Drug Facts for Your Personal Formulary: *Regimens for Malaria Treatment*

Drug Indication	Adult Dosage	Pediatric Dosage[a]	Potential Adverse Effects	Comments
Artemether-lumefantrine *P. falciparum* from chloroquine-resistant or unknown areas	Tablet: 20 mg artemether, lumefantrine. Dose: 4 tablets. Day 1: 2 doses separated by 8 h; thereafter twice daily × 2 days	Wgt (kg) Tablets/dose 5–15 1 15–25 2 25–<35 3 >35 4 Use same 3-day schedule as adults	Adults; headache anorexia, dizziness, asthenia, arthralgia myalgia Children: fever, cough, vomiting, loss of appetite, headache	Take with food or whole milk. If patient vomits within 30 min, repeat dose. Contraindicated in pregnancy.
Artesunate (IV; available from CDC) Severe malaria; see CDC guidelines.	U.S. treatment IND (CDC): 4 equal doses of artesunate (2.4 mg/kg each) over a 3-day period followed by oral treatment with atovaquone-proguanil, doxycycline, clindamycin, or mefloquine (to avoid emergence of resistance)		See Artemether	See Artemether CDC guidelines
Atovaquone-proguanil *P. falciparum* from chloroquine-resistant areas *P. vivax*	Adult tablet 250 mg atovaquone/100 mg proguanil 4 Adult tablets orally per day × 3 days	Pediatric tablet = 62.5 mg atovaquone/25 mg proguanil 5–8 kg: 2 ped tab orally/d × 3 d >8–10 kg: 3 ped tab daily × 3 d >10–20 kg: 1 adult tab daily × 3 d >20–30 kg: 2 adult tab daily × 3 d >30–40 kg: 3 adult tab daily × 3 d >40 kg: 4 adult tab daily × 3 d	Abdominal pain, nausea, vomiting, diarrhea, headache, rash, mild reversible elevations in liver aminotransferase levels	Not indicated for use in pregnant women due to limited data. Contraindicated if hypersensitivity to atovaquone or proguanil; severe renal impairment (creatinine clearance < 30 mL/min). Should be taken with food to increase absorption of atovaquone.
Chloroquine phosphate *P. falciparum* from chloroquine-sensitive areas *P. vivax* from chloroquine-sensitive areas All *P. ovale* All *P malariae* All *P. knowlesi*	600 mg base (1000 mg salt) orally immediately, followed by 300 mg base (500 mg salt) orally at 6, 24, and 48 h Total dose: 1500 mg base (2500 mg salt)	10 mg base/kg orally immediately, followed by 5 mg base/kg orally at 6, 24, and 48 h Total dose: 25 mg base/kg	Nausea, vomiting, rash, headache, dizziness, urticaria, abdominal pain, pruritus	Safe in children and pregnant women. Give for chemoprophylaxis (500 mg salt orally every week) in pregnant women with chloroquine-sensitive *P. vivax*. Contraindicated if retinal or visual field change; hypersensitivity to 4-aminoquinolines. Use with caution in those with impaired liver function since the drug is concentrated in the liver.
Clindamycin (oral or IV) *P. falciparum* from chloroquine-resistant areas *P. vivax* from chloroquine-resistant areas	Oral: 20 mg base/kg/d orally divided 3 times daily × 7 d IV: 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h; switch to oral clindamycin (as above) as soon as patient can take oral meds; duration = 7 d	Oral: 20 mg base/kg/d orally divided 3 times daily × 7 d IV: 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 h; switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication; treatment course = 7 d	Diarrhea, nausea, rash	Always use in combination with quinine-quinidine. Safe in children and pregnant women.
Doxycycline (oral or IV) *P. falciparum* and *P. vivax* from chloroquine-resistant areas	Oral: 100 mg orally twice daily × 7 d. IV: 100 mg IV every 12 h and then switch to oral doxycycline (as above) as soon as patient can take oral medication; treatment course = 7 d.	Oral: 2.2 mg/kg orally every 12 h × 7 d. IV: Only if patient is not able to take oral medication; for children < 45 kg, give 2.2 mg/kg IV every 12 h and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication; for children > 45 kg, use same dosing as for adults; duration = 7 d.	Nausea, vomiting, diarrhea, abdominal pain, dizziness, photosensitivity, headache, esophagitis, odynophagia. Rarely hepatotoxicity, pancreatitis, and benign intracranial hypertension seen with tetracycline class of drugs.	Always use in combination with quinine or quinidine. Contraindicated in children < 8 y, pregnant women, and persons with known hypersensitivity to tetracyclines. Food, milk, and Ca^{2+} antacids decrease absorption and decrease GI disturbances. To prevent esophagitis, take tetracyclines with large amounts of fluids (patients should not lie down for 1 h after taking the drugs). Barbiturates, carbamazepine, or phenytoin may cause reduction in C_p of doxycycline.

Drug Facts for Your Personal Formulary: *Regimens for Malaria Treatment (continued)*

Drug Indication	Adult Dosage	Pediatric Dosage[a]	Potential Adverse Effects	Comments
Hydroxychloroquine (oral) Secondary alternative for treatment of *P. falciparum* and *P. vivax* from chloroquine-sensitive areas All *P. ovale* All *P. malariae*	620 mg base (= 800 mg salt) orally immediately, followed by 310 mg base (= 400 mg salt) orally at 6, 24, and 48 h Total dose: 1550 mg base (= 2000 mg salt)	10 mg base/kg orally immediately, followed by 5 mg base/kg orally at 6, 24, and 48 h Total dose: 25 mg base/kg	Nausea, vomiting, rash, headache, dizziness, urticaria, abdominal pain, pruritus[b]	Safe in children and pregnant women. Contraindicated if retinal or visual field change; hypersensitivity to 4-aminoquinolines. Use with caution in those with impaired liver function.
Mefloquine[c] *P. falciparum* from chloroquine-resistant areas, except Thailand-Burmese and Thailand-Cambodian border regions *P. vivax* from chloroquine-resistant areas	684 mg base (= 750 mg salt) orally as initial dose, followed by 456 mg base (= 500 mg salt) orally given 6–12 h after initial dose Total dose = 1250 mg salt	13.7 mg base/kg (= 15 mg salt/kg) orally as initial dose, followed by 9.1 mg base/kg (= 10 mg salt/kg) orally given 6–12 h after initial dose Total dose = 25 mg salt/kg	Nausea, vomiting, diarrhea, abdominal pain; dizziness, headache, somnolence, sleep disorders; myalgia, mild skin rash, and fatigue; moderate-to-severe neuropsychiatric reactions; ECG changes (sinus arrhythmia, sinus bradycardia, 1° AV block, QTc prolongation, and abnormal T waves.	Contraindicated if hypersensitive to the drug or to related compounds; cardiac conduction abnormalities; psychiatric disorders; and seizure disorders. Do not administer if patient has received related drugs (chloroquine, quinine, quinidine) less than 12 h ago
Primaquine phosphate Radical cure of *P. vivax* and *P. ovale* (to eliminate hypnozoites)	30 mg base orally per day × 14 d	0.5 mg base/kg orally per day × 14 d	GI disturbances, methemoglobinemia (self-limited), hemolysis in persons with G6PD deficiency	Must screen for G6PD deficiency prior to use. Contraindicated in persons with G6PD deficiency; pregnant women. Should be taken with food to minimize GI adverse effects.
Quinine sulfate (oral) *P. falciparum* from chloroquine-resistant areas *P. vivax* from chloroquine-resistant areas	542 mg base (650 mg salt)[d] orally 3 times daily × 3 d (infections acquired outside Southeast Asia) to 7 d (infections acquired in Southeast Asia)	8.3 mg base/kg (10 mg salt/kg) orally 3 times daily × 3 d (infections acquired outside Southeast Asia) to 7 d (infections acquired in Southeast Asia)	Cinchonism,[e] sinus arrhythmia, junctional rhythms, atrioventricular block, prolonged QT interval, ventricular tachycardia, ventricular fibrillation (these are rare and more commonly seen with quinidine), hypoglycemia	Combine with tetracycline, doxycycline, or clindamycin, except for *P. vivax* infections in children < 8 y or pregnant women. Contraindicated in hypersensitivity, including history of blackwater fever, thrombocytopenic purpura, or thrombocytopenia associated with quinine or quinidine use; many cardiac conduction defects and arrhythmias[f]; myasthenia gravis; optic neuritis.
Quinidine gluconate (intravenous) Severe malaria (all species, independently of chloroquine resistance) Patient unable to take oral medication Parasitemia > 10%	6.25 mg base/kg (= 10 mg salt/kg) loading dose IV over 1–2 h, then 0.0125 mg base/kg/min (0.02 mg salt/kg/min) continuous infusion for at least 24 h Note alternative regimen[g]	Same as adult	Cinchonism, tachycardia, prolongation of QRS and QTc intervals, flattening of T wave (effects are often transient). Ventricular arrhythmias, hypotension, hypoglycemia	Combine with tetracycline, doxycycline, or clindamycin. Contraindicated in hypersensitivity; history of blackwater fever including history of blackwater fever, thrombocytopenic purpura or thrombocytopenia associated with quinine or quinidine use; many cardiac conduction defects and arrhythmias[f]; myasthenia gravis; optic neuritis.

Drug Facts for Your Personal Formulary: *Anthelmintics*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Benzimidazoles: β-Tubulin inhibitors		
Albendazole	• Intestinal nematode infections • Cysticercosis • Cutaneous larva migrans • Toxocariasis • Echinococcosis	• Monitor for liver and hemotologic toxicity in long-term therapy • Absorption improved with fatty food
Mebendazole	• Intestinal nematode infections	• Poorly absorbed; useful for intestinal luminal nematode
Triclabendazole	• Fascioliasis	• Available from the CDC under an investigational new drug protocol
Macrocyclic Lactones: Glutamate gated chloride channel blockers		
Ivermectin	• Onchocerciasis • Lymphatic filariasis • Scabies and head lice • Strongyloidiasis	• Safety in pregnancy and children < 15 kg not certain
Moxidectin	• Investigational for onchocerciasis	• Licensed only for veterinary use in the U.S.
Praziquantel		
	• Schistosomiasis • Food-borne trematode infections (opisthorciasis and paragonamiasis) • Intestinal tapeworm infections	• Dizziness is a common adverse effect • May impair mental alertness; avoid tasks such as driving
Miscellaneous Anthelmintics		
Diethylcarbamazine	• Lymphatic filariasis	• Contraindicated in onchocerciasis • Available from CDC under an investigational new drug protocol
Metrifonate	• Second-line drug for *Schistosoma haematobium* infection	• Not licensed for use in the U.S.
Oxamniquine	• Second-line drug for *Schistosoma mansoni* infection	• Discontinued in the U.S.
Niclosamide	• Intestinal tapeworm infection	• Discontinued in the U.S.
Oxantel and pyrantel pamoate	• Second-line drug for intestinal nematode infection	• Oxantel pamoate is not licensed for use in the U.S. • Pyrantel pamoate is sold OTC to treat pinworm infections
Doxycycline	• Filarial infection	• 6-Week course of therapy advised
Levamisole	• Excellent activity against *Ascaris lumbricoides* • Low-to-moderate efficacy against *Trichuris trichiura* and hookworm infections	• May cause agranulocytosis at high doses
Nitazoxanide	• Effective against intestinal helminths • Antiprotozoal and antiviral activity	• Broad-spectrum antiparasitic agent • Side effects are rare

Drug Facts for Your Personal Formulary: *Antiparasitic Agents: Protozoal Infections Other Than Malaria*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Amebiasis		
Metronidazole	• Amoebic colitis and liver abscess	• Always administer with luminal agent • Orally administered: > 80% bioavailable • Common side effects: headache and metallic taste • Can have disulfiram-like effect
Tinidazole	• Amoebic colitis and liver abscess	• Always administer with luminal agent
Paromomycin	• Luminal agent (eradicates *E. histolytica* from gut)	• Drug of choice due to side effects of 8-hydroxyquinolones • Side effects of paromomycin: GI (nausea/vomiting/diarrhea)
Iodoquinol	• Luminal agent	• Use less than 2 g/d for less than 20 days to avoid neurotoxicity
Giardiasis		
Metronidazole	• Giardiasis	• 5-day course • Not FDA-approved for indication, but years of experience
Tinidazole	• Giardiasis	• Single dose sufficient
Paromomycin	• Giardiasis	• Used in pregnancy
Nitazoxanide	• Giardiasis	• Orally bioavailable • Can treat resistant infections • Adverse events are rare
Trichomoniasis		
Metronidazole	• Trichomoniasis	• Drug of choice • 2 g once • If failure, give second dose in 4–6 weeks
Tinidazole	• Trichomoniasis	• 2 g once • Can be used for resistant infection
Toxoplasmosis		
Pyrimethamine	• Acute or congenital toxoplasmosis	• Combine with sulfadiazine or clindamycin • Give with leucovorin • Can cause bone marrow suppression
Sulfadiazine	• Acute or congenital toxoplasmosis	• Combine with pyrimethamine and folic acid • Can cause bone marrow suppression
Clindamycin	• Acute toxoplasmosis	• Combine with pyrimethamine • Use if cannot tolerate sulfonamide
Spiramycin	• Acute toxoplasmosis during early pregnancy	• Prevents fetal transmission • Available via individual investigator IND
Cryptosporidiosis		
Nitazoxanide	• Drug of choice for cryptosporidiosis	• Restore immune function in immunocompromised patients
Leishmaniasis		
Pentavalent antimony compounds (sodium stibogluconate)	• Cutaneous, mucocutaneous leishmaniasis • Visceral leishmaniasis (not in India)	• 20 days IV/IM for cutaneous disease • 28 days IV/IM for visceral disease • Side effects: pancreatitis, elevated hepatic transaminases, bone marrow suppression • Can cause hemolytic anemia and renal failure • Available only through CDC
Amphotericin B	• Visceral leishmaniasis • Second-line agent for cutaneous disease	• Used for antimony-resistant cases • Used during pregnancy • Side effects: renal toxicity, low potassium • Liposomal formulation preferred
Miltefosine	• Cutaneous leishmaniasis • Visceral leishmaniasis	• Only oral agent • GI side effects (vomiting/diarrhea) • Teratogenic: do not use in pregnancy

Trypanosomiasis: African sleeping sickness		
Pentamidine	• Early-stage *T. brucei gambiense* ***before CNS involvement***	• IV administration associated with hypotension, tachycardia, and headache • Hypoglycemia occurs; monitor blood glucose • Nephrotoxic, can cause renal failure
Suramin	• Early-stage *T. brucei rhodesiense* • Second-line agent for early-stage *T. brucei gambiense* (only if pentamidine is contraindicated)	• Immediate reactions: malaise, nausea, and fatigue • Side effects of multiple doses: renal toxicity, delayed neurological complications (headache, metallic taste, paresthesias, peripheral neuropathy) • Only available through CDC
Nifurtimox + eflornithine combination therapy (NECT)	• Late-stage *T. brucei gambiense*	• Safer and more effective than melarsoprol or eflornithine alone • First-line regimen for this indication • Side effects: abdominal pain, headache, tissue infections, pneumonia • Only available through CDC
Melarsoprol	• Late-stage *T. brucei rhodesiense* • Second-line agent for late-stage *T. brucei gambiense* (only if NECT contraindicated)	• Fatal encephalopathy: 2%–10% of patients • Coadminister with prednisolone to reduce the prevalence of encephalopathy • Only available through CDC
Trypanosomiasis: Chagas disease		
Benznidazole	• Drug of choice for Chagas	• Requires 60 days of treatment • Urticarial dermatitis in 30% of patients; coadministration of antihistamines or corticosteroids can help • Better tolerated in children, less well tolerated in adults > 50 years • Most effective if administered early in the course of infection (acute stage) • Efficacy in chronic Chagas is lower • Give with food to minimize GI effects • Monitor blood cell counts • Available only through CDC
Nifurtimox	• Alternative treatment for Chagas	• Requires 60 days of treatment • Less well tolerated than benznidazole
Other Protozoal Infections		
Clindamycin and quinine	• Severe babesiosis	• Quinine: monitor for cardiac effects (prolonged QT interval)
Azithromycin and atovaquone	• Mild-moderate babesiosis	
Tetracycline	• Balatinidiasis	• Drug of choice
Trimethoprim-sulfamethoxazole	• Cyclosporiasis, isosporiasis	• Drug of choice

Drug Facts for Your Personal Formulary: *Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for Urinary Tract Infections*

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Sulfonamides: Competitive inhibitors of bacterial dihydropteroate synthase, thereby disrupting folate synthesis **General: Bacteriostatic; limited efficacy as monotherapy, renal elimination, hypersensitivity reactions**		
Sulfisoxazole (PO)	• Lower UTIs • Otitis media (with erythromycin)	• Some activity vs. *Streptococcus pyogenes, S. pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Escherichia coli, Nocardia* • Rapid renal excretion
Sulfadiazine (PO)	• Toxoplasmosis (with pyrimethamine)	• Similar to sulfisoxazole, with good activity against *Toxoplasma gondii* • Reasonable CSF penetration • Higher risk of crystalluria, requires hydration
Sulfadoxine (PO)	• Prophylaxis and treatment of malaria (with pyrimethamine)	• Similar to sulfisoxazole, with some activity vs. *Plasmodium falciparum* • Long $t_{1/2}$
Sulfacetamide (ophthalmic)	• Treatment of ocular infections	• Activity similar to sulfisoxazole • High penetration into ocular fluids
Silver sulfadiazine (topical) Mafenide (topical)	• Prevention of infection in burn patients	• Activity similar to sulfisoxazole • Burning and itching at application site • Application over large surface may lead to systemic absorption and adverse effects
Sulfonamide and Dihydrofolate Reductase Inhibitor Combination: Sequential inhibition of folate synthesis		
Trimethoprim-sulfamethoxazole (IV, PO)	• UTI • Upper respiratory tract infections • Shigellosis • *Pneumocystis jiroveci* pneumonia • Skin/soft tissue infections due to *S. aureus* • Infections due to *Nocardia, Stenotrophomonas maltophila, Cyclospora, Isospora*	• Excellent activity vs. *S. aureus, Staphylococcus epidermidis, Streptococcus pyogenes* • Good activity vs. *Proteus, E. coli, Klebsiella, Enterobacter, Serratia, Nocardia, Brucella* • Some activity vs. *S. pneumoniae* • Formulated in 5:1 (sulfa:TMP) ratio, giving 20:1 serum levels • Well absorbed on oral administration • Good penetration into CSF • Metabolized and renally eliminated • Hypersensitivity reactions (i.e., rash) common • Dose-related bone marrow suppression, hyperkalemia
Quinolones: Bactericidal inhibitors of bacterial gyrase and topoisomerase, prevent DNA unwinding **General: Drug interactions with cations, neurologic adverse effects, tendonitis/tendon rupture, photosensitivity; typically avoided in children and pregnant women**		
Norfloxacin (PO)	• UTI, prostatitis • Traveler's diarrhea	• Good activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella* • Some activity vs. *Pseudomonas* • Effective concentrations only achieved in GI and urinary tracts
Ciprofloxacin (IV, PO)	• UTI, prostatitis • Traveler's diarrhea • Intra-abdominal infections (with metronidazole) • *Pseudomonas* infections • Anthrax, tularemia	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella* • Good activity vs. *Pseudomonas* • Some activity vs. *S. aureus*, streptococci • Good bioavailability and tissue distribution • Renal and nonrenal elimination
Levofloxacin (IV, PO)	• Respiratory tract infections • UTI, prostatitis • *Chlamydia* • Traveler's diarrhea • Intra-abdominal infections (with metronidazole) • *Pseudomonas* infections	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia, Salmonella, Shigella,* streptococci, *H. influenzae, Legionella, Chlamydia* • Good activity vs. *Pseudomonas, S. aureus* • Good bioavailability and tissue distribution • Renal elimination • S-isomer of ofloxacin

Drug Facts for Your Personal Formulary: *Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for Urinary Tract Infections (continued)*

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Quinolones: Bactericidal inhibitors of bacterial gyrase and topoisomerase, prevent DNA unwinding **General: Drug interactions with cations, neurologic adverse effects, tendonitis/tendon rupture, photosensitivity; typically avoided in children and pregnant women**		
Moxifloxacin (IV, PO)	• Respiratory tract infections • Intra-abdominal infections • Mycobacterial infections	• Excellent activity vs. *E. coli, Klebsiella, Proteus, Serratia,* streptococci, *H. influenzae, Legionella, Chlamydia* • Good activity vs. *S. aureus, Bacteroides fragilis* • Good bioavailability and tissue distribution • Renal and nonrenal elimination; not for UTI • QT prolongation
Urinary Agents: Diverse mechanisms, effective concentrations reached only in urine		
Methenamine (PO)	• Chronic suppression of cystitis	• Forms formaldehyde in urine • Requires acidic urine for activity • Excellent activity against most uropathogens except for *Proteus* and *Enterobacter* • GI distress at high doses
Nitrofurantoin (PO)	• Cystitis treatment • Cystitis prophylaxis	• DNA damage through reactive intermediates • Excellent activity vs. *E. coli, Enterococcus* • Some activity vs. *Klebsiella, Enterobacter* • Rapid absorption and elimination • Colors urine brown • Acute pneumonitis and chronic interstitial pulmonary fibrosis
Fosfomycin (PO)	• Cystitis treatment	• Inhibits early cell wall synthesis • Excellent activity vs. *E. coli, Proteus, Enterococcus* • Some activity vs. *Klebsiella, Enterobacter* • Single-dose treatment of acute uncomplicated cystitis

Drug Facts for Your Personal Formulary: *β-Lactam Antibiotics*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Penicillins—Inhibitors of Bacterial Cell Wall Peptidoglycan Synthesis **General: Bactericidal, renal elimination, hypersensitivity reactions (rash, anaphylaxis)**		
Penicillin G (IV), penicillin V (PO); IM depot formulations (benzathine, procaine)	• Penicillin-susceptible *Streptococcus pneumoniae* infections: pneumonia, meningitis • Streptococcal pharyngitis, endocarditis, skin and soft tissue infection • *Neisseria meningitidis* infections • Syphilis	• Excellent activity vs. *Treponema pallidum*, β-hemolytic streptococci, *N. meningitidis*, gram-positive anaerobes • Good activity vs. *S. pneumoniae*, viridans streptococci • CSF penetration with inflammation
Penicillinase-resistant penicillins Oxacillin (IV), nafcillin (IV), dicloxacillin (PO)	• Skin and soft tissue infections • Serious infections due to MSSA	• Excellent activity vs. MSSA • Good activity vs. streptococci • Nafcillin nonrenal elimination • CSF penetration with inflammation
Aminopenicillins Amoxicillin (PO), ampicillin (PO/IV)	• Upper respiratory tract infections (sinusitis, pharyngitis, otitis media) • *Enterococcus faecalis* infections • *Listeria* infections	• Excellent activity vs. β-hemolytic streptococci, *E. faecalis* • Good activity vs. *S. pneumoniae*, viridans streptococci, *Haemophilus influenzae* • Some activity vs. *Proteus, Escherichia coli* • CSF penetration with inflammation • Rash more common than other penicillins
Aminopenicillin/β-lactamase inhibitors Amoxicillin/clavulanate (PO), ampicillin/sulbactam (IV)	• Upper respiratory tract infections (sinusitis, otitis media) • Intra-abdominal infections	• Activity: amoxicillin and ampicillin plus • Excellent activity vs. *H. influenzae, Bacteroides fragilis, Proteus* • Good activity vs. *E. coli, Klebsiella*, MSSA
Antipseudomonal penicillins Piperacillin/tazobactam (IV)	• Nosocomial infections: pneumonia, intra-abdominal infections, urinary tract infections	• Activity: ampicillin/sulbactam plus • Excellent activity vs. *E. coli, Klebsiella* • Good activity vs. *Pseudomonas, Citrobacter, Enterobacter* • Poor CSF penetration
Cephalosporins—Inhibitors of Bacterial Cell Wall Peptidoglycan Synthesis **General: Bactericidal, renal elimination, hypersensitivity reactions (rash, anaphylaxis)**		
First-generation cephalosporins Cefazolin (IV), cephalexin (PO), cefadroxil (PO)	• Skin and soft tissue infections • Serious infections due to MSSA • Perioperative surgical prophylaxis	• Excellent activity vs. MSSA, streptococci • Some activity vs. *Proteus, E. coli, Klebsiella* • Poor CSF penetration
Second-generation cephalosporins Cefuroxime (IV/PO), cefoxitin (IV), cefotetan (IV), cefaclor (PO), cefprozil (PO)	• Upper respiratory tract infections (sinusitis, otitis media) • Cefoxitin/cefotetan: gynecologic infections, perioperative surgical prophylaxis	• Good activity vs. MSSA, streptococci, *H. influenzae, Proteus, E. coli, Klebsiella* • Cefoxitin/cefotetan: some activity vs. *B. fragilis*
Third-generation cephalosporins Cefotaxime (IV), ceftriaxone (IV), cefpodoxime (PO), cefixime (PO), cefdinir (PO), cefditoren (PO), ceftibuten (PO)	• Community-acquired pneumonia, meningitis, urinary tract infections • Streptococcal endocarditis • Gonorrhea • Severe Lyme disease	• Excellent activity against streptococci, *H. influenzae, Proteus, E. coli, Klebsiella, Serratia, Neisseria* • Good activity vs. MSSA • Some activity vs. *Citrobacter, Enterobacter* • Ceftriaxone renal and nonrenal elimination • Good CSF penetration • Ceftriaxone: neonatal kernicterus (use cefotaxime), biliary pseudolithiasis

Cephalosporins—Inhibitors of Bacterial Cell Wall Peptidoglycan Synthesis General: Bactericidal, renal elimination, hypersensitivity reactions (rash, anaphylaxis) (continued)		
Antipseudomonal cephalosporins Ceftazidime (IV), ceftolozane/tazobactam (IV), ceftazidime/avibactam (IV), cefepime (IV)	• Nosocomial infections: pneumonia, meningitis, urinary tract infections, intra-abdominal infections (with metronidazole)	• Excellent activity against *H. influenzae, Proteus, E. coli, Klebsiella, Serratia, Neisseria,* streptococci,[a] MSSA[a] • Good activity vs. *Pseudomonas, Enterobacter*[b] • Some activity vs. *Enterobacter* (ceftazidime, ceftolozane/tazobactam) • Ceftazidime/avibactam active vs. ESBL and KPC-producing Enterobacteriaceae • Good CSF penetration • Cefepime: encephalopathy at high doses
Anti-MRSA cephalosporins Cefaroline (IV)	• Community-acquired pneumonia • Skin and soft tissue infections	• Excellent activity against streptococci, MSSA, MRSA,[c] *H. influenzae, Proteus, E. coli, Klebsiella, Serratia* • Some activity vs. *Citrobacter, Enterobacter*
Carbapenems—Inhibitors of Bacterial Cell Wall Synthesis **General: Bactericidal, renal elimination, hypersensitivity reactions (rash, anaphylaxis), seizure risk**		
Imipenem/cilastatin (IV), meropenem (IV), doripenem (IV)	• Nosocomial infections: pneumonia, intra-abdominal infections, urinary tract infections • Meningitis (meropenem)	• Excellent activity against streptococci, MSSA, *H. influenzae, Proteus, E. coli, Klebsiella, Serratia, Enterobacter, B. fragilis* • Good activity vs. *Pseudomonas, Acinetobacter, Enterococcus faecalis*[d] • Good CSF penetration • Imipenem coformulated with renal dihydropeptidase inhibitor cilastatin • Seizures at high doses in patients with prior seizure history (imipenem > meropenem, doripenem)
Ertapenem (IV)	• Community-acquired infections and nosocomial infections without *Pseudomonas* risk	• Excellent activity against streptococci, MSSA, *H. influenzae, Proteus, E. coli, Klebsiella, Serratia, Enterobacter, B. fragilis* • Lacks activity against *Pseudomonas, Enterococcus* • Lower seizure risk than imipenem
Monobactam—Bactericidal Inhibitor of Bacterial Cell Wall Synthesis		
Aztreonam (IV)	• Nosocomial infections: pneumonia, urinary tract infections	• Excellent activity against *H. influenzae, Proteus, E. coli, Klebsiella, Serratia* • Good activity vs. *Pseudomonas* • Lacks any gram-positive activity • Lacks cross-allergenicity with other β-lactams (except ceftazidime) • Good CSF penetration, renal elimination

Drug Facts for Your Personal Formulary: *Aminoglycosides*

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Aminoglycosides—Inhibitors of Bacterial Protein Synthesis **General: Bactericidal, no GI absorption (<1%), oral administration used only for bowel decontamination or intestinal parasites, poor CSF penetration, renal elimination, nephrotoxicity, ototoxicity (cochlear and vestibular), neuromuscular blockade**		
Gentamicin (IV)	• UTI • Peritonitis • Endocarditis in combination with a cell-wall active agent • Plague • Tularemia	• Good activity vs. Enterobacteriaceae, *Pseudomonas* • Some activity vs. *Neisseria*, *Haemophilus*, *Moraxella* • Synergistic activity when combined with a cell-wall agent against many organisms • Vestibular > cochlear toxicity • Toxicity primarily renal and reversible
Tobramycin (IV, inhalation)	• UTI • Lung infections, including cystic fibrosis exacerbations • Nosocomial sepsis of unknown origin	• Similar to gentamicin, with better activity against *Pseudomonas aeruginosa* • Cochlear ≈ vestibular toxicity
Amikacin (IV)	• UTI • Lung infections, including cystic fibrosis exacerbations • Nosocomial sepsis of unknown origin • Mycobacterial infections	• Similar to tobramycin, with activity against some gram-negative bacilli resistant to other aminoglycosides • Activity against a variety of mycobacteria • Cochlear > vestibular toxicity
Streptomycin (IV)	• Endocarditis in combination with a cell-wall active agent • Tuberculosis • Plague • Tularemia	• Similar to gentamicin, with activity against some gentamicin-resistant enterococci • Activity against *Mycobacterium tuberculosis* • Vestibular > cochlear toxicity • Vestibular toxicity is irreversible
Neomycin (PO, topical; urologic irrigation)	• Minor skin infections • Bowel preparation prior to intra-abdominal surgery • Bladder irrigation	• Similar activity to gentamicin but only used topically, not systemically • Can cause skin rash
Paromomycin (PO, IM, topical)	• *Cryptosporidia* infection • Intestinal amebiasis • Leishmaniasis	• Diarrhea, nausea, vomiting • IM use for visceral leishmaniasis • Topical use for cutaneous leishmaniasis

Drug Facts for Your Personal Formulary: *Protein Synthesis Inhibitors and Miscellaneous Antibacterial Agents*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Tetracyclines and Glycylcyclines—Inhibitors of Bacterial Protein Synthesis **General: Bacteriostatic; oral formulations interact with orally administered cations (calcium, iron, aluminum); avoid in pregnancy and children < 8 years old due to permanent tooth discoloration, photosensitivity**		
Tetracycline (IV, PO)	• Inflammatory acne • Use for other indications has largely been replaced by doxycycline	• Good activity vs. rickettseae, *Chlamydia, Mycoplasma, Legionella, Ureaplasma, Borrelia, Francisella tularensis, Pasteurella multocida, Bacillus anthracis, Helicobacter pylori* • Some activity vs. *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae* • Good CSF penetration • Renal excretion • Renal toxicity, hepatotoxicity at high doses
Doxycycline (IV, PO)	• Community-acquired pneumonia • Skin/soft-tissue infection • Urogenital chlamydia • Lymphogranuloma venereum • Syphilis (penicillin alternative) • Rocky Mountain spotted fever • Anthrax, tularemia • Lyme disease, leptospirosis	• Similar to tetracycline, with improved activity vs. streptococci and staphylococci • Good CSF penetration • Dual renal/biliary elimination • Preferred tetracycline for most indications due to more favorable activity, tolerability, and frequency of administration
Minocycline (IV, PO)	• Skin/soft-tissue infections • Mycobacterial infections • Nocardiosis	• Similar to doxycycline, with improved activity vs. staphylococci, *Acinetobacter*, and *Stenotrophomonas maltophilia* • Renal elimination • Vestibular toxicity
Tigecycline (IV)	• Intra-abdominal infection • Skin and soft-tissue infection • Pneumonia • Increased risk of death in pooled analysis; reserve as alternative therapy	• Similar to minocycline, with improved activity vs. *Escherichia coli, Klebsiella*, enterococci, *Bacteroides fragilis* • Wide distribution with low serum levels • Hepatic elimination

Chloramphenicol—Inhibitor of Bacterial Protein Synthesis **General: Bacteriostatic; dose-dependent bone marrow suppression, idiosyncratic fatal aplastic anemia, fatal "gray baby syndrome" in neonates receiving high doses**		
Chloramphenicol (IV, PO – not in the U.S.)	• Rickettsial infections • Bacterial meningitis • Because of risk of fatal toxicities, reserve as alternative therapy	• Good activity vs. *S. pneumoniae, H. influenzae, Neisseria meningitidis*, rickettseae, *Vibrio, Enterococcus* • Variable serum levels due to clearance of prodrug before hydrolysis • Excellent CSF penetration • Hepatic clearance
Macrolides and Ketolides—Inhibitors of Bacterial Protein Synthesis **General: Bacteriostatic; widely distributed but with limited CSF penetration, gastrointestinal distress, QT prolongation, major (erythromycin, clarithromycin, telithromycin) to minor (azithromycin) inhibitor of drug-metabolizing CYPs**		
Erythromycin (IV, PO, topical)	• Erysipelas and cellulitis • Ophthalmia neonatorum • Diphtheria • Pertussis	• Good activity against *Mycoplasma, Chlamydia, Legionella, Campylobacter, Bordetella pertussis, Corynebacterium diphtherieae* • Some activity against *S. pneumoniae, S. pyogenes, H. influenzae* • Oral formulations have variable absorption • Stimulates motilin receptors; gastrointestinal prokinetic properties • Chlolestatic hepatitis with long-term use
Clarithromycin (PO)	• Erysipelas and cellulitis • Community-acquired pneumonia • Acute exacerbations of chronic bronchitis • *Helicobacter pylori* gastritis (in combination with other agents) • *Mycobacterium avium* treatment and prophylaxis	• Similar to erythromycin, with improved activity vs. streptococci and staphylococci • Good activity vs. *Moraxella catarrhalis, H. pylori*, and nontuberculous mycobacteria • Active metabolite • Some drug accumulation in severe renal impairment • Tinnitus at high doses
Azithromycin (IV, PO)	• Community-acquired pneumonia • Acute exacerbations of chronic bronchitis • Otitis media • Bacterial pharyngitis • Chlamydia • *Mycobacterium avium* treatment and prophylaxis	• Similar to clarithromycin, improved activity vs. *H. influenzae* • Extensive tissue distribution and concentration in tissues • Anti-inflammatory properties • Long $t_{1/2}$, ~48 h
Telithromycin (PO)	• Community-acquired infection • Due to risk of severe hepatotoxicity, reserve as alternative therapy	• Similar to azithromycin with activity against macrolide-resistant streptococci and staphylococci • Severe hepatotoxicity
Lincosamides—Bacteriostatic Protein Synthesis Inhibitor		
Clindamycin (IV, PO, topical)	• Skin and soft-tissue infection • Inflammatory acne • Lung abscess • Streptococcal pharyngitis • *Pneumocystis* pneumonia • Toxoplasma encephalitis • Nonsevere malaria	• Good activity vs. *S. pneumoniae, S. pyogenes*, viridans streptococci, *Actinomyces, Nocardia* • Some activity versus *S. aureus, Bacteroides* spp., *Toxoplasma, Pneumocystis, Plasmodium* • Wide tissue distribution, especially into bone; modest CSF penetration • Metabolized in liver, excreted in urine and bile • Diarrhea, rarely *Clostridium difficile* colitis
Streptogramins—Bactericidal Protein Synthesis Inhibitor, Components Act Synergistically		
Quinupristin/ dalfopristin (IV)	• Skin and soft-tissue infection • Vancomycin-resistant *Enterococcus faecium* infections	• Good activity against streptococci, staphylococci, *E. faecium, Mycoplasma, Legionella, Chlamydophila* • Hepatic metabolism with biliary excretion • Infusion site phlebitis • Arthralgias, myalgias • CYP inhibitor
Oxazolidininones—Bacteriostatic Protein Synthesis Inhibitors **General: Excellent oral absorption; wide distribution, including to CNS; myelosuppression; peripheral neuropathy with long-term use; risk of serotonin syndrome with concomitant antidepressant use**		
Linezolid (IV, PO)	• Skin and soft-tissue infections • Pneumonia • Vancomycin-resistant enterococcal infections • Nocardiosis • Drug-resistant tuberculosis	• Good activity against streptococci, staphylococci, enterococci, *Nocardia, Listeria* • Some activity against mycobacteria • Nonenzymatic degradation with elimination in urine
Tedizolid (IV, PO)	• Skin and soft-tissue infections	• Similar activity to linezolid but lower risk of myelosuppression and drug interactions • Hepatic metabolism and fecal excretion • Longer $t_{1/2}$ than linezolid

Drug Facts for Your Personal Formulary: *Protein Synthesis Inhibitors and Miscellaneous Antibacterial Agents (continued)*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Polymyxins—Bactericidal Cell Membrane-Disrupting Agents		
Colistin (polymyxin E) (IV, inhaled)	• Serious infections due to multidrug-resistant gram-negative organisms • Prevention of cystic fibrosis exacerbations (inhaled)	• Good activity vs. *Acinetobacter*, *E. coli*, *Klebsiella*, *Pseudomonas*, including multidrug-resistant strains • Prodrug; complex pharmacokinetics with renal and nonrenal elimination • Substantial nephrotoxicity and neurotoxicity
Polymyxin B (IV, topical)	• Serious infections due to multidrug-resistant gram-negative organisms • Topical treatment/prevention of skin and soft-tissue infections	• Similar activity and toxicity as colistin • Nonrenally eliminated; does not achieve high urinary levels
Glycopeptides and Lipoglycopeptides—Bactericidal Inhibitors of Cell Wall Synthesis		
Vancomycin (IV, PO)	• Skin and soft-tissue infections • Bacteremia and endocarditis due to gram-positive bacteria • Pneumonia • Meningitis • *Clostridium difficile* colitis (oral formulation) • Surgical prophylaxis for procedures with high risk of MRSA	• Good activity vs. vast majority of gram-positive bacteria, *Staphylococcus* (including MRSA), streptococci, *E. faecalis* • Oral formulation not well absorbed and only used for treatment of *C. difficile* colitis • Modest CNS penetration in presence of inflammation • Renal elimination • Infusion-related reactions (red man syndrome) associated with rapid infusion • Nephrotoxicity at high doses
Telavancin (IV)	• Skin and soft-tissue infections • Pneumonia	• Similar activity to vancomycin with activity against some vancomycin-resistant strains of *Enterococcus* • Renal elimination • Higher nephrotoxicity relative to vancomycin • QT prolongation • Avoid in pregnancy
Dalbavancin (IV)	• Skin and soft-tissue infections	• Similar activity to vancomycin • Highly protein bound • Extremely long $t_{1/2}$; once-weekly dosing
Oritavancin (IV)	• Skin and soft-tissue infections	• Similar activity to telavancin • Highly protein bound • Extremely long half-life; single-dose therapy for skin infections
Daptomycin (IV)	• Skin and soft-tissue infections • Staphylococcal and streptococcal bacteremia • Vancomycin-resistant enterococcal infections	• Lipopeptide, similar activity to vancomycin • Retains activity against some vancomycin-resistant strains of *Enterococcus* • Protein bound; limited CNS penetration • Inactivated by pulmonary surfactant; not effective for pneumonia • Renal elimination • Rare myositis and rhabdomyolysis
Nitroimidazoles—Disruptors of DNA Synthesis in Anaerobes		
Metronidazole (IV, PO, topical)	• *Clostridium difficile* colitis • Empiric coverage of anaerobic organisms, as in intra-abdominal and skin and soft-tissue infections • *Helicobacter pylori* gastritis (in combination with other agents) • Bacterial vaginosis	• Bacterial spectrum limited to anaerobic organisms, including *B. fragilis* and *Clostridium* • Excellent absorption • Wide distribution, including CNS • Hepatic elimination • CYP inhibitor; drug interactions with warfarin • Peripheral neuropathy with prolonged use
Topical Agents—Inhibitors of Bacterial Cell Wall Synthesis		
Bacitracin (topical)	• Prevention and treatment of skin and soft-tissue infections • Ophthalmic infections	• Activity against broad array of gram-positive and gram-negative organisms • Nephrotoxicity with parenteral use
Mupirocin (topical)	• Treatment of minor skin infections • Eradication of nasal carriage of *S. aureus*	• Activity against broad array of gram-positive and gram-negative organisms • May cause irritation at site of application

TABLE 60–5 ■ PHARMACOTHERAPY OF MYCOBACTERIAL INFECTIONS OTHER THAN TUBERCULOSIS, LEPROSY, AND MAC

MYCOBACTERIAL SPECIES	FIRST-LINE THERAPY	ALTERNATIVE AGENTS
M. kansasii	Isoniazid + rifampin[a] + ethambutol	Trimethoprim-sulfamethoxazole; ethionamide; cycloserine; clarithromycin; amikacin; streptomycin; moxifloxacin or gatifloxacin
M. fortuitum complex	Amikacin + doxycycline	Cefoxitin; rifampin; a sulfonamide; moxifloxacin or gatifloxacin; clarithromycin; trimethoprim-sulfamethoxazole; imipenem
M. marinum	Rifampin + ethambutol	Trimethoprim-sulfamethoxazole; clarithromycin; minocycline; doxycycline
M. ulcerans	Rifampin + streptomycin[c]	Clarithromycin[b]; rifapentine[b]
M. abscessus	Cefoxitin (or imipenem) + amikacin + clarithromycin	Tigecycline, moxifloxacin,
M. malmoense	Rifampin + ethambutol ± clarithromycin	Fluoroquinolone
M. haemophilum	Clarithromycin + rifampin + quinolone	—

[a]In HIV-infected patients, the substitution of rifabutin for rifampin minimizes drug interactions with the HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors.
[b]Based on animal models.
[c]For *M. ulcerans*, surgery is the primary therapy.

Drug Facts for Your Personal Formulary: *Antimycobacterial Drugs*

Drug	Therapeutic Uses	Major Toxicity and Clinical Pearls
Rifamycins		
Rifampin	• Tuberculosis • *M. kansasii* disease • Leprosy • *M. marinum, M. uclerans, M. malmoense,* and *M. haemophilum* diseases • Prophylaxis of meningococcal disease and *Haemophilus influenzae* meningitis • Brucellosis • Combination therapy in selected cases of staphylococcal endocarditis or osteomyelitis, especially those caused by staphylococci "tolerant" of penicillin	• Peak concentration and AUC-driven efficacy • Rifampin potently induces CYPs and thus increases metabolism of many classes of drugs. Prior to putting a patient on rifampin, all the patient's medications and contraception should be examined for potential interactions. • Hypersensitivity reactions, especially with high-dose intermittent therapy, including flu-like symptoms, eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock • Hepatitis, especially in combination with other anti-TB agents, in alcoholics, or preexistent liver disease
Rifapentine	• Treatment of tuberculosis • Prophylaxis of tuberculosis	• 97% protein binding • Long $t_{1/2}$ of ~ 14–18 h, allowing more intermittent dosing (1–2 times weekly) • Moderate CYP3A induction
Rifabutin	• Used as rifampin replacement to avoid drug interactions of rifampin with other medications, especially in HIV coinfection • Treatment of disseminated MAC in patients with AIDS	• Weaker CYP3A induction than rifampin • Concentrations higher in tissue than plasma • $t_{1/2}$ ~ 45 h • Neutropenia in 25% of patients with HIV • Primary reasons for therapy discontinuation include rash, GI intolerance, and neutropenia. • Uveitis and arthralgias in patients receiving rifabutin doses > 450 mg daily
Isoniazid		
Isoniazid	• *M. tuberculosis* infection • *M. kansasii* infection • Prophylaxis of tuberculosis disease	• Patients divided into slow, intermediate, and fast acetylators, which has consequence of efficacy and toxicity. • Hepatotoxicity, increased above age of 42 years • Peripheral neuritis: should be administered with pyridoxine • Reversible vasculitis • Overdose is associated with the clinical triad of (1) seizures refractory to treatment with phenytoin and barbiturates, (2) metabolic acidosis, and (3) coma • Many drug interactions via inhibition and induction of several CYP450 enzymes

Pyrazinamide		
Pyrazinamide	• Tuberculosis	• No activity against *M. bovis* • Activated under acidic conditions; synergizes with rifampin • Pyrazinamide clearance reduced in renal failure; reduce dosing frequency is reduced to 3 x/week at low GFR. • Removed by hemodialysis; redose after each session • Adverse effects: hepatotoxicity and hyperuricemia
Ethambutol		
Ethambutol	• Tuberculosis • *M. avium* complex infections • *M. kansasii* infection • Activity against *M. gordonae, M. marinum, M. scrofulaceum,* and *M. szulgai*	• Incidence of optic neuritis leading to decreased visual acuity and loss of red-green discrimination. Test visual acuity and red-green discrimination prior to the start of therapy and periodically thereafter. • In renal failure, ethambutol should be dosed at 15–25 mg/kg three times a week instead of daily, even in patients receiving hemodialysis.
Bicyclic Nitroimidazoles		
Pretomanid, delaminid	• Treatment of MDR-TB; being tested for regimens used to treat drug-susceptible TB	• Kills both replicating and nonreplicating *M. tuberculosis* • Delaminid: QT segment prolongation
Riminophenazines		
Clofazimine	• Treatment of leprosy	• GI problems are encountered in 40%–50% of patients. • Abdominal pain due to crystal deposition in cavities and tissues • Body secretion, eye, and skin reddish-black discoloration occur in most patients
Diarylquinone		
Bedaquiline	• Treatment of MDR-TB; being tested for regimens used to treat drug-susceptible TB	• Apparent volume of distribution > 10,000 L • Controversy regarding side effects profile and increased number of deaths compared to placebo • QT interval prolongation
Ethionamide		
Ethionamide	• Treatment of MDR-TB and XDR-TB	• Same mutations in ethionamide-resistant bacteria as for isoniazid-resistant bacteria • 50% of patients are unable to tolerate a single dose larger than 500 mg because of GI toxicity. • Adverse effects: postural hypotension, mental depression, drowsiness, asthenia; neurological toxicity • Concomitant administration with pyridoxine is recommended. • Hepatitis in ~ 5% of cases
Para-aminobenzoic Acid Analogues		
Dapsone	• Treatment of leprosy • Combined with chlorproguanil for the treatment of malaria • Treatment of *Pneumocystis jiroveci* infection and prophylaxis • Prophylaxis of *Toxoplasma gondii* infection • Anti-inflammatory effects for treatment of pemphigoid, dermatitis herpetiformis, linear IgA bullous disease, relapsing chondritis, and brown recluse spider bite ulcers	• G6PD deficiency should be tested prior to use. • NADH-dependent methemoglobin reductase deficiency–associated methemoglobinemia • Hemolysis at doses of 200–300 mg of dapsone per day • Used topically for acne
Aminosalicylic acid	• Treatment of MDR-TB	• Should be administered with food • Dose must be reduced in renal dysfunction. • Adverse events incidence is ~ 10%–30%. • GI problems predominate • Hypersensitivity reactions in 5%–10% of patients
Cycloserine		
Cycloserine	• Treatment of MDR-TB	• Oral second-line drug • "Psych-serine": 50% of patients develop neuropsychiatric symptoms; headache, somnolence, severe psychosis, seizures, and suicidal ideas • Must be redosed after dialysis

Drug Facts For Your Personal Formulary: *Antifungal Agents*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Polyenes: Interact with ergosterol in the fungal cell membrane		
Amphotericin B deoxycholate (C-AMB)	• Invasive candidiasis • Invasive aspergillosis • Blastomycosis • Histoplasmosis • Coccidioidomycosis • Cryptococcosis • Mucormycosis • Sporotrichosis • Empirical therapy in the immunocompromised host	• Associated with significant nephrotoxicity, including azotemia, renal tubular acidosis, and hypochromic, normocytic anemia • Associated with acute reactions, including infusion-related fever and chills • C-AMB is better tolerated by premature neonates than by older children and adults
Amphotericin B colloidal dispersion (ABCD) (not available in the U.S.) Liposomal amphotericin B (L-AMB) Amphotericin B lipid complex (ABLC)		• All three amphotericin B lipid formulations are less nephrotoxic than C-AMB. • Infusion-related reactions are highest with ABCD and lowest with L-AMB.
Pyrimidines: Disrupt fungal RNA and DNA synthesis		
Flucytosine	• Cryptococcosis (with amphotericin B)	• Has broad activity but emergence of resistance limits usefulness as single-agent therapy • ↓ Dosage in patients with ↓ renal function • Toxicity more frequent in patients with AIDS or azotemia • Flucytosine may depress bone marrow, lead to leukopenia and thrombocytopenia
Imidazoles and Triazoles: Inhibit ergosterol biosynthesis		
Ketoconazole		
Itraconazole	• Invasive aspergillosis • Blastomycosis • Coccidioidomycosis • Histoplasmosis • Pseudallescheriasis • Sporotrichosis • Ringworm • Onychomycosis	• Substrate for and potent inhibitor of CYP3A4 • Hepatotoxic • Contraindicated in pregnancy and in women considering becoming pregnant

Drug Facts For Your Personal Formulary: *Antifungal Agents (continued)*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Imidazoles and Triazoles: Inhibit ergosterol biosynthesis		
Fluconazole	• Invasive candidiasis • Cryptococcosis • Coccidioidomycosis • Prophylaxis and empirical therapy in immunocompromised host	• Plasma concentrations are essentially the same whether the drug is given orally or intravenously. • Concentrations in CSF = 50%–90% of C_p • Inhibitor of CYP3A4 and CYP2C9 • Contraindicated during pregnancy
Voriconazole	• Invasive aspergillosis • Invasive candidiasis • Pseudallescheriasis	• Oral bioavailability is 96%. • Monitor C_p; serum levels of 1 to 5 mg/L maximize efficacy and minimize toxicity • Metabolized by and inhibits CYPs (2C19 > 2C9 > 3A4) • Can prolong the QTc interval • Transient visual or auditory hallucinations are frequent after the first dose. • Contraindicated in pregnancy
Posaconazole	• Oropharyngeal candidiasis • Prophylaxis in the immunocompromised host against aspergillosis and candidiasis	• Oral bioavailability enhanced by food • Drugs that ↓ gastric acid ↓ posaconazole exposure • Inhibits CYP3A4 • Can prolong the QTc interval • Adverse effects: headache and GI disorders
Isavuconazole (isavuconazonium prodrug)	• Invasive aspergillosis • Mucormycosis	• Oral bioavailability is 98%. • Substrate of and inhibitor of CYP3A4 • Does not appear to prolong QTc
Echinocandins: Inhibit 1,3-β-D-glucan synthesis in the fungal cell wall		
Caspofungin	• Invasive candidiasis • Empirical therapy in the immunocompromised host	• ↓ Dose in moderate hepatic impairment
Micafungin	• Invasive candidiasis • Prophylaxis in the immunocompromised host	• Reduction of micafungin dose in moderate hepatic failure is not required.
Anidulafungin	• Invasive candidiasis	• No dose adjustment is needed for hepatic or renal failure.
Griseofulvin: Inhibits microtubule function, disrupts assembly of the mitotic spindle		
Griseofulvin	• Ringworm • Onychomycosis	• Absorption is reduced by barbiturates • Induces hepatic CYPs
Allylamines: Inhibit fungal squalene epoxidase and reduce ergosterol biosynthesis		
Terbinafine	• Ringworm • Onychomycosis	• Bioavailability is ~ 40% due to first-pass metabolism in the liver. • The drug accumulates in skin, nails, and fat. • The initial $t_{1/2}$ is ~ 12 h but extends to 200–400 h at steady state.
Agents Active Against Microsporidia and *Pneumocystis*		
Albendazole	• Microsporidia infection	• Anthelmintic • Inhibitor of α-tubulin polymerization
Fumagillin	• Microsporidia infection	• Used in immunocompromised individuals with intestinal microsporidiosis due to *Enterocytozoon bieneusi* unresponsive to albendazole • Not approved for human use in the U.S.
Trimethoprim-sulfamethoxazole	• *Pneumocystis jiroveci* pneumonia	• See Chapter 56
Pentamidine	• *Pneumocystis jiroveci* pneumonia	• Prophylaxis use to prevent PJP in at-risk individuals who cannot tolerate trimethoprim-sulfamethoxazole
Topical Antifungal Agents		
Imidazoles and Triazoles Clotrimazole, miconazole, ketoconazole, etc.	• Dermatophytosis (ringworm), candidiasis, tinea versicolor, piedra, tinea nigra, and fungal keratitis	• Available for cutaneous application as creams or solutions • Some are available as vaginal creams or suppositories or as oral troches
Tavaborole	Toenail onychomycosis due to *T. rubrum* or *T. mentagrophytes*	• Apply daily for 48 weeks

Drug Facts for Your Personal Formulary: *Antiviral Agents for Herpes Virus and Influenza*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
ANTIHERPES AGENTS		
Guanine nucleoside analogues		
Acyclovir Valacyclovir (Val, an ester prodrug form of acyclovir)	• Clinical use limited to herpes viruses • Efficacy against: HSV-1 > HSV-2 > VZV > EBV > CMV = –6	• Acyclovir has low bioavailability (~20%); Val has bioavailability ~ 70% • Concentrates in breast milk • Clearance via renal excretion of acyclovir, requires good kidney function; $t_{1/2}$ prolonged in neonates and anuric patients • Safely used long term (10 years)
Cidofovir	• Active against human herpes, papilloma, polyoma, pox, adenoviruses	• Low oral bioavailability • Plasma $t_{1/2}$ ~ 2.6 h, but active diphosphate metabolite has long $t_{1/2}$ in cells, as does a phosphocholine metabolite ($t_{1/2}$ = 86 h) • Major risk: nephrotoxicity, reduced by oral probenecid and saline prehydration (beware interactions of probenecid and other medicines)
Famciclovir (Fam), a prodrug form, rapidly converted to penciclovir (Pen)	• Penciclovir similar to acyclovir against HSV and VZV; also inhibits HBV	• Oral bioavailabilities: Pen, < 5%; Fam, ~ 75% • Food reduces rate but not extent of Pen absorption • Safety in pregnancy not established
Valganciclovir (Val), a prodrug valyl ester of ganciclovor (Gan)	• Gan has inhibitory activity against all herpesviruses, especially CMV	• Gan less active against acyclovir-resistant TK-deficient HSV strains • Active triphosphate form has long cellular $t_{1/2}$ • IV administration gives good levels in vitreous with long dwell time ($t_{1/2}$ ~ 25 h) • Major adverse effects: myelosuppression, neutropenia • Risk in pregnancy not ruled out
Pyrophosphate analogue		
Foscarnet	• Active against all herpesviruses and HIV	• Poorly soluble in water; requires large volumes • Adverse effects: neprotoxicity, hypocalcemia • Safety in pregnancy and childhood uncertain
Other agents		
Fomivirsen (antisense oligonucleotide)	• Inhibits CMV replication	• No longer available in the U.S.
Docosanol (long-chain alcohol)	• 10% cream for labial herpes	• Treatment initiation at papular or later stages provides no benefit
Idoxuridine (iodinated thymidine analogue)	• Ophthalmic HSV keratitis (in the U.S.)	• Averse effects: pain, pruritus, inflammation, edema of eye/eyelid
Trifluridine (trifluoropyrimidine nucleoside)	• Ocular herpes; 1° keratoconjunctivitis, recurrent epithelial keratitis from HSV1/2; for external use	• More active than idoxuridine and comparable to vidarabine in HSV ocular infections • Triphosphate form incorporated into host and viral DNA, so not used systemically
ANTI-INFLUENZA AGENTS		
Inhibitors of viral M2 protein function		
Amantadine (Ama) Rimantadine (Rima)	• Active only against susceptible Influenza A viruses (not B) • Seasonal prophylaxis against Influenza A (70%–90% protective)	• Rima 4- to 10-fold more active than Ama • Resistant Isolates appear after 2–3 days of therapy • Virtually all H3N2 strains of Influenza are resistant to these drugs • Vaccination is more cost-effective
Inhibitors of viral neuraminidase (see PK data in Table 62–3)		
Oseltamivir	• Treatment and prevention of Influenza A and B	• Probenecid doubles plasma $t_{1/2}$
Zanamivir	• Treatment and prevention of Influenza A and B	• Inhalable formulation • IV formulation available as EIND • No clinically significant drug interactions
Peramivir	• Treatment of acute uncomplicated flu in patients ≥ 18 years and symptomatic ≤ 2 days	• Supplied as IV infusion; for patients who cannot absorb or oral agents • Comparable in efficacy and adverse effects to oseltamivir • No clinically significant drug interactions reported
CYTOKINES		
Interferon (recombinant α-IFNs; natural and pegylated IFNs)	• Treatment of condyloma acuminatum, chronic HCV and HBV infection, Kaposi sarcoma (in patients with HIV, other malignancies, multiple sclerosis	• See Chapter 63

Drug Facts for Your Personal Formulary: *Viral Hepatitis (HBV/HCV)*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Hepatitis B Therapy		
Pegylated interferon alfa	• Preferred agent • Approved for adult patients with compensated liver disease and evidence of viral replication and liver inflammation • Administered SC weekly for 48–52 weeks	• Adverse reactions (>40%): fatigue/asthenia, pyrexia, myalgia, and headache • May cause fatal neuropsychiatric, autoimmune, ischemic, and infectious disorders • Frequent hematologic monitoring required • Contraindicated in advanced liver disease and in pregnancy
Entecavir	• Preferred agent • Approved for individuals ≥ 2 years old • Indefinite treatment for patients with cirrhosis	• Use higher dose for decompensated cirrhosis and patients with lamivudine or telbivudine resistance • Take on an empty stomach • Monitor for lactic acidosis in decompensated cirrhosis • Adverse reactions (≥3%): headache, fatigue, dizziness, nausea
Tenofovir disoproxil fumarate	• Preferred agent • Approved for individuals ≥ 2 years old • Indefinite treatment for patients with cirrhosis	• Dose reduction in renal impairment • Monitor renal function • May decrease bone mineral density • Adverse reactions (≥10%) in decompensated cirrhosis: abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia
Adefovir Lamivudine Telbivudine	• Alternative agents due to high incidence of HBV resistance with monotherapy • Indefinite treatment for patients with cirrhosis	• Dose adjust for renal impairment • Abrupt discontinuation causes hepatitis flares • Common adverse reactions: ◦ *Adefovir*: asthenia and impaired renal function ◦ *Lamivudine*: ear, nose, and throat infections; sore throat; and diarrhea ◦ *Telbivudine*: increased CK, nausea, diarrhea, fatigue, myalgia, and myopathy

Drug Facts for Your Personal Formulary: *Viral Hepatitis (HBV/HCV) (continued)*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Hepatitis C Therapy		
Sofosbuvir/ledipasvir	• HCV genotype 1, 4, 5, 6 and individuals with HIV coinfection • Administered as fixed-dose combination tablet for 8 or 12 weeks • Use with ribavirin for 12 weeks in treatment-experienced patients with cirrhosis	• Ledipasvir should not be used with potent Pgp inducers • Ledipasvir absorption requires acid gastric pH • Coadministration of sofosbuvir and amiodarone may cause severe bradycardia and fatal cardiac arrest • Avoid sofosbuvir if CrCl < 30 mL/min • Adverse reactions (≥10%): fatigue, headache
Sofosbuvir/daclatasvir	• HCV genotype 3, HIV coinfection, and advanced liver disease regardless of HCV genotype • 12-week treatment in patients without cirrhosis • Coadministered with ribavirin in patients with cirrhosis for 12 weeks	• Daclatasvir should not be used with potent CYP3A inducers • Daclatasvir dose reduction needed with strong CYP3A inhibitors • Coadministration of sofosbuvir and amiodarone may cause severe bradycardia and fatal cardiac arrest • Avoid sofosbuvir if CrCl < 30 mL/min • Adverse reactions (≥10%): fatigue, headache
Sofosbuvir/simeprevir	• 12-week therapy in patients without cirrhosis • 24-week therapy in patients with cirrhosis	• Cannot be used with potent Pgp inducers • Simeprevir: mild inhibitor of GI; contraindicated in decompensated cirrhosis CYP3A • Coadministration of sofosbuvir and amiodarone may cause severe bradycardia and fatal cardiac arrest • Adverse reactions of simeprevir (≥20%): fatigue, headache, nausea, photosensitivity (limit sun exposure)
Sofosbuvir/velpatasvir	• Approved for use in all HCV genotypes • Administered as a fixed dose combination tablet for 12 weeks • Used with ribavirin for patients with decompensated cirrhosis	• Do not use with potent Pgp or CYP3A inducers • Velpatasvir requires acidic gastric pH • Coadministration of sofosbuvir and amiodarone may cause severe bradycardia and fatal cardiac arrest • Avoid sofosbuvir if CrCl < 30 mL/min • Common adverse reactions: fatigue and headache
Ritonavir-boosted paritaprevir and ombitasvir	• Fixed-dose combination tablets for HCV genotype 4 in combination with ribavirin	• High potential for CYP-mediated drug interactions • Should not be used in patients with decompensated cirrhosis • Adverse reactions (≥5%): nausea, pruritis, and insomnia • With ribavirin, the most common adverse reactions (≥10%) are fatigue, nausea, pruritis, other skin reactions, insomnia, and asthenia
Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir	• HCV genotype 1b (1a in combination with ribavirin) • 12 weeks of therapy • 24 weeks of therapy required for patients with genotype 1a and cirrhosis	
Grazoprevir/elbasvir	• 12-week therapy for patients without baseline NS5A RAVs • 16-week combined therapy with ribavirin for patients with baseline NS5A RAVs • Preferred treatment in renal impairment	• Should not be used with moderate and strong CYP3A and Pgp inducers • Should not be used with OATP1B1 inhibitors • Common adverse reactions: headache, fatigue, nausea
Ribavirin	• Used in combination with other HCV regimens to boost therapeutic efficacy	• May cause hemolytic anemia • Teratogenic • Wide tissue distribution • Long half-life (7–10 days) • Dose adjustment needed for renal impairment

Drug Facts for Your Personal Formulary: *Antiretroviral Agents and Treatment of HIV Infection*

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (phosphorylated to active form to prevent infection of susceptible cells; do not eradicate virus from cells with integrated proviral DNA): Active against HIV-1 and HIV-2 and in some cases HBV		
Zidovudine (AZT) (thymidine analogue)	• HIV in adults and children • Preventing mother-to-child transmission	• Adverse effects: bone marrow (anemia, neutropenia) and muscle toxicity (myopathy); inhibits mitochondrial DNA polymerase γ • Do not use with stavudine
Stavudine (dT4)	• HIV in adults and children	• Adverse effects: sensory neuropathy and lipoatrophy • Do not use with zidovudine • Avoid use because of long-term and potentially irreversible toxicities
Lamivudine	• HIV in adults and children ≥ 3 months • Chronic hepatitis B (adults, children)	• Essentially nontoxic
Abacavir (only guanosine analogue antiretroviral)	• HIV in adults and children • Not active against HBV	• Bioavailability not affected by food • Adverse effects: hypersensitivity syndrome (fever, abdominal pain, rash), associated with HLA B*5701 genotype; discontinue drug immediately and never use again as this is potentially fatal

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (phosphorylated to active form to prevent infection of susceptible cells; do not eradicate virus from cells with integrated proviral DNA): Active against HIV-1 and HIV-2 and in some cases HBV (continued)		
Tenofovir (5′-AMP derivative; supplied as prodrugs: TDF or TAF)	• HIV infection (adults, children > 2 years, in combination with other antiretrovirals) • Chronic hepatitis B (adults, children > 12 years) • HIV preexposure prophylaxis (with emtricitabine) in adults at high risk of infection	• Nephrotoxicty: small decreases in estimated creatinine clearance are common; Fanconi syndrome rare • Decreases in bone mineral density with chronic use
Emtricitabine	• HIV infection (adults, children, in combination with other antiretrovirals) • Chronic hepatitis B (adults, children) • HIV preexposure prophylaxis (with tenofovir) in adults at high risk of infection	• Generally nontoxic
Didanosine	• HIV infection in adults and children	• Adverse effects: sensory neuropathy and pancreatitis • Avoid use because of long-term and potentially irreversible toxicities
Nonnucleoside Reverse Transcriptase Inhibitors: Do not require metabolic activation; HIV-1 specific and not active against HIV-2		
Nevirapine	• HIV-1 infection in infants, children, and adults • Single-dose prevention of mother-to-child transmission	• Autoinducer of metabolism • Commonly produces rash that usually resolves with continued treatment • Can rarely produce life-threatening skin eruptions such as Stevens-Johnson syndrome • Rarely produces life-threatening hepatitis
Efavirenz	• HIV-1 infection in children ≥ 3 years and adults	• Commonly causes CNS toxicity that usually resolves with continued treatment but can be severe enough to warrant discontinuation • Moderate hepatic enzyme inducer
Rilpivirine	• HIV-1 infection in children > 12 years and adults	• Must be given with food • Avoid proton pump inhibitors because of reduced absorption • May cause prolonged QTc interval if concentrations are too high
Etravirine	• Treatment-experienced adults and children ≥ 6 years	• Commonly produces rash that usually resolves with continued treatment • Can rarely produce life-threatening skin eruptions such as Stevens-Johnson syndrome • Moderate inducer of hepatic enzymes
Delavirdine	• Adults with HIV infection	• Rash commonly and rarely Stevens-Johnson syndrome • Rarely used because of the requirement for thrice-daily dosing
Protease Inhibitors: Active against HIV-1 and HIV-2; generally used as second-line agents in treatment-experienced patients		
Saquinavir	• Second-line treatment of HIV in adults and children	• Rarely used because of better-tolerated alternative PIs
Ritonavir	• Used only as a PK-boosting agent in combination with other PIs	• Commonly causes nausea • Associated with elevated cholesterol and triglycerides at higher doses • Potent inhibitor of CYP3A4 • Moderate hepatic enzyme inducer
Fosamprenavir	• HIV-infected adults, treatment-naïve children ≥ 2 years and treatment-experienced children ≥ 6 years	• Adverse effects: diarrhea, nausea, and vomiting • Occasional skin rashes
Lopinavir	• Treatment-naïve or -experienced HIV-infected adults and children ≥ 14 days	• Must be combined with ritonavir • Commonly causes nausea and other GI toxicities • Associated with elevated cholesterol and triglycerides in adults with prolonged use
Atazanavir	• Treatment-naïve or -experienced HIV-infected adults and children ≥ 3 months	• Usually combined with ritonavir or cobicistat • Can be given without a PK booster at a higher dose of 400 mg • Absorption reduced with proton pump inhibitors and H_2 blockers • Commonly causes unconjugated hyperbilirubinemia • Can cause nephrolithiasis and cholelithiasis
Darunavir	• Treatment-naïve or -experienced HIV-infected adults and children > 3 years	• Must be combined with ritonavir or cobicistat • May cause transient rash • Better tolerated than other PIs

Drug Facts for Your Personal Formulary: *Antiretroviral Agents and Treatment of HIV Infection (continued)*

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Protease Inhibitors: Active against HIV-1 and HIV-2; generally used as second-line agents in treatment-experienced patients		
Indinavir	• Treatment-naïve or -experienced HIV-infected adults and children	• Must be taken with ritonavir or while fasting • Adverse effects: crystalluria and nephrolithiasis • Rarely used because of the availability of better-tolerated PIs
Nelfinavir	• Treatment-naïve or -experienced HIV-infected adults and children	• The only PI that does not benefit from PK boosting • Must be taken with food • Adverse effects: diarrhea and other GI toxicity • Rarely used because of the availability of better-tolerated PIs
Tipranavir	• Treatment-experienced HIV-infected adults and children ≥2 years, generally those who have failed all other PIs	• Toxicity: rare but potentially fatal hepatotoxicity; rare but potentially fatal bleeding diathesis, including intracranial hemorrhage • Rarely used because of the availability of better-tolerated PIs
Entry Inhibitors: Generally reserved for second-line or salvage therapy		
Maraviroc	• Treatment-naïve or -experienced HIV-infected adults who have evidence of predominantly CCR5-tropic virus	• CYP3A4 substrate susceptible to drug interactions with other antiretrovirals • Adverse effect: dose- and concentration-dependent orthostatic hypotension
Enfuvirtide	• Treatment-experienced HIV-infected adults and children > 6 years • Generally reserved for those with no other treatment options	• Injected subcutaneously twice daily • Adverse effects: injection site reactions and subcutaneous nodules are common • Not active against HIV-2
Integrase Inhibitors: Widely used in treatment-naïve patients because of excellent tolerability, safety, and antiretroviral activity		
Raltegravir	• HIV-infected adults and children > 4 weeks of age	• Given twice daily without the need for a PK boosting agent • Reduced bioavailability if given concurrently with divalent cations • Generally well tolerated
Elvitegravir	• HIV-infected adults and children > 12 years of age	• Requires cobicistat as a PK booster • Should be taken with food • Reduced bioavailability if given concurrently with divalent cations • Generally well tolerated
Dolutegravir	• HIV-infected adults and children > 12 years of age	• Given once daily without the need for a PK-boosting agent • Reduced bioavailability if given concurrently with divalent cations • Generally well tolerated

Drug Facts for Your Personal Formulary: *Cytotoxic Drugs*

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Section I: Alkylating Agents and Platinum Coordination Complexes		
Mechanism of action: covalent modification of DNA. Adverse effects of all alkylating drugs: myelosuppression and immunosuppression; toxicity to dividing mucosal cells and hair follicles (e.g., oral mucosal ulceration, intestinal denudation, alopecia); delayed pulmonary fibrosis; reproductive system toxicity (premature menopause, sterility); and leukemogenesis (up to 5%, highest for melphalan, procarbazine, nitrosoureas).		
Nitrogen Mustards: DNA alkylation		
Mechlorethamine	• Hodgkin lymphoma • Topical: cutaneous T-cell lymphoma	• Vascular damage during injection due to vesicant properties
Cyclophosphamide	• Acute and chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; neuroblastoma; breast, ovary, Wilms tumor; soft-tissue sarcoma • Autoimmune disease (Wegener granulomatosis, rheumatoid arthritis, nephrotic syndrome)	• Oral or intravenous administration • Active alkylating moieties generated through hepatic metabolism • Nephrotoxic and urotoxic metabolite, acrolein; severe hemorrhagic cystitis in high-dose regimens; prevented by MESNA • Provide vigorous hydration during high-dose treatment • Elimination not affected by renal dysfunction; reduce dose in patients with hepatic dysfunction
Ifosfamide	• Germ cell testicular cancer • Pediatric and adult sarcoma • High-dose chemotherapy with bone marrow rescue	• See cyclophosphamide • Can cause neurotoxicity (including seizures) • Methylene blue treatment of CNS toxicity possibly useful
Melphalan	• Multiple myeloma	• Oral and intravenous administration
Chlorambucil	• Chronic lymphocytic leukemia	• Oral administration
Bendamustine	• Non-Hodgkin lymphoma • Chronic lymphocytic leukemia	• Lacks cross-resistance with other classical alkylators
Alkyl Sulfonate: DNA alkylation		
Busulfan	• Chronic myelogenous leukemia • High-dose chemotherapy regimen with bone marrow transplantation	• Oral administration • Adverse effects: prolonged (up to years) pancytopenia; suppression of stem cells; seizures; ↑ clearance of phenytoin; hepatic VOD
Nitrosoureas: DNA alkylation		
Carmustine (BCNU)	• Malignant gliomas • Hodgkin lymphoma; non-Hodgkin lymphoma	• Vascular damage during injection due to vesicant properties • Profound and delayed myelosuppression
Streptozocin (streptozotocin)	• Malignant pancreatic insulinoma • Carcinoid	• Frequent renal toxicity, sometimes renal failure
Methylhydrazine Derivatives: Monofunctional DNA alkylation		
Procarbazine (*N*-methylhydrazine, MIH)	• Hodgkin lymphoma • Gliomas	• Greater capacity for mutagenesis and carcinogenesis than bifunctional alkylators (e.g., cyclophosphamide)
Triazenes: Methyl transfer to DNA		
Dacarbazine (DTIC)	• Hodgkin lymphoma; soft-tissue sarcomas • Melanoma	• Intravenous administration • Activation by hepatic CYPs • Adverse effects: nausa, vomiting • Rare hepatotoxicity and neurotoxicity
Temozolomide	• Malignant gliomas	• Oral administration • Combined with radiation therapy • Greater capacity for mutagenesis and carcinogenesis than bifunctional alkylators; more active in MGMT-deficient tumors
Platinum Coordination Complexes: Form covalent metal adducts with DNA		
Cisplatin	• Testicular, ovarian, bladder, esophageal, gastric, lung, head and neck, anal, and, breast cancer	• Intravenous administration • Adverse effects: • Nephrotoxicity (reduce by forced pretreatment hydration, diuresis, and use of *amifostine*) • Ototoxicity (tinnitus, high-frequency hearing loss) • Nausea and vomiting (antidote, *aprepitant*) • Peripheral sensory and motor neuropathy (may worsen after discontinuation; may be aggravated by taxane treatment) • Drug resistance due to loss of mismatch repair proteins

Drug Facts for Your Personal Formulary: *Cytotoxic Drugs (continued)*

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Platinum Coordination Complexes: Form covalent metal adducts with DNA		
Carboplatin	• Same as above	• Less nausea, neuro-, oto-, and nephrotoxicity than cisplatin • Dose-limiting toxicity: myelosuppression • May cause hypersensitivity reaction
Oxaliplatin	• Colorectal, gastric, and pancreatic cancer	• Peripheral neuropathy is dose limiting • Some nausea • Efficacy not dependent on intact mismatch repair
Section II: Antimetabolites		
Folic Acid Analogues: Inhibit dihydrofolate reductase		
Methotrexate (amethopterin)	• Acute lymphocytic leukemia; choriocarcinoma; breast, head and neck, ovary, bladder and lung cancers; osteogenic sarcoma • Noncancer use: psoriasis, rheumatoid arthritis	• Oral, intravenous, or intramuscular administration • Adverse effects: myelosuppression, GI toxicity • Leucovorin can reverse toxic effects; used as "rescue" in high-dose therapy • *Glucarpidase*, a methotrexate-cleaving enzyme, is approved to treat toxicity • ↓ Dose in renal insufficiency
Pemetrexed	• Mesothelioma, lung cancer	• Similar effects and side effects as methotrexate • Attenuate toxicity with folate and Vit B12 supplementation
Pyrimidine Analogues		
5-Fluorouracil (5FU) *Thymidylate synthase inhibitor*	• Breast, colon, esophageal, stomach, anal cancer • In FOLFOX or FOLFIRINOX combination to treat pancreatic or colorectal cancer • Combined with cisplatin in head and neck cancer • Premalignant skin lesion (topical)	• Intravenous administration • Nausea, mucositis, diarrhea, myelosuppression, hand-foot syndrome • Combined with leucovorin to enhance efficacy • Enhanced toxicity with DPD deficiency; may rescue with uridine
Capecitabine *Thymidylate synthase inhibitor*	• Metastatic breast, colorectal cancer	• Orally administered prodrug of 5FU • Similar adverse effects as 5FU; hand and foot syndrome more frequent than with 5FU
Cytarabine (cytosine arabinoside) *Interferes with base pairing in DNA; inhibits DNA polymerase*	• Acute myelogenous and acute lymphocytic leukemia; non-Hodgkin lymphoma	• Intravenous administration • Myelosuppressive; can cause acute, severe leukopenia, thrombocytopenia, anemia • GI disturbances • Noncardiogenic pulmonary edema • Dermatitis
Gemcitabine (difluoro analogue of deoxycytidine) *Inhibits DNA polymerase; causes strand termination*	• Pancreatic, ovarian, lung, bladder cancer	• Intravenous administration • Female and elderly patients clear the drug more slowly • Myelosuppression, hepatic toxicity • Rare posterior leukoencephalopathy syndrome; sometimes interstitial pneumonitis • Radiosensitizer; should be used with caution in radiotherapy
5-Azacytidine *Inhibits DNA cytosine methyltransferase*	• Myelodysplasia	• Subcutaneous or intravenous administration • Myelosuppression and mild GI symptoms • After intravenous administration severe nausea possible
Purine Analogues and Related Inhibitors		
6-Mercaptopurine *Inhibits purine nucleotide synthesis and metabolism*	• Acute lymphocytic and myelogenous leukemia; small cell non-Hodgkin lymphoma • Noncancer: Crohn disease, ulcerative colitis	• Oral absorption incomplete, thus intravenous administration • Reduce oral dose by 75% in patients receiving allopurinol; no adjustment needed for intravenous administration • Myelosuppression; anorexia, nausea, vomiting; GI side effects less frequent in children than adults • Secondary malignancy: SCC of the skin, AML
Fludarabine *A chain terminator when incorporated into DNA; inhibits RNA function and processing*	• Chronic lymphocytic leukemia • Follicular B-cell lymphoma • Allogeneic bone marrow transplant	• Oral or intravenous administration • Frequently myelosuppression • Less frequent: nausea, vomiting; altered mental status; seizures • Secondary myelodysplasia and acute leukemias • Adjust dose for renal dysfunction

Purine Analogues and Related Inhibitors (continued)		
Cladribine *Incorporated into DNA, produces strand breaks; inhibits conversion of ribo- to deoxyribonucleotides*	• Hairy cell leukemia • Chronic lymphocytic leukemia • Low-grade lymphoma • CTCL, Waldenström macroglobulinemia	• Intravenous administration • Adjust dose for renal dysfunction • Myelosuppression, opportunistic infections, nausea, high fever, tumor lysis syndrome
Clofarabine (mechanism as above)	• Acute myelogenous or lymphocytic leukemia	• Intravenous administration • Adjust dose to creatinine clearance • Myelosuppression • Capillary leak syndrome: discontinue drug • Nausea, vomiting, diarrhea
Nelarabine *Incorporated into DNA, terminates DNA synthesis*	• T-cell leukemia, lymphoma	• Intravenous administration • Myelosuppression; liver function abnormalities; infrequent neurologic sequelae
Pentostatin (2′-deoxycoformycin) *Inhibits adenosine deaminase; causes immunodeficiency (T and B cells)*	• Hairy cell leukemia; chronic lymphocytic leukemia; small cell non-Hodgkin lymphoma	• Intravenous administration • Adjust dose for renal dysfunction • Myelosuppression, GI symptoms, skin rashes, opportunistic infections • Renal, neurologic, pulmonary toxicity

Section III: Natural Products

Vinca Alkaloids: Inhibit tubulin polymerization and microtubule formation		
Vinblastine	• Hodgkin and non-Hodgkin lymphoma • Breast, bladder, lung, testicular cancer • Kaposi sarcoma, neuroblastoma • Part of ABVD combination with doxorubicin (adriamycin, bleomycin, dacarbazine) for Hodgkin lymphoma	• Intravenous administration; extravasation causes irritation and ulceration • Reduce dose in patients with impaired liver function • Least neurotoxic Vinca alkaloid • Myelosuppressive • GI side effects nausea, vomiting, diarrhea • Vinca alkaloids are substrates of the Pgp efflux pump
Vinorelbine	• Breast cancer • Non–small cell lung cancer	• Intravenous administration • Reduce dose in patients with impaired liver function • Intermediate neurotoxicity amongst the Vinca alkaloids • Myelosuppressive (granulocytopenia)
Vincristine	• Acute lymphocytic leukemia; neuroblastoma; Wilms tumor; rhabdomyosarcoma; Hodgkin and non-Hodgkin lymphoma • part of CHOP regimen: cyclophosphamide, doxorubicin (H), vincristine (O), prednisone	• Intravenous administration; extravasation causes irritation and ulceration • Reduce dose in patients with impaired liver function • Least myelosuppressive Vinca alkaloid • Dose-limiting neurotoxicity • Better tolerated by children than adults
Eribulin	• Breast cancer, liposarcoma	• Side effects overlap with vinca but less sensitive to extrusion by Pgp
Taxanes: Stabilize microtubules, inhibit depolymerization		
Paclitaxel	• Ovarian, breast, lung, prostate, bladder, head and neck cancer	• Intravenous administration • Metabolized by hepatic CYPs, ↓ dose in patients with hepatic dysfunction • Substrate of Pgp efflux pump • Myelosuppressive, alleviated by G-CSF • Peripheral neuropathy is dose limiting • Mucositis
Docetaxel	• Same as above	• No effect on doxorubicin clearance • Pharmacokinetics similar to paclitaxel's • ↓ Neutropenia, ↓ neuropathy than paclitaxel
Camptothecins: Inhibit topoisomerase I; DNA religation is inhibited: accumulation of single-strand breaks		
Topotecan	• Ovarian cancer; small cell lung cancer	• Intravenous or oral administration • Reduce dose in patients with renal dysfunction • Neutropenia, GI side effects, nausea, vomiting • Substrate for Pgp
Irinotecan	• Colorectal cancer, small cell lung cancer • Part of FOLFIRI or FOLFIRINOX combination for GI tumors	• Intravenous administration • Prodrug activated in the liver; CYP substrate • Diarrhea and neutropenia • Acetylcholinesterase inhibition results in cholinergic syndrome: treat with atropine
Antibiotics		
Dactinomycin (actinomycin D) *Intercalates between GC base pairs of DNA*	• Wilms tumor; rhabdomyosarcoma; Ewing, Kaposi, and other sarcoma; choriocarcinoma	• Intravenous administration; severe injury on extravasation • Nausea, vomiting; myelosuppression; GI side effects; erythema, inflammation of the skin

Drug Facts for Your Personal Formulary: *Cytotoxic Drugs (continued)*

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Anthracyclines and Anthracenediones: Inhibit topoisomerase II and intercalate DNA		
Daunorubicin (daunomycin, rubidomycin)	• Acute myelogenous and acute lymphocytic leukemia	• Intravenous administration • Impart a red color to the urine • Myelosuppression, GI side effects • Most important long-term side effect is cardiotoxicity, including tachycardia, arrhythmias, congestive heart failure • Alopecia
Doxorubicin	• Soft-tissue, osteogenic, and other sarcoma; Hodgkin and non-Hodgkin lymphoma; acute leukemia; breast, genitourinary, thyroid, and stomach cancer; neuroblastoma	
Mitoxantrone (an anthracenedione)	• Acute myelocytic leukemia; breast and prostate cancer	• Similar side effects as above • Less cardiotoxic
Epipodophyllotoxins: Inhibit topoisomerase II and religation of cleaved DNA strand		
Etoposide	• Testicular and lung cancer; Hodgkin lymphoma; non-Hodgkin lymphomas; acute myelogenous leukemia; Kaposi sarcoma	• Oral and intravenous administration • Reduce dose in patients with renal dysfunction • Leukopenia, GI side effects; hepatic toxicity after high doses • Secondary leukemia
Teniposide	• Acute lymphoblastic leukemia in children; glioblastoma, neuroblastoma	• Intravenous administration • Myelosuppression, nausea, vomiting
Drugs With Diverse Mechanism of Action		
Bleomycin *Binds to DNA, generates free radicals, and induces DNA cleavage via deoxyribose ring damage*	• Testicular cancer; Hodgkin and non-Hodgkin lymphoma; local treatment of bladder cancer • Part of the ABVD regimen (doxorubicin [Adriamycin], Bleomycin, Vinblastine, and Dacarbazine)	• IV, IM or SC administration; instilled into bladder • Reduce dose in patients with renal dysfunction • Most serious: pulmonary toxicity • Cutaneous toxicity (erythema, ulcerations) • Less myelosuppression than other cytotoxics
L-Asparaginase *Hydrolyzes asparagine; deprives leukemia cells that lack asparagine synthase*	• Acute lymphocytic leukemia	• IV and IM administration • Hypersensitivity reactions, anaphylaxis • Hyperglycemia, clotting abnormalities
Hydroxyurea *Inhibits RNR (conversion of ribo- to deoxyribonucleotides)*	• Chronic myelogenous leukemia; polycythemia vera; essential thrombocytosis; sickle cell disease in adults	• Oral administration • Reduce dose in patients with renal dysfunction • Myelosuppression; some GI side effects
Tretinoin (all-*trans* retinoic acid) *Promotes degradation of PML-RARA fusion protein*	• Acute promyelocytic leukemia	• Oral administration • CYP substrate • Leukocyte maturation syndrome, pulmonary distress, effusions, fever, dyspnea • Dry skin, cheilitis • Hypercalcemia and renal failure
Arsenic trioxide *Inhibits thioredoxin and generates reactive oxygen species*	• Acute promyelocytic leukemia	• Oral or intravenous administration • Leukocyte maturation syndrome as above with ATRA • QT prolongation; rare torsade de pointes

[a]For drugs that are subject to hepatic metabolism by CYP enzymes, drug exposure of a patient can be affected by coadministration of inhibitors or inducers of CYP3A4 and can then reduce efficacy or increase side effects.

[b]Embryo-fetal toxicity: Consider that all of these drugs can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug and for 1 month after cessation of therapy. Advise men to avoid fathering a child during the same time period. Avoid lactation during therapies.