options exist.

Gastrointestinal infections caused by *Salmonella* and *Shigella* spp. and enteropathogenic strains of *E. coli* often were treated successfully with TMP-SMX in the past; however, the value of TMP-SMX has decreased as resistance in these gastrointestinal pathogens has increased.[83,155] The intracellular activity of TMP-SMX has been particularly advantageous in the treatment of susceptible strains of *Salmonella*. *Yersinia enterocolitica* and *Vibrio cholera* often are susceptible to TMP-SMX. Susceptibility of enteric bacterial pathogens should be assessed before TMP-SMX is selected for therapy in serious infections. For parasitic infections of the gastrointestinal tract caused by *Cyclospora* sp. and *Cystoisospora* (formerly *Isospora*), TMP-SMX remains the treatment of choice.[194]

TMP-SMX remains effective therapy for brucellosis, nocardiosis (with exceptions), and some infections caused by the nontuberculous mycobacteria. Prophylaxis and treatment of *Pneumocystis* pneumonia in immunocompromised children remains highly effective.

Sulfadiazine plus Pyrimethamine

The combination of sulfadiazine and pyrimethamine is active against a number of protozoa, including *Toxoplasma* and *Plasmodium*. Clinical use in children is primarily limited to congenital toxoplasmosis, with treatment starting as soon as physiologic jaundice has resolved, and to older children who have documented toxoplasmosis associated with immune deficiencies (primarily HIV-related).

Miscellaneous

Nitrofurantoin

Nitrofurantoin is a unique antibiotic, characterized by a hydantoin ring with a nitro-substituted furanyl side chain that is metabolized within the bacteria to produce reactive compounds that are bactericidal. The mechanism of antibacterial activity is not well understood, but presumably occurs by altering ribosomal proteins and other important intracellular structures. Both gram-positive bacteria (including staphylococci and streptococci) and gram-negative bacteria (*E. coli*, *Klebsiella*, and *Citrobacter* spp.) are susceptible. Mechanisms of resistance have not been well defined, but no cross-resistance occurs with other antibiotic classes. Recent data from the U.S. on susceptibility of pediatric uropathogens document that, overall, resistance to nitrofurantoin across all pathogens and pediatric age groups is approximately 5% to 10%.[195]

Nitrofurantoin was originally FDA-approved in 1953 for the treatment of uncomplicated UTIs. Nitrofurantoin is well absorbed orally and is rapidly cleared from the serum, producing subtherapeutic concentrations in serum, but bactericidal concentrations in urine. Currently available formulations include a rapidly absorbed monohydrate salt, a monohydrate salt in slow-release matrix, and crystalline nitrofurantoin that is also more slowly absorbed. Dosages should be decreased in children with any degree of renal insufficiency.

In clinical practice, nitrofurantoin has been used primarily for prophylaxis of UTI, although few prospective comparative data are available on which to base recommendations.[196–199] Serious pulmonary toxicities, both acute and chronic, were reported in the decade following availability of nitrofurantoin.[166,167] Acute lung

injury, felt to be immune-mediated, and chronic fibrosis have been reported in adults during long-term therapy. The rate and severity of these multiple pulmonary toxicities have not been evaluated prospectively in children. However, no reports of pulmonary toxicity in young children receiving nitrofurantoin prophylaxis for UTI have been published in the past two decades, despite continued use. In addition to pulmonary toxicity, hemolysis secondary to glucose-6-phosphate dehydrogenase deficiency has also been documented.

Methenamine

Methenamine hippurate is used exclusively for the prevention of UTI. Initially available in 1967 and FDA-approved for patients ≥12 years of age, methenamine is a salt that ultimately exerts an antibacterial effect in the urine as it becomes converted into formaldehyde. This effect occurs when the urine pH is below 5.5. Formaldehyde has nonspecific bactericidal activity on both gram-positive and gram-negative bacteria. However, as the generation of formaldehyde is dependent on an acidic urinary pH, methenamine may not be active in situations in which a more alkaline pH is created by diet, or by urea-splitting bacteria in the urine, such as *Proteus* and *Pseudomonas*. A recent review of previously published data on clinical trials of methenamine prophylaxis, some of which were published as early as 1975, suggested efficacy for short-term use (<1 week), in adults with normal urinary tract anatomy.[200] Data collected in children in Finland from 1960 to 1974 suggest a benefit that is equivalent to, or superior to sulfa and nitrofurantoin, although failures were not uncommon.[201] The clinical use of methenamine in children is not well defined currently due to lack of high quality data on the safety and efficacy in children, and particularly for long-term prophylaxis.

APPENDIX 292-1. Dosage of Antibacterial Drugs for Infants, Older Children, and Adolescents

Drug Generic (Trade)	Route	Dosage (per kg/day)[a]	Comments
Aminoglycosides[b]			Dosage adjusted according to serum concentration(s).
Amikacin (Amikin)	IV, IM	15–22.5 mg divided into 3 doses	
Gentamicin (Garamycin)	IV, IM	3–7.5 mg divided into 3 doses	8–10 mg for cystic fibrosis
	Intraventricular	1–2 mg per dose (adult 3 mg)	
Kanamycin (Kantrex)	IV, IM	15–30 mg divided into 3 doses (adult maximum 1.5 g/day)	
Neomycin (numerous)	PO	100 mg divided into 4 doses (adult, 4–8 g/day)	Minimally absorbed from GI tract
Streptomycin	IM, IV	20–30 mg divided into 2 doses (adult 1–2 g/day)	
Tobramycin (Nebcin)	IV, IM	3–7.5 mg divided into 3 doses	8–10 mg for cystic fibrosis
β-Lactam agents[c]			
Monolactams			
Aztreonam (Azactam)	IV, IM	90–120 mg divided into 4 doses (adult 3–6 g/day, maximum 8 g/day)	
Carbapenems[c]			
Doripenem (Doribax)	IV	Adults 1500 mg per day in 3 doses	
Ertapenem (Invanz)	IV, IM	30 mg divided into 2 doses, maximum 1 g/day (children ≥12 years and adults, 1 g/day once daily)	
Imipenem-cilastatin (Primaxin)	IV, IM	60–100 mg divided into 4 doses (adult 1–2 g/day)	Seizures at high doses; not used for meningitis
Meropenem (Merrem)	IV	60 mg divided into 3 doses (adult 3–6 g/day)	120 mg for meningitis
Cephalosporins[c]			Methicillin-resistant staphylococci are resistant to all currently available cephalosporins, except ceftaroline
Cefaclor (Ceclor)	PO	20–40 mg divided into 2 or 3 doses (adult 1–1.5 g/day, maximum 4 g/day)	
Cefadroxil (Duricef, Ultracef)	PO	30 mg divided into 2 doses (adult 1–2 g/day, maximum 4 g/day)	
Cefazolin (Kefzol, Ancef)	IV, IM	50–100 mg divided into 3 doses (adult 1.5–6 g/day, maximum 12 g/day)	
Cefdinir (Omnicef)	PO	14 mg once daily, maximum 600 mg/day	
Cefditoren (Spectracef)	PO	400–800 mg (not per kg) divided into 2 doses	
Cefepime (Maxipime)	IV, IM	100–150 mg divided into 2–3 doses (adult 2–6 g/day, maximum 6 g/day)	
Cefixime (Suprax)	PO	8 mg divided into 1 or 2 doses (adult 400 mg/day)	Poor antistaphylococcal activity Single-dose gonorrhea treatment 400 mg ×1 in children ≥45 kg
Cefotaxime (Claforan)	IV, IM	50–180 mg divided into 3 or 4 doses (adult 3–6 g/day, maximum 12 g/day)	200–300 mg divided into 4 doses for meningitis
Cefotetan (Cefotan)	IV, IM	60–100 mg divided into 2 doses (adult 2–4 g/day, maximum 6 g/day)	
Cefoxitin (Mefoxin)	IV, IM	80–160 mg divided into 4 doses (adult 4–6 g/day, maximum 12 g/day)	

Continued

APPENDIX 292-1. Dosage of Antibacterial Drugs for Infants, Older Children, and Adolescents—cont'd

Drug Generic (Trade)	Route	Dosage (per kg/day)[a]	Comments
Cefpodoxime proxetil (Vantin)	PO	10 mg divided into 2 doses (adult 200–400 mg/day, maximum 800 mg/day)	
Cefprozil (Cefzil)	PO	15–30 mg divided into 2 doses (adult 0.5–1 g/day, maximum 1 g/day)	
Ceftazidime (Fortaz, Tazicef, Tazidime)	IV, IM	100–150 mg divided into 3 doses (adult 3–6 g/day, maximum 6 g/day)	200–300 mg for serious *Pseudomonas* infection
Ceftibuten (Cedax)	PO	9 mg once daily (adult 400 mg/day)	
Ceftizoxime (Cefizox)	IV, IM	150–200 mg divided into 3 doses (adult 3–6 g/day, maximum 12 g/day)	
Ceftriaxone (Rocephin)	IV, IM	50–100 mg divided into 1 or 2 doses (adult 1–2 g/day, maximum 4 g/day)	100 mg for meningitis and penicillin-resistant pneumococcal pneumonia
Cefuroxime (Zinacef)	IV, IM	75–150 mg divided into 3 doses (adult 2.25–4.5 g/day)	Should not be used for meningitis
Cefuroxime axetil (Ceftin)	PO	20–30 mg divided into 2 doses, maximum 1 g/day	
Cephalexin (Keflex)	PO	25–50 mg divided into 3 or 4 doses (adult 1–4 g/day)	100 mg for oral step-down therapy to replace parenteral therapy
PENICILLINS[c]			
PENICILLIN G and V			
Penicillin G, crystalline K or Na	IV, IM	100,000–300,000 units divided into 4–6 doses (adult 8–24 million units/day)	
Penicillin G, procaine	IM	25,000–50,000 units divided into 1–2 doses (adult 600,000–1.2 million units/day, maximum 4.8 million units/day)	
Penicillin G, benzathine (Bicillin LA)	IM	50,000 units/kg once for neonates/infants <27 kg (60 lb) 300,000–600,000 units (not per kg) once ≥27 kg (60 lb) 900,000 units (not per kg) once (adult 1.2–2.4 million units once)	
Penicillin G benzathine/procaine (Bicillin CR)	IM	<14 kg (30 lb) 600,000 units (not per kg) once 14–27 kg (30–60 lb) 900,000–1,200,000 units (not per kg) once ≥27 kg (60 lb) 2,400,000 units (not per kg) once	
Penicillin V K (numerous)	PO	25–50 mg divided into 3 or 4 doses (adult 0.5–2 g/day)	Optimal administration on empty stomach
PENICILLINASE-RESISTANT PENICILLINS			Methicillin-resistant staphylococci are resistant to all penicillins
Oxacillin (Bactocill)	IV, IM	100–200 mg divided into 4–6 doses (adult 4–6 g/day, maximum 12 g/day)	
Nafcillin (Unipen, Nafcil)	IV, IM	100–200 mg divided into 4–6 doses (adult 4–6 g/day, maximum 12 g/day)	
Dicloxacillin (Dynapen, Pathocil)	PO	12.5–25 mg divided into 4 doses (adult 0.5–2 g/day, maximum 4 g/day)	100 mg for oral step-down therapy to replace parenteral therapy
AMINOPENICILLINS			
Amoxicillin (Amoxil)	PO	25–50 mg divided into 3 doses (adult 0.75–3 g/day)	90 mg in 2 doses for AOM 80–100 mg in 3 doses for oral step-down therapy to replace parenteral therapy
Amoxicillin-clavulanate (Augmentin)	PO	14:1 formulation: 90 mg amoxicillin component divided into 2 doses 7:1 formulation: 25–45 mg amoxicillin component divided into 2 doses 4:1 formulation: 20–40 mg amoxicillin component divided into 3 doses	
Ampicillin	IV, IM	100–200 mg divided into 4 doses (adult 4–12 g/day)	200–400 mg divided into 4 doses for meningitis
Ampicillin-sulbactam (Unasyn)	IV	100–200 mg ampicillin component divided into 4 doses (adult 4–8 g day)	
Ampicillin/ampicillin trihydrate (Principen)	PO	50–100 mg divided into 4 doses (adult 2–4 g/day)	
BROAD-SPECTRUM PENICILLINS			
Piperacillin (Pipracil)	IV, IM	200–400 divided into 3–6 doses (adult 6–18 g/day, maximum 24 g/day)	

Continued

APPENDIX 292-1. Dosage of Antibacterial Drugs for Infants, Older Children, and Adolescents—cont'd

Drug Generic (Trade)	Route	Dosage (per kg/day)[a]	Comments
Piperacillin-tazobactam (Zosyn)	IV	240–300 mg piperacillin component divided into 3–4 doses (adult 9–16 g piperacillin/day)	
Ticarcillin-clavulanate (Timentin)	IV	200–300 mg ticarcillin component divided into 4–6 doses (adult 12–18 g ticarcillin/day, maximum 24 g/day)	300–600 mg divided into 4 doses for cystic fibrosis
Chloramphenicol (Chloromycetin) sodium-succinate	IV	50–100 mg divided into 4 doses (adult 2–4 g/day)	Dosage adjusted according to serum concentration(s)
FLUOROQUINOLONES			Arthropathy is a potential fluoroquinolone-class side effect in children
Norfloxacin (Noroxin)	PO	9–14 mg divided into 2 doses (adult 400–800 mg/day, maximum 1.2 g/day)	
Ciprofloxacin (Cipro)	PO	20–40 mg divided into 2 doses, maximum 2 g/day	
	IV	20–30 mg divided into 2–3 doses, maximum 1.2 g/day	
Levofloxacin (Levaquin)	PO, IV	20 mg divided into 2 doses (children <5 years); 10 mg once-daily (children ≥5 years) (adult 500–750 mg/day)	
LINCOSAMIDES			
Clindamycin (Cleocin)	IM, IV	20–40 mg divided into 3 doses (adult 900 mg–2.7 g/day, maximum 4.8 g/day)	
	PO	10–30 mg divided into 3–4 doses (adult 600 mg–1.8 g/day, maximum 2.7 mg/day)	30–40 mg for AOM and CA-MRSA infection
LIPOPEPTIDES			
Daptomycin (Cubicin)	IV	4–6 mg once daily for children ≥12 years; 7 mg once daily for 6–12 years; 8–10 mg once daily for 2–6 years (adult 4–6 mg/kg once daily)	
MACROLIDES/AZALIDES			
Erythromycin (numerous)	PO	50 mg divided into 2–4 doses (adult 1–2 g/day, maximum 4 g/day)	Available as base, stearate, ethyl succinate preparations, and as erythromycin-sulfisoxazole
	IV	20 mg divided into 4 doses (adult 1–2 g/day, maximum 4 g/day)	Administer over at least 60 min to potentially prevent cardiac arrhythmias
Clarithromycin (Biaxin)	PO	15 mg divided into 2 doses (adult 0.5–1 g/day)	
Azithromycin (Zithromax)	PO, IV	All doses once daily: AOM: 10 mg × 3 days; *or* 30 mg × 1 day; *or* 10 mg × 1 day, then 5 mg × 4 days Pharyngitis: 12 mg × 5 days Sinusitis: 10 mg × 3 days; *or* 10 mg ×1 days, then 5 mg × 4 days Pneumonia: 10 mg × 1 day, then 5 mg × 4 days; *or* 60 mg × 1 day of Zmax susp if >6 months of age Shigellosis: 12 mg × 1 day, then 6 mg × 4 days	
MISCELLANEOUS			
Methenamine mandelate (Mandelamine)	PO	50–75 mg divided into 2–4 doses (adult 2–4 g/day)	For UTI prophylaxis
Nitrofurantoin (Furadantin)	PO	5–7 mg divided into 4 doses (adult 200–400 mg/day, maximum 7 mg/kg per day)	1–2 mg once-daily for UTI prophylaxis
NITROIMIDAZOLES			
Metronidazole (Flagyl)	PO	30–50 mg divided into 3 doses (adult 0.75–2.25 g/day)	
	IV	22.5–40 mg divided into 3 doses (adult 1–2 g/day, maximum 4 g/day)	
OXAZOLIDINONES			
Linezolid (Zyvox)	PO, IV	For children <12 years of age: 30 mg in 3 doses For adolescents ≥12 years and adults: 1200 mg per day (not per kg) in 2 doses	Myelosuppression increases with duration of therapy over 10 days
POLYMYXINS			
Colistin (as Colistimethate, Coly-Mycin M)	IV, IM	5–7 mg colistin base, divided into 3 doses	Reserved for multidrug-resistant gram-negative pathogens because of neuro- and nephrotoxicity
Quinupristin-dalfopristin (Synercid)	IV	15–22.5 mg divided into 2–3 doses (adult dose same)	

Continued

APPENDIX 292-1. Dosage of Antibacterial Drugs for Infants, Older Children, and Adolescents—cont'd

Drug Generic (Trade)	Route	Dosage (per kg/day)[a]	Comments
RIFAMYCINS			
Rifampin (Rifadin)	PO, IV	10–20 mg divided into 1–2 doses (adult 600 mg/day)	
Rifaximin (Xifaxan)	PO	≥12 years of age:600 mg/day (not per kg) divided into 3 doses	
SULFONAMIDES			
Sulfadiazine	PO	120–150 mg divided into 4 doses (adult 4–6 g/day)	
Sulfisoxazole (Gantrisin)	PO	120–150 mg divided into 4 doses (adult 2–4 g/day)	10–20 mg in 2 doses for UTI prophylaxis
Trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim, Septra)	IV, PO	8–12 mg TMP divided into 2 doses (adult 160–320 mg TMP/day, maximum 15 mg TMP/kg per day)	20 mg TMP divided into 4 doses for *Pneumocystis* pneumonia (PCP) 2 mg TMP once daily for UTI prophylaxis 5 mg TMP divided into 2 doses for 3 consecutive days per week for PCP prophylaxis
TETRACYCLINES			Tetracycline-class antibiotics stain unerupted teeth; use in children <8 years of age if benefits exceed risks
Tetracycline (numerous)	PO	25–50 mg divided into 4 doses (adult 1–2 g/day)	
Minocycline (Minocin)	PO, IV	4 mg divided into 2 doses (adult 200 mg/day PO, 200–400 mg/day IV)	
Doxycycline (numerous)	PO, IV	2–4 mg divided into 1–2 doses (adult 100–200 mg/day)	
Tigecycline (Tygacil)	IV	2 mg divided into 2 doses (adult 100 mg/day)	
VANCOMYCIN (VANCOCIN)	IV	40 mg divided into 3–4 doses (adult 1–2 g/day)	Dosage adjusted according to serum concentration(s) Consider dose of 60 mg/kg per day for meningitis, and for invasive CA-MRSA
	PO	40 mg divided into 4 doses (adult, 500 mg divided into 4 doses)	Not absorbed from GI tract
	Intraventricular	1–2 mg daily	

AOM, acute otitis media; GI, gastrointestinal; IV, intravenous; IM, intramuscular; PO, orally; UTI, urinary tract infection.

[a]Doses for children are listed as the number of dosing units (e.g. mg, µg, etc.) per kilogram per day along with an absolute maximum dose if known. The corresponding parenthetic adult doses are the common adult dose range (not per kg per day, unless specified) followed by the adult maximum dose, if known.

[b]Once daily IV aminoglycoside dosing (amikacin 15–20 mg/kg; gentamicin/tobramycin 4.5–7.5 mg/kg) may provide equal efficacy with reduced toxicity and can be used as an alternative to multiple daily dosing.[202]

[c]In patients with a history of immediate hypersensitivity (anaphylaxis) to penicillin, other penicillins, cephalosporins, or carbapenems should not be used.

Data for Appendix 293–1 from references 126, 203–208.

APPENDIX 292-2. Table of Antibiotic Dosages for Neonates

		Dosage (mg/kg per dose) and Frequency of Administration[a]			
		Body weight ≤2 kg		Body weight >2 kg	
Drug	**Route**	**≤7 days old**	**8–28 days old[b]**	**≤7 days old**	**8–28 days old**
AMINOGLYCOSIDES[c,d]					
Amikacin	IV, IM	15 every 48 h	15 every 24–48 h	15 every 24 h	15 every 12–24 h
Gentamicin	IV, IM	5 every 48 h	4–5 every 24–48 h	4 every 24 h	4 every 12–24 h
Tobramycin	IV, IM	5 every 48 h	4–5 every 24–48 h	4 every 24 h	4 every 12–24 h
CARBAPENEMS					
Imipenem/cilastatin	IV	25 every 12 h	25 every 12 h	25 every 12 h	25 every 8 h
Meropenem[e]	IV	20 every 12 h	20 every 8 h	20 every 8 h	20 every 8 h
for meningitis		40 every 12 h	40 every 8 h	40 every 8 h	40 every 8 h
CEPHALOSPORINS					
Cefepime[e]	IV, IM	30 every 12 h	30 every 12 h	30 every 12 h	30 every 12 h
Cefotaxime	IV, IM	50 every 12 h	50 every 8–12 h	50 every 12 h	50 every 8 h
for meningitis	IV	50 every 12 h	50 every 8 h	50 every 8 h	50 every 6 h
Cefazolin	IV, IM	25 every 12 h	25 every 12 h	25 every 12 h	25 every 8 h

Continued

APPENDIX 292-2. Table of Antibiotic Dosages for Neonates—cont'd

Drug	Route	Dosage (mg/kg per dose) and Frequency of Administration[a]			
		Body weight ≤2 kg		Body weight >2 kg	
		≤7 days old	8–28 days old[b]	≤7 days old	8–28 days old
Ceftazidime	IV, IM	50 every 12 h	50 every 8–12 h	50 every 12 h	50 every 8 h
Ceftriaxone[f]	IV, IM	50 every 24 h	50 every 24 h	50 every 24 h	50 every 24 h
Cefuroxime	IV, IM	50 every 12 h	50 every 8–12 h	50 every 12 h	50 every 8 h
Penicillins					
Ampicillin	IV, IM	50 every 12 h[g]	50 every 8 h	50 every 8 h	50 every 6 h
for meningitis	IV	100 every 12 h	100 every 8 h	100 every 8 h	75 every 6 h
Nafcillin, Oxacillin	IV, IM	25 every 12 h	25 every 8 h	25 every 8 h	25 every 6 h
for meningitis	IV	50 every 12 h	50 every 8 h	50 every 8 h	50 every 6 h
Penicillin G crystalline[h]	IV, IM	50,000 units every 12 h	50,000 units every 8 h	50,000 units every 12 h	50,000 units every 8 h
for meningitis	IV	100,000 units every 12 h	100,000 units every 8 h	100,000 units every 8 h	100, 000 units every 6 h
Penicillin G procaine	IM only	50,000 units every 24 h	50,000 units every 24 h	50,000 units every 24 h	50,000 units every 24 h
Piperacillin-Tazobactam	IV	100 every 12 h	100 every 8 h	100 every 12 h	100 every 8 h
Ticarcillin-Clavulanate	IV	75 every 12 h	75 every 8 h	75 every 12 h	75 every 8 h
Other agents					
Azithromycin	PO, IV	10 every 24 h	10 every 24 h	10 every 24 h	10 every 24 h
Aztreonam[e]	IV, IM	30 every 12 h	30 every 8–12 h	30 every 8 h	30 every 6 h
Clindamycin	IV, IM, PO	5 every 12 h	5 every 8 h	5 every 8 h	5 every 6 h
Erythromycin	PO, IV	10 every 12 h	10 every 8 h	10 every 12 h	10 every 8 h
Linezolid	IV	10 every 12 h	10 every 8 h	10 every 8 h	10 every 8 h
Metronidazole	IV	7.5 every 24–48 h[i]	15 every 24 h	15 every 24 h	15 every 12 h
Vancomycin	IV	See comment[j]			

IV. intravenous; IM, intramuscular; PO, oral.

[a]*In milligrams (mg) unless otherwise specified. Dosages may need to be adjusted in neonates with severe renal or hepatic impairment.*

[b]*May use the longer dosing interval (if given) in extremely low-birthweight (less than 1000 g) neonates until 2 weeks of life.*

[c]*Dosages for aminoglycosides may differ from those recommended by the manufacturer and approved by the FDA.*

[d]*Optimal, individualized dosage should be based on determination of serum concentrations.*

[e]*50 mg/kg/dose may be required for* Pseudomonas *infections.*

[f]*Neonates should not receive ceftriaxone intravenously if they are also receiving, or are expected to receive, intravenous calcium in any form, including parenteral nutrition. See* Pediatrics *2009;123;e609. Cefotaxime is the preferred 3rd generation cephalosporin in neonates.*

[g]*100 mg/kg/dose every 12 hours is also acceptable for empiric therapy of early onset sepsis.*

[h]*Dosage applies to treatment of congenital syphilis and empiric therapy of early onset sepsis. Some experts recommend 200–300,000 units/kg/day for other invasive infections.*

[i]*May begin therapy with a 15 mg/kg loading dose, then use the longer dosing interval for extremely low-birthweight (less than 1000 g) neonates.*

[j]*Dosing algorithm based on serum creatinine; if <0.7 then 15 mg/kg every 12 h, if 0.7–0.9 then 20 mg/kg every 24 h, if 1–1.2 then 15 mg/kg every 24 h, if 1.3–1.6 then 10 mg/kg every 24h, if >1.6 then 15 mg/kg every 48h. Add 0.2 to serum creatinine when using algorithm in neonates ≤28 weeks gestational age.*

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