
# ANTIBIOTIC ESSENTIALS

FOURTEENTH EDITION

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- Immunizations and prophylaxis
- Antibiotic susceptibility profiles
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2015

BURKE A. CUNHA, MD, MACP

# ANTIBIOTIC ESSENTIALS

**Fourteenth Edition**

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## DEDICATION

*for*
*Marie*

*"Grace in her steps,*
*Heaven in her eye,*
*In every gesture, dignity and love"*

*Milton*

## TABLE OF CONTENTS

## EDITORS

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**Cheston B. Cunha, MD**
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Burke A. Cunha, MD

## NOTICE

The clinical recommendations set forth in this book are those of the authors and are offered as general guidelines, not specific instructions for individual patients. Clinical judgement should always guide the physician in the selection, dosing, and duration of antimicrobial therapy for individual patients.

***Not all recommendations in this book are approved indications by the U.S. Food and Drug Administration, and antimicrobial recommendations are not limited to indications in the package insert. The use of any drug should be preceded by careful review of the package insert, which provides indications and dosing approved by the U.S. Food and Drug Administration***.

The information provided in this book is essential not exhaustive, and the reader is referred to other medical references and the manufacturer's product literature for further information. *Clinical use of the information provided and any consequences that may arise from its use is the responsibility of the prescribing physician. The authors, editors, and publisher do not warrant or guarantee the information herein contained and do not assume and expressly disclaim any liability for errors or omissions or any consequences that may occur from use of this information.*

## BASIS OF RECOMMENDATIONS

***The therapeutic recommendations in Antibiotic Essentials are based on the contributors' clinical expertise and experience as well as the literature and clinical guidelines.***

## ABBREVIATIONS

| | |
|---|---|
| ABE | acute bacterial endocarditis |
| ABM | acute bacterial meningitis |
| ADA | adenosine deaminase |
| AFB | acid fast bacilli |
| AIH | autoimmune lupoid hepatitis |
| AIHA | autoimmune hemolytic anemia |
| AML | acute myelogenous leukemia |
| ANA | antinuclear antibody |
| ARDS | adult respiratory distress syndrome |
| AG | Aspergillus galactomannan |
| A-V | atrio-ventricular |
| β-lactams | penicillins, cephalosporins, cephamycins (not monobactams or carbapenems) |
| BAL | bronchoalveolar lavage |
| BG | β 1, 3 D-glucan |
| BMT | bone marrow transplant |
| BPH | benign prostatic hypertrophy |
| CAB | catheter associated bacteriuria |
| CABG | coronary artery bypass grafting |
| CAC | catheter associated candiduria |
| CAH | chronic active hepatitis |
| CA-MRSA | community-acquired MRSA |
| CAP | community-acquired pneumonia |
| $CD_4$ | $CD_4$ T-cell lymphocyte |
| CE | California encephalitis virus |
| CFS | chronic fatigue syndrome |
| CGD | chronic granulomatous disease |
| CIE | counter-immunoelectrophoresis |
| CLL | chronic lymphocytic leukemia |
| CML | chronic myelogenous leukemia |
| CMV | Cytomegalovirus |
| CNS | central nervous system |
| CO-MRSA | community onset MRSA |
| CoNS | coagulase negative staphylococci |
| CPH | chronic persistent hepatitis |
| CPK | creatine phosphokinase |
| CrCl | creatinine clearance |
| CRE | carbapenemase resistant Enterobacteriaceae |
| CSD | cat scratch disease |
| CSF | cerebrospinal fluid |
| CT | computerized tomography |
| CVA | costovertebral angle |
| CVC | central venous catheter |
| CVID | common variable immune deficiency |
| CVVH | continuous veno venous hemo filtration |
| CXR | chest x-ray |
| DFA | direct fluorescent antibody |
| DI | diabetes insipidus |
| DIC | disseminated intravascular coagulation |
| DM | diabetes mellitus |
| DOT | directly observed therapy |
| e.g. | for example |
| EBV | Ebstein-Barr virus |
| EEE | Eastern equine encephalitis |
| EEG | electroencephalogram |
| EIA | enzyme immunoassay |
| ELISA | enzyme-linked immunosorbent assay |
| EM | erythema migrans |
| EMB | ethambutol |
| Enterobacteriaceae: | Citrobacter, Edwardsiella, Enterobacter, E. coli, Klebsiella, Proteus, Providencia, Shigella, Salmonella, Serratia, Hafnia, Morganella, Yersinia |
| ESBLs | extended spectrum β-lactamases |
| esp | especially |
| ESR | erythrocyte sedimentation rate |
| ESRD | end-stage renal disease |
| ET | endotracheal |
| EV | enterovirus |
| EVD | external ventricular drain |
| FTA-ABS | fluorescent treponemal antibody absorption test |
| FUO | fever of unknown origin |
| G6PD | glucose-6-phosphate dehydrogenase |
| GC | gonococcus/gonorrhea |
| GCA | giant cell arteritis |
| GI | gastrointestinal |
| gm | gram |
| GU | genitourinary |
| GVHD | graft versus host disease |
| HA-MRSA | hospital acquired MRSA |
| HAP | hospital acquired pneumonia |
| HAV | hepatitis A virus |
| HBcAb | hepatitis B core antibody |
| HBoV | human bocavirus |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HD | hemodialysis |
| HDV | hepatitis D virus |
| HEV | hepatitis E virus |
| HFHD | high flux hemodialysis |
| HFV | hepatitis F virus |
| HFM | hand foot mouth disease |

| | |
|---|---|
| HGA | human granulocytic anaplasmosis |
| HHV-6,7,8 | human herpes virus 6,7,8 |
| HME | human monocytic ehrlichiosis |
| hMPV | human metapneumovirus |
| HPS | Hanta virus pulmonary syndrome |
| HPV | human papilloma virus |
| HTLV-1 | human T-cell leukemia virus |
| HRIG | human rabies immune globulin |
| HSV | herpes simplex virus |
| I & D | incision and drainage |
| IFA | immunofluorescent antibody |
| IgA | immunoglobulin A |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IM | intramuscular |
| INH | isoniazid |
| IP | intraperitoneal |
| IT | intrathecal |
| ITP | idiopathic thrombocytopenic purpura |
| IV | intravenous |
| IV/PO | IV or PO |
| IVDA | intravenous drug abuser |
| IVIG | intravenous immunoglobulin |
| JE | Japanese encephalitis |
| kg | kilogram |
| L | liter |
| LCM | lymphocytic choriomeningitis |
| LDH | lactate dehydrogenase |
| LFTs | liver function tests |
| LGV | lymphogranuloma venereum |
| MAI | Mycobacterium avium-intracellulare |
| MCD | multicentric Castleman's disease |
| mcg | microgram |
| mcL | microliter |
| MDR | multidrug resistant |
| MDRSP | multidrug resistant S. pneumoniae |
| MERS | middle east respiratory syndrome |
| mg | milligram |
| mL | milliliter |
| MIC | minimum inhibitory concentration |
| min | minute |
| MMR | measles, mumps, rubella |
| MPD | myeloprolifevative disorder |
| MRI | magnetic resonance imaging |
| MRSA | methicillin-resistant S. aureus |
| MRSE | methicillin-resistant S. epidermidis |
| MS | multiple sclerosis |
| MSSA | methicillin-sensitive S. aureus |
| MSSE | methicillin-sensitive S. epidermidis |
| MTT | methlytetrathiazole |
| MU | million units |
| MVP | mitral valve prolapse |
| NDM | New Delhi metallo-β-lactamase |
| NHAP | nursing home acquired pneumonia |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NP | nosocomial pneumonia |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| OI | opportunistic infection |
| OPAT | outpatient parenteral antibiotic therapy |
| PAN | polyarteritis nodosa |
| PBC | primary biliary cirrhosis |
| PBS | protected brush specimen |
| PCEC | purified chick embryo cells |
| PCN | penicillin |
| PCP | Pneumocystis (carinii) jiroveci pneumonia |
| PCR | polymerase chain reaction |
| PD | peritoneal dialysis |
| PDA | patent ductus arteriosus |
| PE | Powassan encephalitis |
| PEP | post-exposure prophylaxis |
| PI | protease inhibitor |
| PID | pelvic inflammatory disease |
| PML | progressive multifocal leukoencephalopathy |
| PMN | polymorphonuclear leucocytes |
| PO | oral |
| PPD | tuberculin skin test |
| PPIs | proton pump inhibitors |
| PPNG | penicillinase-producing N. gonorrhoeae |
| PTBM | partially treated bacterial meningitis |
| PVE | prosthetic valve endocarditis |
| PVL | Panton-Valentine leukocidin |
| PZA | pyrazinamide |
| q__d | every __ days |
| q__h | every __ hours |
| q month | once a month |
| q week | once a week |
| RA | rheumatoid arthritis |
| RBC | red blood cells |
| RE | regional ileitis (Crohn's disease) |
| RMSF | rocky mountain spotted fever |
| RSV | respiratory syncytial virus |
| RUQ | right upper quadrant |
| RVA | rabies vaccine absorbed |
| SARS | severe acute respiratory syndrome |
| SBE | subacute bacterial endocarditis |
| SCID | severe combined immune deficiency |
| SGOT/SGPT | serum transaminases |
| SLE | systemic lupus erythematosus |
| St. LE | Saint Louis encephalitis |
| SOT | solid organ transplant |
| sp. | species |
| SPB | spontaneous bacterial peritonitis |
| SPEP | serum protein electrophoresis |
| SQ | subcutaneous |
| STD | sexually transmitted diseases |
| TA | temporal arteritis |
| TAA | teichoic acid antibody titers |

| | |
|---|---|
| TAH/BSO | total abdominal hysterectomy/bilateral salpingoophorectomy |
| TB | M. tuberculosis |
| TDF | tenofovir disoproxil fumarate |
| TEE | transesophageal echocardiogram |
| TEN | toxic epidermal necrolysis |
| TID | three times per day |
| TMP | trimethoprim |
| TMP–SMX | trimethoprim-sulfamethoxazole |
| TPN | total parenteral nutrition |
| TRNG | tetracycline-resistant N.gonorrhoeae |
| TSS | toxic shock syndrome |
| TTE | transthoracic echocardiogram |
| TTP | thrombotic thrombocytopenic purpura |
| TURP | transurethral resection of prostate |
| UC | ulcerative colitis |
| UTI | urinary tract infection |
| VA | ventriculoatrial |
| VAP | ventilator associated pneumonia |
| VCA | viral capsid antigen |
| VEE | Venezuelan equine encephalitis virus |
| VISA | vancomycin intermediate S. aureus |
| VLM | visceral larval migrans |
| VP | ventriculoperitoneal |
| VRE | vancomycin resistant enterococci |
| VRSA | vancomycin resistant S. aureus |
| VSE | vancomycin-sensitive enterococci |
| VZV | varicella zoster virus |
| WBC | white blood cells |
| WEE | western equine encephalitis |
| WNE | west nile encephalitis |
| XMRV | xenotropic murine leukemia related virus |
| yrs | years |

Chapter 1

# Overview of Antimicrobial Therapy

**Burke A. Cunha, MD**
**Cheston B. Cunha, MD**

# Overview of Antimicrobial Therapy

## FACTORS IN ANTIBIOTIC SELECTION

**A. Spectrum.** Antibiotic spectrum refers to the range of microorganisms an antibiotic is usually effective against, and is the basis for empiric antibiotic therapy (Chapter 2). Antibiotic susceptibilities are a guide to predicting antibotic effectiveness in blood/well vascularized organs. *In vitro* testing does not always predict *in vivo* effectiveness (see p. 6).

**B. Tissue Penetration.** Antibiotics that are effective against a microorganism in vitro but unable to reach the site of infection are of little or no benefit to the host. Antibiotic tissue penetration depends on properties of the antibiotic, e.g., lipid solubility, molecular size and tissue, e.g., adequacy of blood supply, presence of inflammation. Antibiotic tissue penetration is rarely problematic in acute infections due to increased microvascular permeability from local release of chemical inflammatory mediators. In contrast, chronic infections, e.g., chronic pyelonephritis, chronic prostatitis, chronic osteomyelitis and infections caused by intracellular pathogens often rely on chemical properties of an antibiotic, e.g., high lipid solubility, small molecular size for adequate tissue penetration. Antibiotics cannot be expected to eradicate organisms from areas that are difficult to penetrate or have impaired blood supply, such as abscesses, which usually require surgical drainage for cure. In addition, implanted foreign materials associated with infection usually need to be removed for cure, since microbes causing infections associated with prosthetic joints, shunts, and intravenous lines produce a slime/biofilm on plastic/metal surfaces that permits organisms to survive despite antimicrobial therapy.

**C. Antibiotic Resistance.** Bacterial resistance to antimicrobial therapy may be classified as natural/intrinsic or acquired relative or absolute. Pathogens not covered by the usual spectrum of an antibiotic are termed *naturally/intrinsically* resistant, e.g., 25% of S. pneumoniae are naturally resistant to macrolides; *acquired* resistance refers to a previously susceptible pathogen that is no longer susceptible to an antibiotic, e.g., ampicillin resistant H. influenzae. Organisms with *intermediate level (relative)* resistance manifests as an increase in minimum inhibitory concentrations (MICs), but are susceptible if achievable serum/tissue concentrations > MIC, e.g., penicillin-resistant S. pneumoniae. In contrast, organisms with *high level (absolute)* resistance manifests as a sudden increase in MICs during therapy, and cannot be overcome by higher-than-usual antibiotic doses, e.g., gentamicin-resistant P. aeruginosa. Most acquired antibiotic resistance is *agent-specific*, not a class specific, and is usually limited to one or two species. Resistance is *not* related, per se, to volume or duration of use. Some antibiotics have little resistance potential i.e., "low resistance" potential even when used in high volume; other antibiotics can induce resistance, e.g., "high resistance" potential with little use.

**The Antibiotic Resistance Potential of each antibiotic is included in each Drug Summary (see Chapter 11).**

**Table 1.1. Resistance Potential of Selected Antibiotics**

| "High Resistance Potential" Antibiotics | Usual Organism(s) Resistant for Each Antibiotic | Preferred "Low Resistance Potential" Antibiotic Alternatives in Same Class | Preferred "Low Resistance Potential Antibiotic Alternatives in Different Classes |
|---|---|---|---|
| **Aminoglycosides** | | | |
| Gentamicin or Tobramycin | P. aeruginosa | Amikacin | Levofloxacin or Colistin or Cefepime |
| **Cephalosporins** | | | |
| Ceftazidime | P. aeruginosa | Cefepime | Levofloxacin or Colistin |
| **Tetracyclines** | | | |
| Tetracycline | S. pneumoniae S. aureus | Doxycycline or Minocycline | Levofloxacin or Moxifloxacin |
| **Quinolones** | | | |
| Ciprofloxacin | S. pneumoniae | Levofloxacin or Moxifloxacin | Doxycycline |
| Ciprofloxicin | P. aeruginosa | Levofloxican | Amikacin or Colistin or Cefepime |
| **Glycopeptides** | | | |
| Vancomycin | MSSA MRSA | None | Linezolid or Daptomycin or Minocycline or Tigecycline |
| **Carbapenems** | | | |
| Imipenem | P. aeruginosa | Meropenem or Doripenem | Amikacin or Cefepime or Colistin |

**Table 1.1. Resistance Potential of Selected Antibiotics** (Cont'd)

| "High Resistance Potential" Antibiotics | Usual Organism(s) Resistant for Each Antibiotic | Preferred "Low Resistance Potential" Antibiotic Alternatives in Same Class | Preferred "Low Resistance Potential Antibiotic Alternatives in Different Classes |
|---|---|---|---|
| **Macrolides** | | | |
| Azithromycin | S. pneumoniae | None | Doxycycline or Levofloxacin or Moxifloxacin |
| **Dihydrofolate Reductase Inhibitors** | | | |
| TMP-SMX | S. pneumoniae | None | Doxycycline or Levofloxacin or Moxifloxacin |

Adapted from: Cunha BA. Antibiotic Resistance: Effective Control Strategies. Lancet 357:1307-1308, 2001; Cunha BA (Ed). Antibiotic Essentials (12th ed) Jones & Bartlett. Sudbury, MA 2013. p. 521-719

**D. Safety Profile.** Whenever possible, avoid antibiotics with serious/frequent side effects.

**E. Cost.** Switching early from IV to PO antibiotics is the single most important cost saving strategy in hospitalized patients, as the institutional cost of IV administration (~$10/dose) may exceed the cost of the antibiotic itself. Antibiotic costs can also be minimized by using antibiotics with long half-lives, and by choosing monotherapy over combination therapy.

## FACTORS IN ANTIBIOTIC DOSING

**A. Renal Insufficiency.** Since most antibiotics eliminated by the kidneys have a wide "toxic-to-therapeutic ratio," dosing strategies are frequently based on formula-derived estimates of creatinine clearance, rather than precise quantitation of glomerular filtration rates. Dosage adjustments are especially important for antibiotics with narrow toxic-to-therapeutic ratios, and for patients who are receiving other nephrotoxic medications or have preexisting renal disease.

1. **Initial and Maintenance Dosing in Renal Insufficiency.** For drugs eliminated by the kidneys, ***the initial dose is unchanged***, and the ***maintenance dose/dosing interval are modified in proportion to the degree of renal insufficiency (CrCl)***. Dosing adjustment problems in renal insufficiency can be circumvented by selecting an antibiotic with a similar spectrum that is eliminated by the hepatic route.

2. **Aminoglycoside Dosing.** Single daily dosing—adjusted for the degree of renal insufficiency after the loading dose is administered–has virtually eliminated the nephrotoxic potential of aminoglycosides, and is recommended for all patients, including the critically ill (a possible exception is enterococcal endocarditis, where gentamicin dosing every 8 hours may be preferable). Aminoglycoside-induced tubular dysfunction is best assessed by quantitative renal tubular cast counts in urine, which more accurately reflect aminoglycoside nephrotoxicity than serum creatinine.

**Table 1.2. Dosing Strategies in Hepatic/Renal Insufficiency***

**Hepatic Insufficiency**
- Decrease total daily dose of hepatically-eliminated antibiotic by 50% in presence of clinically severe liver disease.
- **Alternative: Use antibiotic eliminated/inactivated by the renal route in usual dose.**

**Renal Insufficiency (Examples)**
- If creatinine clearance ~ 40–60 mL/min, decrease dose of renally-eliminated antibiotic by 50% and maintain the usual dosing interval.
- If creatinine clearance ~10–40 mL/min, decrease dose of renally-eliminated antibiotic by 50% and double the dosing interval.
- **Alternative: Use antibiotic eliminated/inactivated by the hepatic route in usual dose.**

| Major Route of Elimination | | | |
|---|---|---|---|
| **Hepatobiliary** | | **Renal** | |
| Chloramphenicol | Pyrazinamide | Most β-lactams | Amantadine |
| Cefoperazone | Linezolid | β-lactam/β-lactamase inhibitors | Rimantadine |
| Ceftriaxone† | Tedizolid | Aminoglycosides | Acyclovir |
| Doxycycline | Itraconazole | TMP–SMX | Valacyclovir |
| Minocycline | Isavuconazole | Azthreonam | Famciclovir |
| Telithromycin | Caspofungin | Carbapenems | Valganciclovir |
| Moxifloxacin | Micafungin | Polymyxin B | Oseltamavir |
| Macrolides | Anidulafungin | Colistin | Zanamavir |
| Nafcillin | Ketoconazole | Ciprofloxacin | Peramavir |
| Clindamycin | Voriconazole | Levofloxacin | Tetracycline |
| Metronidazole | Posaconazole | Gatifloxacin | Oxacillin |
| Tigecycline | | | Daptomycin |

**Table 1.2. Dosing Strategies in Hepatic/Renal Insufficiency*** (Cont'd)

| Major Route of Elimination | | |
|---|---|---|
| **Hepatobiliary** | **Renal** | |
| Quinupristin/dalfopristin | Gemifloxacin | Telavancin |
| Isoniazid | Flucytosine | Dalbavancin |
| Ethambutol | Fluconazole | Oritavancin |
| Rifampin | Amphotericin | Ceftaroline fosamil |
| | Vancomycin | Fosfomycin |
| | Cycloserine | Nitrofurantoin |

* CrCl (mL/min) = [(140 – age) × weight (kg)] / [72 × serum creatinine (mg/dL)]. Multiply by 0.85 if female. It is important to recognize that due to age-dependent declines in renal function, elderly patients with "normal" serum creatinines may have CrCls requiring dosage adjustment. For example, a 70-year-old, 50-kg female with a serum creatinine of 1.2 mg/dL has an estimated CrCl of 34 mL/min.

† ~½ eliminated renally.

**B. Hepatic Insufficiency.** Antibiotic dosing for patients with hepatic dysfunction is problematic, since there is no hepatic counterpart to the serum creatinine to accurately assess liver function. In practice, antibiotic dosing is based on clinical assessment of the severity of liver disease. For practical purposes, dosing adjustments are usually not required for mild or moderate hepatic insufficiency. For severe hepatic insufficiency, dosing adjustments are usually made for antibiotics with hepatotoxic potential.

**C. Combined Renal and Hepatic Insufficiency.** There are no good dosing adjustment guidelines for patients with hepatorenal insufficiency. If renal insufficiency is worse than hepatic insufficiency, antibiotics eliminated by the liver are often administered at half the total daily dose. If hepatic insufficiency is more severe than renal insufficiency, renally eliminated antibiotics are usually administered and dosed in proportion to renal function.

**D. Mode of Antibiotic and Excretion/Excretory Organ Toxicity.** The mode of elimination/excretion does not predispose to excretory organ toxicity per se, e.g., nafcillin (hepatically eliminated) is not hepatotoxic, and it's main side effect is nephrotoxicity (interstitial nephritis). In contrast, oxacillin (renally eliminated), is not nephrotoxic and it's main side effect is hepatotoxicity (hepatitis).

## MICROBIOLOGY AND SUSCEPTIBILITY TESTING

**A. Overview.** In vitro susceptibility testing provides information about microbial sensitivities of a pathogen to various antibiotics and is useful in guiding therapy.

**B. Limitations of Microbiology Susceptibility Testing**

1. ***In vitro* data do not differentiate between colonizers and pathogens.** Before responding to a culture report from the microbiology laboratory, it is important to determine whether the organism is a pathogen or a colonizer in the clinical context. As a rule, colonization should not be treated.

2. ***In vitro* data do not necessarily translate into *in vivo* efficacy.** Reports which indicate an organism is "susceptible" or "resistant" to a given antibiotic in vitro do not necessarily reflect in vivo activity.

3. ***In vitro* susceptibility testing is dependent on the microbe, methodology, and antibiotic concentration.** *In vitro* susceptibility testing by the microbiology laboratory *assumes* the isolate was recovered from *blood*, and is being exposed to *serum* concentrations of an antibiotic given in the *usual* dose. Since some body sites e.g., bladder urine contains higher antibiotic concentrations than found in serum, and other body sites. CSF contain lower antibiotic concentrations than found in serum, i.e., *in vitro* data may be misleading for non-bloodstream infections. For example, a Klebsiella pneumoniae isolate obtained from the CSF may be reported as "sensitive" to cefazolin even though cefazolin does not penetrate the CSF. Likewise, E. coli and Klebsiella urinary isolates are often reported as "resistant" to ampicillin/sulbactam despite *in vivo* efficacy, due to high antibiotic concentrations in the urinary tract. Antibiotics should be prescribed at the usual recommended doses; attempts to lower cost by reducing dosage may decrease antibiotic efficacy e.g., cefoxitin 2 gm IV inhibits ~ 85% of B. fragilis isolates, whereas 1 gm IV inhibits only ~ 20% of strains.

**Table 1.3. Antibiotic-Organism Combinations for Which *In Vitro* Susceptibility Testing Does Not Predict *In Vivo* Effectiveness[1]**

| Antibiotic | "Susceptible" Organism |
|---|---|
| Penicillin | H. influenzae, Yersinia pestis |
| TMP–SMX | Klebsiella, Enterococci, Bartonella |
| Polymyxin B | Proteus, Salmonella |
| Imipenem | Stenotrophomonas maltophilia[2] |
| Gentamicin | Mycobacterium tuberculosis |
| Vancomycin | Erysipelothrix rhusiopathiae |
| Aminoglycosides | Streptococci, Salmonella, Shigella |
| Clindamycin | Fusobacteria, Clostridia, enterococci, Listeria |
| Macrolides | P. multocida |
| 1st, 2nd generation cephalosporins | Salmonella, Shigella, Bartonella |

**Table 1.3. Antibiotic-Organism Combinations for Which *In Vitro* Susceptibility Testing Does Not Predict *In Vivo* Effectiveness[1]** (Cont'd)

| Antibiotic | "Susceptible" Organism |
|---|---|
| 3rd, 4th generation cephalosporins[4] | Enterococci, Listeria, Bartonella |
| All antibiotics | MRSA[3] |

1. *In vitro* susceptibility *does not* predict *in vivo* activity; susceptibility data cannot be relied upon to guide therapy for antibiotic-organism combinations in this table.
2. Formerly Pseudomonas.
3. In spite of apparent *in vitro* susceptibility of antibiotics against MRSA, only vancomycin, minocycline, quinupristin/dalfopristin, linezolid, tedizolid, daptomycin, ceftaroline fosamil, telavancin, dalbavancin, oritavancin, and tigecycline are effective *in vivo*.
4. Cefoperazone is the only cephalosporin with clinically useful anti-enterococcal activity against E. faecalis (VSE), *not* E. faecium (VRE).

**Table 1.4. CLSI Susceptibility Breakpoints for Streptococcus pneumoniae**

| Antibiotic | MIC (mcg/mL) | | |
|---|---|---|---|
| | Sensitive | Intermediate | Resistant |
| Amoxicillin (non-meningitis) | ≤ 2 | 4 | ≥ 8 |
| Penicillin (meningitis) | ≤ 0.06 | – | ≥ 0.12 |
| Penicillin (non-meningitis) | ≤ 2 | 4 | ≥ 8 |
| Doxycycline | ≤ 2 | 4 | ≥ 8 |
| Cefepime (non-meningitis) | ≤ 1 | 2 | ≥ 4 |
| Cefepime (meningitis) | ≤ 0.5 | 1 | ≥ 2 |
| Cefotaxime (non-meningitis) | ≤ 1 | 2 | ≥ 4 |
| Cefotaxime (meningitis) | ≤ 0.5 | 1 | ≥ 2 |
| Ceftriaxone (non-meningitis) | ≤ 1 | 2 | ≥ 4 |
| Ceftriaxone (meningitis) | ≤ 0.5 | 1 | ≥ 2 |
| Meropenem | ≤ 0.25 | 0.5 | ≥ 1 |
| Vancomycin | ≤ 1 | – | – |
| Moxifloxacin | ≤ 1 | 2 | ≥ 4 |
| Levofloxacin | ≤ 2 | 4 | ≥ 8 |
| Chloramphenicol | ≤ 4 | – | ≥ 8 |
| Clindamycin | ≤ 0.25 | 0.5 | ≥ 1 |
| Linezolid | ≤ 2 | – | – |

CLSI = Clinical and Laboratory Standards Institute (formerly NCCLS = National Committee for Clinical Laboratory Standards) M100–S20 (2010).

**C. Summary.** In vitro susceptibility testing is useful in most situations, but should not be followed blindly. Many factors need to be considered when interpreting in vitro microbiologic data, and infectious disease consultation is recommended for all but the most straightforward susceptibility interpretation problems. IV-to-PO switch changes using antibiotics of the same or other antibiotic class is best made when the oral antibiotic can achieve similar blood/tissue levels as the IV antibiotic.

## PK/PD AND OTHER CONSIDERATIONS IN ANTIMICROBIAL THERAPY

**A. Bactericidal vs. Bacteriostatic Therapy.** For most infections, bacteriostatic and bactericidal antibiotics inhibit/kill organisms at the same rate, and **should not be a factor in antibiotic selection**. Bactericidal antibiotics have an advantage in certain infections, such endocarditis, meningitis, and febrile leukopenia, but there are exceptions even in these cases.

**B. Monotherapy vs. Combination Therapy. Monotherapy is preferred to combination therapy for nearly all infections.** In addition to cost savings, monotherapy results in less chance of medication error and fewer missed doses/drug interactions. Combination therapy may be useful for drug synergy or for extending spectrum beyond what can be obtained with a single drug. However, since drug synergy is difficult to assess and the possibility of antagonism always exists, antibiotics should be combined for synergy if synergy is based on actual testing. Combination therapy is not effective in preventing antibiotic resistance, except in very few situations.

**Table 1.5. Combination Therapy and Antibiotic Resistance**

| |
|---|
| **Examples of Antibiotic Combinations That Prevent Resistance** |
| Anti-pseudomonal penicillin (carbenicillin) + aminoglycoside (gentamicin, tobramycin, amikacin) |
| Rifampin + other TB drugs (INH, ethambutol, pyrazinamide) |
| 5-flucytosine + amphotericin B |
| **Examples of Antibiotic Combinations That Do Not Prevent Resistance*** |
| TMP–SMX |
| Aztreonam + ceftazidime |
| Cefepime + ciprofloxacin |
| Aminoglycoside + imipenem |
| Most other antibiotic combinations |

* These combinations are often prescribed to prevent resistance when, in actuality, they do not.

**C. Pharmacokinetic (PK)/Pharmacodynamic (PD) Antibiotic Dosing Considerations**

**Table 1.6. Antibiotic Dosing: Pharmacokinetic/Pharmacodynamic (PK/PD) Considerations**

| Antibiotic-Dependent Antibiotics | | Optimal Dosing Strategies |
|---|---|---|
| **Concentration-Dependent Antibiotics (Cmax: MIC)** | | |
| • Quinolones<br>• Aminoglycosides<br>• Vancomycin (if MIC ≥ 1 mcg/ml) | • Doxycycline<br>• Tigecycline<br>• Colistin | **Use highest effective dose (without toxicity)** |
| **Time Dependent Antibiotics (T > MIC)** | | |
| • PCN concentrations > MIC for ≥ 60% of the dosing interval<br>• β-lactam concentrations > MIC for ≥ 75% of the dosing interval<br>• Carbapenems concentrations > MIC for ≥ 40% of the dosing interval<br>• Vancomycin (if MIC ≤ 1 mcg/ml) | | **Use high doses (which increase serum concentrations and also increases T > MIC for more of the dosing interval)** |
| **Other Antibiotics (Cmax: MIC/T>MIC and/or AUC $_{0\text{-}24}$/MIC)** | | |
| • Quinolones<br>> 125 (effective)<br>> 250 (more effective) | | **Use highest effective dose (without toxicity)** |

Adapted from: Roberts JA, Lipman J. Optimizing use of beta-lactam antibiotics in the critically ill. Semin Respir Crit Care Med 28:579-85,2007; Roberts JA, Pharm B, Kruger P, Paterson DL, Lipman J. Antibiotic resistance – What's dosing got to do with it? Crit Care Med 36:2433-40,2008; Roberts JA, Pharm B, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37:840-851,2009.

**D. Intravenous vs. Oral Switch Therapy.** Patients admitted to the hospital are usually started on IV antibiotic therapy, then switched to equivalent oral therapy after clinical improvement/defervescence (usually within 72 hours). **Advantages of early IV-to-PO switch programs include reduced cost, early hospital discharge, less need for home IV therapy, and virtual elimination of IV line infections**. Drugs well-suited for IV-to-PO switch or for treatment entirely by the oral route include doxycycline, minocycline, clindamycin, metronidazole, chloramphenicol, amoxicillin, trimethoprim-sulfamethoxazole, quinolones, and linezolid.

**Most infectious diseases should be treated orally unless the patient is critically ill, cannot take antibiotics by mouth, or there is no equivalent oral antibiotic**. If the patient is able to take/absorb oral antibiotics, there is no difference in clinical outcome using equivalent IV or PO antibiotics. It is more important to think in terms of antibiotic spectrum, bioavailability and tissue penetration, rather than route of administration. **Nearly all non-critically ill patients should be treated in part or entirely with oral antibiotics.** When

**Table 1.7. Bioavailability of Oral Antimicrobials**

| Bioavailability | Antimicrobials | | |
|---|---|---|---|
| Excellent (> 90%) | Amoxicillin<br>Cephalexin<br>Cefprozil<br>Cefadroxil<br>Clindamycin<br>Quinolones<br>Chloramphenicol | TMP<br>TMP–SMX<br>Doxycycline<br>Minocycline<br>Fluconazole<br>Metronidazole<br>Cycloserine | Linezolid<br>Tedizolid<br>Isavuconazole<br>Voriconazole<br>Rifampin<br>Isoniazid<br>Pyrazinamide |
| Good (60–90%) | Cefixime<br>Cefpodoxime<br>Ceftibuten<br>Cefuroxime | Valacyclovir<br>Famciclovir<br>Valganciclovir<br>Macrolides<br>Cefaclor<br>Nitrofurantoin | Ethambutol<br>5-Flucytosine<br>Posaconazole<br>Itraconazole (solution)<br>Nitazoxanide (with food) |
| Poor (< 60%) | Vancomycin<br>Acyclovir | Cefdinir<br>Cefditoren | Nitazoxanide (without food)<br>Fosfomycin |

switching from IV to PO therapy, **the oral antibiotic chosen should have the same spectrum/degree of activity against the presumed/known pathogen and achieve the same blood and tissue levels as the equivalent IV antibiotic.**

**E. OPAT (outpatient parenteral antibiotic therapy).** OPAT has been used to treat infections IV on an outpatient basis or to complete IV therapy begun during hospitalization. Preferred OPAT antibiotics are those with few adverse effects and those with a long serum half life (t1/2). The most frequently used OPAT antibiotics are ceftriaxone and vancomycin. Other agents with long t1/2 ideal for OPAT of Gram positive cSSSIs due to MRSA are telavancin 10 mg (IV) q 24 h, dalbavancin 1 gm (IV) × 1 doses then 500 mg (IV) × 1 dose 7 days later; tedizolid 200 mg (IV) q 24 h × 6 days, then 200 mg (PO) q 24 h × 6 days; and oritavancin 1200 mg (IV) × 1 dose. The alternative to OPAT is oral antibiotic therapy, e.g., for MRSA, minocycline or linezolid are equally efficacious as OPAT regimens.

**F. Duration of Therapy.** Most bacterial infections in normal hosts are treated with antibiotics for 1–2 weeks. The duration of therapy may need to be extended in patients with impaired immunity e.g., diabetes, SLE, alcoholic liver disease, neutropenia, diminished splenic function, etc., chronic bacterial infections e.g., endocarditis, osteomyelitis, chronic viral and fungal infections, or certain bacterial intracellular pathogens.

**Table 1.8. Infectious Diseases Requiring Prolonged Antimicrobial Therapy**

| Therapy | Infectious Diseases |
|---|---|
| 3 weeks | Lymphogranuloma venereum (LGV), syphilis (late latent), H. pylori, chronic prostatitis |
| 4 weeks | Chronic otitis media, chronic sinusitis, acute osteomyelitis, chronic pyelonephritis, brain abscess, SBE |
| 4–6 weeks | Acute bacterial endocarditis (S. aureus, Listeria, enterococcal), chronic osteomyelitis[4] |
| 3 months | Lung abscess[1], melioidosis, bartonella |
| 6 months | Pulmonary TB, extrapulmonary TB, actinomycosis[2], nocardia[3], prosthetic-related infections[5] |
| 12 months | Whipple's disease |
| > 12 months | Lepromatous leprosy, HIV, Q fever (SBE/PVE) |

1. Treat until resolved or until chest x-ray is normal/nearly normal and remains unchanged.
2. May require longer treatment; treat until resolved.
3. May require longer treatment in compromised hosts.
4. Adequate surgical debridement is required for cure.
5. Implanted foreign materials associated with infection (prosthetic valves, vascular grafts, joint replacements, hemodialysis shunts) should be removed as soon as possible after diagnosis. If removal is not feasible, then chronic suppressive therapy may be attempted, although clinical failure is the rule.

## EMPIRIC VS SPECIFIC ANTIBIOTIC THERAPY

*Always treat the usual pathogens* (related to body site flora) rather than just "covering the cultured organism" (*particularly if the specimen is not representative of the infected tissue)*.

**Examples:**

**Diabetic foot chronic osteomyelitis**

**Cover the usual pathogens:** GAS, GBS, common coliforms, S. aureus, and B. fragilis (*not P. aeruginosa*)

**Do not cover surface colonizers cultured:** P. aeruginosa, acinetobactor, VSE/VRE, Enterobacter, Burkholderia, Stenotrophomonas

Do not rely on deep ulcer/fistula cultures which represent skin flora (and are not reflective of bone pathogens, i.e., osteomyelitis). If P. aeruginosa is cultured from deep ulcer/fistula, do not cover only for P. aeruginosa. Over 95% of diabetic foot ulcers/fistulas will be culture positive from P. aeruginosa (due to P. aeruginosa colonization from wet socks, wet dressings, whirlpool baths). In aseptically collected bone specimens in the OR, P. aeruginosa is NOT a bone pathogen in diabetics with chronic osteomyelitis.

**Sacral decubitus ulcers (stage III/IV) = chronic osteomyelitis**

**Cover' the usual pathogens:** GAS, GBS, S. aureus, common coliforms, and B. fragilis.

**Do not cover surface colonizers cultured:** Stenotrophomonas, Acinetobacter, Enterobacter, P. aeruginosa, Burkholderia

**Table 1.9. Positive Blood Cultures vs. Bacteremia (MSSA, MRSA, CoNS)**

| Factors Favoring + Blood Cultures (not bacteremia) | Factors Favoring Bacteremia (not BC contaminants) |
|---|---|
| **MSSA/MRSA** (+ BCs skin contamination likely) with:<br>• Intermittently positive BCs<br>• Low level/low grade BC positivity (1/4 – 2/4 BCs +)<br>• TTP = > 2 days<br>• No clinical source of MSSA/MRSA bacteremia (CVC, abscesses, osteomyelitis, ABE) | **MSSA/MRSA Bacteremia** with:<br>• Persistently positive BCs<br>• High level/high grade bacteremia (3/4 – 4/4 BCs +)<br>• TTP = < 2 days<br>• Clinical source of MSSA/MRSA bacteremia clinically apparent (CVC, abscesses, osteomyelitis, ABE) |
| **CoNS** (skin contamination likely) with:<br>• Intermittently positive BCs<br>• Low level/low grade BC positivity (1/4 - 2/4 + BCs)<br>• TTP = > 2 days<br>• No clinical source of CoNS + BCs (CVC, implanted orthopedic/cardiac devices, prosthetic materials, severe/prolonged neutropenia) | **CoNS Bacteremia** (infection likely) with:<br>• Persistently positive BCs<br>• High level/high grade bacteremia (3/4 – 4/4 BCs +)<br>• TTP = > 2 days<br>• Clinical source of + BCs for CoNS apparent (CVC, implanted orthopedic/cardiac devices, prosthetic materials, severe/prolonged neutropenia) |

Implanted/prosthetic device associated: Dx = gallium or indium scans.
ABE: Dx = cardiac vegetation
Abscess Dx = Gallium scan or CT scan
CVC associated: Dx = SQ removed CVC tip culture with > 15 col of same organism as in BCs not drawn from the CVC
TTP = time to blood culture positivity

**Table 1.10. Clinical Features of Drug Fever**

**History**

Many but not all individuals are atopic

Patients have been on a sensitizing medication for days or years "without a problem"

**Physical exam**

Relative bradycardia

Fevers may be low- or high-grade, but usually range between 102°–104°F and may exceed 106°F

Patient appears "inappropriately well" for degree of fever

**Laboratory tests**

Elevated WBC count (usually with left shift)

Eosinophils almost always present, but eosinophilia is uncommon

Elevated erythrocyte sedimentation rate in majority of cases

Early, transient, mild elevations of serum transaminases (common)

Negative blood cultures (excluding contaminants)

## Relative Bradycardia*

### Temperature-Pulse Relationships

| Temperature | Appropriate Pulse Response (beats/min) | If Relative Bradycardia Pulse (beats/min) |
|---|---|---|
| 106°F (41.1°C) | 150 | < 140 |
| 105°F (40.6°C) | 140 | < 130 |
| 104°F (40.7°C) | 130 | < 120 |
| 103°F (39.4°C) | 120 | < 110 |
| 102°F (38.9°C) | 110 | < 100 |

* Relative bradycardia refers to heart rates that are inappropriately slow relative to body temperature (pulse must be taken simultaneously with temperature elevation). Applies to adult patients with temperature ≥ 102°F; does not apply to patients with second/third-degree heart block, pacemaker-induced rhythms, or those taking beta-blockers, diltiazem, or verapamil.

## ANTIBIOTIC FAILURE

### Table 1.11. Causes of Apparent/Actual Antibiotic Failure

**Microbiologic Factors**

- *In vitro* susceptibility but ineffective *in vivo*
- Antibiotic "tolerance" with gram-positive cocci
- Treating colonization (not infection)

**Antibiotic Factors**

- Inadequate coverage/spectrum
- Inadequate antibiotic blood tissue levels
- Decreased antibiotic activity in tissue
- Drug-drug interactions (inactivation/antagonism)

**Antibiotic Penetration Problems**

- Undrained abscess
- Foreign body-related infection
- Protected focus e.g., cerebrospinal fluid
- Organ hypoperfusion/diminished blood supply

**Noninfectious Diseases**

- Medical disorders mimicking infection e.g., SLE
- Drug fever

**Antibiotic-unresponsive Infectious Diseases**

- Viral or Fungal infections

## PITFALLS IN ANTIBIOTIC PRESCRIBING

- Do not **use antibiotics *to "treat" colonization or non-infectious/diseases.***
- **Overuse of combination therapy**. *Monotherapy is preferred over combination therapy unless compelling reasons prevail*, such as drug synergy or extended spectrum beyond what can be obtained with a single drug. *Monotherapy reduces the risk of drug interactions and side effects, and is usually less expensive.*
- **Use of antibiotics for persistent fevers**. For patients with persistent fevers on an antimicrobial regimens that appears to be failing, it is important to reassess the patient rather than add additional antibiotics. Causes of prolonged fevers include undrained septic foci, noninfectious medical disorders, and drug fevers. *Undiagnosed causes of leukocytosis/low-grade fevers should not be treated with prolonged courses of antibiotics.*
- **Inadequate surgical therapy**. Infections involving infected prosthetic materials or fluid collections e.g., abscesses often require surgical therapy for cure. *For infections such as chronic osteomyelitis, surgery is the only way to cure the infection*; antibiotics are useful only for suppression or to prevent local infectious complications.

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# Chapter 2

# Empiric Therapy Based on Clinical Syndrome

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This chapter is organized by clinical syndrome, patient subset, and in some cases, specific organism. Clinical summaries immediately follow each treatment grid. Unless otherwise specified, **this chapter pertains to infectious diseases and antimicrobial agents in adults. For pediatric infectious diseases and antimicrobial therapy see Chapter 7.** Therapeutic recommendations are based on antimicrobial effectiveness, reliability, cost, safety, and resistance potential. The antimicrobial dosages in this section represent the usual dosages for normal renal and hepatic function in adults. For any treatment category (i.e., preferred IV therapy, alternate IV therapy, PO therapy), ***in any given grid category drugs listed are equivalent alternatives and not ranked.*** Dosage adjustments, side effects, drug interactions, and other important prescribing information are

described in the individual drug summaries in Chapter 11. Use of any drug should be preceded by careful review of the package insert, which provides indications and dosing approved by the U.S. Food and Drug Administration. *"IV-to-PO Switch"* in the last column of the shaded title bar in each treatment grid indicates the clinical syndrome should be treated either by IV therapy alone or IV followed by PO therapy, but *not* by PO therapy alone. *"PO Therapy or IV-to-PO Switch"* indicates the clinical syndrome can be treated by IV therapy alone, PO therapy alone, or IV followed by PO therapy (unless otherwise indicated in the footnotes under each treatment grid). Most patients on IV therapy should be switched to PO equivalent therapy after clinical improvement.

## Empiric Therapy of CNS Infections

### **Acute Bacterial Meningitis (ABM)** (see Color Atlas for CSF Gram stains)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Normal host | N. meningitidis<br>H. influenzae<br>S. pneumoniae | Ceftriaxone 2 gm (IV) q12h × 2 weeks | Meropenem 2 gm (IV) q8h × 2 weeks<br>**or**<br>Cefotaxime 3 gm (IV) q6h × 2 weeks<br>**or**<br>Ceftizoxime 3 gm (IV) q6h × 2 weeks | Chloramphenicol 500 mg (PO) q6h × 2 weeks |
| Elderly or malignancy | Listeria monocytogenes plus usual meningeal pathogens in normal hosts | Before culture results<br>Ceftriaxone 2 gm (IV) q12h × 3 weeks<br>**plus**<br>Ampicillin 2 gm (IV) q4h × 3 weeks<br>After culture results<br>*Listeria present*<br>Ampicillin 2 gm (IV) q4h × 3 weeks<br>*Listeria not present*<br>Treat as normal host | After culture results<br>*Listeria present*<br>TMP–SMX 5 mg/kg (IV) q6h × 3 weeks<br>**or**<br>Meropenem 2 gm (IV) q8h × 3 weeks<br>**or**<br>Chloramphenicol 500 mg (IV) q6h × 3 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 3 weeks<br>*Listeria not present*<br>Treat as for normal host, above | For Listeria meningitis only<br>TMP–SMX 5 mg/kg (PO) q6h × 3 weeks<br>**or**<br>Chloramphenicol 500 mg (PO) q6h × 3 weeks<br>**or**<br>Linezolid 600 mg (PO) q12h × 3 weeks<br>For usual meningeal pathogens<br>Chloramphenicol 500 mg (PO) q6h × 3 weeks |

## **Acute Bacterial Meningitis (ABM)** (cont'd) (see Color Atlas for CSF Gram stains)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| CNS shunt infections (VA shunts) (Treat initially for MSSA; if later identified as MRSA, MSSE, or MRSE, treat accordingly) | S. aureus<br>S. epidermidis (coagulase-negative staphylococci) CoNS | MSSA/MSSE<br>Meropenem 2 gm (IV) q8h*<br>**or**<br>Ceftizoxime 3 gm (IV) q6h*<br>MRSA/MRSE<br>Linezolid 600 mg (IV) q12h* | MSSA/MSSE<br>Cefepime 2 gm (IV) q8h*<br>**or**<br>Cefotaxime 3 gm (IV) q6h*<br>MRSA/MRSE<br>Vancomycin 2 gm (IV) q12h*<br>**plus**<br>20 mg (IT) q24h until shunt removal | MSSE/MRSE<br>Linezolid 600 mg (PO) q12h*<br>MSSA/MRSA<br>Minocycline 100 mg (PO) q12h*<br>**or**<br>Linezolid 600 mg (PO) q12h* |
| CNS shunt infections (VP shunts) | E. coli<br>K. pneumoniae<br>Enterobacter<br>S. marcescens | Ceftriaxone 2 gm (IV) q12h × 2 weeks (after shunt removal) | TMP–SMX 5 mg/kg (IV) q6h × 2 weeks (after shunt removal) | TMP–SMX 5 mg/kg (PO) q6h × 2 weeks (after shunt removal) |
| | MDR<br>P. aeruginosa | Meropenem 2 gm (IV) q8h ± Colistin 5 mg/kg (IV) q8h<br>**plus**<br>Colistin 10 mg (IT) q24h × 2 weeks (after shunt removal) | Meropenem 2 gm (IV) q8h ± Amikacin 1 gm (IV) q24h<br>**plus**<br>Amikacin 10 mg (IT) q24h × 2 weeks (after shunt removal) | |
| | MDR<br>Acinetobacter baumanii | Meropenem 2 gm (IV) q8h<br>**or**<br>Ampicillin/sulbactam 4.5 gm (IV) q6h ± Colistin 5 mg/kg (IV) q8h<br>**plus**<br>Colistin 10 mg (IT) q12h × 2 weeks (after shunt removal) | Meropenem 2 gm (IV) q8h<br>**plus**<br>Ampicillin/sulbactam 4.5 gm (IV) q6h × 2 weeks (after shunt removal) | |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis.*

* Treat for 1 week after shunt removal.

**Clinical Presentation:** Abrupt onset of fever, headache, stiff neck.
**Diagnosis:** CSF gram stain/culture.

## Acute Bacterial Meningitis (Normal Hosts)

**Diagnostic Considerations:** Gram stain of centrifugated CSF is still the best diagnostic test. CSF antigen/CIE are unhelpful in establishing the diagnosis (many false-negatives). Blood cultures are positive for ABM pathogen in 80–90%. Typical CSF findings include a WBC count of 100–5000 cells/$mm^3$, elevated opening pressure, elevated protein and lactic acid levels (> 4–6 mmol/L), and a positive CSF gram stain. If the WBC is extremely high (> 20,000 cells/$mm^3$), suspect brain abscess with rupture into the ventricular system, and obtain a CT/MRI to confirm. S. pneumoniae meningitis is associated with cranial nerve abnormalities, mental status changes, and neurologic sequelae. With H. influenzae or S. pneumoniae meningitis, obtain a head CT/MRI to rule out other CNS pathology.
**Pitfalls:** If ABM is suspected, always perform lumbar puncture (LP) *before* obtaining a CT scan, since early antibiotic therapy is critical to prognosis. A CT/MRI should be obtained before LP *only* if a mass lesion/suppurative intracranial process is of primary concern, after blood cultures have been drawn. A stiff neck on physical examination has limited diagnostic value in the elderly, since nuchal rigidity may occur without meningitis (e.g., cervical arthritis) and meningitis may occur without nuchal rigidity. Recurrence of fever during the first week of H. influenzae meningitis is commonly due to subdural effusion, which usually resolves spontaneously over several days. Meningococcal meningitis may occur with or without meningococcemia. On gram stain, S. pneumoniae may be mistaken for H. influenzae, and Listeria may be mistaken for S. pneumoniae. Meningococcal meningitis may occur in those who received the meningococcal vaccine especially serogroup B not in meningococcal vaccine.
**Therapeutic Considerations:** Do not reduce meningeal antibiotic dosing as the patient improves. Repeat LP if the patient is not responding to antibiotics after 48 hours; lack of response may be due to therapeutic failure, relapse, or a Noninfectious CNS disorder. For S. pneumoniae meningitis, obtain penicillin MICs on all CSF isolates. Penicillin-resistant strains are susceptible to meningeal doses of beta-lactam antibiotics (e.g., ceftriaxone). All but the most highly penicillin-resistant pneumococci are still effectively treated with meningeal doses of beta-lactams. Highly resistant pneumococcal strains (rare in the CSF) may be treated for 2 weeks with meropenem 2 gm (IV) q8h, or, linezolid 600 mg (IV) q12h. Dexamethasone 0.15 mg/kg (IV) q6h × 4 days may be given to children with ABM to reduce the incidence/severity of neurologic sequelae, although the value of steroids in adult ABM is unclear; if used, give dexamethasone 30 minutes *before* the initial antibiotic dose.
**Prognosis:** Often fatal without treatment. Case-fatality rates in treated adults are 10–20%.
Neurological deficits on presentation are associated with a poor prognosis. Permanent neurological deficits are more frequent with S. pneumoniae than H. influenzae, even with prompt therapy. In meningococcal meningitis with meningococcemia, prognosis is related to the number of petechiae, with few or no neurological deficits in survivors.

## Acute Bacterial Meningitis (Elderly Malignancy)

**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture. ABM pathogens include usual pathogens in normal hosts plus Listeria monocytogenes, a gram-positive, aerobic, bacillus. Listeria is the most common ABM pathogen in patients with malignancies, and is a common pathogen in the elderly. With Listeria meningitis, CSF cultures are positive in 100%, but CSF gram stain is negative in 50%. Meningeal carcinomatosis is suggested by multiple cranial nerve abnormalities.
**Pitfalls:** "Diphtheroids" isolated from CSF should be speciated to rule out Listeria. Listeria are motile and hemolytic on blood agar plate, diphtheroids are not.

**Therapeutic Considerations:** Elderly patients and cancer patients with ABM require empiric coverage of Listeria plus other common pathogens in normal hosts (N. meningitidis, H. influenzae, S. pneumoniae). Third-generation cephalosporins are not active against Listeria.
**Prognosis:** Related to underlying health of host.

### Acute Bacterial Meningitis (CNS Shunt Infections)

**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture. S. epidermidis meningitis usually occurs only with infected prosthetic implant material (e.g., CNS shunt).
**Pitfalls:** Blood cultures are usually negative for shunt pathogens. CSF P. acnes cultures usually represent skin contamination. P. acnes is rarely a CNS shunt pathogen.
**Therapeutic Considerations:** 15% of S. epidermidis strains are resistant to nafcillin/clindamycin. In addition to systemic antibiotics in meningeal doses, adjunctive intraventricular/intrathecal antibiotics are sometimes given to control shunt infections before shunt removal. If vancomycin is used to treat CNS S. aureus (MSSA/MRSA) infection, I.T. dosing needed in addition to IV therapy.
**Prognosis:** Good if prosthetic material is removed.

## Acute Nonbacterial Meningitis/Chronic Meningitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Viral (aseptic) | EBV, LCM, Parvo B19, mumps, Enteroviruses, WNE. No effective therapy for most. For HIV (see Chapter 5) | | | |
| | HSV-1<br>HSV-2 | IV Therapy: Acyclovir 10 mg/kg (IV) q8h × 10 days<br>**or**<br>Ganciclovir 5 mg/kg (IV) q12h × 10 days. IV → PO: Valacyclovir 1 gm (PO) q8h × 10 days | | |
| | VZV | Acyclovir 10 mg/kg (IV) q8h × 10 days. IV → PO: Valacyclovir 2 gm (PO) q6h × 10 days | | |
| | HHV-6 | Gangciclovir: 5 mg/kg (IV) of 12h × 2 weeks<br>**or**<br>Foscarnet 90 mg/kg (IV) q12h × 2 weeks | | |
| Primary amebic meningo-encephalitis | Naegleria fowleri | Amphotericin B deoxycholate 1 mg/kg (IV) q24h until cured **plus** Amphotericin B deoxycholate 1 mg into ventricles via Ommaya reservoir q24h until cured | | |
| Lyme neuro-borreliosis | Borrelia burgdorferi | Ceftriaxone 1 gm (IV) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days | | Minocycline 100 mg (PO) q12h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then<br>100 mg (PO) q12h × 11 days |

## Acute Nonbacterial Meningitis/Chronic Meningitis (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Granulomatous amebic meningoencephalitis | Acanthamoeba | No proven treatment (amphotericin B, fluconazole, ketoconazole, itraconazole, flucytosine, rifampin, isoniazid, aminoglycosides, sulfonamides, pentamidine mostly with little success. Success reported in transplant recipient with IV pentamidine followed by itraconazole, and in AIDS patient with ketoconazole plus flucytosine) | | |
| Neurobrucellosis | Brucella sp. | Ceftriaxone 2 gm (IV) q12h **plus** Doxycycline 100 mg (PO) q12h **plus** Rifampin 600 mg (PO) q24th × 4 weeks, then Doxycycline **plus** Rifampin (same doses) × 4 weeks | | |
| TB | M. tuberculosis | INH 300 mg (IV/PO) q24h × 6 months **plus** Rifampin 600 mg (IV/PO) q24h × 6 months **plus** PZA 25 mg/kg (PO) q24h × 2 months **plus** EMB 15 mg/kg (PO) q24h (until susceptibilities known) | | |
| | | Begin with 4 drugs, as for pulmonary TB, but extend treatment for 9–12 months. Corticosteroids tapered over 1–2 months is helpful. If resistance is demonstrated or suspected, ID consultation is advised | | |
| Fungal<br>*Non-HIV* | Cryptococcus neoformans | Amphotericin B 0.7–1 mg/kg (IV) q24h × 2–6 weeks*<br>**plus**<br>Flucytosine 25 mg/kg (PO) q6h × 6 weeks*,<br>**followed by**<br>Fluconazole 800 mg (IV or PO) × 1 dose, then 400 mg (PO) q24h × 10 weeks* | Liposomal amphotericin B (AmBisome) 6 mg/kg (IV) q24h × 6–10 weeks†<br>**or**<br>Fluconazole 800 mg (IV or PO) × 1 dose, then 400 mg (PO) q24h × 10 weeks* | <u>PO therapy alone</u><br>Fluconazole may be given PO* |
| *HIV* | Cryptococcus neoformans (see p. 329)<br>Blastomyces dermatitidis (see p. 269) | | | |
| Chronic meningitis | Coccidioidomycosis (see p. 271), Histoplasmosis (see p. 269), Neurocysticercosis (see p. 262) | | | Do not treat empirically |

* The 6-week amphotericin B deoxycholate plus flucytosine regimen is the classical approach to achieving a durable cure. Anecdotal data suggest that a shorter course followed by Fluconazole × 10 weeks (or longer) may be successful. ID consultation is advised.

† Other lipid-associated Amphotericin B formulations at 3–5 mg/kg (IV) q24h may also be used (see p. 525).

‡ Levofloxacin 500 mg or Moxifloxacin 400 mg.

## Viral (Aseptic) Meningitis

**Clinical Presentation:** Headache, low-grade fever, mild meningismus, photophobia. Natalizumab (NTZ) predisposes to HSV and VZV meningitis or meningoencephalitis.

**Diagnostic Considerations:** Diagnosis by specific serological tests/viral culture. HSV-2 genital infections are often accompanied by mild CNS symptoms, which usually do not require anti-viral therapy. HSV-1, usually more severe, causes meningitis, meningoencephalitis, or encephalitis. HSV HHV-6, and WNE meningitis is indistinguishable clinically from other causes of viral meningitis. EBV meningitis is usually associated with clinical/laboratory features of EBV infectious mononucleosis; suspect the diagnosis in a patient with a positive monospot and unexplained meningoencephalitis. VZV meningitis is typically associated with cutaneous vesicular lesions (H. zoster). VZV meningitis may be later (weeks/months) followed by a CVA. LCM meningitis begins as a "flu-like" illness usually in the fall after hamster contact, and may have low CSF glucose. Enterovirus meningitis is often associated with a maculopapular rash, non-exudative pharyngitis, diarrhea, and rarely low CSF glucose. Aseptic meningitis due to mumps may present without parotid swelling ± acute deafness. Drug induced aseptic meningitis may have eosinophils in the CSF and little/no fever.

**Pitfalls:** Consider NSAIDs, TMP–SMX, and IV immunoglobulin as causes of drug induced aseptic meningitis.

**Therapeutic Considerations:** Treat specific pathogen.

**Prognosis:** Without neurological deficits, full recovery is the rule.

## Primary Amebic Meningoencephalitis (PAM) (Naegleria fowleri)

**Clinical Presentation:** Acquired by freshwater exposure containing the protozoa, often by jumping into a lake/pool. Affects healthy children/young adults. Organism penetrates cribriform plate and enters CSF. Symptoms occur within 7 days of exposure and may be indistinguishable from fulminant bacterial meningitis, including headache, fever, anorexia, vomiting, signs of meningeal inflammation, altered mental status, coma. May complain of unusual smell/taste sensations early in infection. CSF has RBCs and very low glucose.

**Diagnostic Considerations:** Diagnosis by demonstrating organism in CSF. Worldwide distribution. Free-living freshwater amoeba flourish in warmer climates. Key to diagnosis rests on clinical suspicion based on history of freshwater exposure in previous 1–2 weeks.

**Pitfalls:** CSF findings resemble bacterial meningitis, but RBCs present.

**Therapeutic Considerations:** Often fatal despite early treatment.

**Prognosis:** Frequently fatal.

## Granulomatous Amebic Meningoencephalitis (Acanthamoeba sp.)

**Clinical Presentation:** Insidious onset with focal neurologic deficits ± mental status changes, seizures, fever, headache, hemiparesis, meningismus, ataxia, visual disturbances. May be associated with Acanthamoeba keratoconjunctivitis, skin ulcers, or disseminated disease. Usually seen only in immunocompromised/debilitated patients.

**Diagnostic Considerations:** Diagnosis by demonstrating organism in brain biopsy specimen. CT/MRI shows mass lesions. "Stellate cysts" characteristic of Acanthamoeba. Worldwide distribution. Strong association with extended wear of contact lenses. Differentiate from N. fowleri by culture.

**Pitfalls:** Not associated with freshwater exposure, unlike primary amebic meningoencephalitis (Naegleria fowleri). Resembles subacute/chronic meningitis. No trophozoites in CSF. Skin lesions may be present for months before onset of CNS symptoms.

**Therapeutic Considerations:** No proven treatment. Often fatal despite early treatment.
**Prognosis:** Usually fatal.

## Neuroborreliosis (CNS Lyme Disease)

**Clinical Presentation:** May have mild neck stiffness not frank nucal rigidity. Low grade fever < 102˚F usually ~ 100–101˚F. Recent tick exposure. Often without rash. Sore throat in some, WBC count WNL, mildly ↑ AST/ALT in some.
**Diagnostic Considerations:** Diagnosed by demonstrating B. burgdorferi antibody production in the CNS. A CSF-to-serum IgM Lyme titer ratio > 1:1 is diagnostic.
**Pitfalls:** If CNS symptoms present with acute Lyme disease, rash may be absent and serology may be negative early. Neuroborreliosis cannot be reliably diagnosed using CSF-to-serum IgM if antibiotics given before the LP (antibiotics change the ratio and render it useless).
**Therapeutic Considerations:**
**Prognosis:** Related to underlying health of host. Prognosis with neuroborreliosis is good even with delayed treatment.

## TB Meningitis (Mycobacterium tuberculosis)

**Clinical Presentation:** Subacute onset of nonspecific symptoms. Fever usually present ± headache, nausea, vomiting. Acute presentation and cranial nerve palsies uncommon.
**Diagnostic Considerations:** Diagnosis by CSF AFB smear/culture; PCR of CSF is specific but not very sensitive. CSF may be normal but usually shows a mild lymphocytic pleocytosis, ↓ glucose, ↑ protein, and few RBCs. Adenosine deaminase (ADA) levels ↑.
**Pitfalls:** CSF may have PMN predominance early, before developing typical lymphocytic predominance. Eosinophils in CSF is not a feature of TB, and should suggest another diagnosis. Chest x-ray, PPD, and CSF smear/culture may be negative. ADA levels more highly elevated in TB than in ABM, listeria, neurobrucellosis.
**Therapeutic Considerations:** Dexamethasone 4 mg (IV or PO) q6h × 4–8 weeks is useful to reduce CSF inflammation if given early. Proteinaceous TB exudates may obstruct ventricles and cause hydrocephalus, which is diagnosed by CT/MRI and may require shunting.
**Prognosis:** Poor prognostic factors include delay in treatment, neurologic deficits, or hydrocephalus.

## Fungal (Cryptococcal) Meningitis (Cryptococcus neoformans)

**Clinical Presentation:** Insidious onset of nonspecific symptoms. Headache most common. Chronic cases may have CNS symptoms for weeks to months with intervening asymptomatic periods. Acute manifestations are more common in AIDS, chronic steroid therapy, lymphoreticular malignancies. 50–80% of patients are abnormal hosts.
**Diagnostic Considerations:** C. neoformans is the most common cause of fungal meningitis, and the only encapsulated yeast in the CSF to cause meningitis. Diagnosis by CSF India ink preparations showing encapsulated yeasts/cryptococcal latex antigen by latex agglutination/culture. Rule out HIV and other underlying immunosuppressive diseases.
**Pitfalls:** False + crytococcal antigen may occur with BBL Port-A-Cul transport vials**.** CSF latex antigen titer may not return to zero. Continue treatment until titers decline/do not decrease further, and until CSF culture is negative for cryptococci. India ink preparations showing encapsulated yeasts of CSF are useful for initial infection, but should not be relied on to diagnose recurrent episodes, since smears may be positive despite negative CSF cultures (dead cryptococci may remain in CSF for years). Diagnosis of recurrences rests on CSF culture.

**Therapeutic Considerations:** Treat until CSF is sterile or CSF latex antigen titer is zero or remains near zero on serial lumbar punctures. After patient defervesces on amphotericin B/5FC, switch to oral fluconazole × 10 weeks. Lipid amphotericin may be used if amphotericin B cannot be tolerated. HIV patients require life-long suppressive therapy with fluconazole 200 mg (PO) q24h. Expert consultation is strongly advised.

**Prognosis:** Good. Poor prognostic factors include no CSF pleocytosis, many organisms in CSF, and altered consciousness on admission.

## Encephalitis

| Subset | Usual Pathogens | IV-to-PO Switch | | |
|---|---|---|---|---|
| Herpes simplex | HSV-1<br>HSV-2 | IV Therapy: Acyclovir 10 mg/kg (IV) q8h × 10 days*<br>**or** Ganciclovir 5 mg/kg (IV) q12h × 10 days.*<br>IV → PO: Valacyclovir 1 gm (PO) q8h × 10 days* | | |
| Herpes zoster (VZV) | VZV | IV Therapy: Acyclovir (IV) q8h 10 mg/kg × 10 days.*<br>IV → PO: Valacyclovir 2 gm (PO) q6h × 10 days* | | |
| | HHV-6 | Ganciclovir 5 mg/kg (IV) q12h × 2 weeks **or** Foscarnet 90 mg/kg (IV) q12h × 2 weeks | | |
| Arbovirus | Mosquito borne: California encephalitis (CE), Western equine encephalitis (WEE), Venezuelan equine encephalitis (VEE), Eastern equine encephalitis (EEE), St. Louis encephalitis (St. LE), Japanese encephalitis (JE), West Nile encephalitis (WNE)<br>Tick borne: Powassan (PE), TBE (RSSE/CCE)<br>IV/PO Therapy: None | | | |
| Mycoplasma | M. pneumoniae | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 2 weeks | Minocycline 100 mg (IV) q12h × 2 weeks | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |
| Listeria | L. monocytogenes | Treat as for Listeria meningitis (see p. 18) but treat for 6–8 weeks | | |
| HIV | see Chapter 5 (p. 304) | | | |
| Transplants, HIV | CMV<br>HHV-6<br>Toxoplasma gondii | Transplants (see p. 160) HIV (see p. 304) | | |

* Severe HSV encephalitis may require a longer duration of therapy, i.e., 14-21 days.

## Herpes Encephalitis (HSV-1)

**Clinical Presentation:** Acute onset of fever and change in mental status without nuchal rigidity. Natalizumab (NTZ) predisposes to HSV meningitis, meningoencephalitis, or encephalitis.
**Diagnostic Considerations:** EEG is best early (< 72 hours) presumptive test, showing unilateral temporal lobe abnormalities. Brain MRI is abnormal before CT scan, which may require several days before a temporal lobe focus is seen. Definitive diagnosis is by CSF PCR for HSV-1 DNA. Usually presents as encephalitis or meningoencephalitis; RBCs in CSF ~ CNS damage Early/mild HSE may have no RBCs in CSF. CSF may have PMN predominance and low glucose levels, unlike other viral causes of meningitis.
**Pitfalls:** HSV-2 HSE rare in young adults; HSV-2 aseptic menigitis common HSV-2 HSE occurs in the elderly/immunosuppres. In normal hosts, HHV-6 may mimic HSV-1 encephalitis with a frontal/temporal focus on EEG.
**Therapeutic Considerations:** HSV is treatable. Treat as soon as possible, since neurological deficits may be mild and reversible early on, but severe and irreversible later.
**Prognosis:** Related to extent of brain injury and early anti-HSV therapy.

## Arboviral Encephalitis

**Clinical Presentation:** Acute onset of fever, headache, change/decrease in mental status days to weeks after insect bite (e.g., mosquito/tick). WNE is suggested by encephalitis ± with highly elevated ferritin levels ± new onset tremors or flaccid paralysis. EEG: diffuse slowing ± ↑ activity basal ganglia/thalamus. Prognosis ~ severity of neurologic deficits and degree/duration of relative lymphopenia/ferritin levels.
**Diagnostic Considerations:** Diagnosis by specific arboviral serology.
**Pitfalls:** Usually occurs in summer/fall. SIADH common, may occur.
**Therapeutic Considerations:** Only supportive therapy is available at present.
**Prognosis:** Permanent neurological deficits are common, but not predictable. May be fatal.

## Mycoplasma Encephalitis

**Clinical Presentation:** Acute onset of fever and change in mental status without nuchal rigidity.
**Diagnostic Considerations:** Diagnosis suggested by CAP with sore throat, otitis, E. multiforme, soft stools/diarrhea—with elevated IgM mycoplasma titers, and very high (≥ 1:1024) cold agglutinin titers. CSF shows mild mononucleosis/pleocytosis and normal/low glucose.
**Pitfalls:** CNS findings may overshadow pulmonary findings.
**Therapeutic Considerations:** Macrolides not effective for CNS infection. Doxycycline rapidly ↓ mycoplasma shedding in oropharyngeal secretions (vs. prolonged shedding with macrolides).
**Prognosis:** With early treatment, prognosis is good without neurologic sequelae.

## Listeria Encephalitis

**Clinical Presentation:** Fever/mental confusion (encephalitis/cerebritis) ± nuchal rigidity (meningoencephalitis).
**Diagnostic Considerations:** Diagnosis by LP. Suspect Listeria if CSF with "purulent profile" plus RBCs. Listeria seen on Gram stain of CSF in 50%; but culture positive in 100%.
**Pitfalls:** Not to be confused with other gram-positive bacilli (skin contaminants) isolated from CSF (diphtheroids). Listeria are motile and hemolytic on blood agar.
**Therapeutic Considerations:** 3rd generation cephalosporins not active against Listeria. In penicillin-tolerant patients, use meningeal dose ampicillin (not penicillin).
**Prognosis:** Good with early/adequate treatment. Related to degree of T lymphocyte dysfunction.

**CMV Encephalitis** (see p. 329)

**Toxoplasma Encephalitis** (see p. 331)

## Brain Abscess/Subdural Empyema/Cavernous Vein Thrombosis/Intracranial Suppurative Thrombophlebitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| **Brain Abscess (Single Mass Lesion)** | | | | |
| Open trauma | S. aureus (MSSA) Enterobacteriaceae P. aeruginosa | Meropenem 2 gm (IV) q8h × 2 weeks **or** Cefepime 2 gm (IV) q8h × 2 weeks | | Not applicable |
| Neurosurgical procedure (Treat initially for MSSA; if later identified as MRSA, MSSE, or MRSE, treat accordingly) | S. aureus S. epidermidis (CoNS) | MSSA Nafcillin 2 gm (IV) q4h × 2 weeks **or** MRSA/MSSE/MRSE Linezolid 600 mg (IV) q12h × 2 weeks **or** Minocycline 100 mg (IV) q12h × 2 weeks | | MSSA/MRSA/MSSE/MRSE Linezolid 600 mg (PO) q12h × 2 weeks **or** Minocycline 100 mg (PO) q12h × 2 weeks |
| Mastoid/otitic source | Enterobacter Proteus | Treat the same as for open trauma (see above) | | |
| Dental source | Oral anaerobes Actinomyces | Ceftriaxone 2 gm (IV) q12h × 2 weeks **plus** Metronidazole 500 mg (IV) q12h × 2 weeks | | Ceftizoxime 3 gm (IV) q6h × 2 weeks |
| Subdural empyema/sinus source | Oral anaerobes H. influenzae | Treat the same as for dental source (see above) | | |
| Cardiac source (ABE; right-to- left shunt) | S. aureus (MSSA) S. pneumoniae H. influenzae | Ceftriaxone 2 gm (IV) q12h × 2 weeks **or** Meropenem 2 gm (IV) q8h × 2 weeks | | |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h × 2 weeks **or** Vancomycin 2 gm (IV) q12h × 2 weeks **or** Minocycline 100 mg (IV) q12h × 2 weeks | | Linezolid 600 mg (PO) q12h × 2 weeks **or** Minocycline 100 mg (PO) q12h × 2 weeks |

## Brain Abscess/Subdural Empyema/Cavernous Vein Thrombosis/Intracranial Suppurative Thrombophlebitis (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| **Brain Abscess (Single Mass Lesion)** | | | | |
| Pulmonary source | Oral anaerobes Actinomyces | Ceftriaxone 2 gm (IV) q12h × 2 weeks **plus** Metronidazole 500 mg (IV) q12h × 2 weeks | | Ceftizoxime 3 gm (IV) q6h × 2 weeks |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis.* Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

**Clinical Presentation:** Variable presentation, with fever, change in mental status, cranial nerve abnormalities ± headache.
**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture. If brain abscess is suspected, obtain head CT/MRI. Lumbar puncture may induce herniation.
**Pitfalls:** CSF analysis is negative for bacterial meningitis unless abscess ruptures into ventricular system.
**Therapeutic Considerations:** Treatment with meningeal doses of antibiotics is required. Large single abscesses may be surgically drained; multiple small abscesses are best treated medically.
**Prognosis:** Related to underlying source and health of host.

### Brain Abscess (Mastoid/Otitic Source)

**Diagnostic Considerations:** Diagnosis by head CT/MRI demonstrating focus of infection in mastoid.
**Pitfalls:** Rule out associated subdural empyema.
**Therapeutic Considerations:** ENT consult for possible surgical debridement of mastoid.
**Prognosis:** Good. May require mastoid debridement for cure.

### Brain Abscess (Dental Source)

**Diagnostic Considerations:** Diagnosis by Panorex x-rays/gallium scan of jaw demonstrating focus in mandible/erosion into sinuses.
**Pitfalls:** Apical root abscess may not be apparent clinically.
**Therapeutic Considerations:** Large single abscess may be surgically drained. Multiple small abscesses are best treated medically. Treat until lesions on CT/MRI resolve or do not become smaller on therapy.
**Prognosis:** Good if dental focus is removed.

### Brain Abscess (Subdural Empyema/Sinus Source)

**Diagnostic Considerations:** Diagnosis by sinus films/CT/MRI to confirm presence of sinusitis/bone erosion (cranial osteomyelitis/epidural abscess). Usually from paranasal sinusitis.

**Pitfalls:** Do not overlook underlying sinus infection, which may need surgical drainage.
**Therapeutic Considerations:** Obtain ENT consult for possible surgical debridement of sinuses.
**Prognosis:** Good prognosis if sinus is drained.

### Brain Abscess (Cardiac Source; Acute Bacterial Endocarditis)

**Diagnostic Considerations:** Blood cultures often positive if brain abscess due to acute bacterial endocarditis (ABE) pathogen. Head CT/MRI shows multiple mass lesions.
**Pitfalls:** Do not overlook right-to-left cardiac shunt (e.g., patent foramen ovale, atrial septal defect) as source of brain abscess. Cerebral embolization results in aseptic meningitis in SBE, but septic meningitis/brain abscess in ABE (due to high virulence of pathogens).
**Therapeutic Considerations:** Multiple lesions suggest hematogenous spread. Use susceptibility of blood culture isolates to determine coverage. Meningeal doses are the same as endocarditis doses.
**Prognosis:** Related to location/size of CNS lesions and extent of cardiac valvular involvement.

### Brain Abscess (Pulmonary Source)

**Diagnostic Considerations:** Diagnosis suggested by underlying bronchiectasis, empyema, cystic fibrosis, or lung abscess in a patient with a brain abscess.
**Pitfalls:** Brain abscesses are most often due to chronic suppurative lung disease (e.g., bronchiectasis, lung abscess/empyema), not chronic bronchitis/AECB. If patient doesn't have a cardiopulmonary disorder predisposing to brain abscess, look for a clinically silent dental (apical root) abscess by gallium scan of jaws/Panorex dental x-rays.
**Therapeutic Considerations:** Lung abscess may need surgical drainage.
**Prognosis:** Related to extent/location of CNS lesions, drainage of lung abscess/empyema, and control of lung infection.

## Empiric Therapy of HEENT Infections

## Facial/Periorbital Cellulitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Facial cellulitis | Group A streptococci<br>H. influenzae | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Cefotaxime 2 gm (IV) q6h × 2 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 2 weeks | Respiratory quinolone* (IV) q24h × 2 weeks | Any oral 2nd or 3rd gen. cephalosporin × 2 weeks<br>**or**<br>Respiratory quinolone* (PO) q24h × 2 weeks |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

* Levofloxacin 500 mg or Moxifloxacin 400 mg.

**Clinical Presentation:** Acute onset of warm, painful, facial rash without discharge, swelling, pruritus.
**Diagnostic Considerations:** Diagnosis by clinical appearance. May spread rapidly across face. Purplish hue suggests H. influenzae.
**Pitfalls:** If periorbital cellulitis, obtain head CT/MRI to rule out underlying sinusitis/CNS involvement. If secondary to an abrasion after contact with a saliva-contaminated surface, consider Herpes gladiatorum; lesions are painful/edematous and do not respond to antibiotic therapy for cellulitis.
**Therapeutic Considerations:** May need to treat × 3 weeks in compromised hosts (chronic steroids, diabetics, SLE, etc.).
**Prognosis:** Good with early treatment; worse if underlying sinusitis/CNS involvement.

## Bacterial Sinusitis

| Subset | Usual Pathogens | IV Therapy (Hospitalized) | PO Therapy or IV-to-PO Switch (Ambulatory) |
|---|---|---|---|
| Acute | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Respiratory quinolone† (IV) q24h × 1–2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 1– 2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days | Respiratory quinolone† (PO) q24h × 1–2 weeks<br>**or**<br>Amoxicillin 1gm (PO) q8h × 10 days<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days*<br>**or**<br>Cephalosporin‡ (PO) × 2 weeks<br>**or**<br>Clarithromycin XL 1 gm (PO) q24h × 2 weeks |
| Chronic | Same as acute + oral anaerobes | Requires prolonged antimicrobial therapy (2–4 weeks) | |

Duration of therapy represents total time IV, PO, or IV + PO in adults. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours). See Chapter 7 for pediatric therapy.

* Loading dose is not needed PO if given IV with the same drug.

† Moxifloxacin 400 mg × 7 days or Levofloxacin 750 mg × 5 days.

‡ Cefdinir 300 mg q12h or Cefditoren 400 mg q12h or Cefixime 400 mg q12h or Cefpodoxime 200 mg q12h.

### Acute Bacterial Sinusitis

**Clinical Presentation:** Nasal discharge and cough frequently with headache, facial pain, and low-grade fever lasting > 10–14 days. Can also present acutely with high fever (≥ 104°F) and purulent nasal discharge ± intense headache lasting for ≥ 3 days. Other manifestations depend on the affected sinus: maxillary sinus: percussion tenderness of molars; maxillary toothache; local extension may cause osteomyelitis of facial bones with proptosis, retroorbital cellulitis, ophthalmoplegia; direct intracranial extension is rare; frontal sinus: prominent headache; intracranial extension may cause epidural/brain abscess, meningitis, cavernous sinus/superior sagittal sinus thrombosis; orbital extension may cause periorbital cellulitis; ethmoid sinus: eyelid edema and prominent tearing; extension may cause retro-orbital pain/periorbital cellulitis and/or cavernous sinus/superior sagittal sinus thrombosis; sphenoid

sinus: severe headache; extension into cavernous sinus may cause meningitis, cranial nerve paralysis [III, IV, VI], temporal lobe abscess, cavernous sinus thrombosis). Cough and nasal discharge are prominent in children.

**Diagnostic Considerations:** Diagnosis by sinus x-rays or CT/MRI showing complete sinus opacification, air-fluid levels, mucosal thickening. Consider sinus aspiration in immunocompromised hosts or treatment failures. In children, acute sinusitis is a clinical diagnosis; imaging studies are not routine.

**Pitfalls:** May present as periorbital cellulitis (obtain head CT/MRI to rule out underlying sinusitis). If CT/MRI demonstrates "post-septal" involvement, treat as acute bacterial meningitis. In children, transillumination, sinus tenderness to percussion, and color of nasal mucus are not reliable indicators of sinusitis.

**Therapeutic Considerations:** Treat for full course to prevent relapses/complications. Macrolides and TMP–SMX may predispose to drug-resistant S. pneumoniae (DRSP), and ≥ 30% of S. pneumoniae are naturally resistant to macrolides. Consider local resistance rates before making empiric antibiotic selections.

**Prognosis:** Good if treated for full course. Relapses may occur with suboptimal treatment. For frequent recurrences, consider radiologic studies and ENT consultation.

### Chronic Bacterial Sinusitis

**Clinical Presentation:** Generalized headache, fatigue, nasal congestion, post-nasal drip lasting > 3 months with little/no sinus tenderness by percussion. Local symptoms often subtle. Fever is uncommon.

**Diagnostic Considerations:** Sinus films and head CT/MRI are less useful than for acute sinusitis (chronic mucosal abnormalities may persist after infection is treated). Many cases of chronic maxillary sinusitis are due to a dental cause; obtain odontogenic x-rays if suspected.

**Pitfalls:** Clinical presentation is variable/nonspecific. Malaise and irritability may be more prominent than local symptoms. May be mistaken for allergic rhinitis. Head CT/MRI can rule out sinus tumor.

**Therapeutic Considerations:** Therapeutic failure/relapse is usually due to inadequate antibiotic duration, dose, or tissue penetration. Treat for full course. If symptoms persist after 4 weeks of therapy, refer to ENT for surgical drainage procedure.

**Prognosis:** Good if treated for full course. Relapses may occur with suboptimal treatment. For frequent recurrences, consider radiologic studies and ENT consultation.

## Keratitis

| Subset | Pathogens | Topical Therapy |
|---|---|---|
| Bacterial | S. aureus<br>S. pneumoniae<br>Bacillus cereus<br>M. catarrhalis<br>P. aeruginosa | Antibacterial eyedrops (ciprofloxacin, ofloxacin, or tobramycin/bacitracin/polymyxin B) hourly while awake × 2 weeks |
| Viral | HSV-1 | Trifluridine 1% solution 1 drop hourly while awake × 2 days, then 1 drop q6h × 14–21 days ***or*** viral ophthalmic topical ointment (e.g., vidarabine) at bedtime × 14–21 days |

## Keratitis (cont'd)

| Subset | Pathogens | Topical Therapy |
|---|---|---|
| Amebic | Acanthamoeba | Propamidine (0.1%), neomycin, gramicidin, or polymyxin B eyedrops hourly while awake × 1–2 weeks **or** polyhexamethylene biguanide (0.02%) eyedrops hourly while awake × 1–2 weeks **or** chlorhexidine (0.02%) eyedrops hourly while awake × 1–2 weeks |

**Clinical Presentation:** Corneal haziness, infiltrates, or ulcers.
**Diagnosis:** Appearance of corneal lesions/culture.

### Bacterial Keratitis

**Diagnostic Considerations:** Usually secondary to eye trauma. Always obtain ophthalmology consult.
**Pitfalls:** Be sure to culture ulcer. Unusual organisms are common in eye trauma.
**Therapeutic Considerations:** Treat until lesions resolve. Ointment easier/lasts longer than solutions. Avoid topical steroids.
**Prognosis:** Related to extent of trauma/organism. S. aureus, B. cereus, P. aeruginosa have worst prognosis.

### Viral Keratitis (HSV-1)

**Diagnostic Considerations:** "Dendritic" corneal ulcers characteristic. Obtain ophthalmology consult.
**Pitfalls:** Small corneal ulcers may be missed without fluorescein staining.
**Therapeutic Considerations:** Treat until lesions resolve. Oral acyclovir is not needed. Avoid ophthalmic steroid ointment.
**Prognosis:** Good if treated early (before eye damage is extensive).

### Amebic Keratitis (Acanthamoeba)

**Diagnostic Considerations:** Usually associated with extended use of soft contact lenses. Corneal scrapings are positive with calcofluor staining. Acanthamoeba keratitis is painful with typical circular, hazy, corneal infiltrate. Always obtain ophthalmology consult.
**Pitfalls:** Do not confuse with HSV-1 dendritic ulcers. Avoid topical steroids.
**Therapeutic Considerations:** If secondary bacterial infection, treat as bacterial keratitis.
**Prognosis:** No good treatment. Poor prognosis.

## Conjunctivitis

| Subset | Usual Pathogens | PO/Topical Therapy |
|---|---|---|
| Bacterial | M. catarrhalis<br>H. influenzae<br>S. pneumoniae<br>N. meninsititis<br>N. gonorrhea | Antibacterial eyedrops (ciprofloxacin, ofloxacin, moxifloxacin, or tobramycin/bacitracin/polymyxin B) q12h × 1 week plus antibacterial ointment (same antibiotic) at bedtime × 1 week |

## **Conjunctivitis** (cont'd)

| Subset | Usual Pathogens | PO/Topical Therapy |
|---|---|---|
| Viral | Adenovirus | Not applicable |
| | VZV | Valacyclovir 1 gm (PO) q8h × 10–14 days **or** Famciclovir 500 mg (PO) q8h × 10–14 days |
| Chlamydial | C. trachomatis (trachoma) | Doxycycline 100 mg (PO) q12h × 1–2 weeks **or** Azithromycin 1 gm (PO) × 1 dose |

### Bacterial Conjunctivitis

**Clinical Presentation:** Profuse, purulent exudate from conjunctiva.
**Diagnostic Considerations:** Reddened conjunctiva; culture for specific pathogen.
**Pitfalls:** Do not confuse with allergic conjunctivitis, which itches and has a clear discharge.
**Therapeutic Considerations:** Obtain ophthalmology consult. Ointment lasts longer in eye than solution. Do not use topical steroids without an antibacterial.
**Prognosis:** Excellent when treated early, with no residual visual impairment.

### Viral Conjunctivitis

#### *Adenovirus*

**Clinical Presentation:** Reddened conjunctiva, watery discharge, negative bacterial culture.
**Diagnostic Considerations:** Diagnosis by cloudy/steamy cornea with negative bacterial cultures. Clue is punctate infiltrates with a cloudy cornea. Extremely contagious; careful handwashing is essential. Obtain viral culture of conjunctiva for diagnosis.
**Pitfalls:** Pharyngitis a clue to adenoviral etiology (pharyngoconjunctival fever).
**Therapeutic Considerations:** No treatment available. Usually resolves in 1–2 weeks.
**Prognosis:** Related to degree of corneal haziness. Severe cases may take weeks to clear.

#### *VZV Ophthalmicus*

**Diagnostic Considerations:** Vesicles on tip of nose predict eye involvement.
**Pitfalls:** Do not miss vesicular lesions in external auditory canal in patients with facial palsy (Ramsey-Hunt Syndrome).
**Therapeutic Considerations:** Obtain ophthalmology consult. Topical steroids may be used if given with anti-VZV therapy.
**Prognosis:** Good if treated early with systemic antivirals.

### Trachoma (C. trachomatis) Conjunctivitis

**Diagnostic Considerations:** Diagnosis by direct fluorescent antibody (DFA)/culture of conjunctiva.
**Pitfalls:** Do not confuse bilateral, upper lid, granular conjunctivitis of Chlamydia with viral/bacterial conjunctivitis, which involves both upper and lower eyelids.
**Therapeutic Considerations:** Ophthalmic erythromycin treatment is useful for neonates. Single-dose azithromycin may be associated with recurrence.
**Prognosis:** Excellent with early treatment.

## Chorioretinitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Viral | CMV | See p. 327 | | |
| Fungal† | Candida albicans | Fluconazole 800 mg (IV) × 1 dose, then 400 mg (IV) q24h × 2 weeks‡ **or** Voriconazole 6 mg/kg (IV) q12h × 1 day, then 4 mg/kg (IV) q12h × 2 weeks‡ | Amphotericin B 0.6 mg/kg (IV) q24h for total of 1 gm **or** Lipid amphotericin (see p. 525) (IV) q24h × 3 weeks‡ | Fluconazole 800 mg (PO) × 1 dose, then 400 mg (PO) q24h × 2 weeks*‡ |
| Protozoal | Toxoplasma gondii | IV Therapy<br>Not applicable | PO Therapy<br>Pyrimethamine 75 mg (PO) × 1 dose, then 25 mg (PO) q24h × 6 weeks **plus either** Sulfadiazine 1 gm (PO) q6h × 6 weeks **or** Clindamycin 300 mg (PO) q8h × 6 weeks | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† Treat IV or IV-to-PO switch.

* Loading dose is not needed PO if given IV with the same drug.

‡ Duration of therapy is approximate and should be continued until resolution of infection. Close follow-up with an ophthalmologist is required.

### CMV Chorioretinitis (see p. 327)

### Candida Chorioretinitis

**Clinical Presentation:** Small, raised, white, circular lesions on retina.

**Diagnostic Considerations:** Fundus findings similar to white, raised colonies on blood agar plates.

**Pitfalls:** Candida endophthalmitis signifies invasive/disseminated candidiasis.

**Therapeutic Considerations:** Treat as disseminated candidiasis.

**Prognosis:** Good with early treatment.

### Toxoplasma Chorioretinitis

**Clinical Presentation:** Grey/black pigmentation of macula.

**Diagnostic Considerations:** Diagnosis by IgM IFA toxoplasmosis titers.

**Pitfalls:** Unilateral endophthalmitis usually indicates acquired toxoplasmosis; congenital toxoplasmosis is usually bilateral.

**Therapeutic Considerations:** Obtain ophthalmology consult. Treat only acute/active toxoplasmosis with visual symptoms; do not treat chronic chorioretinitis. Add folinic acid 10 mg (PO) q24h to prevent folic acid deficiency.

**Prognosis:** Related to degree of immunosuppression.

## Endophthalmitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Bacterial<br><br>(Treat initially for MSSA; if later identified as MRSA or S. epidermidis, treat accordingly) | Streptococci<br>H. influenzae<br>S. aureus (MSSA) | **Intravitreal injection:** Cefepime 2.25 mg/0.1 mL sterile saline × 1 dose; repeat × 1 if needed in 2–3 days **plus** **Subconjunctival injection:** Cefepime 100 mg/0.5 mL sterile saline q24h × 1–2 weeks **plus** Levofloxacin 500 mg (IV/PO) q12h × 1–2 weeks | | |
| | S. aureus (MRSA)<br>S. epidermidis (CoNS) | **Intravitreal injection:** Vancomycin 1 mg/0.1 mL sterile saline × 1 dose; repeat × 1 if needed in 2–3 days **plus Subconjunctival injection:** Vancomycin 2.5 mg/0.5 mL sterile saline q24h × 1–2 weeks **plus** Linezolid 600 mg (IV/PO) q12h × 1–2 weeks | | |
| Fungal‡ | C. albicans | Fluconazole 800 mg (IV) × 1 dose, then 400 mg (IV) q24h × 2 months | Voriconazole (see "usual dose," p. 714) × 2 months | Fluconazole (same as IV dose)<br>**or**<br>Voriconazole (see p. 714) × 2 months |
| | A. fumigatus<br>A. flavus | Amphotericin B (intravitreal) 10 mcg (in 0.1 mL of saline ) q2–3 days | Voriconazole (see "usual dose," p. 714) × 2 months | Voriconazole (see "usual dose," p. 714) × 2 months |
| TB | M. tuberculosis | Treat the same as for TB pneumonia (see p. 53) | | |
| Infected lens implant*<br><br>(Treat initially for MSSA; if later identified as MRSA, treat accordingly) | Entero-bacteriaceae<br>S. aureus (MSSA) | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Cefepime 2 gm (IV) q8h × 2 weeks | Chloramphenicol 500 mg (IV) q6h × 2 weeks | Chloramphenicol 500 mg (PO) q6h × 2 weeks |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h × 2 weeks | Minocycline 100 mg (IV) q12h × 2 weeks | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement (usually < 72 hours).

* Treat only IV or IV-to-PO switch.

‡ Duration of therapy is approximate and should be continued until resolution of disease. Close follow-up with an ophthalmologist is required.

## Bacterial Endophthalmitis

**Clinical Presentation:** Ocular pain/sudden vision loss.

**Diagnosis:** Post-op endophthalmitis occurs 1–7 days after surgery. Hypopyon seen in anterior chamber.

**Pitfalls:** Delayed-onset endophthalmitis may occur up to 6 weeks post-op. White intracapsular plaque is characteristic.

**Therapeutic Considerations:** Use steroids (dexamethasone 0.4 mg/0.1 mL intravitreal and 10 mg/1 mL subconjunctival) with antibiotics in post-op endophthalmitis. Also use systemic antibiotics for severe cases. Vitrectomy is usually necessary.

**Prognosis:** Related to pathogen virulence.

## Fungal Endophthalmitis

**Clinical Presentation:** Slow deterioration in visual acuity ± eye pain. N fever. Antecedent/concomitant TPN, central IV line, prolonged antibiotic/immunosuppressive therapy, steroids, IVDA, or post-cataract surgery.

**Diagnostic Considerations:** Blood cultures frequently positive in Candida endophthalmitis. Small/round white lesions near retinal vessels. Cultures of aqueous/vitreous humors diagnostic.

**Pitfalls:** Symptoms develop insidiously with little/no eye pain or fever. Blood cultures negative with Aspergillus endophthalmitis.

**Therapeutic Considerations:** Penetration of antibiotic into vitreous humor requires high lipid solubility and inflammation. IV/intravitreous/subconjunctival antimicrobial choice depends on physiochemical properties of drug selected. Vitrectomy preferred by some.

If using intravitreal amphotericin B, there is no benefit in adding systemic IV therapy. Voriconazole penetrates CSF/eye, but clinical experience is limited. Based on limited data, caspofungin appears to have poor penetration into the vitreous and should not be relied upon to treat fungal endophthalmitis.

**Prognosis:** Best results with vitrectomy plus intravitreal antifungal therapy.

## Tuberculous (TB) Endophthalmitis

**Clinical Presentation:** Raised retinal punctate lesions ± visual impairment.

**Diagnostic Considerations:** Signs of extraocular TB are usually present. Confirm diagnosis of miliary TB by liver/bone biopsy.

**Pitfalls:** TB endophthalmitis is a sign of disseminated TB.

**Therapeutic Considerations:** Treat as disseminated TB. Systemic steroids may be used if given with anti-TB therapy.

**Prognosis:** Related to degree of immunosuppression.

## Infected Lens Implant

**Diagnostic Considerations:** Diagnosis by clinical appearance and culture of anterior chamber. Obtain ophthalmology consult.

**Pitfalls:** Superficial cultures are inadequate. Anterior chamber aspirate may be needed for culture.

**Therapeutic Considerations:** Infected lens must be removed for cure.
**Prognosis:** Good with early lens removal and recommended antibiotics.

## External Otitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | Topical Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Benign | P. aeruginosa | Use otic solutions only (ofloxacin 0.3%, tobramycin, polymyxin B); apply ear drops q6h × 1 week | | |
| Malignant | P. aeruginosa | **One "A" drug ± one "B" drug: "A" drugs:** Meropenem 1 gm (IV) q8h<br>**or**<br>Cefepime 2 gm (IV) q8h<br>**or**<br>Piperacillin 4 gm (IV) q8h × 4–6 weeks<br>**"B" drugs:** Ciprofloxacin 400 mg (IV) q8h<br>**or**<br>Levofloxacin 750 mg (IV) q24h × 4–6 weeks<br>**or**<br>Amikacin 1 gm (IV) q24h × 4–6 weeks | | Ciprofloxacin 750 mg (PO) q12h<br>**or**<br>Levofloxacin 750 mg (PO) q24h × 4–6 weeks |

Duration of therapy represents total time topically (benign), or IV + PO (malignant). Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

### Benign External Otitis (Pseudomonas aeruginosa)

**Clinical Presentation:** Acute external ear canal drainage without perforation of tympanic membrane or bone involvement.

**Diagnostic Considerations:** Diagnosis suggested by external ear drainage after water exposure. Usually acquired from swimming pools ("swimmers ear"). Not an invasive infection.

**Pitfalls:** Be sure external otitis is not associated with perforated tympanic membrane, which requires ENT consultation and systemic antibiotics.

**Therapeutic Considerations:** Treat topically until symptoms/infection resolve.

**Prognosis:** Excellent with topical therapy.

### Malignant External Otitis (Pseudomonas aeruginosa)

**Clinical Presentation:** External ear canal drainage with bone involvement.

**Diagnostic Considerations:** Diagnosis by demonstrating P. aeruginosa in soft tissue culture from ear canal plus bone/cartilage involvement on x-ray. Usually affects diabetics. CT/MRI of head shows bony involvement of external auditory canal.

**Pitfalls:** Rare in non-diabetics.

**Therapeutic Considerations:** Requires surgical debridement plus antibiotic therapy for cure.

**Prognosis:** Related to control of diabetes mellitus.

## Acute Otitis Media

| Subset | Usual Pathogens | IM Therapy | PO Therapy |
|---|---|---|---|
| Initial uncomplicated bacterial infection | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Ceftriaxone 50 mg/kg (IM) × 1 dose | Amoxicillin 1 gm or 10 mg/kg (PO) q8h × 10 days<br>**or**<br>Clarithromycin 7.5 mg/kg (PO) q12h × 10 days<br>**or**<br>Azithromycin 10 mg/kg (PO) × 1 dose, then 5 mg/kg (PO) q24h × 4 days |
| Treatment failure or resistant organism* | MDRSP<br>β-lactamase +<br>H. influenzae | Ceftriaxone 50 mg/kg (IM) q24h × 3 doses | Amoxicillin/clavulanate ES-600 90 mg/kg/day (PO) in 2 divided doses × 10 days†<br>**or**<br>Cephalosporin† (PO) × 10 days |

*MDRSP = multidrug-resistant S. pneumoniae.* Pediatric doses are provided; acute otitis media is uncommon in adults. For chronic otitis media, prolonged antimicrobial therapy is required.

* Treatment failure = persistent symptoms and otoscopy abnormalities 48–72 hours after starting initial antimicrobial therapy. For risk factors for MDRSP, see Therapeutic Considerations.

† ES-600 = 600 mg amoxicillin/5 mL. Cephalosporins: Cefuroxime axetil 15 mg/kg (PO) q12h or Cefdinir 7 mg/kg (PO) q12h or 14 mg/kg (PO) q24h or Cefpodoxime 5 mg/kg (PO) q12h may be used.

### Acute Otitis Media

**Clinical Presentation:** Fever, otalgia, hearing loss. Nonspecific presentation is more common in younger children (irritability, fever). Key to diagnosis is examination of the tympanic membrane. Uncommon in adults.

**Diagnostic Considerations:** Diagnosis is made by finding an opaque, hyperemic, bulging tympanic membrane with loss of landmarks and decreased mobility on pneumatic otoscopy.

**Pitfalls:** Failure to remove cerumen (inadequate visualization of tympanic membrane) and reliance on history of ear tugging/pain are the main factors associated with overdiagnosis of otitis media. Otitis media with effusion (i.e., tympanic membrane retracted or in normal position with decreased mobility or mobility with negative pressure; fluid present behind the drum but normal in color) usually resolves spontaneously and should not be treated with antibiotics.

**Therapeutic Considerations:** Risk factors for infection with MDRSP S. pneumoniae include antibiotic therapy in past 30 days, failure to respond within 48–72 hours of therapy, day care attendance, and antimicrobial prophylaxis. Macrolides and TMP–SMX may predispose to DRSP, and 25% of S. pneumoniae are naturally resistant to macrolides.

**Prognosis:** Excellent, but tends to recur. Chronic otitis, cholesteatomas, mastoiditis are rare complications. Tympanostomy tubes/adenoidectomy for frequent recurrences of otitis media are the leading surgical procedures in children.

## Mastoiditis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute | S. pneumoniae<br>H. influenzae<br>S. aureus (MSSA) | Ceftriaxone 1–2 gm (IV) q24h × 2 weeks<br>**or**<br>Cefotaxime 2 gm (IV) q6h × 2 weeks<br>**or**<br>Cefepime 2 gm (IV) q12h × 2 weeks | Moxifloxacin 400 mg (IV) q24h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (IV) q24h × 2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (PO) q12h × 2 weeks | Moxifloxacin 400 mg (PO) q24h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 2 weeks<br>**or**<br>Doxycycline 100 mg (PO) q12h × 2 weeks |
| Chronic | S. pneumoniae<br>H. influenzae<br>P. aeruginosa<br>S. aureus (MSSA)<br>Oral anaerobes | Meropenem 1 gm (IV) q8h × 4 weeks<br>**or**<br>Cefepime 2 gm (IV) q8h × 4 weeks | Moxifloxacin 400 mg (IV) × 4–6 weeks<br>**or**<br>Levofloxacin 750 mg (IV) q24h | Moxifloxacin 400 mg (PO) × 4–6 weeks |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

### Acute Mastoiditis

**Clinical Presentation:** Pain/tenderness over mastoid with fever.

**Diagnostic Considerations:** Diagnosis by CT/MRI showing mastoid involvement.

**Pitfalls:** Obtain head CT/MRI to rule out extension into CNS presenting as acute bacterial meningitis.

**Prognosis:** Good if treated early.

### Chronic Mastoiditis

**Clinical Presentation:** Subacute pain/tenderness over mastoid with low-grade fever.

**Diagnostic Considerations:** Diagnosis by CT/MRI showing mastoid involvement. Rarely secondary to TB (diagnose by AFB smear/culture of bone biopsy or debrided bone).

**Pitfalls:** Obtain head CT/MRI to rule out CNS extension.

**Therapeutic Considerations:** Usually requires surgical debridement for cure. Should be viewed as chronic osteomyelitis. If secondary to TB, treat as skeletal TB.

**Prognosis:** Progressive without surgery. Poor prognosis with associated meningitis/brain abscess.

## Suppurative Parotitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Parotitis (bacterial) | S. aureus (MSSA)<br>Entero-bacteriaceae<br>Oral anaerobes | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Respiratory quinolone* (IV) q24h × 2 weeks | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 2 weeks | Respiratory quinolone* (PO) q24h × 2 weeks |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

* Levofloxacin 500 mg or Moxifloxacin 400 mg.

**Clinical Presentation:** Unilateral parotid pain/swelling with discharge from Stensen's duct ± fever.
**Diagnostic Considerations:** Diagnosis by clinical presentation, ↑ amylase, CT/MRI demonstrating stone in parotid duct/gland involvement.
**Pitfalls:** Differentiate from unilateral mumps by purulent discharge from Stensen's duct.
**Therapeutic Considerations:** If duct is obstructed, remove stone.
**Prognosis:** Good with early therapy/hydration.

## Pharyngitis

| Subset | Usual Pathogens | PO Therapy |
|---|---|---|
| Bacterial | Group A streptococci | Amoxicillin 1 gm (PO) q8h × 7–10 days **or** Cefprozil 500 mg (PO) q12h × 7–10 days **or** Clindamycin 300 mg (PO) q8h × 7–10 days **or** Clarithromycin XL 1 gm (PO) q24h × 7–10 days **or** Azithromycin 500 mg (PO) × 1 dose, then 250 mg (PO) q24h × 4 days |
| Membranous | Arcanobacterium (Corynebacterium) hemolyticum | Doxycycline 100 mg (IV or PO) q12h × 1–2 weeks **or** Clarithromycin XL 1 gm (PO) q24h × 1–2 weeks **or** Azithromycin 500 mg (IV or PO) × 1 dose then 250 mg (IV or PO) q24h × 1–2 weeks **or** Cephalosporin (IV or PO) × 1–2 wks |
| | C. diphtheriae<br>C. ulcerans | Diphtheria antitoxin (see p. 170) ± penicillin or macrolide |
| Viral | Respiratory viruses, EBV, CMV, HHV-6 | Not applicable. EBV/CMV do not cause primary pharyngitis, but pharyngitis part of infectious mononucleosis syndrome, along with hepatitis and lymph node involvement. Viral hepatitis (see pp. 97–98) |

## **Pharyngitis** (cont'd)

| Subset | Usual Pathogens | PO Therapy |
|---|---|---|
| Other | M. pneumoniae<br>C. pneumoniae | Respiratory quinolone* (PO) q24h × 1 week **or** Doxycycline 100 mg (PO) q12h × 1 week **or** Clarithromycin XL 1 gm (PO) q24h × 1 week **or** Azithromycin 500 mg (PO) × 1 dose, then 250 mg (PO) q24h × 4 days |
| Chronic fatigue syndrome.† | | |

* Levofloxacin 500 mg or Moxifloxacin 400 mg.

† Not a cause of pharyngitis, pathogen unknown (not EBV) but may be caused by xenotropic murine leukemia related virus (XMRV). For therapeutic considerations (see p. 43).

### Bacterial Pharyngitis

**Clinical Presentation:** Acute sore throat with fever, bilateral anterior cervical adenopathy, and elevated ASO titer. No hoarseness.

**Diagnostic Considerations:** Diagnosis of Group A streptococcal pharyngitis by elevated ASO titer after initial sore throat and positive throat culture. Rapid strep tests unnecessary, since delay in culture results (~1 week) still allows adequate time to initiate therapy and prevent acute rheumatic fever. Group A streptococcal pharyngitis is rare in adults > 30 years.

**Pitfalls:** Gram stain of throat exudate differentiates Group A streptococcal colonization (few or no PMNs) from infection (many PMNs) in patients with a positive throat culture or rapid strep test. Neither throat culture nor rapid strep test alone differentiates colonization from infection.

**Therapeutic Considerations:** Benzathine penicillin 1.2 mu (IM) × 1 dose can be used as an alternative to oral therapy. Penicillin, erythromycin, and ampicillin fail in 15% of cases due to poor penetration into oral secretions or beta-lactamase producing oral organisms.

**Prognosis:** Excellent. Treat within 10 days to prevent acute rheumatic fever.

### Membranous Pharyngitis

**Clinical Presentation:** A. hemolyticum presents with a scarlet fever-like rash and membranous pharyngitis. C. diphtheriae pharyngitis has no fever/rash.

**Diagnostic Considerations:** Diagnosis by throat culture/recovery of organism in patients with scarlatiniform rash.

**Pitfalls:** A. hemolyticum must be differentiated from C. diphtheriae on culture.

**Therapeutic Considerations:** For A. hemolyticum, doxycycline or erythromycin are more active than beta-lactams. Penicillin or macrolides are preferred for C. diphtheriae. C. diphtheriae should be treated with antitoxin ASAP since antibiotic therapy is adjunctive.

**Prognosis:** Related to degree of airway obstruction. Good with early treatment of A. hemolyticum. Diphtheria prognosis related to early antitoxin treatment and to presence/severity of toxic myocarditis.

## Viral Pharyngitis

**Clinical Presentation:** Acute sore throat. Other features depend on specific pathogen.

**Diagnostic Considerations:** Most cases of viral pharyngitis are caused by respiratory viruses, and are frequently accompanied by hoarseness, but not high fever, pharyngeal exudates, palatal petechiae, or posterior cervical adenopathy. Other causes of viral pharyngitis (EBV, CMV, HHV-6) are usually associated with posterior cervical adenopathy and ↑ SGOT/SGPT. EBV mono may present with exudative or non-exudative pharyngitis, and is diagnosed by negative ASO titer with a positive mono spot test or elevated EBV IgM viral capsid antigen (VCA) titer. Before mono spot test turns positive (may take up to 8 weeks), a presumptive diagnosis of EBV mono can be made by ESR and SGOT, which are elevated in EBV and normal in Group A streptococcal pharyngitis. If EBV mono spot is negative, retest weekly × 8 weeks; if still negative, obtain IgM CMV/toxoplasmosis titers to diagnose the cause of "mono spot negative" pharyngitis.

**Pitfalls:** 30% of patients with viral pharyngitis have Group A streptococcal colonization. Look for viral features to suggest the correct diagnosis (leukopenia, lymphocytosis, atypical lymphocytes).

**Therapeutic Considerations:** Symptomatic care only. Short-term steroids should only be used in EBV infection if airway obstruction is present/imminent. Since 30% of patients with viral pharyngitis are colonized with Group A streptococci, do not treat throat cultures positive for Group A streptococci if non-streptococcal pharyngitis features are present (e.g., bilateral posterior cervical adenopathy).

**Prognosis:** Related to extent of systemic infection. Post-viral fatigue is common. CMV may remain active in liver for 6–12 months with mildly elevated serum transaminases.

## Mycoplasma/Chlamydophilia (Chlamydia) Pharyngitis

**Clinical Presentation:** Acute sore throat ± laryngitis. Usually non-exudative.

**Diagnostic Considerations:** Diagnosis by elevated IgM M. pneumoniae or C. pneumoniae titers. Consider diagnosis in patients with non-exudative pharyngitis without viral or streptococcal pharyngitis. Mycoplasma pharyngitis is often accompanied by otitis/bullous myringitis.

**Pitfalls:** Patients with C. pneumoniae frequently have laryngitis, which is not a feature of EBV, CMV, Group A streptococcal, or M. pneumoniae pharyngitis.

**Therapeutic Considerations:** Treatment of C. pneumoniae laryngitis results in rapid (~ 3 days) return of normal voice, which does not occur with viral pharyngitis.

**Prognosis:** Excellent.

## Chronic Fatigue Syndrome (CFS)

**Clinical Presentation:** Fatigue > 1 year with cognitive impairment and no pharyngitis.

**Diagnostic Considerations:** Rule out other causes of chronic fatigue (cancer, adrenal/thyroid disease, etc.) before diagnosing CFS. HHV-6/Coxsackie B titers are usually elevated. Some have ↓ natural kill (NK) cells/activity. ESR ~ 0. Crimson crescents in the posterior pharynx are common.

**Pitfalls:** ↑ VCA IgG EBV titers is common in CFS, but EBV does not cause CFS. Do not confuse CFS with fibromyalgia, which has muscular "trigger points" and no cognitive impairment. CFS and fibromyalgia may coexist. In presumed CFS, if there is pharyngitis or if the ESR is elevated, consider an alternate diagnosis.

**Therapeutic Considerations:** No specific therapy is available. Patients with ↓ NK cells may benefit from β-carotene 50,000 U (PO) q24h × 3 weeks. Patients with ↑ C. pneumoniae IgG titers may benefit from doxycycline 100 mg (PO) q24h × 3 weeks.

**Prognosis:** Cyclical illness with remissions (precipitated by exertion, stress, or sleep lack). Avoid exercise.

## Thrush (Oropharyngeal Candidiasis)

| Subset | Pathogens | PO Therapy |
|---|---|---|
| Fungal | C. albicans | Fluconazole 200 mg (PO) × 1 dose, then 100 mg (PO) q24h ×† weeks **or** Posaconazole 100 mg (PO) q12h × 1 day, then 100 mg (PO) q24h × 13 days **or** Clotrimazole 10 mg troches (PO) 5x/day ×† weeks **or** Itraconazole 200 mg (PO) q24h ×† weeks |
| | Fluconazole-resistant Candida species | Posaconazole 400 mg (PO) q12h ×† weeks* **or** Voriconazole 200 mg (PO) q12h ×† weeks* **or** Caspofungin 70 mg (IV) × 1, then 50 mg (IV) q24h ×† weeks* **or** Itraconazole 200 mg (PO) q12h ×† weeks* |

* Duration of therapy depends on underlying disease and clinical response.

† See Fluconazole unresponsive esophagitis (see p. 612).

### Thrush (Oropharyngeal Candidiasis)

**Clinical Presentation:** White coated tongue or oropharynx. White adherent plaques may be on any part of the oropharynx.

**Diagnostic Considerations:** Gram stain/culture of white plaques demonstrates yeasts (Candida). Culture and susceptibility testing of causative fungus is useful in analyzing failure to respond to therapy.

**Pitfalls:** Lateral, linear, white, striated tongue lesions may resemble thrush but really represent hairy leukoplakia. Hairy leukoplakia should suggest HIV. Thrush may occur in children, alcoholics, diabetics, those receiving steroids/antibiotic therapy, or HIV.

**Therapeutic Considerations:** Almost all infections are caused by C. albicans, a species that is usually susceptible to fluconazole. Fluconazole-unresponsive infections may be caused by infection with fluconazole-resistant C. albicans (most common explanation), infection with a fluconazole-resistant non-albicans species (rare), noncompliance with therapy (common), or drug interactions (e.g., concomitant usage of rifampin, which markedly reduced azole blood levels). For suspected fluconazole-resistance, a trial with another azole is appropriate as cross-resistance is not universal.

**Prognosis:** Non-HIV patients respond well to therapy, particularly when the predisposing factor is eliminated/decreased (i.e., antibiotics discontinued, steroids reduced, etc.). HIV patients may require longer courses of therapy and should be treated until cured. Relapse is frequent in HIV patients, and institution of effective antiretroviral therapy is the most effective general strategy.

## Mouth Ulcers/Vesicles

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Vincent's angina | Borrelia<br>Fusobacterium | Clindamycin 600 mg (IV) q8h × 2 weeks | Ceftizoxime 2 gm (IV) q8h × 2 weeks<br>**or**<br>Any β-lactam (IV) × 2 weeks | Clindamycin 300 mg (PO) q8h × 2 weeks<br>**or**<br>Amoxicillin/clavulanic acid 500/125 mg (PO) q8h × 2 weeks |
| Ludwig's angina | Group A streptococci | Clindamycin 600 mg (IV) q8h × 2 weeks | Ceftizoxime 2 gm (IV) q8h × 2 weeks<br>**or**<br>Any β-lactam (IV) × 2 weeks | Clindamycin 300 mg (PO) q8h × 2 weeks<br>**or**<br>Amoxicillin/clavulanic acid 500/125 mg (PO) q8h × 2 weeks |
| Stomatitis | Normal mouth flora | Not applicable | | |
| Herpangina | Coxsackie A virus | Not applicable | | |
| Herpes gingivo-stomatitis | HSV-1 | PO Therapy<br>Valacyclovir 500 mg (PO) q12h × 1 week<br>**or**<br>Famciclovir 500 mg (PO) q12h × 1 week<br>**or**<br>Acyclovir 400 mg (PO) 5x/day × 1 week | | |
| Herpes labialis (cold sores/ fever blisters) | HSV-1 (recurrent) | PO Therapy<br>Valacyclovir 2 gm (PO) q12h × 1 day (2 doses) started at onset of symptoms (tingling/burning)<br>**or**<br>Acyclovir 400 mg (PO) 5x/day × 1 week<br>**or**<br>Famciclovir 500 mg (PO) q12h × 1 week<br><br>Topical Therapy<br>Penciclovir 1% cream q2h while awake × 4 days<br>**or**<br>Acyclovir 5% cream 5x/d × 4 days | | |
| Aphthous ulcers | Normal mouth flora | Not applicable | | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

### Vincent's Angina (Borrelia/Fusobacterium)

**Clinical Presentation:** Painful/bleeding gums without fever.
**Diagnostic Considerations:** Foul breath, poor dental hygiene/pyorrhea.
**Pitfalls:** Do not attribute foul breath to poor dental hygiene without considering other serious causes (e.g., lung abscess, renal failure).
**Therapeutic Considerations:** After control of acute infection, refer to dentist.
**Prognosis:** Excellent with early treatment.

### Ludwig's Angina (Group A streptococci)

**Clinical Presentation:** Painful floor of mouth with fever.
**Diagnostic Considerations:** Elevated floor of mouth is diagnostic. Massive neck swelling may be present.
**Pitfalls:** $C_{1q}$ deficiency has perioral/tongue swelling, but no fever or floor of mouth elevation. Rarely, Ludwig's, angina may be due to F. necrophorum.
**Therapeutic Considerations:** Surgical drainage is not necessary. May need airway emergently; have tracheotomy set at bedside.
**Prognosis:** Early airway obstruction has adverse impact on prognosis.

### Stomatitis (normal mouth flora)

**Clinical Presentation:** Painful mouth ulcers with fever.
**Diagnostic Considerations:** Diagnosis based on clinical appearance.
**Pitfalls:** Do not miss a systemic cause (e.g., acute leukemia).
**Therapeutic Considerations:** Painful; treat symptomatically.
**Prognosis:** Related to severity of underlying systemic disease.

### Herpangina (Coxsackie A virus)

**Clinical Presentation:** Painful mouth ulcers/vesicles with fever.
**Diagnostic Considerations:** Ulcers located posteriorly in pharynx. No gum involvement or halitosis.
**Pitfalls:** Do not confuse with anterior vesicular lesions of HSV.
**Therapeutic Considerations:** No good treatment available. Usually resolves spontaneously in 2 weeks.
**Prognosis:** Good, but may be recurrent.

### Herpes Gingivostomatitis (HSV-1)

**Clinical Presentation:** Painful gums with fever.
**Diagnostic Considerations:** Anterior ulcers in pharynx. Associated with bleeding gums, not halitosis.
**Pitfalls:** Do not miss a systemic disease associated with bleeding gums (e.g., acute myelogenous leukemia). Periodontal disease is not usually associated with oral ulcers.
**Therapeutic Considerations:** Oral analgesic solutions may help in swallowing.
**Prognosis:** Excellent with early treatment.

### Herpes Labialis (Cold Sores/Fever Blisters) (HSV-1)

**Clinical Presentation:** Painful vesicles along vermillion border of upper or lower lip with fever.
**Diagnostic Considerations:** Caused by recurrent HSV-1 infection, which appears as painful vesicular lesions on/near the vermillion border of lips. Attacks may be triggered by stress, sun exposure, menstruation, and often begin with pain or tingling before vesicles appear. Vesicles crust over and attacks usually resolve by 1 week. "Fever blisters" are not triggered by temperature elevations per se, but may accompany malaria, pneumococcal/meningococcal meningitis. Diagnosis is clinical.
**Pitfalls:** Do not confuse with perioral impetigo; impetigo has crusts (not vesicles), is itchy (not painful), and does not involve the vermillion border of the lips.
**Therapeutic Considerations:** Treatment is not always needed. If valacyclovir if used, it should be started when pain/tingling appear to decrease symptoms/vesicles/duration of attack. Valacyclovir is of no proven value once vesicles have appeared. Non-prescription topical products (docosanol 10%,

tetracaine cream) may decrease pain/itching. Once-daily suppressive therapy may be considered for frequent recurrences or during times of increased risk (e.g., sun exposure). Sun screen may be helpful.
**Prognosis:** Tends to be recurrent in normal hosts. May be severe in compromised hosts.

### Aphthous Ulcers (normal mouth flora)

**Clinical Presentation:** Painful mouth ulcers/vesicles without fever.
**Diagnostic Considerations:** Usually an isolated finding. Ulcers are painful.
**Pitfalls:** May be a clue to systemic disorder, e.g., Behcet's syndrome. Mouth ulcers in SLE are painless.
**Therapeutic Considerations:** Usually refractory to all treatment and often recurrent. Steroid ointment (Kenalog) may be helpful.
**Prognosis:** Good, but tends to recur.

## Deep Neck Infections, Lemierre's Syndrome, Severe Dental Infections

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Deep neck infections (lateral pharyngeal, retro-pharyngeal, space) | Oral anaerobes<br>Oral streptococci | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Tigecycline 100 mg (IV) × 1 dose, then 100 mg (IV) q24h or 50 mg (IV) q12h × 2 weeks<br>**or**<br>Piperacillin/tazobactam 3.375 mg (IV) q6h × 2 weeks | Clindamycin 600 mg (IV) q8h × 2 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks | Clindamycin 300 mg (PO) q8h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days* |
| Lemierre's Syndrome | Fusobacterium necrophorum | Treat as deep neck infection, see above | | |
| Severe dental infections | Oral anaerobes<br>Oral streptococci | Clindamycin 600 mg (IV) q8h × 2 weeks<br>**or**<br>Piperacillin/tazobactam 3.375 mg (IV) q6h × 2 weeks | Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks | Clindamycin 300 mg (PO) q8h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days* |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.
* Loading dose is not needed PO if given IV with the same drug.

### Deep Neck Infections (lateral pharyngeal, retropharyngeal)

**Diagnostic Considerations:** Lateral pharyngeal space infection: Anterior → fever/chills, trismus, dysphagia, swelling or angle of mandible, ± parotid swelling, and bulging of lateral pharyngeal wall. Posterior pharyngeal space infection → bacteremic septic, no trismus/pain, and no pharyngeal wall bulging. Retropharyngeal space infection: fever/chills, dysphagia, dyspnea,± mucal rigidity, esophageal regurgitation, and bulging of posterior pharyngeal wall.

**Pitfalls:** Retropharyngeal "danger space" infection may extend to mediastinum and present as mediastinitis.

**Therapeutic Considerations:** Obtain ENT consult for surgical drainage.

**Prognosis:** Worst prognosis with posterior lateral and retropharyngeal space infections.

### Lemierre's Syndrome

**Clinical Presentation:** Severe sore throat with fever, toxemic appearance, and tenderness over jugular vein. Jugular vein septic thrombophlebitis and septic pulmonary emboli.

**Diagnostic Considerations:** May present as multiple septic pulmonary emboli. Usually follows recent dental infection. Jugular vein tenderness diagnostic. Blood cultures positive for F. necrophorum or F. nucleatum; rarely MSSA/MRSA.

**Pitfalls:** Suspect Lemierre's syndrome in patients with concurrent/antecedent dental/oropharyhngeal infection with severe sore throat and jugular vein tenderness.

**Therapeutic Considerations:** If unresponsive to antibiotic therapy, may need venotomy.

**Prognosis:** Good with prompt treatment. May be more severe with concurrent M. pneumoniae or EBV pharyngitis.

### Severe Dental Infections

**Diagnostic Considerations:** Obtain CT/MRI of jaws to rule out osteomyelitis or abscess.

**Pitfalls:** Chronic drainage in a patient with an implant is diagnostic of chronic osteomyelitis/abscess until proven otherwise.

**Therapeutic Considerations:** Abscesses should be drained for cure.

**Prognosis:** Poor prognosis and recurrent without adequate surgical drainage.

## Epiglottitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Epiglottitis | S. pneumoniae<br>H. influenzae<br>Respiratory viruses | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 2 weeks | Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (IV) q24h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (IV) q24h × 2 weeks | Moxifloxacin 400 mg (PO) q24h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 2 weeks<br>**or**<br>Cefprozil 500 mg (PO) q12h × 2 weeks |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

**Clinical Presentation:** Stridor with upper respiratory infection.
**Diagnostic Considerations:** Lateral film of neck shows epiglottic edema. Neck CT/MRI may help if neck films are non-diagnostic.
**Pitfalls:** Do not attempt to culture the epiglottis (may precipitate acute upper airway obstruction).
**Therapeutic Considerations:** Treat empirically as soon as possible. Obtain ENT consult.
**Prognosis:** Early airway obstruction is associated with an adverse prognosis.

## Empiric Therapy of Lower Respiratory Tract Infections

### Acute Bacterial Exacerbation of Chronic Bronchitis (AECB)

| Subset | Pathogens | PO Therapy |
|---|---|---|
| AECB | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Respiratory quinolone* (PO) q24h × 5 days<br>**or**<br>Amoxicillin/clavulanic acid 500/125 mg (PO) q12h × 5 days<br>**or**<br>Clarithromycin XL 1 gm (PO) q24h × 5 days<br>**or**<br>Doxycycline 100 mg (PO) q12h × 5 days<br>**or**<br>Azithromycin 500 mg (PO) × 3 days |

* Moxifloxacin 400 mg or Levofloxacin 500 mg.

**Clinical Presentation:** Productive cough and negative chest x-ray in a patient with chronic bronchitis.
**Diagnostic Considerations:** Diagnosis by productive cough, purulent sputum, and chest x-ray negative for pneumonia. H. influenzae is relatively more common than other pathogens.
**Pitfalls:** Do not obtain sputum cultures in chronic bronchitis; cultures usually reported as normal/mixed flora and should not be used to guide therapy.
**Therapeutic Considerations:** Treated with same antibiotics as for community-acquired pneumonia, since pathogens are the same (even though H. influenzae is relatively more frequent). Respiratory viruses/C. pneumoniae may initiate AECB, but is usually followed by bacterial infection, which is responsible for symptoms and is the aim of therapy. Bronchodilators are helpful for bronchospasm. Macrolide-resistant S. pneumoniae is an important clinical problem (prevalence ≥ 30%).
**Prognosis:** Related to underlying cardiopulmonary status.

## Mediastinitis

| Subset | Usual Pathogens | IV Therapy | IV-to-PO Switch |
|---|---|---|---|
| Following esophageal perforation or thoracic surgery | Oral anaerobes | Preferred:<br>Piperacillin/tazobactam 3.375 gm (IV) q6h × 2 wks **or** Ampicillin/sulbactam 3 gm (IV) q6h × 2 wks<br>Alternate:<br>Meropenem 1 gm (IV) q8h × 2 weeks or Ertapenem 1 gm (IV) q24h × 2 weeks | Amoxicillin/clavulanate 500/125 mg (PO) q8h × 2 weeks **or** Respiratory quinolone* (PO) q24h × 2 weeks |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Moxifloxacin 400 mg or Levofloxacin 500 mg.

**Diagnostic Considerations:** Chest x-ray usually shows perihilar infiltrate in mediastinitis. Pleural effusions from esophageal tears have elevated amylase levels.
**Pitfalls:** Do not overlook esophageal tear in mediastinitis with pleural effusions.
**Therapeutic Considerations:** Obtain surgical consult if esophageal perforation is suspected.
**Prognosis:** Related to extent, location, and duration of esophageal tear/mediastinal infection.

## Community-Acquired Pneumonia (CAP) (see Color Atlas for Sputum Gram stains and Chapter 8 for Differential Diagnosis of CXR patterns)

| Subset | Usual Pathogens* | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|
| Pathogen unknown | S. pneumoniae¶<br>H. influenzae<br>M. catarrhalis<br>B. pertussis<br>Legionella sp.<br>Mycoplasma pneumoniae | Respiratory quinolone† (IV) q24h<br>**or**<br>**combination therapy with**<br>Ceftriaxone 1 gm (IV) q24h × 1–2 week<br>**plus either**<br>Doxycycline‡ (IV) × 1–2 weeks<br>**or**<br>Azithromycin 500 mg (IV) q24h × 1–2 weeks (minimum 2 doses before switching to PO therapy) | Respiratory quinolone† (PO) q24h<br>**or**<br>Doxycycline‡ (PO) × 1–2 weeks<br>**or**<br>Macrolide††¶ (PO) q24h × 1–2 weeks |

Duration of therapy represents total time IV or IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Compromised hosts may require longer courses of therapy.
† Moxifloxacin 400 mg × 1–2 weeks or Levofloxacin 750 mg × 5 days (or 500 mg × 1–2 weeks).
†† Azithromycin 500 mg or Clarithromycin XL 1 gm.
¶ Macrolide monotherapy should be avoided in areas where *macrolide-resistant S. pneumoniae (MRSP) or multidrug-resistant S. pneumoniae (MDRSP)* strains are prevalent.
‡ Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) q12h × 4–11 days.

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Typical bacterial pathogens | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days<br>**or**<br>Respiratory quinolone† (IV) q24h × 1–2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 1–2 wks | Doxycycline‡ (IV) × 1–2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 1–2 weeks<br>**or**<br>Tigecycline** 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 1–2 weeks | (see unknown pathogen)<br>**or**<br>Amoxicillin/clavulanate XR 2 tablets (PO) q12h × 7–10 days<br>**or**<br>Cefprozil 500 mg (PO) q12h × 1–2 weeks |
| | K. pneumoniae* | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Respiratory quinolone§ (IV) q24h × 2 weeks | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Doripenem 1 gm (IV) q8h | Respiratory quinolone§ (PO) q24h × 2 weeks<br>**or**<br>Doxycycline‡ (PO) × 1–2 weeks |
| | MDR K. pneumoniae CRE | Ceftazidime/avibactam 2.5 gm (IV) q8h × 1-2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 1–2 weeks** | Colistin 5 mg/kg (IV) q8h¶<br>**or**<br>Polymyxin B 1.25 mg/kg (IV) q12h¥ | None |

* Compromised hosts may require longer courses of therapy.
† Moxifloxacin 400 mg × 1–2 weeks or Levofloxacin 750 mg × 5 days (or 500 mg × 1–2 weeks).
§ Moxifloxacin 400 mg or Levofloxacin 500 mg.
¥ 1 mg Colistin = 12,500 IU; 1 mg Polymyxin B = 10,000 IU.
‡ Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) q12h × 4–11 days.
** Depending on MIC, higher doses of tigecycline (LD: 400 mg (IV) × 1 dose, then MD: 200 mg (IV) q24h) may be necessary for susceptible MDR GNBs.

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Atypical pathogens *Zoonotic* | C. psittaci (psittacosis)<br>Coxiella burnetii (Q fever)<br>Francisella tularensis (tularemia) | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 2 weeks | Respiratory quinolone† (IV) q24h × 2 weeks | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days<br>**or**<br>Quinolone† (PO) q24h × 2 weeks |
| *Non-zoonotic* | Legionella sp.‡<br>Mycoplasma pneumoniae‡<br>C. pneumoniae‡ | Moxifloxacin 400 mg (IV) q24h × 1–2 weeks<br>**or**<br>Levofloxacin 500 mg (IV) q24h × 1–2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 4–11 days | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 1–2 weeks<br>**or**<br>Azithromycin 500 mg (IV) q24h × 1–2 weeks (minimum of 2 doses before switching to PO) | Respiratory quinolone† (PO) q24h × 1–2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4–11 days<br>**or**<br>Azithromycin 500 mg (PO) q24h × 1–2 weeks |
| | CMV | Valganciclovir 900 mg (PO) q12h until cured | | |
| Influenza (*mild or moderate*) *without bacterial CAP* | Influenza A/B | Oseltamivir (Tamiflu) 75 mg (PO) q24h × 5 days | Zanamivir (Relenza) 10 mg (2 puffs via oral inhaler) q12h × 5 days | Oseltamivir may be ineffective against avian influenza ($H_5N_1$), but effective against swine influenza ($H_1N_1$) and swine-like influenza ($H_3N_2$) |

* Compromised hosts may require longer courses of therapy.
† Moxifloxacin 400 mg or Levofloxacin 500 mg.
‡ May require prolonged therapy: Legionella (2–3 weeks); Mycoplasma (2 weeks); Chlamydia (2 weeks).

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Influenza (*severe with **simultaneous** CAP*)¶ | Influenza A pneumonia | Peramivir 600 mg (IV) q24h × 1 days<br>**or**<br>Oseltamivir 75 mg (PO) q12h × 5 days<br>**plus**<br>Amantadine 200 mg (PO) q24h × 7–10 days¶¶ | | Start treatment as soon as possible after onset of symptoms, preferably within 3 days. Rimantadine/ amantadine inactive against Influenza B. |
| | with MSSA/ MRSA CAP | *MSSA*<br>Nafcillin 2 gm (IV) q4h × 2 weeks<br>**or**<br>Cefazolin 1 gm (IV) q8h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks<br>*MRSA*<br>Vancomycin 1 gm (IV) q12h × 2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose then 100 mg (IV) q24h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks | | |
| Post-influenza *(with **subsequent** bacterial CAP). Recovering from influenza/treated previously* | S. pneumoniae H. influenzae | Respiratory quinolone‡ (IV) q24h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 wks | Doxycycline 200 mg (IV) × 3 days, then 100 mg (IV) q12h × 11 days | Respiratory quinolone‡ (PO) q24h × 2 weeks |
| | | Plus influenza therapy (see preceeding page) | | |
| Chickenpox pneumonia | VZV | Acyclovir 5–10 mg/kg (IV) q8h × 10 days | | Valacyclovir 1–2 gm (PO) q8h × 10 days |

Duration of therapy represents total time IV or IV, PO, or IV + PO.

* Compromised hosts predisposed to organisms listed, but may be infected by usual pathogens in normal hosts.

‡ May require prolonged therapy: Legionella (2–3 weeks); Mycoplasma (2 weeks); Chlamydia (2 weeks).

¶ If CXR shows multiple rapidly cavitating infiltrates < 72 hours, begin empiric anti-MSSA/CA-MRSA therapy with anti-influenza therapy.

¶¶ Although resistance common, may improve oxygenation in severe influenza A.

§ Dose for CrCl > 30 ml/min = 30 mg (PO) q12h; for CrCl > 10–30 ml/min = 30 mg (PO) q24h.

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Aspiration | Oral anaerobes<br>S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Respiratory quinolone‡ (IV) q24h × 2 weeks | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days | Respiratory quinolone‡ (PO) q24h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4–11 days**<br>**or**<br>Amoxicillin 1 gm (PO) q8h × 2 weeks |
| Tuberculosis (TB) | M. tuberculosis | INH 300 mg (PO) q24h (and pyridoxine 50 mg (PO) q24h) × 6 months **plus** RIF 600 mg (PO) q24h × 6 months **plus** PZA 25 mg/kg (PO) q24h × 2 months **plus** EMB 15 mg/kg (PO) q24h (until susceptibilities known)†† | | |
| MDR TB | M. tuberculosis | Bedaquiline (Sirturo) 400 mg (PO) q24h (D.O.T.) × 2 weeks, then 200 mg (PO) 3 × per week × 22 weeks*. | | |
| Non-tuberculous (atypical tuberculosis) Mycobacteria | | Treat for 12 months after sputum negative for MAI: EMB 15 mg/kg (PO) q24h **plus either** Clarithromycin 500 mg (PO) q12h **or** Azithromycin 500 mg (PO) q24h **plus either** (Rifampin or Rifabutin). May substitute a quinolone (PO)‡ q24h for rifamycin | | |
| | M. kansasii | Preferred therapy<br>RIF 600 mg (PO) q24h **plus** INH 300 mg (PO) q24h **plus** pyridoxine 50 mg (PO) q24h **plus** EMB 15 mg/kg (PO) q24h. Treat × 12 months after negative sputum<br>Alternate therapy<br>RIF 600 mg (PO) thrice weekly **or** daily **plus** EMB 15 mg/kg (PO) thrice weekly **or** daily **plus** clarithromycin 500–1000 mg (PO) thrice weekly **or** daily. Treat × 12 months after negative sputum | | |

* May be used in adults as part of a multidrug TB regimen (>3 drugs). Take with food. Side effects include nausea, headache, arthralgias, $QT_c$ prolongation.

‡ Moxifloxacin 400 mg or Levofloxacin 500 mg.

†† If isolate is sensitive, discontinue EMB and continue as above to complete 6 months. If INH-resistant, continue EMB, RIF and PZA to complete 6 months. If any other resistance is present (MDR-TB), obtain infectious disease or pulmonary consult.

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Chronic alcoholics | K. pneumoniae<br>S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Meropenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1, then 100 mg (IV) q24h | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Respiratory quinolone‡ (IV) q24h × 2 weeks | Respiratory quinolone (PO)‡ q24h × 2 weeks |
| | MDR<br>K. pneumoniae<br>CRE | Ceftazidime/avibactam 2.5 gm (IV) q8h × 1-2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, 100 mg (IV) q24h × 1–2 weeks | Colistin 5 mg/kg (IV) q8h × 1-2 weeks¥<br>**or**<br>Polymyxin B 1.25 mg/kg (IV) q12h × 1-2 weeks¥ | None |
| Bronchiectasis, cystic fibrosis | S. maltophilia<br>B. cepacia<br>Alcaligenes xyloxidans | Preferred:<br>TMP–SMX 2.5 mg/kg (IV) q6h¶<br>**or**<br>Minocycline 100 mg (IV) q12h¶<br>Alternate:<br>Doxycycline 100 mg (IV) q12h¶ | | TMP–SMX 1 SS tablet (PO) q6h¶<br>**or**<br>Minocycline 100 mg (PO) q12h¶<br>**or**<br>Respiratory quinolone‡ (PO) q24h¶ |
| | P. aeruginosa | Meropenem 2 gm (IV) q8h¶ | Levofloxacin 750 mg (IV) q24h¶<br>**or**<br>Cefepime 2 gm (IV) q8h¶ ± Amikacin 1 gm (IV) q24h¶ | Levofloxacin 750 mg (PO) q24h¶<br>**or**<br>Ciprofloxacin 750¶ mg (PO) q12h |
| | MDR<br>P. aeruginosa | Ceftazidime/avibactam 2.5 gm (IV) q8h × 1-2 weeks<br>**or**<br>Doripenem 1 gm (IV) q8h¶ | Polymyxin B 1.25 mg/kg (IV) q12h¶¥<br>**or**<br>Colistin 5 mg/kg (IV) q8h¶ | None |

* Compromised hosts predisposed to organisms listed but may be infected by usual pathogens in normal hosts.
¶ Treat until cured.
‡ Moxifloxacin 400 mg or Levofloxacin 500 mg.
¥ Colistin 1 mg = 12,500 IU; Polymyxin B 1 mg = 10,000 IU.

## Community-Acquired Pneumonia (CAP) (cont'd)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Chronic steroid therapy† | Aspergillus sp. | Voriconazole (see "usual dose," p. 714)¶ | Lipid amphotericin (see p. 525)¶ **or** Caspofungin 70 mg (IV) × 1 then 50 mg (IV) q24h¶ **or** amphotericin B 1–1.5 mg/kg (IV) q24h¶ | Voriconazole (see "usual dose," p. 714)¶ **or** Posaconazole 200 mg (PO) q6h initially, then 400 mg (PO)q12h¶ **or** Itraconazole 200 mg (IV) q12h × 2 days then 200 mg (PO) q12h**¶ |
| | P. (carinii) jiroveci (PCP) | TMP–SMX 5 mg/kg (IV) q6h × 3 weeks‡ | Pentamidine 4 mg/kg (IV) q24h × 3 weeks‡ | TMP–SMX 5 mg/kg (PO) q6h × 3 weeks **or** Atovaquone 750 mg (PO) of q12h **or** Dapsone 100 mg (PO) of q24h |
| | CMV | Valganciclovir 900 mg (PO) q12h until cured | | |
| HIV | Typical/atypical CAP pathogens | | see pp. 50–51 | |
| | P. (carinii) jiroveci (PCP) | | see p. 325 | |
| Other pathogens | For Cytococcus neoformans, Blastomyces, Histoplasma, Coccidioides, Paracoccidioides, Actinomyces, Nocardia, Pseudallescheria boydii, Sporothrix, Mucor (see pp. 267–269). | | | |

¶ Treat until cured.
† Treat IV or IV-to-PO switch.
* Compromised hosts predisposed to organisms listed, but may be infected by usual pathogens of normal hosts.
** Loading dose is not needed PO if given IV with the same drug.
‡ Steroid dosage: prednisone 40 mg (PO) q12h on days 1–5, then 40 mg (PO) q24h on days 6–10, then 20 mg (PO) q24h on days 11–21. Methylprednisolone (IV) can be substituted at 75% of prednisone dose.
†† Moxifloxacin 400 mg or Levofloxacin 500 mg.

**Clinical Presentation:** Fever, cough, respiratory symptoms, chest x-ray consistent with pneumonia. Typical CAPs present only with pneumonia without extrapulmonary findings.
**Diagnosis:** Identification of organism on sputum gram stain/culture. Same organism is found in blood if blood cultures are positive. Also see Chapter 8 for typical chest x-ray patterns.

## Community-Acquired Pneumonia (Typical Bacterial Pathogens)

**Diagnostic Considerations:** Sputum is useful if a single organism predominates and is not contaminated by saliva. Purulent sputum, pleuritic chest pain, pleural effusion favor typical pathogens.
**Pitfalls:** Obtain chest x-ray to verify the diagnosis and rule out noninfectious mimics (e.g., heart failure).
**Therapeutic Considerations:** Do not switch to narrow-spectrum antibiotic after organism is identified on gram stain/blood culture. Pathogen identification is important for prognostic and public health reasons, not for therapy. Severity of CAP is related to the degree of cardiopulmonary/immune dysfunction and impacts the length of hospital stay, not the therapeutic approach or antibiotic choice.
**Prognosis:** Related to cardiopulmonary status and splenic function.

## Community-Acquired Pneumonia (Pertussis)

**Clinical Presentation:** Rhinorrhea over 1–2 weeks (catarrhal stage) progressing to paroxysms of cough (paroxysmal stage) lasting 2–4 weeks, often without a characteristic inspiratory whoop, followed by a convalescent stage lasting 1–2 weeks during which cough paroxysms decrease in frequency/severity. Fever is low grade or absent. In children < 6 months, whoop is frequently absent and apnea may occur. Older children/adults may present with persistent cough (without whoop) lasting 2–6 weeks.
**Diagnostic Considerations:** A positive PCR or DFA for Bordetella pertussis from a nasopharyngeal swab (NP). May be cultured by beside inoculation from NP swab of Bordet-Gengou media. "Shaggy heart" on chest x-ray is characteristic. The only CAP with lymphocytosis > 60%.
**Pitfalls:** Consider pertussis in older children and adults with prolonged coughing. Hoarseness uncommon, but may be misleading by mimicing viral laryngitis or C. pneumoniae.
**Therapeutic Considerations:** By the paroxysmal stage, antibiotics have minimal effect on the course of the illness but are indicated to decrease transmission.
**Prognosis:** Good, despite the prolonged course.

## Community-Acquired Pneumonia (Atypical Pathogens)

**Clinical Presentation:** CAP with extrapulmonary symptoms, signs, or laboratory abnormalities.
**Diagnosis:** Confirm by specific serological tests.

## Legionnaire's Disease (Legionella sp.)

Legionella organisms live in a fresh water environment and survive in a symbiotic relationship with freshwater amoeba. Legionella infection may be introduced into humans via droplet aerosolization of Legionella-contaminated water supplies (e.g., cooling towers, water systems, whirlpools, showers, air conditioners, respiratory therapy devices). LD can occur in isolated cases or in outbreaks (community-acquired or nosocomial). Legionella has a seasonal predisposition and is most common in the late summer/early fall. LD is rare in young children, uncommon in young adults, but is most common in adult/elderly patients. Individuals with impaired cell-mediated immunity (↓ T-lymphocyte function) e.g., TNF-∝ antagonists are predisposed to LD, but normal hosts can be infected as well.
**Clinical Presentation:** LD is more severe than M. pneumoniae or C. pneumoniae CAP. Onset is usually acute, with high fever (≥ 102°F) and relative bradycardia Myalgias and chills are not uncommon. Like other atypical pneumonias, LD has a characteristic pattern of extrapulmonary

manifestations, which is the key to presumtive clinical diagnosis. On chest x-ray, LD is suggested not by the appearance of the infitrate, but by its rapid, asymmetric progression. With LD, bilateral involvement is usual, consolidation/pleural effusion are not uncommon, and cavitation is rare. Extrapulmonary LD findings include, otherwise unexplained, mental confusion, watery diarrhea, abdominal pain, relative lymphopenia ↑ ESR/CRP, mild/transient ↑ SGOT/SGPT, early/transient ↓ serum phosphorus, ↑ ferritin levels (> 2 × n) ↑ CPK, and early microscopic hematuria.

**Diagnostic Considerations:** Lack of response to beta-lactam therapy in a CAP patient suggests the possibility of LD and should prompt specific testing. Diagnosis is confirmed by Legionella DFA of sputum/respiratory secretions, Legionella IgM/IgG titers (a single titer ≥ 1:256 or ≥ 4 fold increase between acute and convalescent titers) is diagnostic. Legionella may also be cultured on BCYE agar from sputum/respiratory secretions, pleural effusion, or lung tissue. Legionella pneumophila (serotypes 01-06) may also be diagnosed by urinary antigen test.

**Pitfalls:** As no individual finding is pathognomonic the constellation of signs/symptoms of LD are often overlooked. The characteristic pattern of extrapulmonary organ involvement differentiates LD from other CAPs. Hyponatremia is common but nonspecific, but serum phosphorus is a more specific for LD. Findings suggestive of an alternate (non-Legionella) cause of CAP include ↑ cold agglutinin titer, normal SGOT/SGPT, normal serum phosphorus, normal CPK level, upper respiratory tract involvement (non-exudative pharyngitis, laryngitis, otitis) or splenomegaly. Legionella DFA of sputum/respiratory secretions is positive early, but rapidly becomes negative with treatment. Legionella titers, may be negative if ordered early (usually at the time of presentation). Antimicrobial therapy may eliminate/blunt a titer rise. Legionella urinary antigen testing is useful but has limitations, as it is not always positive early when the patient presents, and detects only Legionella pneumophila (serotypes 01-06), but not other Legionella species.

**Therapeutic Considerations:** Antimicrobial agents with a high degree of anti-Legionella activity are quinolones, doxycycline, tigecycline, and macrolides. Rifampin has in vitro anti-Legionella activity, but as part of combination therapy (erythromycin + rifampin) has not been shown to offer any advantage over well selected monotherapy (quinolone, doxycycline). LD does not respond to beta-lactams and only somewhat to erythromycin. Patients treated with a quinolone, doxycycline, or tigecycline typically defervesce slowly (5–7 days). Therapy is usually continued for 2–3 weeks depending upon clinical severity/host factors.

**Prognosis:** In immunocompetent hosts with good cardiopulmonary function, prognosis is good. Prognosis is guarded in the elderly and those with impaired CMI (HIV, organ transplants, corticosteroid therapy) and in those severe cardiopulmonary disease (CAD, valvular heart disease, COPD, chronic bronchiectasis).

## Mycoplasma pneumoniae

**Epidemiology:** M. pneumoniae primarily affects young adults and the elderly. M. pneumoniae is spread from person-to-person via aerosolized droplets.

**Clinical Presentation:** Onset is subacute with a characteristic dry/nonproductive cough that lasts for weeks, low-grade fever (< 102°F) /chills, and mild myalgias. As with other atypical CAPs, M. pneumoniae is characterized by its pattern of extrapulmonary organ involvement, which may include sore throat (non-exudative pharyngitis), bullous myringitis, otitis media, and/or watery loose stools/diarrhea (Table 2.1). Features that argue against the diagnosis of M. pneumoniae CAP include high fevers (>102°F), relative bradycardia, laryngitis, abdominal pain, ↑ SGOT/SGPT, low serum phosphorus, or renal abnormalities. Chest x-ray typically shows ill-defined unilateral infiltrates without pleural effusion, consolidation or cavitation. M. pneumoniae may present as severe CAP in compromised hosts, the elderly, and those with advanced COPD.

**Diagnostic Considerations:** M. pneumoniae testing is recommended for patients with otherwise unexplained protracted nonproductive cough, low-grade fevers, loose stools/watery diarrhea, and an ill-defined infiltrate on chest x-ray. Cold agglutinin titers are elevated early/transiently (75%) and provide a rapid presumptive diagnosis; titers ≥ 1:64 are due to M. pneumoniae. An elevated M. pneumoniae IgM ELISA titer suggests acute infection, but an elevated IgG titer indicates only past exposure; M. pneumoniae may be cultured from respiratory secretions on viral media (requires 1–2 weeks for growth).
**Pitfalls:** A dry, nonproductive cough also suggests an ILI or C. pneumoniae. Before ascribing E. multiforme to M. pneumoniae, be sure that it is not due to other causes (e.g., drug induced). Features that argue against the diagnosis of M. pneumoniae include temperature > 102°F, relative bradycardia, moderate/large pleural effusion, consolidation/cavitation, otherwise unexplained abdominal pain, ↑ SGOT/SGPT or low serum phosphorus. Suspect M. pneumoniae in chronic dry cough/new onset asthma.
**Therapeutic Considerations:** Doxycycline, macrolides, quinolones, or tigecycline result in rapid clinical response: in < 72 hours, but dry cough usually persists for weeks. Because Mycoplasma organisms reside on/in the bronchial epithelium, antimicrobial therapy should be continued for 2 weeks to eliminate carriage from oropharyngeal secretions and reduce the risk of transmission via aerosolized droplets.
**Prognosis:** M. pneumoniae is usually a mild, self-limiting illness in immunocompetent adults. M. pneumoniae may be severe in compromised hosts, the elderly, and those with advanced lung disease. Patients with M. pneumoniae and meningoencephalitis (headaches/stiff neck, mental confusion, very high cold agglutinin titers [often ≥ 1:1024]) have a good prognosis. M. pneumoniae may be complicated by transverse myelitis, brain stem/cerebellar ataxia, or Guillain-Barré syndrome after M. pneumoniae some patients develop permanent asthma.

## Chlamydophilia (Chlamydia) pneumoniae

**Epidemiology:** C. pneumoniae is may occur as sporadic cases part of an outbreak NHAP. C. pneumoniae is spread from person-to-person via aerosolized droplets. C. pneumoniae has no seasonal predisposition. Some patients with C. pneumoniae CAP develop permanent asthma.
**Clinical Presentation:** C. pneumoniae presents as a "mycoplasma-like" illness. Like other atypical CAPs, C. pneumoniae CAP is characterized by extrapulmonary findings, particularly nasal discharge, sore throat, and hoarseness (Table 2.1). Temperature is usually ≤ 102°F. Chest x-ray findings typically show a unilateral ill-defined infiltrate without consolidation, cavitation, or pleural effusion. C. pneumoniae testing is recommended in a patient with a "mycoplasma-like" illness and hoarseness.
**Diagnostic Considerations:** The diagnosis of C. pneumoniae CAP requires a single IgM titer of ≥ 1:16 or an IgG titer > 1:512 (ELISA or MIF). C. pneumoniae may be cultured from respiratory secretions using viral culture media.
**Pitfalls:** IgG titers indicate past exposure, not current infection. ↑ IgM and ↑ IgG titers may be delayed for more than 3 and 6 weeks, respectively. False negatives may occur if IgM titers are obtained too early. Recovery of C. pneumoniae from respiratory secretions does not differentiate carriage from infection. In a CAP patient with otherwise unexplained wheezing should suggest the possibility of C. Pneumoniae.
**Therapeutic Considerations:** Doxycycline, or quinolones are effective. C. pneumoniae is sensitive to erythromycin in vitro, but erythromycin is often ineffective in vivo. C. pneumoniae also responds to newer macrolides.
**Prognosis:** C. pneumoniae CAP is usually a mild/moderate pneumonia with an excellent prognosis. Severe CAP may occur in compromised hosts, the elderly, or those with severe lung disease some develop permanent asthma.
**Clinical Presentation:** CAP with extrapulmonary symptoms, signs, or laboratory abnormalities (Table 2.2).

**Table 2.1. Diagnostic Features of Non-zoonotic Atypical Pneumonias**

| Key Characteristics | Mycoplasma pneumoniae | Legionnaire's Disease | C. pneumoniae |
|---|---|---|---|
| **Symptoms** | | | |
| Mental confusion | –[†] | + | – |
| Prominent headache | – | ± | – |
| Meningismus | – | – | – |
| Myalgias | ± | ± | ± |
| Ear pain | + | – | ± |
| Pleuritic pain | – | ± | – |
| Abdominal pain | – | ± | – |
| Loose stools/watery diarrhea | ± | ± | – |
| **Signs** | | | |
| Rash | ± [a] | – | – |
| Non-exudative pharyngitis | + | – | + |
| Hemoptysis | – | ± | – |
| Wheezing | – | – | + |
| Lobar consolidation | – | ± | – |
| Cardiac involvement | ± [b] | – [c] | – |
| Splenomegaly | – | – | – |
| Relative bradycardia | – | + | – |
| **Laboratory Abnormalities** | | | |
| WBC count | ↑/N | ↑ | N |
| Acute thrombocytosis | ± | – | – |
| Hyponatremia | – | + | – |
| Hypophosphatemia (early) | – | + | – |
| ↑ AST/ALT (SGOT/SGPT) | – | + | – |
| ↑ CPK | – | ± | – |
| ↑ ESR (> 100 mm/h) | – | + | – |
| ↑ Ferritin (> 2 x n) | – | + | – |
| ↑ Cold agglutinins (≥ 1:64) | + | – | – |
| Microscopic hematuria (early) | – | ± | – |
| **Chest X-Ray** | | | |
| Infiltrate | Patchy | Patchy | Circumscribed lesions |
| Bilateral hilar adenopathy | – | – | – |
| Pleural effusion | ± (small) | ± | – |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = normal; WBC = white blood cell.
+ = usually present; ± = sometimes present; – = usually absent.
↑ = increased; ↓ = decreased; ↑↑↑ = markedly increased.
a = erythema multiforme; b = myocarditis, heart block, or pericarditis; c = unless endocarditis.
† = mental confusion only if meningoencephalitis.
†† = often not be positive early, but antigenuria persists for weeks. Useful only to diagnose L. pneumophila (serogroups 1-6), not other species/serogroups.

## **Zoonotic Atypical Pneumonia** (see Chapter 8 for Differential Diagnosis of Chest X-Ray patterns)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Zoonotic pathogens (zoonotic vector) | C. psittaci (psittacosis)<br>Coxiella burnetii (Q fever)<br>Francisella tularensis (tularemia) | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days | Levofloxacin 500 mg (IV) × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (IV) × 2 weeks | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days†<br>**or**<br>Levofloxacin 500 mg (PO) × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (PO) × 2 weeks |

Duration of therapy represents total time IV, PO, or IV + PO.
* *Compromised hosts may require longer courses of therapy.*
† *Loading dose is not needed PO if give IV with the same drug.*

**Diagnostic Considerations:** Zoonotic contact history is key to presumptive diagnosis: psittacosis (parrots and psittacine birds); Q fever (sheep, parturient cats); tularemia (rabbit, deer, deer fly bite). The diagnosis is confirmed by specific serological testing. Zoonotic CAP with splenomegaly/relative bradycardia suggests Q fever or psittacosis.

**Pitfalls:** Organisms are difficult/dangerous to grow. Do not culture. Use serological tests for diagnosis. The diagnosis of acute Q fever is by demonstrating elevated IgG (phase II) C. burnetii titers. Most patients with acute Q fever do not become chronic e.g., Q fever SBE. The diagnosis of chronic Q fever is made by demonstrating elevated IgG (phase I) titers ≥ 1:1024 at 6 months following acute Q fever. C. burnetii (Q fever) titers may cross react with Bartonella titers.

**Therapeutic Considerations:** Q fever endocarditis requires prolonged therapy.

**Prognosis:** Good except for Q fever with complications, e.g., myocarditis, SBE.

**Table 2.2. Diagnostic Features of Zoonotic Atypical Pneumonias**

| Key Characteristics | Psittacosis | Q Fever | Tularemia |
|---|---|---|---|
| **Symptoms** | | | |
| Mental confusion | – | ± | – |
| Prominent headache | + | + | + |
| Meningismus | – | – | – |
| Myalgias | + | + | + |
| Ear pain | – | – | – |
| Pleuritic pain | ± | ± | + |
| Abdominal pain | – | – | – |
| Diarrhea | – | – | – |
| **Signs** | | | |
| Rash | ± a | – | – |
| Nonexudative pharyngitis | – | – | ± |
| Hemoptysis | – | – | ± |
| Lobar consolidation | + | + | + |
| Cardiac involvement | ± b | ± c | – |
| Splenomegaly | ± | + | – |
| Relative bradycardia | ± | ± | – |
| **Chest X-Ray** | | | |
| Infiltrate | Patchy consolidation | "Round" infiltrates or consolidation | "Ovoid infiltrates" |
| Bilateral hilar adenopathy | – | – | ± |
| Pleural effusion | – | – | Bloody |
| **Laboratory Abnormalities** | | | |
| WBC count | ↓ | ↑/N | ↑/N |
| Thrombocytosis | – | + | – |
| Hyponatremia | ± | ± | ± |
| Hypophosphatemia | – | – | – |
| ↑ AST/ALT (SGOT/SGPT) | + | + | – |
| ↑ Cold agglutinins | – | ± | – |
| Anti-smooth muscle antibodies (anti-SMA) | – | ± | – |
| Microscopic hematuria | – | – | – |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = normal; WBC = white blood cell.
+ = usually present; ± = sometimes present; – = usually absent.
↑ = increased; ↓ = decreased; ↑↑↑ = markedly increased.
a = Horder's spots (facial spots, resemble the abdominal rash of typhoid fever (rose spots); b = Mycocarditis; c = endocarditis.

## Severe Acute Respiratory Syndrome (SARS)

**Presentation:** Fever, dry cough, myalgias, diarrhea in some. Auscultation of the lungs resembles viral influenza (i.e., quiet, no rales). Biphasic infection: fever decreases after few days, patient improves, then fever recurs in a few days and patients become short of breath/hypoxic. Chest x-ray shows bilateral interstitial (diffuse) infiltrates. WBC and platelet counts are usually normal or slightly decreased. Relative lymphopenia present early. Mild increases in SGOT/SGPT, LDH, CPK are common.
**Diagnostic Considerations:** Diagnosis by viral isolation or specific SARS serology. Important to exclude influenza A, Legionnaires' disease and tularemic pneumonia.
**Pitfalls:** Should not be confused with viral influenza (a 3-day illness). Patients with SARS deteriorate during week 2 when influenza patients are recovering. Early, chest x-ray in SARS has discrete infiltrates (unlike influenza unless superimposed CAP) that may be ovoid. Late, ARDS on chest x-ray.
**Therapeutic Considerations:** Most patients are severely hypoxemic and require oxygen/ventilatory support. In a preliminary study, some patients benefitted from corticosteroids (pulse-dosed methylprednisolone 500 mg [IV] q24h × 3 days followed by taper/step down with prednisone [PO] to complete 20 days) plus Interferon alfacon-1 (9 mcg [SQ] q24h × at least 2 days, increased to 15 mcg/d if no response) × 8–13 days. Ribavirin of no benefit.
**Prognosis:** Related to underlying cardiopulmonary/immune status/ARDS. Frequently fatal.
**Pitfalls:** Failure to respond to beta-lactams should suggest diagnosis of atypical CAP.
**Therapeutic Considerations:** Treat Legionella × 4 weeks. Treat Mycoplasma or Chlamydia × 2 weeks.
**Prognosis:** Related to severity of underlying cardiopulmonary disease.

## Middle East Respiratory Syndrome (MERS)

**Clinical Presentation:** Presents as an influenza like illness (ILI) with acute onset of fever, chills, dry cough/SOB, myalgias ± N/V/D. Headache/sore throat common. Hemoptysis in some. Rapidly progressive respiratory failure/ARDS is typical (~ 1 week). WBC counts usually normal, thrombocytopenia, ↑LFTs, ↑LDH, relative lymphopenia, but lymphocytosis in some. CXR: basilar unilateral (initially) or bilateral dense interstitial/nodular infiltrates (later). Consolidation common ± pleural effusions.
**Diagnostic Considerations:** MERS resembles an ILI clinically (unlike SARS-CoA). Contact with dromedary camels (MERS reservoir). Dx is by RT-PCR of MERS-CoA virus in respiratory secretions (lower > upper). MERS, in respiratory secretions (lower > upper), but not in stools/urine (unlike SARS-CoA).
**Pitfalls:** Resembles severe influenza A. Not a biphasic illness (like SARS-CoA).
**Therapeutic Considerations:** Ventilatory support, but no effective treatment available. No bacterial co-infections, i.e., no antibiotics for superimposed bacterial CAP. IC measures important to prevent person-to-person/nosocomial spread.
**Prognosis:** High mortality rate with rapidly progressive severe respiratory failure/ARDS especially with comorbidities.

## Avian Influenza (Influenza A ($H_5N_1$, $H_7N_9$) Pneumonia

**Clinical Presentation:** Influenza following close contact with infected poultry. Recent outbreaks in humans in Asia. Human-to-human transmission reported. Often fulminant respiratory illness rapidly followed by ARDS/death.
**Diagnostic Considerations:** Often acute onset of severe influenza illness ± diarrhea/conjunctival suffusion with leukopenia, lymphopenia, mildly ↑ serum transaminases and ↑ LDH. Diagnosis by hemagglutin-specific RT-PCR for avian influenza or culture of respiratory secretions. Not complicated by bacterial CAP. No need for empiric antibiotic therapy.
**Pitfalls:** Although avian influenza is caused by influenza A virus, the hemagglutinin inhibition serological test used to diagnose influenza A is insensitive to avian hemagglutinin, resulting in negative testing.
**Therapeutic Considerations:** Antivirals must be given early to be effective. Avian influenza strains may be resistant to oseltamivir and amantadine/rimantadine. Oseltamivir 150 mg dose may be more effective than 75 mg dose. Even if resistant, amantadine/rimantadine should be given to increase peripheral airway dilatation/oxygenation.
**Prognosis:** Often fulminant with ARDS/death. Unlike human/swine influenza, avian influenza is often rapidly/highly lethal but *not* complicated by MSSA/MRSA CAP.

## Influenza A/B Pneumonia

**Clinical Presentation:** Acute onset of fever, headache, myalgias/arthralgias, sore throat, prostration, dry cough. Myalgias most pronounced in lower back/legs. Eye pain is common. Rapid high fever initially, which decreases in

2–3 days. Severity ranges from mild flu to life-threatening pneumonia. Chest x-ray in early influenza is normal/near normal without focal/segmental infiltrates or pleural effusion.

**Diagnostic Considerations:** Mild cases with headache, sore throat, and rhinorrhea resemble the common cold/respiratory viruses (influenza-like illnesses) and can be caused by type A or B. Severe flu is usually due to type A. Rapid diagnosis by DFA of respiratory secretions (nasopharyngeal swabs). Influenza virus may be cultured in viral media from respiratory secretions and typed.

**Pitfalls:** Influenza pneumonia has no chest auscultatory findings and the chest x-ray is normal/near normal. Severe influenza pneumonia is accompanied by an oxygen diffusion defect (↑ A-a gradient), and patients are hypoxemic/cyanotic. Pleuritic chest pain may be present. Influenza can invade the intercostal muscles to mimic pleuritic chest pain. Labor/segmental infiltrates on CXR with influenza pneumonia indicate simultaneous or subsequent bacterial CAP. If CAP presents with fulminant/severe necrotizing pneumonia in a normal host look for antecedent or concomitant influenza pneumonia.

**Therapeutic Considerations:** Mild/moderate influenza can be treated with neuraminidase inhibitors (Tamiflu/Relenza), which reduce symptoms by 1–2 days. Start treatment within 2 days of symptom onset. Reduce the dose of Tamiflu to 75 mg (PO) q48h for CrCl 10–30 ml/min. Relenza is generally not recommended for patients with underlying COPD/asthma (increased risk of bronchospasm) and should be discontinued if bronchospasm or a decline in respiratory function occurs. For severe influenza pneumonia, amantadine may increase peripheral airway dilatation/oxygenation. Reduce the dose of rimantadine to 100 mg (PO) q24h in the elderly, severe liver dysfunction, or CrCl < 10 ml/min. Peramivir may be given in severe cases. Flu *with simultaneous bacterial CAP is due to MSSA/MRSA* and *post-influenza CAP usually due to S. pneumoniae or H. influenzae* (Table 2.3).

**Prognosis:** Good for mild/moderate flu. Severe flu may be fatal due to influenza pneumonia with profound hypoxemia. Prognosis is worse if presents with simultaneous MSSA/MRSA. Influenza with necrotizing community-acquired (CA) MSSA/MRSA CAP is frequently fatal. Prognosis is worst for CA-MRSA Panton-Valentine Leukocidin (PVL)-positive strains. Dry cough/fatigue may persist for weeks after influenza.

**Table 2.3. The 3 Clinical Presentations of Influenza A Pneumonia in Adults**

| Clinical features at time of onset | Severity | Usual Pathogens |
|---|---|---|
| • Influenza pneumonia (***no focal/lobar infiltrates***) | **Mild/moderate** → *rarely fatal* | **Influenza** (human, avian, swine†) |
| • Influenza pneumonia with **simultaneous** bacterial CAP (***with multiple rapidly cavitating infiltrates***) | **Severe** → *often rapidly fatal* | **Influenza** (human, swine *not* avian) **plus MSSA/CA-MRSA*** |
| • Influenza pneumonia with **sequential** bacterial CAP (***followed by non-cavitating focal/lobar infiltrates*** (*after ~1 week of improvement*)) | **Mild/moderate** → *rarely fatal* (unless underlying cardiopulmonary disease/ Immunodeficiency). Same prognosis as in S. pneumoniae/H. influenzae CAP without influenza. | **S. pneumoniae H. influenzae** |

† Avian influenza ($H_5N_1$) often rapidly fatal in young/healthy adults.

* CA-MRSA PVL + strains highly virulent.

## Swine Influenza ($H_1N_1$) Pneumonia

**Clinical Presentation:** Swine influenza ($H_1N_1$) may present with a mild illness with fever, cough, and loose stools/diarrhea to severe viral pneumonia requiring ventilation that may rapidly progress to ARDS/death. Because the clinical presentation resembles that of human seasonal influenza, patients with swine influenza ($H_1N_1$) pneumonia as well as other viral pneumonias typically present as influenza-like illnesses (ILIs). Unlike human seasonal influenza, swine influenza ($H_1N_1$) pneumonia affects primarily young healthy adults. As with human seasonal influenza, swine influenza ($H_1N_1$) may affect children, pregnant females, and the elderly with co-morbid conditions. In admitted adults, swine influenza ($H_1N_1$) pneumonia typically presents with high fevers > 102°F often with shaking chills and myalgias. Patients may also complain of headache or sore throat. Dry cough is characteristic but a mildly productive cough with thin mucoid sputum is also common. Patients are variably short of breath. Conjunctival suffusion is rare. Lungs are clear to auscultation. Patients often have loose stools/diarrhea but not abdominal pain. Swine influenza ($H_1N_1$) pneumonia clinically resembles human seasonal influenza, avian influenza, CMV or adenoviral CAP. CXR early (< 48 hours) typically is clear or may show accentuated bibasilar lung markings resembling basilar atelectasis. CXR later (> 48 hours) typically shows bilateral patchy interstitial infiltrates. Consolidation may occur later, but cavitation or moderate/large pleural effusions are not features. Degree of hypoxemia is related to the severity of pneumonia. In adults, nonspecific laboratory clues include otherwise unexplained relative lymphopenia, thrombocytopenia, elevated CPKs or mildly elevated serum transaminases (SGOT/SGPT). Atypical lymphocytes are not present in adults. Unlike in human seasonal and avian influenza ($H_2N_1$), leukopenia is uncommon in swine influenza ($H_1N_1$) pneumonia in adults. Serum LDH is variably elevated. Elevated cold agglutinin titers are not elevated. Nosocomial transmission may occur.

**Diagnostic Considerations:** Definitive diagnosis is by RT-PCR of oropharyngeal/respiratory secretions/lung. Rapid influenza diagnostic screening tests (RIDTs), if positive, correlate well with RT-PCR positivity. However, ~30% of (RIDTs) are false negative. Discordant testing results with rapid influenza A, respiratory FA viral panel, and RT-PCR may be due to variability of specimens rather than differences in test sensitivity/specificity. All respiratory secretion diagnostic tests may be negative in autopsy proven cases of swine influenza ($H_1N_1$) pneumonia whose lungs are RT-PCR positive.

**Pitfalls:** Since swine influenza ($H_1N_1$) pneumonia presents as an ILI, care must be taken to rule out other viral pneumonias as well as mimics of viral pneumonia. The CXR is important in identifying possible mimics of swine flu. While human seasonal influenza may present simultaneously with MSSA/MRSA CAP or subsequently after an interval (5–7 days) of improvement with *S. pneumoniae* or *H. influenzae* CAP, this and has been uncommon with swine influenza ($H_1N_1$) pneumonia and has not been a complication of avian influenza ($H_5N_1$) pneumonia. Swine influenza ($H_1N_1$) pneumonia on CXR appears initially with clear lung fields and with subsequent bilateral patchy infiltrates. Cold agglutinins and atypical lymphocytes may occur in pediatric cases but in adults should suggest an alternate diagnosis, e.g., adenoviral or CMV pneumonia.

**Therapeutic Considerations:** Swine influenza ($H_1N_1$) appears to respond to oseltamivir. There are no benefits to steroids. Although amantadine or rimantadine are ineffective against swine influenza ($H_1N_1$), patients who are severely hypoxemic may benefit from amantadine or rimantadine by increasing peripheral airway dilatation/oxygenation. If the CXR in swine influenza ($H_1N_1$) pneumonia has no lobar/focal infiltrates, there is no need to treat with empiric antimicrobial therapy. Swine influenza ($H_1N_1$) pneumonia with multiple lobar/focal infiltrates that rapidly cavitate (< 72 hours) empiric anti-MSSA/CA-MRSA therapy should be given with oseltamivir. For patients with swine influenza ($H_1N_1$) pneumonia that

improves and after 5–7 days re-present with focal segmental/lobar (non-cavitating) infiltrates, treat as for typical CAP to cover S. pneumoniae or H. influenzae.

In patients unable to take oval oseltamivir, IV peramivir may be given. (See p. 665 for dosing recommendations.)

**Prognosis:** In immuncompetent adults, prognosis is related to severity of swine influenza ($H_1N_1$) pneumonia. With swine influenza ($H_1N_1$), prognosis is directly related to the severity of pneumonia (degree/duration of severe hypoxemia) and degree/persistence of relative lymphopenia. Prognosis worst with simultaneous MSSA/MRSA CAP, but is not worse with subsequent S. pneumoniae or H. influenzae CAP.

### *S. aureus* (MSSA/MRSA) Pneumonia

**Clinical Presentation:** Only occurs with an antecedent ILI or concurrent influenza pneumonia. Does not occur in DM or those on chronic steroids/immunosuppressive therapy. Presents as a fulminant necrotizing CAP with high fevers, hemoptysis, cyanosis, and hypotension. CXR shows unilateral/bilateral rapid cavitation of pulmonary infiltrates < 72 hrs.

**Diagnostic Considerations:** Patient severely hypoxemic with ↑ A-a gradient ( >35 ) due to underlying influenza pneumonia. Blood/sputum cultures + for MSSA/MRSA.

**Pitfalls:** Culture of MSSA/MRSA from sputum in CAP without rapid cavitation < 72 hrs on CXR, represents colonization, not diagnostic of MSSA/MRSA CAP. Patients CAP due to MSSA/MRSA are critically ill with high spiking fevers, hemoptysis, cyanosis, and hypotension. Diagnosis not supported by MSSA/MRSA in sputum/blood cultures unless accompanied by the clinical features of MSSA/MRSA pneumonia.

**Therapeutic Considerations:** Treat underlying influenza as well as the superimposed MSSA/MRSA pneumonia with an antibiotic with a high degree of anti- MSSA/MRSA activity, e.g., linezolid (avoid daptomycin). Resection of necrotic lung segments may be life saving.

**Prognosis:** Poor (independent of host factors). Worst prognosis is with PVL + strains.

### Aspiration Pneumonia

**Diagnostic Considerations:** Sputum not diagnostic. No need for transtracheal aspirate culture.

**Pitfalls:** Lobar location varies with patient position during aspiration.

**Therapeutic Considerations:** Oral anaerobes are sensitive to all beta-lactams and most antibiotics used to treat CAP. Additional anaerobic (B. fragilis) coverage is not needed.

**Prognosis:** Related to severity of CNS/esophageal disease.

### HIV with CAP (*Sputum Negative for AFB*) *(PCP see p. 325)*

**Clinical Presentation:** Bacterial CAP in HIV patient with focal infiltrate(s) and normal/slightly depressed $CD_4$.

**Diagnostic Considerations:** Diagnosis by sputum gram stain/culture ± positive blood cultures (bacterial pathogens) or Legionella/Chlamydia serology (atypical pathogens). S. pneumoniae and H. influenzae are particularly common.

**Pitfalls:** Atypical chest x-ray appearance is not uncommon. Treat syndrome of CAP, not chest x-ray. Bacterial CAP (focal/segmental infiltrates) in HIV does not resemble PCP (bilateral patchy interstitial infiltrates). PCP presents with profound hypoxemia and ↑ LDH. β 1,3 D-glucan +, aspergillus galactomannan –.

**Therapeutic Considerations:** R/O TB/MAI with negative sputum AFB stain. If AFB negative, treat same as bacterial CAP in normal hosts.

**Prognosis:** Same as bacterial CAP in normal hosts.

## Tuberculous (TB) Pneumonia

**Clinical Presentation:** Community-acquired pneumonia with single/multiple infiltrates.

**Diagnostic Considerations:** Diagnosis by sputum AFB smear/culture. Primary TB is lower lobe usually with a pleural effusion. Reactivation TB is usually bilateral/apical ± old, healed Ghon complex; cavitation/fibrosis are common, but adenopathy or pleural effusions uncommon. TB reactivation ↑ with steroids, immunosuppressive drugs, HIV, gastorectomy, jejunoileal bypass, silicosis, DM, CRI, advanced age.

**Pitfalls:** Primary TB may present as CAP and improve transiently with quinolone therapy. Primary TB patients with large pleural effusion usually anergic.

**Therapeutic Considerations:** Usually sputum becomes smear negative in 1–2 weeks of therapy.

**Prognosis:** Related to underlying health status.

## Mycobacterium avium-intracellulare (MAI) Pneumonia

**Clinical Presentation:** Community-acquired pneumonia in normal hosts or immunosuppressed/HIV patient with focal single/multiple infiltrates indistinguishable from TB.

**Diagnostic Considerations:** Diagnosis by AFB culture. In HIV, MAI may disseminate, resembling miliary TB. MAI typically lingular with "tree in bud" appearance on chest CT. BHA more frequent than with TB.

**Pitfalls:** May mimic reactivation TB. Must differentiate TB from MAI by AFB culture, since therapy for MAI differs from TB.

**Therapeutic Considerations:** Should be treated until sputum cultures are negative × 1 year.

**Prognosis:** Good in normal hosts. In HIV related to degree of immunosuppression/$CD_4$ count.

## Mycobacterium kansasii Pneumonia

**Clinical Presentation:** Subacute CAP resembling reactivation TB.

**Diagnostic Considerations:** Chest x-ray infiltrates/lung disease plus M. kansasii in a single sputum specimen. M. kansasii can cause disseminated infection, like TB, and is diagnosed by culturing M. kansasii from sputum, blood, liver, or bone marrow.

**Pitfalls:** M. kansasii in sputum with a normal chest x-ray and no symptoms does not indicate infection.

**Therapeutic Considerations:** Should be treated until sputum cultures are negative × 1 year.

**Prognosis:** Good in normal hosts. May be rapidly progressive/fatal without treatment in HIV patients.

## Pneumonia in Chronic Alcoholics

**Diagnostic Considerations:** Klebsiella pneumoniae usually occurs only in chronic alcoholics, and is characterized by blood-flecked "currant jelly" sputum and cavitation (typically in 3–5 days).

**Pitfalls:** Suspect Klebsiella in "pneumococcal" pneumonia that cavitates. Empyema is more common than pleural effusion.

**Therapeutic Considerations:** Monotherapy with newer anti-Klebsiella agents, e.g., 3rd GC, carbapenems, colistin, tigecycline, are as effective or superior to "double-drug" therapy with older agents.

**Prognosis:** Related to degree of hepatic/splenic dysfunction.

## Bronchiectasis/Cystic Fibrosis

**Diagnostic Considerations:** Cystic fibrosis/bronchiectasis is characterized by viscous secretions ± low grade fevers; less commonly may present as lung abscess. Onset of pneumonia/lung abscess heralded by cough/decrease in pulmonary function.

**Pitfalls:** Sputum colonization is common (e.g., S. maltophilia, B. cepacia, P. aeruginosa); may not reflect pathogens.

**Therapeutic Considerations:** Important to select antibiotics with low resistance potential and good penetration into respiratory secretions (e.g., quinolones, meropenem).

**Prognosis:** Related to extent of underlying lung disease/severity of infection.

### Pneumonia in Organ Transplants

**Clinical Presentation:** CAP with perihilar infiltrates and hypoxemia.

**Diagnostic Considerations:** CMV is diagnosed by stain/culture of lung biopsy.

**Therapeutic Considerations:** Treat as CMV pneumonia if CMV is predominant pathogen on lung biopsy. CMV may progress despite ganciclovir therapy.

**Prognosis:** Related to degree of immunosuppression.

### Pneumonia in Chronic Steroid Therapy

If fungal infection is suspected, obtain lung biopsy to confirm diagnosis/identify causative organism. Non-responsiveness to appropriate antibiotics should suggest fungal infection. Avoid empirically treating fungi; due to the required duration of therapy, it is advantageous to confirm the diagnosis by lung biopsy first. Prognosis related to degree of immunosuppression.

#### *Acute Aspergillus Pneumonia*

**Clinical Presentation:** Chest x-ray shows progressive necrotizing pneumonia (bilateral in half) unresponsive to antibiotics. Characteristic of early Apsergillus pneumonia is the "halo sign". A few days later the halo decreases in size. After a week after the appearance of the halo sign, the "air crescent sign" is typically present. Usually seen only in compromised hosts.

**Diagnostic Considerations:** Diagnosis by lung biopsy (not bronchoalveolar lavage) demonstrating hyphae invading lung parenchyma/blood vessels. Usually occurs only in patients on chronic steroids, cancer chemotherapy, organ transplants, leukopenic compromised hosts, or with chronic granulomatous disease (CGD). β 1,3 D-glucan +, aspergillus galactomannan +. Aspergillus galactomannan (GM) may XR with Geotrichum, Blastomyces, Penicillium, or Alternaria. ↑ GM levels with cyclophosphamide and if enteritis/colitis (↑ absorption of GM).

**Pitfalls:** Invasive Aspergillus pneumonia does not occur in normal/non-immunosuppressed hosts. PCP has ↑ LDH levels and β 1,3 D-glucan +, aspergillus galactomannan –.

**Prognosis:** Cavitation is a good prognostic sign. Prognosis related to degree of immunosuppression.

## Lung Abscess/Empyema

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Lung abscess/ empyema | Oral anaerobes<br>S. aureus<br>K. pneumoniae<br>S. pneumoniae | Clindamycin 600 mg (IV) q8h* **or** Piperacillin/ tazobactam 3.375 gm (IV) q8h* | Meropenem 1 gm (IV) q8h* **or** Ertapenem 1 gm (IV) q24h* | Clindamycin 300 mg (PO) q8h* **or** Quinolone† (PO) q24h* |

Bronchiectasis, cystic fibrosis (P. aeruginosa): see p. 54

* Treat until resolved. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

† Moxifloxacin 400 mg or Levofloxacin 500 mg.

**Clinical Presentation:** Lung abscess presents as single/multiple cavitary lung lesion(s) with fever. Empyema presents as persistent fever/pleural effusion without layering on lateral decubitus chest x-ray.
**Diagnostic Considerations:** In lung abscess, plain film/CT scan demonstrates cavitary lung lesions appearing > 1 week after pneumonia. Most CAPs are not associated with pleural effusion, and few develop empyema. In empyema, pleural fluid pH is ≤ 7.2; culture purulent exudate for pathogen.
**Pitfalls:** Pleural effusions secondary to CAP usually resolve rapidly with treatment. Suspect empyema in patients with persistent pleural effusions with fever.
**Therapeutic Considerations:** Chest tube/surgical drainage needed for empyema. Treat lung abscess until it resolves (usually 3–12 months).
**Prognosis:** Good if adequately drained.

## Nursing Home-Acquired Pneumonia (NHAP)

| Subset | Usual Pathogens* | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Nursing home-acquired pneumonia (NHAP) | H. influenzae<br>S. pneumoniae<br>M. catarrhalis | Ceftriaxone 1 gm (IV) q24h × 2 weeks **or** Respiratory quinolone†† (IV) q24h × 2 weeks **or** Doxycycline 200 mg (IV) q12h × 3 days; then 100 mg (IV) q12h × 2 weeks | Ertapenem 1 gm (IV) q24h × 2 weeks **or** Cefepime 2 gm (IV) q12h × 2 weeks | Respiratory quinolone†† (PO) q24h × 2 weeks **or** Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days |

**Diagnostic Considerations:** H. influenzae is common.
**Pitfalls:** Resembles community-acquired pneumonia in terms of pathogens and length of stay, not nosocomial pneumonia. NHAP outbreaks may be due to H. influenzae, C. pneumoniae, hMPV, or Legionnaire's disease.
**Therapeutic Considerations:** Treat as community-acquired pneumonia, not nosocomial pneumonia. No need to cover P. aeruginosa or GNBs which are common colonizers of nursing home patients, but not causes of NHAP.
**Prognosis:** Related to underlying cardiopulmonary status.

## Nosocomial Pneumonia (NP) / Hospital-Acquired Pneumonia (HAP) / Ventilator-Associated Pneumonia (VAP)§

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Empiric therapy | P. aeruginosa*<br>E. coli<br>K. pneumoniae<br>S. marcescens<br>(S. aureus)† | Meropenem 1 gm (IV) q8h × 1–2 weeks<br>**or**<br>Doripenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Levofloxacin 750 mg (IV) q24h × 1–2 weeks<br>**or**<br>Piperacillin/tazobactam 4.5 gm (IV) q6h ***plus*** amikacin 1 gm (IV) q24h × 1–2 wks | | Levofloxacin 750 mg (PO) q24h × 1–2 weeks<br>**or**<br>Ciprofloxacin 750 mg (PO) q12h × 1–2 weeks |

* For *confirmed* P. aeruginosa NP/VAP, combination therapy *preferred*.
† **MSSA/MRSA are common colonizers of respiratory secretions. In ventilated patients with fever, leukocytosis, and infiltrates on CXR, are *not* diagnostic of MSSA/MRSA NP/HAP/VAP. *MSSA/MRSA NP/HAP/VAP is clinically distinctive and rare.***
§ Treat aspiration NP same as NP/VAP. Anerobes not pathogens in aspiration NP.

## Nosocomial Pneumonia (NP) / Hospital-Acquired Pneumonia (HAP) / Ventilator-Associated Pneumonia (VAP) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Specific therapy | P. aeruginosa*‡ | Meropenem 1 gm (IV) q8h × 2 weeks **plus either** Levofloxacin 750 mg (IV) q24h × 2 weeks **or** Amikacin 1 gm (IV) q24h × 2 weeks | | Levofloxacin 750 mg (PO) q24h × 2 weeks **or** Ciprofloxacin 750 mg (PO) q12h × 2 weeks |
| | MDR Klebsiella or MDR Acinetobacter | Meropenem 1 gm (IV) q8h × 2 weeks **or** Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks¶ **or** Ceftolozane/tazobactam 1.5 gm (IV) q8h × 2 weeks **or** Colistin 5 mg/kg (IV) q8h × 2 weeks | | |
| | MDR P. aeruginosa | Doripenem 1 gm (IV) q8h × 2 weeks† **or** Meropenem 1 gm (IV) q8h × 2 weeks§ **or** Ceftolozane/tazobactam 1.5 gm (IV) q8h × 2 weeks | | |
| | CRE | Ceftazidime/avibactam 2.5 gm (IV) q8h × 2 weeks **or** Colistin 5 mg/kg (IV) q8h × 2 weeks | | |
| | HSV-1** | Acyclovir 10 mg/kg (IV) q8h × 10 days | | Valacyclovir 1 gm (PO) q8h × 10 days |

* **For empiric P. aeruginosa coverage, monotherapy sufficient.** For *proven* P. aeruginosa NP/VAP, *combination therapy preferred.*

‡ P. aeruginosa NP/VAP shows multiple infiltrates with rapid cavitation in <72 h on CXR ± otherwise unexplained blood cultures for P. aeruginosa (BCs negative with inhalation acquired P. aeruginosa VAP and BCs + with in hematogenously acquired P. aeruginosa NP/VAP).

† Give as a 4 hour infusion.

** Presents late in course of VAP as "failure to wean", does *not* present as early VAP.

§ If susceptible.

¶ Higher than usual doses of tigecycline may be necessary for non-susceptible/relatively resistant MDR GNBs.

**Clinical Presentation:** Pulmonary infiltrate compatible with a bacterial pneumonia occurring ≥ 1 week in-hospital ± fever/leukocytosis.

**Diagnostic Considerations:** CXR infiltrates with leukocytosis and fever are nonspecific/nondiagnostic of NP/VAP. Definitive diagnosis by lung biopsy. P. aeruginosa is a common colonizer in ventilated patients. P. aeruginosa VAP manifests as a necrotizing pneumonia with rapid cavitation (< 72 hours), microabscesses, and blood vessel invasion. S. aureus (MSSA/MRSA) NP/VAP remains rare. MSSA/MRSA common colonizers of respiratory secretions. Acinetobacter/Legionella NP/VAP usually occur in clusters/outbreaks.

**Pitfalls:** No rationale for "covering" non-pulmonary pathogens colonizing respiratory secretions in ventilated patients (Enterobacter, B. cepacia, S. maltophilia, Citrobacter, Flavobacterium, Enterococci); these organisms rarely if ever cause NP/VAP. Semi-quantitative BAL/protected brush specimens often reflect airway colonization. Characteristic clinical presentation (necrotizing pneumonia with rapid cavitation < 72 hrs) or tissue biopsy is needed for diagnosis of P. aeruginosa NP/VAP. MSSA/MRSA are common colonizers of respiratory secretions and are not uncommon causes of tracheobronchitis in ventilated patients. While MSSA/MRSA colonization of respiratory secretions is common, MSSA/MRSA necrotizing/rapidly cavitating NP/VAP is rare.

**Therapeutic Considerations:** NP (HAP/VAP) is defined as pneumonia acquired > 5 hospital days. So called "early" NP occurring < 5 days of hospitalization, usually due to S. pneumoniae or H. influenzae, represents CAP that manifests early after hospital admission. Empiric therapy recommendations cover usual NP/VAP pathogens. Monotherapy is as effective as combination therapy for non-P. aeruginosa NP/VAP, but 2-drug therapy is recommended for confirmed P. aeruginosa NP/VAP. If MSSA/MRSA nectorizing/rapidly cavitating NP/VAP present, may be treated with vancomycin, quinupristin/dalfopristin, tigecycline, or linezolid. After 2 weeks of appropriate antibiotic therapy, nonprogressive/stable pulmonary infiltrates with fever and leukocytosis are usually due to a noninfectious cause, rather than persistent infection. Treat aspiration NP/VAP the same as NP/VAP since anaerobes are not important pathogens in NP/VAP.

**Prognosis:** Related to underlying cardiopulmonary status.

## Empiric Therapy of Cardiovascular Infections

### Native Valve Subacute Bacterial Endocarditis (SBE)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| No obvious source or oral | Viridans streptococci*† Groups B, C, G streptococci, S. bovis (PCN MIC < 0.12 mcg/ml) | Ceftriaxone 2 gm (IV) q24h × 2 weeks*‡ **plus** Gentamicin 240 mg or 3 mg/kg (IV) q24h × 2 weeks* **or monotherapy with** Ceftriaxone 2 gm (IV) q24h × 4 weeks | Penicillin G 3 mu (IV) q4h × 2 weeks*‡ **plus** Gentamicin 240 mg or 3 mg/kg (IV) q24h × 2 weeks* **or** Vancomycin 1 gm (IV) q12h × 2 weeks **or** Linezolid 600 mg (IV) q12h × 4 weeks | Linezolid§ 600 mg (PO) q12h × 4–6 weeks **or** Amoxicillin§ 1 gm (PO) q8h × 4–6 weeks |

* If *relatively* PCN resistant (MIC 0.12–0.5 mcg/ml) or if *no intra/extra cardiac complications* treat × 4 weeks.

† S. mitis (S. mitior), S. oralis, S. gordonii, S. parasanguis, S. sanguis, S. mutans, S. sobrinus, S. thermophilus, S. angiosus, S. milleri, S. intermedius, S. constellatus.

‡ In PCN allergic patients, Vancomycin 1 gm (IV) q12h × 2 weeks.

§ IV therapy preferred. PO therapy if no IV access or if patient not a surgical candidate.

## Native Valve Subacute Bacterial Endocarditis (SBE) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| | Nutritionally-variant streptococci (NVS) pyridoxal $B_6$ dependent streptocci‡ | As above, but treat × 6 weeks | As above, but treat × 6 weeks | As above§, but treat × 6 weeks |
| | Listeria monocytogenes | Ampicillin 2 gm (IV) q4h × 4–6 weeks **or** TMP-SMX 5 mg/kg (IV) q6h | Meropenem 1 gm (IV) q8h × 4–6 weeks | Amoxicillin§ 1 gm (PO) q8h × 4–6 weeks **or** Linezolid§ 600 mg (PO) q12h × 4–6 weeks |
| GI/GU source likely (Treat initially for E. faecalis (VSE); if later identified as E. faecium (VRE), treat accordingly) | E. faecalis (VSE)† | Ampicillin 2 gm (IV) q4h × 4–6 weeks **plus** Gentamicin* 120 mg or 1 mg/kg (IV) or 80 mg (IV) q8h × 4–6 weeks | Vancomycin 1 gm or 15 mg/kg (IV) q12h × 4–6 weeks **plus** Gentamicin* 120 mg or 1 mg/kg (IV) q24h × 2 weeks | Amoxicillin§ 1 gm (PO) q8h × 4–6 weeks **or** Linezolid§ 600 mg (PO) q12h × 4–6 weeks |
| | E. faecium (VRE)† | Linezolid 600 mg (IV) q12h × ≥ 8 weeks **or** Daptomycin 12 mg/kg (IV) q24h × 6-8 weeks | | Linezolid§ 600 mg (PO) q12h × ≥ 8 weeks |
| GI source | S. (bovis) gallolyticus (Non-enterococcal group D streptococci) | Treat the same as "no obvious source" subset (see p. 70) | | |

VRE = vancomycin-resistant enterococci. Duration of therapy represents total time IV, PO, or IV + PO.

† Symptoms < 3 months → treat × 4 weeks.
Symptoms > 3 months → treat × 6 weeks.

‡ *NVS (nutritionally variant streptococci)* include: Abiotrophia defectivus, Granulicata adjacens/elegans.

§ IV therapy preferred. PO therapy if no IV access or if patient not a surgical candidate.

* If gentamicin resistant, give streptomycin 7.5 mg/kg (IV/1M) q12h.

## Native Valve Subacute Bacterial Endocarditis (SBE) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| "Culture negative" SBE* | Pathogen unknown (Abiotrophia, enterococci) PCN resistant organisms | Ampicillin/ Sulbactam 3 gm (IV) q6h × 4–6 weeks **plus** Gentamicin§ 120 mg or 1 mg/kg (IV) q24h × 2 weeks | Quinolone† (IV) q24h × 4–6 weeks | Quinolone†§ (PO) q24h × 4–6 weeks |
| | Hemophilus sp.<br>Actinobacillus actinomycetem-comitans<br>Cardiobacterium hominis<br>Eikenella corrodens<br>Kingella kingae<br>(HACEK organisms) | Ceftriaxone 2 gm (IV) q24h × 4–6 weeks **or** Any 3rd generation cephalosporin (IV) × 4–6 weeks **or** Cefepime 2 gm (IV) q12h × 4–6 weeks | Ampicillin 2 gm (IV) q4h × 4–6 weeks **plus** Gentamicin§ 120 mg or 1 mg/kg (IV) q24h × 2 weeks **or monotherapy with** Ampicillin/ Sulbactam 3 gm (IV) q6h × 4–6 weeks **or** Quinolone† (IV) q24h × 4–6 weeks | Quinolone†§ (PO) q24h × 4–6 weeks |
| | Legionella<br>Chlamydophilia (Chlamydia) psittaci | Doxycycline** 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 3 months | Quinolone† (IV) q24h × 3 months | Doxycycline**§ 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 3 months |
| | Coxiella burnetii (Q fever) | Doxycycline** 200 mg (IV/PO) q12h × 3 days, then 100 mg (PO) q12h × 24 months **plus** Hydroxchloroquin 200 mg (PO) q8h × 24 months | | |

* Slow growing/fastidious organisms may require ↑ $CO_2$ and prolonged incubation.
† Levofloxacin 500 mg or Moxifloxacin 400 mg.
** Loading dose is not needed PO if given IV with the same drug.
§ IV therapy preferred. PO therapy if no IV access or if patient not a surgical candidate.

## Native Valve Subacute Bacterial Endocarditis (SBE) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Brucella SBE† | Brucella melitensis, abortus, canis, suis | Doxycycline 200 mg** (IV) q12h × 3 days, then 100 mg (PO) q12h × ≥ 6 weeks<br>**plus**<br>Rifampin 300 mg (PO) q8h × ≥ 6 weeks<br>**plus**<br>Gentamicin§§ 3 mg/kg (IV) q24h × ≥ 6 weeks | | |

† Levofloxacin 500 mg or Moxifloxacin 400 mg.
** Loading dose is not needed PO if given IV with the same drug or if patient not a surgical candidate.
§§ May be given as a once daily dose or given as divided doses q8h.

### Native Valve SBE

**Clinical Presentation:** Subacute febrile illness ± localizing symptoms/signs in a patient with a heart murmur. Peripheral manifestations are commonly absent with early diagnosis/treatment.
**Diagnosis:** High grade/continuous bacteremia (due to a endocarditis pathogen) plus vegetation on TTE/TEE is diagnostic.

### SBE (No Obvious Source)

**Diagnostic Considerations:** Most common pathogen is viridans streptococci. Source is usually the mouth, although oral/dental infection is usually inapparent clinically.
**Pitfalls:** Vegetations without positive blood cultures or peripheral manifestations of SBE are not diagnostic of endocarditis. SBE vegetations may persist after antibiotic therapy, but are sterile.
**Therapeutic Considerations:** In penicillin-allergic (anaphylactic) patients, vancomycin may be used alone or in combination with gentamicin. Follow ESR weekly to monitor antibiotic response. No need to repeat blood cultures unless patient has persistent fever or is not responding clinically. Two-week treatment is acceptable for uncomplicated viridans streptococcal SBE. Treat nutritionally-variant streptococci (NVS) ($B_6$/pyridoxal dependent streptococci) same as viridans streptococcal SBE.
**Prognosis:** Related to extent of embolization/severity of heart failure.

### SBE (GI/GU Source Likely)

**Diagnostic Considerations:** Commonest pathogens from GI/GU source are Enterococci (especially) E. faecalis). If S. bovis, look for GI polyp, tumor source. Enterococcal SBE commonly follows GI/GU instrumentation.
**Pitfalls:** Low back pain prominent with enterococcal/S. bovis SBE, S. bovis associated with CNS embolization, Vertebral osteomyelitis, and large valvular vegetations.
**Therapeutic Considerations:** For penicillin-allergic patients, use vancomycin plus gentamicin. Vancomycin alone is inadequate for enterococcal (E. faecalis) SBE. Treat enterococcal PVE the same as for native valve enterococcal SBE. Treat S. bovis SBE the same as S. viridans SBE.
**Prognosis:** Related to extent of embolization.

### "Culture Negative" SBE (Culturable Pathogens)

**Diagnostic Considerations:** Culture of organisms may require enhanced $CO_2$/special media (Castaneda vented bottles) and prolonged incubation (2–4 weeks). True "culture negative" SBE is rare, and is characterized by peripheral signs of SBE, a murmur, vegetation (by TTE/TEE), and negative blood cultures.

**Pitfalls:** Most cases of "culture negative" SBE are not, in fact, culture negative SBE, but are due to slow growing organisms. Vegetations may not be visible by TTE/TEE with Q fever SBE.

**Therapeutic Considerations:** Follow clinical improvement with serial ESRs, which should return to pretreatment levels with therapy. Serial TTEs/TEEs show decreasing vegetation size during effective therapy. Sterile vegetations may persist after antibiotic therapy.

**Prognosis:** Related to extent of embolization.

### "Culture Negative" SBE Non-Culturable/(Serologically Diagnosed Pathogens)

**Diagnostic Considerations:** Diagnosis by specific serology. Large vessel emboli suggests culture negative SBE in patients with negative blood cultures but signs of SBE, e.g., splenomegaly/peripheral manifestation's.

**Pitfalls:** Do not diagnose culture negative SBE in patients with a heart murmur and negative blood cultures if peripheral SBE manifestations are absent. Vegetations may not be visible on TTE/TEE in Q fever SBE. The diagnosis of chronic Q fever is made by demonstrating elevated IgG (phase I) titers ≥ 1:1024 at 6 months following acute Q fever. Since Bartonella titers may cross react with C. burnetii (Q fever) titers and vice versa, an elevation of either titer may be a clue to the other and should prompt testing for both.

**Therapeutic Considerations:** Treatment is based on specific organism identified by diagnostic tests.

**Prognosis:** Related to extent of embolization/severity of heart failure.

## Native Valve Acute Bacterial Endocarditis (ABE)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch Therapy |
|---|---|---|---|---|
| Normal hosts*<br><br>(Treat initially for MRSA; if later identified as MSSA, treat accordingly) | S. aureus (MRSA) | Daptomycin 12 mg/kg (IV) q24h × 4–6 weeks<br>**or**<br>Linezolid 600 mg (IV) q24h × 4–6 weeks<br>**or**<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h × 4–6 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 4–6 weeks | | Linezolid 600 mg (PO) q12h × 4–6 wks<br>**or**<br>Minocycline 100 mg (PO) q12h × 4–6 wks |
| | S. aureus (MSSA) | Nafcillin 2 gm (IV) q4h × 4–6 weeks<br>**or**<br>Cefazolin 1 gm (IV) q8h × 4–6 weeks | | Linezolid 600 mg (PO) q12h × 4–6 wks<br>**or**<br>Cephalexin 1 gm (PO) q6h × 4–6 weeks |

MRSA/MSSA = methicillin-resistant/sensitive S. aureus. Duration of therapy represents total time IV, PO, or IV + PO.

* Treat IV or with IV-to-PO switch therapy or if patient not a surgical candidate.

## Native Valve Acute Bacterial Endocarditis (ABE) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch Therapy |
|---|---|---|---|---|
| IV drug abusers (IVDAs)†<br><br>(Treat as MRSA before culture results; treat according to pathogen after culture results) | S. aureus (MRSA) | Before culture results<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h<br>**or**<br>Daptomycin 12 mg/kg (IV) q24h × 4–6 weeks | After culture results<br>Linezolid 600 mg (IV) q12h × 4–6 weeks<br>**or**<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h × 4–6 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 4–6 weeks | After culture results<br>Linezolid 600 mg (PO) q12h × 4–6 weeks |
| | S. aureus (MSSA) | Before culture results<br>Meropenem 1 gm (IV) q8h | After culture results<br>Nafcillin 2 gm (IV) q4h × 4–6 weeks **or** Cefazolin 1 gm (IV) q8h × 4–6 weeks **or** Daptomycin 6 mg/kg (IV) q24h × 4–6 weeks **or** Linezolid 600 mg (IV) q12h × 4–6 weeks **or** Meropenem 1 gm (IV) q8h × 4–6 weeks | After culture results<br>Linezolid 600 mg (PO) q12h × 4–6 weeks<br>**or**<br>Cephalexin 1 gm (PO) q6h × 4–6 weeks<br>**or**<br>Minocycline† 100 mg (PO) q12h × 4–6 weeks |
| | P. aeruginosa*<br>S. marcesens<br>Aerobic GNBs | Before culture results<br>Meropenem 1 gm (IV) q8h | After culture results<br>**One "A" drug ± one "B" drug**<br>**"A" Drugs**<br>Meropenem 1 gm (IV) q8h × 4–6 weeks **or** Doripenem 1 gm (IV) q8h × 4–6 weeks<br>**"B" Drugs**<br>Amikacin 1 gm or 15 mg/kg (IV) q24h × 4–6 weeks **or** Aztreonam 2 gm (IV) q8h × 4–6 weeks | None |

MRSA/MSSA = methicillin-resistant/sensitive S. aureus. Duration of therapy represents total time IV, PO, or IV + PO.

* Treat IV or with IV-to-PO switch therapy or if patient not a surgical candidate.

† *MSSA/MRSA TV ABE may be treated IV/PO × 2 weeks if no intra-cardiac or CNS complications.* Pulmonary septic emboli are a feature of TV ABE e.g., and are *not*, per se, an extracardiac complication.

## Acute Bacterial Endocarditis (ABE)

**Diagnostic Considerations:** Clinical criteria for MRSA/MSSA ABE: continuous/high-grade bacteremia (repeatedly 3/4 or 4/4 positive blood cultures), fever (temperature usually ≥ 102°F), no, new or changing murmur, and vegetation by transesophageal/transthoracic echocardiogram.

**Pitfalls:** Obtain a baseline TTE for comparative purposes should ABE be complicated by valve destruction, heart failure or ring/perivalvular abscess. On TTE/TEE a vegetation may not be visible until > 1 week of ABE. In MSSA/MRSA ABE, resistance to deptomycin may occur during therapy particularly in patients initially treated with vancomycin.

**Therapeutic Considerations:** Treat for 4–6 weeks. Follow teichoic acid antibody titers (TAA) weekly in MSSA/MRSA ABE, which ↓ (along with the ESR) with effective therapy. If MSSA/MRSA ABE unresponsive (persistent high grade bacteremia) to appropriate MSSA/MRSA therapy or if a myocardial/paravalvular abscess present that cannot be surgically drained, "high dose" daptomycin 12 mg/kg (IV) q24h may be effective. With daptomycin resistant MSSA/MRSA strains, Quinupristin/dalfopristin, linezolid or minocycline may be effective.

**Prognosis:** Related to extent of embolization/severity of valve destruction/heart failure.

## Acute Bacterial Endocarditis (IVDAs)

**Diagnostic Considerations:** Clinically IVDAs with S. aureus usually have relatively mild ABE, permitting oral treatment.

**Pitfalls:** IVDAs with new aortic or tricuspid regurgitation should be treated IV ± valve replacement.

**Therapeutic Considerations:** After pathogen is isolated, may switch from IV to PO regimen to complete treatment course.

**Prognosis:** Prognosis is better than ABE in normal hosts if not complicated by abscess, valve regurgitation, or heart failure.

**Clinical Presentation:** Prolonged fevers and chills following prosthetic valve replacement (PVR).

**Diagnosis:** High-grade blood culture positivity (3/4 or 4/4) with endocarditis pathogen and no other source of infection.

## Prosthetic Valve Endocarditis (PVE)

### Early PVE (< 60 days post-PVR)

**Diagnostic Considerations:** Blood cultures persistently positive. Temperature usually ≤ 102°F.

**Pitfalls:** Obtain baseline TTE/TEE. Premature closure of mitral leaflet is early sign of impending aortic valve regurgitation. Rifampin should be given 2 days after strain shown to be susceptible.

**Therapeutic Considerations:** Patients improve clinically on treatment, but prosthetic valve removal may be necessary for cure.

**Prognosis:** Related to extent of embolization/severity of heart failure.

### Late PVE (> 60 days post-PVR)

**Pitfalls:** Culture of removed valve may be negative, but valve gram stain will be positive.

**Therapeutic Considerations:** Clinically, late PVE resembles viridans streptococcal SBE. Patients improve clinically on treatment, but prosthetic valve removal may be necessary for cure.

**Prognosis:** Related to extent of embolization/severity of heart failure.

## Prosthetic Valve Endocarditis (PVE)

| Subset | Usual Pathogens | Before Culture Results | After Culture Results |
|---|---|---|---|
| Early PVE (< 60 days post-PVR)§ | S. aureus (MSSA/MRSA)<br>S. epidermidis (CoNS)<br>Enterobacteriaceae | Vancomycin 1 gm or 15 mg/kg (IV) q12h<br>**plus**<br>Gentamicin 120 mg or 1 mg/kg (IV) q24h | Enterobacteriaceae<br>Meropenem 1 gm (IV) q8h × 6 weeks<br>**or**<br>MSSA<br>Cefazolin 1 gm (IV) q8h × 6 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 6 weeks<br>MRSA†<br>Daptomycin 12 mg/kg (IV) q24h × 6 weeks<br>**or**<br>Linezolid 600 mg (IV or PO) q12h × 6 weeks<br>**or**<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h × 6 weeks<br>**plus**<br>Gentamicin 120 mg (IV) q24h × 2 weeks<br>**plus**<br>Rifampin 300 mg (IV) q24h × 6 weeks* |
| | Candida species§ | Mycafungin 150 mg or 3 mg/kg (IV) q24h | Lipid amphotericin 3–5 mg/kg (IV) q24h × 6 weeks<br>**plus**<br>5-FC 25 mg/kg (PO) q6h × 6 weeks |
| Late PVE (> 60 days post-PVR)§ | Viridans streptococci<br>S. epidermidis (CoNS) | Vancomycin 1 gm or 15 mg/kg (IV) q12h **plus** Gentamicin 120 mg or 1 mg/kg (IV) q24h | Viridans streptococci<br>Ceftriaxone 2 gm (IV) q24h × 6 weeks<br>CoNS<br>Linezolid 600 mg (IV or PO) q12h × 6 weeks<br>**or**<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h × 6 weeks<br>**plus**<br>Rifampin 300 mg (PO) q8h × 6 weeks |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis. Duration of therapy represents total time IV or IV + PO.

† MRSA drugs also effective against MSSA.

§ Valve removal usually needed for cure.

* Begin 2 days after pathogen known to be susceptible.

## Pericarditis/Myocarditis

| Subset | Usual Pathogens | Preferred Therapy |
|---|---|---|
| Diphtheritic myocarditis | C. diphtheriae | Treat same as diphtheriae (see p. 170) |
| Viral | Coxsackie, influenza | No treatment for Coxsackie, for influenza therapy |
| Lyme myocarditis | B. burgdorferi | Ceftriaxone 2 gm (IV) q24h × 2 weeks<br>**or**<br>Doxycycline 100 mg (IV) q12h × 2 weeks |
| TB pericarditis | M. tuberculosis | Treat same as pulmonary TB (see p. 53). Add a tapering dose of corticosteroids × 4–8 weeks |
| Suppurative pericarditis | S. pneumoniae<br>S. aureus | Treat same as lung abscess/empyema (see p. 67) |

**Clinical Presentation:** Viral pericarditis presents with acute onset of fever/chest pain (made worse by sitting up) following a viral illness. TB pericarditis is indolent in presentation, with ↑ jugular venous distension (JVD), pericardial friction rub (40%), paradoxical pulse (25%), and chest x-ray with cardiomegaly ± left-sided pleural effusion. Suppurative pericarditis presents as acute pericarditis (patients are critically ill). Develops from contiguous (e.g., pneumonia) or hematogenous spread e.g., S. aureus bacteremia. Viral myocarditis presents with heart failure, arrhythmias ± emboli.

**Diagnostic Considerations:** Pericarditis/effusion manifests cardiomegaly with decreased heart sounds ± tamponade. Diagnosis by culture/biopsy of pericardial fluid or pericardium for viruses, bacteria, or acid-fast bacilli (AFB). Diagnosis of myocarditis is clinical ± myocardial biopsy.

**Pitfalls:** Consider other causes of pericardial effusion (malignancy, esp. if bloody effusion, uremia, etc). Otherwise unexplained tachycardia should suggest myocarditis until proven otherwise. Rule out treatable non-viral causes of myocarditis e.g., RMSF, Lyme, diphtheria. Suspect Lyme disease in any person without heart disease with exposure to endemic area who presents with otherwise unexplained heart block. Lyme IgM titers may be negative early when patients present with heart block.

**Therapeutic Considerations:** No specific treatment for viral myocarditis/pericarditis. TB pericarditis is treated the same as pulmonary TB ± pericardiectomy. Suppurative pericarditis is treated the same as lung abscess plus surgical drainage (pericardial window). Heart block in Lyme disease rapidly reverses with therapy, but a temporary pacemaker may be needed until heart block is reversed.

**Prognosis:** For viral pericarditis, the prognosis is good, but viral myocarditis may be fatal. For TB pericarditis, the prognosis is good if treated before constrictive pericarditis/adhesions develop. Suppurative pericarditis is often fatal without early pericardial window/antibiotic therapy. With Lyme myocarditis/heart block, prognosis is good if treatment is started early when diagnosis is suspected.

## Central Venous Catheter (CVC) and Pacemaker/Lead Infections

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| **CVC (temporary) Infections*** <br> <u>Bacterial</u> <br> (Treat initially for MSSA; if later identified as MRSA, treat accordingly) | S. aureus (MSSA) Aerobic GNBs | Meropenem 1 gm (IV) q8h** **or** Cefepime 2 gm (IV) q12h** | Ceftriaxone 2 gm (IV) q24h** | Quinolone‡ (PO) q24h**† |
| | S. aureus (MRSA/MSSA§) | Daptomycin 12 mg/kg (IV) q24h** **or** Linezolid 600 mg (IV) q12h** **or** Vancomycin 1 gm or 15 mg/kg (IV) q12h** | | Linezolid 600 mg (PO) q12h**† **or** Minocycline 100 mg (PO) q12h**† |
| <u>Candida</u>¶ <br> (Treat initially for C. albicans; if later identified as non-albicans Candida, treat accordingly). | C. albicans | Treat the same as for Candidemia (see p. 153) | | |
| | Non-albicans Candida | Treat the same as for Candidemia (see p. 153) | | |
| **CVC (semi-permanent Hickman/ Broviac/Tessio) Infections*** <br> <u>Bacterial</u> | S. aureus (MSSA/MRSA) | Daptomycin 12 mg/kg (IV) q24h** **or** Linezolid 600 mg (IV) q12h** **or** Vancomycin 1 gm or 15 mg/kg (IV) q12h** **or** Minocycline 100 mg (IV) q12h** | | Linezolid 600 mg (PO) q12h**† **or** Minocycline 100 mg (PO) q12h**† |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus.*

† IV therapy preferred. PO therapy if no IV access

‡ Levofloxacin 500 mg or Moxifloxacin 400 mg.

* If clinically possible, CVC should be removed if CVC suspected source of bacteremia in a septic patient. If high grade/sustained bacteremia obtain TTE/TEE to rule out ABE.

** Treat × 2 weeks after CVC removal if no ABE.

¶ For candidemia not associated with CVCs, (see pp. 153–154).

§ MRSA drugs also effective against MSSA.

## Central Venous Catheter (CVC) and Pacemaker/Lead Infections (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| | S. epidermidis (CoNS) | Daptomycin 6 mg/kg (IV) q24h** **or** Linezolid 600 mg (IV) q12h** **or** Vancomycin 1 gm or 15 mg/kg (IV) q12h** | | Linezolid 600 mg (PO) q12h**† |
| Pacemaker wire/generator infection, LVAD, ICD (Treat initially for S. aureus; if later identified as S. epidermidis, treat accordingly) | S. aureus (MSSA/MRSA) | Daptomycin 6 mg/kg (IV) q24h†§ **or** Linezolid 600 mg (IV) q12h†§ **or** Vancomycin 1 gm or 15 mg/kg (IV) q12h† | | Linezolid 600 mg (PO) q12h†§* **or** Minocycline 100 mg (PO) q12h†§* |
| | S. epidermidis (CoNS) | Daptomycin 6 mg/kg (IV) q24h† **or** Linezolid 600 mg (IV) q12h† **or** Vancomycin 1 gm or 15 mg/kg (IV) q12h† | | Linezolid 600 mg (PO) q12h†* |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis.

† IV therapy preferred. PO therapy if no IV access.

** Treat × 2 weeks after CVC removal if no IE.

* Treat × 2 weeks after wire/generator removal if no IE.

§ Obtain teichoic acid antibody titers (TAA) after 2 weeks. If titers are < 1:4, 2 weeks of therapy is sufficient. If titers are ≥ 1:4 rule out endocarditis and complete 4–6 weeks of therapy.

## Central Venous Catheter (CVC) and Pacemaker/Lead Infections (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Septic thrombophlebitis<br><br>(Treat initially for MSSA; if later identified as MRSA, treat accordingly) | S. aureus (MSSA) | Nafcillin 2 gm (IV) q4h × 2 weeks*<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks*<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks* | Cefazolin 1 gm (IV) q8h × 2 weeks*<br>**or**<br>Ceftriaxone 1 gm (IV) q12h × 2 weeks*<br>**or**<br>Minocycline 100 mg (IV) q12h × 2 weeks | Linezolid 600 mg (PO) q12h × 2 weeks*†<br>**or**<br>Clindamycin 300 mg (PO) q8h × 2 weeks*†<br>**or**<br>Cephalexin 1 gm (PO) q6h × 2 weeks*† |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h × 2 weeks*<br>**or**<br>Vancomycin 1 gm or 15 mg/kg (IV) q12h × 2 weeks*<br>**or**<br>Minocycline 100 mg (IV) q12h × 2 weeks* | | Linezolid 600 mg (PO) q12h × 2 weeks*†<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks*† |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus. Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Obtain teichoic acid antibody titers after 2 weeks. If titers are < 1:2, 2 weeks of therapy is sufficient. If titers are ≥ 1:2, TTE/TEE to rule out ABE and complete 4–6 weeks of therapy.

† IV therapy preferred. PO therapy if no IV access.

### CVC (Temporary) Infections

**Clinical Presentation:** Temperature ≥ 102°F ± IV site erythema.

**Diagnostic Considerations:** Diagnosis by semi-quantitative catheter tip culture with ≥ 15 colonies plus blood cultures with same pathogen. If no other explanation for fever and line has been in place ≥ 7 days, remove line and obtain semi-quantitative catheter tip culture. Suppurative thrombophlebitis presents with hectic/septic fevers and pus at IV site ± palpable venous cord.

**Pitfalls:** Temperature ≥ 102°F with IV line infection, in contrast to phlebitis.

**Therapeutic Considerations:** Line removal is usually curative, but antibiotic therapy is usually given for 1 week after IV line removal for gram-negative bacilli or 2 weeks after IV line removal for S. aureus (MSSA/MRSA). Antifungal therapy is usually given for 2 weeks after IV line removal for Candidemia.

**Prognosis:** Good if line is removed before endocarditis/metastatic spread.

### CVC (Semi-Permanent) Hickman/Broviac Infections

**Clinical Presentation:** Fever ± IV site erythema.
**Diagnostic Considerations:** Positive blood cultures plus gallium scan pickup on catheter is diagnostic.
**Pitfalls:** Antibiotics will lower temperature, but patient will usually not be afebrile without line removal.
**Therapeutic Considerations:** Lines usually need to be removed for cure. Rifampin 600 mg (PO) q24h may be added to IV/PO regimen if pathogen is S. aureus.
**Prognosis:** Good with organisms of low virulence.

### Pacemaker/Lead Infections

**Clinical Presentation:** Persistently positive blood cultures without endocarditis in a pacemaker patient.
**Diagnostic Considerations:** Positive blood cultures with gallium scan pickup on wire/pacemaker generator is diagnostic. Differentiate wire from pacemaker pocket infection by chest CT/MRI.
**Pitfalls:** Positive blood cultures are more common in wire infections than pocket infections. Blood cultures may be negative in both, but more so with pocket infections.
**Therapeutic Considerations:** Wire alone may be replaced if infection does not involve pacemaker generator. Replace pacemaker generator if involved; wire if uninvolved can usually be left in place.
**Prognosis:** Good if pacemaker wire/generator replaced before septic complications develop.

### Septic Thrombophlebitis

**Clinical Presentation:** Temperature ≥ 102°F with local erythema and signs of sepsis.
**Diagnostic Considerations:** Palpable venous cord and pus at IV site when IV line is removed.
**Pitfalls:** Suspect diagnosis if persistent bacteremia and no other source of infection in a patient with a peripheral IV.
**Therapeutic Considerations:** Remove IV catheter. Surgical venotomy is usually needed for cure.
**Prognosis:** Good if removed early before septic complications develop.

## Vascular Graft Infections

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| AV graft/shunt infection<br><br>(Treat initially for MRSA, etc.; if later identified as MSSA, treat accordingly) | S. aureus (MRSA) | Daptomycin*†§ 12 mg/kg (IV) q24h **plus** Rifampin 300 mg (PO) q8h **or** Linezolid†§ 600 mg (IV) q12h **plus** Rifampin†§ 300 mg (PO) q8h | Vancomycin*†§ 1 gm or 15 mg/kg (IV) q12h **plus** Rifampin 300 mg (PO) q8h **or** Minocycline†§ 100 mg (IV) q12h **plus** Rifampin†§ 300 mg (PO) q8h | Linezolid†§ 600 mg (PO) q12h **plus** Rifampin 300 mg (PO) q8h **or** Minocycline†§ 100 mg (PO) q12h **plus** Rifampin†§ 300 mg (PO) q8h |

MRSA/MSSA = methicillin-resistant/sensitive S. aureus. Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Follow with maintenance dosing for renal failure (CrCl < 10 mL/min) and type of dialysis.

† If ABE not present, treat for 2 weeks after graft is removed/replaced. If ABE present, treat for 6 weeks.

§ IV therapy preferred. PO therapy if no IV access.

## Vascular Graft Infections (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| | S. aureus (MSSA) | Nafcillin 3 gm (IV) q12h† | Vancomycin 1 gm or 15 mg/kg (IV) q12h*† | Moxifloxacin 400 mg (IV or PO) q24h*†§ |
| | E. faecalis (VSE)<br>Aerobic GNBs | Ampicillin 2 gm (IV) q4h*†<br>**plus**<br>Gentamicin 240 mg or 3 mg/kg (IV) q24h*† | Vancomycin 1 gm or 15 mg/kg (IV) q24h†<br>**plus**<br>Gentamicin 120 mg or 3 mg/kg (IV) q24h*† | |
| Aortic graft infection | S. aureus (MSSA)<br>Aerobic GNBs<br>P. aeruginosa | Meropenem 1 gm (IV) q8h†**<br>**or**<br>Cefepime 2 gm (IV) q12h†** | Levofloxacin 750 mg (IV) q24h† | Levofloxacin 750 mg (PO) q24h†<br>**or**<br>Ciprofloxacin 750 mg (PO) q12h† |

*MRSA/MSSA = methicillin-resistant/sensitive S. aureus.* Duration of therapy represents total time IV or IV

* Follow with maintenance dosing for renal failure (CrCl < 10 mL/min) and type of dialysis.

** Depending on susceptibilities.

† If ABE not present, treat for 2 weeks after graft is removed/replaced. If graft not removable/replaceable, treat for 6 weeks.

§ IV therapy preferred. PO therapy if no IV access.

### AV Graft Infection

**Clinical Presentation:** Persistent fever/bacteremia without endocarditis in a patient with an AV graft on hemodialysis.

**Diagnostic Considerations:** Diagnosis by persistently positive blood cultures and gallium scan pickup over infected AV graft. Gallium scan will detect deep AV graft infection not apparent on exam.

**Pitfalls:** Antibiotics will lower temperature, but patient will usually not become afebrile without AV graft replacement.

**Therapeutic Considerations:** Graft usually must be removed for cure. MRSA is a rare cause of AV graft infection; if present, treat with linezolid 600 mg (IV or PO) q12h until graft is removed/replaced.

**Prognosis:** Good if new graft does not become infected at same site.

### Aortic Graft Infection

**Clinical Presentation:** Persistently positive blood cultures without endocarditis in a patient with an aortic graft.

**Diagnostic Considerations:** Diagnosis by positive blood cultures plus gallium scan pickup over infected aortic graft or abdominal CT/MRI scan.

**Pitfalls:** Infection typically occurs at anastomotic sites.

**Therapeutic Considerations:** Graft must be removed for cure. Operate as soon as diagnosis is confirmed (no value in waiting for surgery). MRSA is a rare cause of AV graft infection; if present, treat with linezolid 600 mg (IV or PO) q12h until graft is replaced.
**Prognosis:** Good if infected graft is removed before septic complications develop.

## Empiric Therapy of GI Tract Infections

### Esophagitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Fungal | Candida albicans | Fluconazole 200 mg (IV or PO) × 1 dose, then 100 mg (IV or PO) q24h × 2–3 weeks | Micafungin 150 mg (IV) q24h × 2–3 weeks **or** Caspofungin 50 mg (IV) q24h × 2–3 weeks **or** Anidulafungin 100 mg (IV or PO) × 1 dose then 50 mg (IV) q24h × 2–3 weeks **or** Amphotericin B deoxycholate 0.5 mg/kg (IV) q24h × 2–3 weeks **or** Itraconazole 200 mg (IV) q12h × 2 days, then 200 mg (IV) q24 h × 2–3 weeks | Fluconazole 200 mg (PO) × 1 dose, then 100 mg (PO) q24h × 2–3 weeks* **or** Posaconazole 100 mg (PO)q12h × 1 day, then 100 mg (PO) q24h × 2 weeks **or** Itraconazole 200 mg (PO) solution q24h × 2–3 weeks |
| Viral | HSV-1 | Acyclovir 5 mg/kg (IV) q8h × 3 weeks | Valacyclovir 500 mg (PO) q12h × 3 weeks **or** Famciclovir 500 mg (PO) q12h × 3 weeks | |
| | CMV | Ganciclovir 5 mg/kg (IV) q12h × 3 weeks | Valganciclovir 900 mg (PO) q12h × 3 weeks | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).
* Loading dose is not needed PO if given IV with the same drug.

**Clinical Presentation:** Pain on swallowing.
**Diagnosis:** Stain/culture for fungi/HSV/CMV on biopsy specimen.

#### Fungal (Candida) Esophagitis

**Diagnostic Considerations:** Rarely if ever in normal hosts. Often (but not always) associated with Candida in mouth. If patient is not alcoholic or diabetic and is not receiving antibiotics, test for HIV.
**Pitfalls:** Therapy as a diagnostic trial is appropriate. Suspect CMV-related disease and proceed to endoscopy if a patient with a typical symptom complex fails to respond to antifungal therapy.

**Therapeutic Considerations:** In normal hosts, treat for 1 week after clinical resolution. HIV patients respond more slowly than normal hosts and may need higher doses/treatment for 2–3 weeks after clinical resolution (see p. 336).
**Prognosis:** Related to degree of immunosuppression.

### Viral Esophagitis

**Diagnostic Considerations:** Rarely in normal hosts. May occur in the immunosuppressed.
**Pitfalls:** Viral and non-viral esophageal ulcers look similar; need biopsy for specific viral diagnosis.
**Therapeutic Considerations:** In normal hosts, treat for 2–3 weeks after clinical resolution. HIV patients respond more slowly and may need treatment for weeks after clinical resolution.
**Prognosis:** Related to degree of immunosuppression.

## Peptic Ulcer Disease (H. pylori)

| Triple Therapy | Quadruple Therapy | Sequential Therapy |
|---|---|---|
| PPI + amoxicillin 1 gm (PO) q12h **plus either** clarithromycin 500 mg (PO) q12h **or** tinidazole (or metronidazole) 500 mg (PO) q12h all × 2 weeks | PPI + metronidazole 500 mg (PO) q12h + doxycycline 100 mg (PO) q12h + bismuth subsalicylate 525 mg tabs (PO) q6h all × 2 weeks | ***5 days:*** PPI + amoxicillin 1 gm (PO) q12h; ***next 5 days:*** PPI **plus** either clarithromycin 500 (PO) q12h **or** levofloxacin 500 mg (PO) q24h |

**Diagnostic Considerations: Invasive:** rapid urease test, histology, culture. **Noninvasive:** serum ELISA test, urea breath test, stool (monoclonal antibody) antigen test.
**Pitfalls:** *False negative H. pylori tests with antibiotics, bismuth, PPIs.*
**Therapeutic Considerations:** See above grid. **Therapeutic failure:** *substitute* bismuth (for amoxicillin) or *substitute* nitazoxanide 1 gm (PO) q12h (for clarithromycin, metronidazole or tinidazole) all × 2 weeks. ***1 week of therapy often fails*.**
**Tests of Cure:** Urea breath test → 4–6 weeks post-therapy. Stool antigen test → 6–8 weeks post-therapy. *Stop PPIs 2 weeks before re-testing*.

## Gastric Perforation

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Gastric perforation | Oral anaerobes | Cefazolin 1 gm (IV) q8h × 1–3 days | Any beta-lactam (IV) × 1–3 days | Amoxicillin 1 gm (PO) q8h × 1–3 days **or** Cephalexin 500 mg (PO) q6h × 1–3 days **or** Quinolone* (PO) q24h × 1–3 days |

* Levofloxacin 500 mg or Moxifloxacin 400 mg.

**Clinical Presentation:** Presents acutely with fever and peritonitis.
**Diagnostic Considerations:** Obtain CT/MRI of abdomen for perforation/fluid collection.
**Pitfalls:** No need to cover B. fragilis with perforation of stomach/small intestine.
**Therapeutic Considerations:** Obtain surgical consult for possible repair.
**Prognosis:** Good if repaired.

## Infectious Diarrhea/Typhoid (Enteric) Fever

| Subset | Usual Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Acute watery diarrhea | E. coli (ETEC, EHEC)<br>Campylobacter<br>Yersinia Salmonella<br>Vibrio sp. | Quinolone† (IV or PO) × 5 days | Doxycycline 100 mg (IV or PO) q12h × 5 days<br>**or**<br>TMP–SMX 1 DS tablet (PO) q12h × 5 days |
| C. difficile diarrhea/ colitis | Clostridium difficile | **Diarrhea** †§<br>**Initial episode:**<br>Vancomycin 250 mg (PO) q6h × 7–10 days* (If no improvement in 3 days, ↑ dose to 500 mg (PO) q6h × 7 days)**<br>**Relapse:**<br>Vancomycin 500 mg (PO) q6h × 14 days**<br>**Recurrence:††**<br>Vancomycin 500 mg (PO) q6h × 1 month **(*do not taper vancomycin dose*).**<br>If another recurrence, *re-treat* with Vancomycin 500 mg (PO) q6h × *2 months*.<br>If another recurrence, *re-treat* with Vancomycin 500 mg (PO) q6h × *3 months*.<br>*If dose not tapered and if no colitis*, **this regimen will not fail!** If diarrhea continues, rule out C. difficile *colitis* or look for alternate diagnosis. | **Diarrhea**<br>**Initial episode:**<br>Nitazoxanide 500 mg (PO) q12h × 7–10 days<br>**or**<br>Metronidazole 250 mg (PO) q6h × 7–10 days*<br>**Relapse:**<br>Nitazoxanide 500 mg (PO) q12h × 7–10 days<br>**Recurrence:**<br>Nitazoxanide 500 mg (PO) q12h × 7–10 days<br>**or**<br>Rifaximin 400 mg (PO) q8h × 10 days<br>**or**<br>Fidoxamicin 200 mg (PO) q12h × 10 days |

* **Treatment failure common with Vancomycin 125 mg (PO) q6h and with Metronidazole at any dose, (*Flagyl frequently fails!*).**

** *If no improvement after 3 days with Vancomycin 500 mg (PO) q6h*, **rule out *colitis* with abdominal CT scan.** If abdominal CT scan shows **colitis** treat as C. difficile **colitis.**

† When treating C. difficile diarrhea or colitis, ***discontinue antibiotics with a high C. difficile potential***, e.g., **cilndamycin, ciprofloxacin, α-lactams** (*excluding* ceftriaxone).
Patients being treated with levofloxacin or moxifloxacin *should not concurrently be taking PPIs*. Either discontinue PPI or switch to a $H_2$ blocker during quinolone therapy.

†† **Avoid C. difficile "prophylaxis."** Do ***not*** treat **"history of C. difficile."** Instead, *repeat C. difficile stool PCR to verify diagnosis*. Treat C. difficile diarrhea **only if** PCR + for C. difficile.

§ **Avoid anti-spasmatics in C. difficile diarrhea;** use may result in C. difficile **colitis.**

§§ Colectomy may be lifesaving in severe C. difficile pancolitis.

## Infectious Diarrhea/Typhoid (Enteric) Fever (cont'd)

| Subset | Usual Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| | | **Colitis**<br>**Initial episode:**<br>Metronidazole 1 gm (IV) q24h until cured<br>**plus**<br>Ertapenem 1 gm (IV) 124h (until associated peritonitis component resolves)<br><br>**Severe Pancolitis:**§§<br>Metronidazole 500 mg (IV/PO) q6h–8h until cured<br>**plus**<br>Nitazoxanide 500 mg (PO) q12h × until cured<br>**plus**<br>Tigecycline 200 mg (IV) × 1 dose, then, 100 mg (IV) q24h until cured<br><br>**Relapse or Recurrence:**<br>Re-treat with Metronidazole 500 mg (IV/PO) q6–8h until cured | **Colitis**<br>**Initial Episode:**<br>Metronidazole 250 mg (PO) q6h until cured<br>**plus**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h until cured<br>**or**<br>Nitazoxanide 500 mg (PO) q12h until cured<br><br>**Relapse or Recurrence:**<br>Nitazoxanide 500 mg (PO) q12h until cured |
| Cytomegalovirus colitis | CMV | Valganciclovir 900 mg (PO) q12h × 21 days; for HIV, see p. 334 | |

§ Colectomy may be lifesaving in severe *C. difficile* pancolitis.

## Infectious Diarrhea/Typhoid (Enteric) Fever (cont'd)

| Subset | Usual Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Typhoid (enteric) fever | Salmonella typhi/ paratyphi | Quinolone† (IV or PO) × 10–14 days **or** TMP–SMX 5 mg/kg (IV or PO) q6h × 10–14 days | Chloramphenicol 500 mg (IV or PO) q6h × 10–14 days **or** any 3rd gen cephalosporin (IV or PO) × 10–14 days **or** Azithromycin 1 gm (PO) q24h × 5 days |
| Chronic watery diarrhea | Giardia lamblia* | Tinidazole 2 gm (PO) × 1 dose **or** Nitazoxanide 500 mg (PO) q12h × 3 days **or** Metronidazole 2 gm (PO) q24h × 3 days | Albendazole 400 mg (PO) q24h × 5 days **or** Quinacrine 100 mg (PO) q8h × 5 days |
| | Cryptosporidia* | Nitazoxanide 500 mg (PO) q12h × 5 days§ | Paromomycin 500–750 mg (PO) q8h until response **or** Azithromycin 600 mg (PO) q24h × 4 weeks |
| | Isospora* Cyclospora* | TMP–SMX 1 DS tablet (PO) q12h × 10 days‡ | |
| Acute dysentery | Entamoeba histolytica | Preferred therapy: Metronidazole 750 mg (PO) q8h × 10 days **followed by either** Iodoquinol 650 mg (PO) q8h × 20 days **or** Paromomycin 500 mg (PO) q8h × 7 days Alternate therapy: Tinidazole 1 gm (PO) q12h × 3 days | |
| | Shigella | Quinolone† (IV or PO) × 3 days | TMP–SMX 1 DS tablet (PO) q12h × 3 days **or** Azithromycin 500 mg (IV or PO) q24h × 3 days |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

* May also present as acute watery diarrhea.

† Ciprofloxacin 400 mg (IV) or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h or Moxifloxacin 400 mg (IV or PO) q24h.

§ Longer duration of therapy may be needed in immunosuppressed patients (treat until cured).

## Acute Watery Diarrhea

**Clinical Presentation:** Acute onset of watery diarrhea without blood/mucus.

**Diagnostic Considerations:** Diagnosis by culture of organism from stool specimens.

**Pitfalls:** Recommended antibiotics are active against most susceptible enterotoxigenic bacterial pathogens causing diarrhea, but not viruses/parasites. Concomitant transient lactase deficiency may prolong diarrhea if dairy products are taken during an infectious diarrhea.

**Therapeutic Considerations:** Avoid norfloxacin and ciprofloxacin due to resistance potential. V. cholerae may be treated with a single dose of any oral respiratory quinolone or doxycycline.

**Prognosis:** Excellent. Most recover with supportive treatment.

## Clostridium difficile Diarrhea/Colitis

**Clinical Presentation:** Voluminous watery diarrhea following exposure to C. difficile contaminated fomites, exposure to patients with C. difficile, recent cancer chemotherapy or antibiotic therapy with some, *but not most*, antibiotics. Most often associated with clindamycin, ciprofloxacin, and β-lactams (excluding ceftriaxone).

**Diagnostic Considerations:** Watery diarrhea with positive C. difficile stool toxin. A single positive PCR C. difficile stool toxin test is sufficiently sensitive/specific for diagnosis (endpoint is end of diarrhea, not stool toxin negativity); *If negative, no need to retest*. If C. difficile colitis suspected in C. difficile positive patients with fever/prominent leukocytosis/abdominal pain, confirm diagnosis by abdominal CT scan.

**Pitfalls:** C. difficile colitis is suggested by the presence of otherwise unexplained leukocytosis, ↑ ESR, abdominal pain and often temperature > 102°F; confirm diagnosis with CT/MRI of abdomen. Virulent strains of C. difficile may present with colitis with temperature ≤ 102°F, leukocytosis (often very high, i.e., 25–50 K/mm$^3$), and little/no abdominal pain; confirm diagnosis with CT/MRI of abdomen. Radiographically C. difficile colitis typically is a pancolitis. Segmental colitis suggests a non-C. difficile etiology, i.e., ischemic colitis. C. difficile toxin test may remain positive in stools following resolution of diarrhea; In patients receiving enteral feeds, diarrhea is likely due to enteral feeds (high infusion rates/high osmotic loads) rather than C. difficile. Norovirus diarrhea may mimic C. difficile diarrhea or concurrent outbreaks may occur. Vancomycin may be *ineffective* in C. difficile *colitis*.

**Therapeutic Considerations:** For **C. difficile diarrhea** oral vancomycin or nitazoxanide are preferred; *Flagyl frequently fails.* Rifaxamin and Fidaxomycin have no advantage over vancomycin. With effective therapy, C. difficile diarrhea begins to improve (≤ 3 days) and usually resolves by 5–7 days, although some patients require 10 days of therapy. If no improvement with vancomycin 250 mg (PO) q6h, ↑ dose to 500 mg (PO) q6h or use nitazoxanide. *Do not treat C. difficile negative diarrhea with oral vancomycin or metronidazole*. For **C. difficle colitis**, treat until colitis resolves (follow with serial ESRs/abdominal and or CT scans). Add aerobic GNB coverage for microscopic/gross peritonitis with ESRs ertapenem. Tigecycline highly effective monotherapy for C. difficle colitis; and also provides anti-B fragilis coverage (for associated microscopic/clinical peritonitis). ***Avoid*** *anti-motility agents, e.g., loperamide with C. difficile diarrhea which may result in C. difficile colitis/toxic megacolon.*

**Prognosis:** Prognosis with C. difficile diarrhea is excellent. C. difficile colitis prognosis is related to strain virulence/and extent of the colitis.

## Typhoid (Enteric) Fever (Salmonella typhi/Paratyphi)

**Clinical Presentation:** High fevers (> 102°F) increasing in a stepwise fashion accompanied by relative bradycardia (without chills) with watery diarrhea/constipation, headache, anorexia, abdominal pain, dry cough/sore throat, tender hepatomegaly, ± Rose spots. Dull mental affect ("apathetic facies") peculiar to typhoid fever. Thrombocytopenia should suggest another diagnosis. e.g. malaria or viral coinfection, e.g. dengue.

**Diagnostic Considerations:** Most community-acquired watery diarrheas are not accompanied by temperatures > 102°F and relative bradycardia. Diagnosis is confirmed by demonstrating Salmonella in blood, bone marrow, Rose spots, or stool cultures. Culture of bone marrow is the quickest/most reliable method of diagnosis. WBC count is usually low/low normal. Leukocytosis should suggest another diagnosis or bowel perforation, which may occur during 2nd week of typhoid fever. Eosinopenia characteristic of typhoid/enteric fever. In patients with suspected typhoid fever, eosinophilia should suggest an alternate diagnosis or parasitic coinfection.
**Pitfalls:** Rose spots are few/difficult to see and not present in all cases. Typhoid fever usually presents with constipation, not diarrhea. Severe rigors not a feature of typhoid fever.
**Therapeutic Considerations:** 2nd generation cephalosporins, aztreonam, and aminoglycosides are ineffective. Since Salmonella strains causing enteric fever are intracellular pathogens, treat for a full 2 weeks to maximize cure rates/minimize relapses. Treat relapses with the suggested antibiotics × 2–3 weeks. Salmonella excretion into feces usually persists < 3 months. Persistent excretion > 3 months suggests a carrier state—rule out hepatobiliary/urinary calculi.
**Prognosis:** Good if treated early. Poor with late treatment/bowel perforation.

## Chronic Watery Diarrhea

**Clinical Presentation:** Watery diarrhea without blood/mucus lasting > 1 month.
**Diagnostic Considerations:** Diagnosis by demonstrating organisms/cysts in stool specimens. Multiple fresh daily stool samples often needed for diagnosis especially for protozoan parasites.
**Pitfalls:** Concomitant transient lactase deficiency may prolong diarrhea if dairy products are consumed during an infectious diarrhea.
**Therapeutic Considerations:** Cryptosporidia and Isospora are being recognized increasingly in acute/chronic diarrhea in normal hosts.
**Prognosis:** Excellent in well-nourished patients. Untreated patients may develop malabsorption.

### *Giardia lamblia*

**Clinical Presentation:** Acute/subacute onset of diarrhea, abdominal cramps, bloating, flatulence. Incubation period 1–2 weeks. Malabsorption may occur in chronic cases. No eosinophilia.
**Diagnostic Considerations:** Diagnosis by demonstrating trophozoites or cysts in stool/antigen detection assay. If stool exam and antigen test are negative and Giardiasis is suspected, perform "string test"/duodenal aspirate and biopsy.
**Pitfalls:** Cysts intermittently excreted into stool. Usually need multiple stool samples for diagnosis. Often accompanied by transient lactose intolerance.
**Therapeutic Considerations:** Nitazoxanide effective therapy. Diarrhea may be prolonged if milk (lactose-containing) products are ingested after treatment/cure. May need repeat courses of therapy.
**Prognosis:** Related to severity of malabsorption and health of host.

### *Cryptosporidia*

**Clinical Presentation:** Acute/subacute onset of diarrhea. Usually occurs in HIV patients with $CD_4$ counts < 200. Biliary cryptosporidiosis is seen only in HIV; may present as acalculous cholecystitis or sclerosing cholangitis with RUQ pain, fever, ↑ alkaline phosphatase, but bilirubin is normal.
**Diagnostic Considerations:** Diagnosis by demonstrating organism in stool/intestinal biopsy specimen. Cholera-like illness in normal hosts. Chronic watery diarrhea in compromised hosts.
**Pitfalls:** Smaller than Cyclospora. Oocyst walls are smooth (not wrinkled) on acid fast staining.
**Therapeutic Considerations:** Nitazoxanide effective therapy.
**Prognosis:** Related to adequacy of fluid replacement/underlying health of host.

### *Cyclospora*

**Clinical Presentation:** Acute/subacute onset of diarrhea. Incubation period 1–14 days.
**Diagnostic Considerations:** Diagnosis by demonstrating organism in stool/intestinal biopsy specimen. Clinically indistinguishable from cryptosporidial diarrhea (intermittent watery diarrhea without blood or mucus). Fatigue/weight loss common.
**Pitfalls:** Oocysts only form seen in stool and are best identified with modified Kinyoun acid fast staining. Acid fast fat globules stain pink with acid fast staining. "Wrinkled wall" oocysts are characteristic of Cyclospora, not Cryptosporidia. Oocysts are twice the size of similar appearing Cryptosporidia (~ 10 µm vs. 5 µm).
**Therapeutic Considerations:** Nitazoxanide effective therapy.
**Prognosis:** Related to adequacy of fluid replacement/underlying health of host.

## Acute Dysentery

### *Entamoeba histolytica*

**Clinical Presentation:** Acute/subacute onset of bloody diarrhea/mucus. Fecal WBC/RBCs due to mucosal invasion. E. histolytica may also cause chronic diarrhea. Colonic ulcers secondary to E. histolytica are round and may form "collar stud" abscesses.
**Diagnostic Considerations:** Diagnosis by demonstrating organism/trophozoites in stool/intestinal biopsy specimen. Serology is negative with amebic dysentery, but positive with extra-intestinal forms. Test to separate E. histolytica from non-pathogenic E. dispar cyst passers. On sigmoidoscopy, ulcers due to E. histolytica are round with normal mucosa in between, and may form "collar stud" abscesses. In contrast, ulcers due to Shigella are linear and serpiginous without normal intervening mucosa. Bloody dysentery is more subacute with E. histolytica compared to Shigella.
**Pitfalls:** Intestinal perforation/abscess may complicate amebic colitis. Rule out infectious causes of bloody diarrhea with mucus before diagnosing/treating inflammatory bowel disease (IBD). Obtain multiple stool cultures for bacterial pathogens/parasites. Do not confuse E. histolytica in stool specimens with E. hartmanni, a non-pathogen protozoa similar in appearance but smaller in size.
**Therapeutic Considerations:** E. histolytica cyst passers should be treated, but metronidazole is ineffective against cysts. Recommended antibiotics treat both luminal and hepatic E. histolytica. Use paromomycin 500 mg (PO) q8h × 7 days for asymptomatic cysts.
**Prognosis:** Good if treated early. Related to severity of dysentery/ulcers/extra-intestinal amebiasis.

### *Shigella*

**Clinical Presentation:** Acute onset of bloody diarrhea/mucus.
**Diagnostic Considerations:** Diagnosis by demonstrating organism in stool specimens. Shigella ulcers in colon are linear, serpiginous, and rarely lead to perforation.
**Therapeutic Considerations:** Shigella dysentery is more acute/fulminating than amebic dysentery. Shigella has no carrier state, unlike Entamoeba.
**Prognosis:** Good if treated early. Severity of illness related to Shigella species: S. dysenteriae (most severe) > S. flexneri > S. boydii/S. sonnei (mildest).

## Cholecystitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Normal host | E. coli<br>Klebsiella<br>E. faecalis (VSE) | Meropenem 1 gm (IV) q8h*<br>**or**<br>Piperacillin/tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h* | Cefazolin 1 gm (IV) q8h* ± Ampicillin 1 gm (IV) q6h*<br>**or**<br>Quinolone‡ (IV)* | Quinolone‡ (PO)* |
| Emphysematous cholecystitis† | Clostridium perfringens<br>E. coli | Meropenem 1 gm (IV) q8h¶<br>**or**<br>Piperacillin/tazobactam 3.375 gm (IV) q6h¶ | Ertapenem 1 gm (IV) q24h¶<br>**or**<br>Ticarcillin/clavulanate 3.1 gm (IV) q6h¶ | Clindamycin 300 mg (PO) q8h¶ |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† Treat only IV or IV-to-PO switch.

‡ Ciprofloxacin 400 mg (IV) or Levofloxacin 500 mg (IV or PO) q24h or Moxifloxacin 400 mg (IV or PO) q24h.

* If no cholecystectomy, treat × 5–7 days. If cholecystectomy is performed, treat × 3–4 days postoperatively.

¶ Treat × 4–7 days after cholecystectomy.

### Cholecystitis

**Clinical Presentation:** RUQ pain, fever usually ≤ 102°F, positive Murphy's sign, no percussion tenderness over right lower ribs.
**Diagnostic Considerations:** Diagnosis by RUQ ultrasound/positive HIDA scan.
**Pitfalls:** No need to cover B. fragilis.
**Therapeutic Considerations:** Obtain surgical consult for possible cholecystectomy.
**Prognosis:** Related to cardiopulmonary status.

### Emphysematous Cholecystitis

**Clinical Presentation:** Clinically presents as cholecystitis. Usually in diabetics.
**Diagnostic Considerations:** RUQ/gallbladder gas on flat plate of abdomen.
**Pitfalls:** Requires immediate cholecystectomy.
**Therapeutic Considerations:** Usually a difficult/prolonged post-op course.
**Prognosis:** Related to speed of gallbladder removal.

## Cholangitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Normal host | E. coli<br>Klebsiella<br>E. faecalis (VSE) | Meropenem 1 gm (IV) q8h*<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h*<br>**or**<br>Piperacillin/tazobactam 3.375 gm (IV) q6h* | Ampicillin/sulbactam 3 gm (IV) q6h*<br>**or**<br>Cefoperazone 2 gm (IV) q12h*<br>**or**<br>Doripenem 1 gm (IV) q8h | Ciprofloxacin 500 mg (PO) q12h*<br>**or**<br>Levofloxacin 500 mg (PO) q24h*<br>**or**<br>Moxifloxacin 400 mg (PO) q24h* |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Treat until resolved (usually 5–7 days).

**Clinical Presentation:** RUQ pain, fever > 102°F, positive Murphy's sign, percussion tenderness over right lower ribs.
**Diagnostic Considerations:** Obstructed common bile duct on ultrasound/CT/MRI of abdomen.
**Pitfalls:** Charcot's triad (fever, RUQ pain, jaundice) is present in only 50%.
**Therapeutic Considerations:** Obtain surgical consult to relieve obstruction. Continue antibiotics for 4–7 days after obstruction is relieved.
**Prognosis:** Related to speed of surgical relief of obstruction.

## Gallbladder Wall Abscess/Perforation

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Gallbladder wall abscess/ perforation | E. coli<br>Klebsiella E. faecalis (VSE) | Piperacillin/ tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h*<br>**or**<br>Meropenem 1 gm (IV) q8h* | Ampicillin/ sulbactam 3 gm (IV) q6h*<br>**or**<br>Cefoperazone 2 gm (IV) q12h*<br>**or**<br>Doripenem 1 gm (IV) q8h | Ciprofloxacin 500 mg (PO) q12h*<br>**or**<br>Levofloxacin 500 mg (PO) q24h*<br>**or**<br>Moxifloxacin 400 mg (PO) q24h* |

Duration of therapy represents total time IV or IV + PO.

* Treat until resolved (usually 1–2 weeks).

**Clinical Presentation:** RUQ pain, fever ≤ 102°F, positive Murphy's sign, no percussion tenderness over right lower ribs.
**Diagnostic Considerations:** Diagnosis by CT/MRI of abdomen. Bile peritonitis is common.
**Pitfalls:** Bacterial peritonitis may be present.
**Therapeutic Considerations:** Obtain surgical consult for possible gallbladder removal. Usually a difficult and prolonged post-op course.
**Prognosis:** Related to removal of gallbladder/repair of perforation.

## Acute Pancreatitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Edematous pancreatitis | None | Not applicable | Not applicable | Not applicable |
| Hemorrhagic/ necrotizing pancreatitis | Aerobic GNBs<br>B. fragilis | Meropenem 1 gm (IV) q8h*<br>**or**<br>Ertapenem 1 gm (IV) q24h* | Piperacillin/tazobactam 3.375 mg (IV) q6h*<br>**or**<br>Ampicillin/sulbactam 1.5 gm (IV) q6h*<br>**or**<br>Ticarcillin/clavulanate 3.1 gm (IV) q6h* | Clindamycin 300 mg (PO) q8h*<br>**plus**<br>Levofloxacin 500 mg (PO) q24h*<br>**or monotherapy with**<br>Moxifloxacin 400 mg (PO) q24h* |

Duration of therapy represents total time IV or IV + PO and varies depending on the clinical response. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Treat until resolved (usually 1–2 weeks).

### Edematous Pancreatitis

**Clinical Presentation:** Sharp abdominal pain with fever ≤ 102°F ± hypotension.
**Diagnostic Considerations:** Diagnosis by elevated serum amylase and lipase levels with normal methemalbumin levels. May be drug-induced (e.g., steroids).
**Pitfalls:** Amylase elevation alone is not diagnostic of acute pancreatitis.
**Therapeutic Considerations:** NG tube is not needed. Aggressively replace fluids.
**Prognosis:** Good with adequate fluid replacement.

### Hemorrhagic/Necrotizing Pancreatitis

**Clinical Presentation:** Sharp abdominal pain with fever ≤ 102°F ± hypotension. Grey-Turner/ Cullen's sign present in some.
**Diagnostic Considerations:** Mildly elevated serum amylase and lipase levels with high methemalbumin levels.
**Pitfalls:** With elevated lipase, amylase level is inversely related to severity of disease.
**Therapeutic Considerations:** Obtain surgical consult for possible peritoneal lavage as adjunct to antibiotics. Serum albumin/dextran are preferred volume expanders.
**Prognosis:** Poor with hypocalcemia or shock.

## Pancreatic Abscess/Infected Pancreatic Pseudocyst

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Infected pancreatic pseudocyst/ pancreatic abscess | Aerobic GNBs<br>B. fragilis | Meropenem 1 gm (IV) q8h*<br>**or**<br>Piperacillin/ tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Ertapenem 1 gm (IV) q24h* | Ampicillin/sulbactam 1.5 gm (IV) q6h*<br>**or**<br>Ticarcillin/clavulanate 3.1 gm (IV) q6h*<br>**or**<br>Doripenem 1 gm (IV) q8h | Moxifloxacin 400 mg (PO) q24h*<br>**or combination therapy with**<br>Clindamycin 300 mg (PO) q8h*<br>**plus**<br>Quinolone† (PO)* |

Duration of therapy represents total time IV or IV + PO.
† Ciprofloxacin 500 mg q12h or Levofloxacin 500 mg q24h.
* Treat until resolved.

**Clinical Presentation:** Follows acute pancreatitis or develops in a pancreatic pseudocyst. An infected pancreatic pseudocyst is an abscess equivalent. Fevers usually ≥ 102°F.
**Diagnostic Considerations:** CT/MRI of abdomen demonstrates pancreatic abscess.
**Pitfalls:** Peritoneal signs are typically absent.
**Prognosis:** Related to size/extent of abscess and adequacy of drainage.

## Liver Abscess

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Liver abscess | Aerobic GNBs<br>Enterococci (VSE)<br>B. fragilis | Piperacillin/ tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Tigecycline 100 mg (IV) × 1 dose, then 50 mg (IV) q12h*<br>**or**<br>Meropenem 1 gm (IV) q8h* **or** | Quinolone† (IV)*<br>**plus either**<br>Metronidazole 1 gm (IV) q24h*<br>**or**<br>Clindamycin 600 mg (IV) q8h*<br>Moxifloxacin 400 mg (IV) q24h*<br>**or**<br>Sulbactam/ampicillin 3 gm (IV) q6h | Amoxicillin/clavulanic acid 875/125 mg (PO) q12h*<br>**or**<br>Moxifloxacin 400 mg (PO) q24h*<br>**or combination therapy with**<br>Quinolone† (PO)*<br>**plus either**<br>Metronidazole 500 mg (PO) q12h*<br>**or**<br>Clindamycin 300 mg (PO) q8h* |
| | E. histolytica | See p. 274 | | |

Duration of therapy represents total time IV, PO, or IV + PO.
* Treat until abscess(es) are no longer present or stop decreasing in size on serial CT scans.
† Ciprofloxacin 400 mg (IV) or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h.

## Liver Abscess (cont'd)

**Clinical Presentation:** Fever, RUQ tenderness, negative Murphy's sign, and negative right lower rib percussion tenderness.

**Diagnostic Considerations:** Diagnosis by CT/MRI scan of liver and aspiration of abscess. CT shows multiple lesions in liver. Source is usually either the colon (diverticulitis or diverticular abscess with portal pyemia) or retrograde infection from the gallbladder (cholecystitis or gallbladder wall abscess).

**Pitfalls:** Bacterial abscesses are usually multiple and involve multiple lobes of liver; amebic abscesses are usually solitary and involve the right lobe of liver.

**Therapeutic Considerations:** Liver laceration/trauma usually requires ~ 2 weeks of antibiotics.

**Prognosis:** Good if treated early.

## Hepatosplenic Candidiasis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Hepato-splenic candidiasis | Candida albicans | Fluconazole 800 mg (IV) × 1 dose, then 400 mg (IV) q24h × 2–4 weeks<br>**or**<br>Micafungin 100 mg (IV) q24h × 2–4 weeks<br>**or**<br>Caspofungin 70 mg (IV) × 1 dose, then 50 mg (IV) q24h × 2–4 weeks | Ambisome (L-Amb) (see p. 540) (IV) q24h × 2–4 weeks<br>**or**<br>Amphotericin B 0.7 mg/kg (IV) q24h × 2–4 weeks | Fluconazole 800 mg (PO) × 1 dose, then 400 mg (PO) q24h × 2–4 weeks*<br>**or**<br>Itraconazole 200 mg (PO) solution q12h × 2–4 weeks |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Loading dose is not needed PO if given IV with the same drug.

**Clinical Presentation:** New high spiking fevers with RUQ/LUQ pain after 2 weeks in a patient with afebrile leukopenia.

**Diagnostic Considerations:** Diagnosis by abdominal CT/MRI showing mass lesions in liver/spleen.

**Pitfalls:** Do not overlook RUQ tenderness and elevated alkaline phosphatase in leukopenic cancer patients as a clue to the diagnosis.

**Therapeutic Considerations:** Treat until liver/spleen lesions resolve. Should be viewed as a form of disseminated disease.

**Prognosis:** Related to degree/duration of leukopenia.

## Granulomatous Hepatitis (BCG)

| Subset | Pathogen | Preferred Therapy |
|---|---|---|
| BCG hepatitis | Bacille Calmette-Guérin (BCG) | INH 300 mg (PO) q24h × 6 months + rifampin 600 mg (PO) q24h × 6 months |

**Clinical Presentation:** Fever, chills, anorexia, weight loss, hepatomegaly ± RUQ pain days to weeks after intravesicular BCG for bladder cancer.
**Diagnostic Considerations:** ↑ alkaline phosphatase > ↑ SGOT/SGPT. Liver biopsy is negative for AFB/positive for granulomas.
**Pitfalls:** Exclude other causes of hepatomegaly.
**Therapeutic Considerations:** INH plus rifampin × 6 months is curative.
**Prognosis:** Excellent with early treatment.

## Leptospirosis

**Clinical Presentation:** After incubation period of 1–2 weeks, abrupt onset of fever, no chills, severe headache, conjunctival suffusion, meningismus, dry cough, intense myalgias (gastroc myalgias/tenderness) ± abdominal pain. 1st (leptospiremic) phase (4–9 days); 2nd (immune) phase (6–12 days). Leukocytosis with no thrombocytopenia usual. Hepatic (↑ bilirubin/transaminases) and renal (azotemia, proteinuria, sterile, pyuria) involvement. Meningitis (early) → ABM with CSF + for leptospires; meningitis (late) → aseptic meningitis CSF—for leptospires. Progressive vomiting, epistaxis, jaundice/hepatosplenomegaly only with Weil's syndrome (icteric leptospirosis). Intense myalgias with hepatic and renal involvement should suggest leptospirosis.
**Diagnostic Considerations:** Recent occupational or contaminated water (rat urine) exposure. Leptospiruria (after 2 weeks) seen in dark-field of urine. BCs + early (– late); UCs + late. Leptospires die rapidly in acid urine (add buffered saline before culture). Diagnosis by blood/urine culture or ↑ MAT IgM titers (after 1 week). Antibiotic therapy may blunt, delay or abort titer rise.
**Pitfalls:** Like influenza (headache, sore throat, myalgias), patients can recall exact hour of onset. Unlike influenza, no chills but conjunctival suffusion. CXR—in influenza (early) but CXR often + in leptospirosis. Differentiate from viral hepatitis ( < 102°F, no conjunctival suffusion, leukopenia, highly ↑ transaminases, no renal involvement). Differentiate from EBV, CMV, HSV hepatitis by + atypical lymphocytes ( – with leptospirosis) and specific serologies. Like aseptic (viral) meningitis (normal glucose, WBCs < 500/hpf). Only ID with CSF bilirubin > serum. Clinically irrelevant serologic XR with Borrelia/treponeme titers.
**Therapeutic Considerations:** Penicillin or doxycycline (± Jarisch-Herxheimer reaction).
**Prognosis:** Excellent if treated early, 5–40% mortality for Weil's syndrome and elderly.

## Viral Hepatitis

| Subset | Pathogens | Therapy |
|---|---|---|
| Acute | HAV (none); HBV (consider nucleos(t)ides for HBV-acute liver failure); HCV (consider pegylated interferon +/– ribavirin if no viral clearance after 12–16 weeks); HDV (none); HEV (consider ribavirin fir severe hepatitis) | |
| Chronic | HBV* | Preferred:<br>Tenofovir 300 mg (PO) **or** Entecavir 0.5 mg (PO) q24h × ≥ 12 months<br>For lamivudine resistant strains use **either**<br>Entecavir 1.0 mg q24h **or** Pegylated interferon alfa-2a 180 mcg (SQ)/week *without* ribavirin × 12 months<br>Alternate: Telbivudine 600 mg (PO) q24h **or** Adefovir 10 mg (PO) q24h **or** Lamivudine 100 mg (PO) for × ≥ 12 months |

* HBeAg+ with ALT > 2 × n and HBV DNA > 20,000 IU/ml or alternately, chronic HBV with moderate/severe inflammation or significant fibrosis on liver biopsy. Primary therapeutic response (< 2 log ↓) in a HBV DNA levels after ≥ 6 months of therapy. Treatment failures should be treated with an alternate regimen or additional treatment.

## Viral Hepatitis (cont'd)

| Subset | Pathogens | Therapy |
|---|---|---|
| | HCV | **Genotype 1 (includes 1a & 1b)**<br>Preferred therapy (similar efficacy):<br>Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg (PO) q24h + dasabuvir 250 mg (Viekira Pak) (PO) q12h + ribavirin[1,2] x weeks[3]<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + simeprevir[4] 150 mg (Olysio) (PO) q24h ± ribavirin[1] × weeks[3]<br>**Genotype 2**<br>Preferred therapy:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + ribavirin[1] x 12 weeks (16 weeks in cirrhosis)<br>**Genotype 3**<br>Preferred therapies:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + ribavirin[1] x 24 weeks<br>Alternate therapy:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + pegylated IFN alfa-2a/2b[5] ribavirin[1] x 12 weeks<br>**Genotype 4**<br>Preferred therapies (similar efficacy):<br>Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg (Viekira Pak minus dasabuvir) (PO) q24h + ribavirin[1] x 12 weeks<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + ribavirin[1] x 24 weeks<br>Alternate therapy:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirin[1] x 12 weeks,<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + simeprevir 150 mg (Olysio) (PO) q24h ± ribavirin[1] x 12 weeks<br>**Genotype 5**<br>Preferred therapy:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirin[1] x 12 weeks<br>Alternate therapy:<br>Pegylated IFN alfa-2a/2b[5] + ribavirin[1] × 48 weeks<br>**Genotype 6**<br>Preferred therapy:<br>Ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Alternate therapy:<br>Sofosbuvir 400 mg (Sovaldi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirin[1] x 12 weeks |
| | HDV | Prolonged therapy with pegylated interferon alfa-2a *without* ribavirin as for chronic hepatitis B (see above) |
| | HEV | Ribavirin 600–1200 mg daily × 12 weeks or pegylated interferon weekly × 12 weeks +/– ribavirin |

[1]Ribavirin should be dosed as following:
Weight < 75 kg: Ribavirin 1000 mg (PO) daily in 2 divided doses (400 mg in am, 600 mg in pm)
Weight > 75 kg: Ribavirin 1200 mg (PO) daily in 2 divided doses (600 mg q12h)

[2]In Genotype Ib, ribavirin is only Indicated in cirrhosis

[3]12 week therapy without cirrhosis; 24 week therapy with cirrhosis

[4]Simperevir may be ineffective in patients with HCV genotype 1a Q80K polymorphism

[5]Pegylated IFN alfa-2a should be dosed 180 µg (SC) weekly. Pegylated IFN alfa-2b should be dosed 1.5 µg/kg (SC) weekly. Both types of pegylated IFN alfa are approved to treat genotype 1

Adapted from: American Association for the Study of Liver Disease and Infectious Disease Society of America. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org, 2014

## Acute Viral Hepatitis

**Clinical Presentation:** Asymptomatic or anorexia, malaise, nausea, serum-sickness like syndrome, ± jaundice, dark urine.

**Diagnostic Considerations:** Diagnosis by presence in HAV of IgM anti-HAV or in HBV of HBsAg and IgM anti-HBc or in HCV of anti-HCV and HCV RNA or in HDV of HBsAg, anti-HDV and HDV RNA or in HEV of anti-HEV and HEV RNA, with markedly elevated serum aminotransferases (ALT > 400). Serum alkaline phosphatase normal/mildly elevated; albumin normal or mildly depressed; INR normal or minimally elevated.

**Pitfalls:** Rule out other hepatitis-causing agents (EBV, CMV, HSV, etc) and drug-induced liver injury if serologic tests for HAV, HBV, HCV, HDV, and HEV are negative.

**Therapeutic Considerations:** For patients who develop encephalopathy and/or a prolonged INR (acute liver failure) admit to liver transplantation center.

**Prognosis:** Hepatitis A generally self-limited; Hepatitis B, C, D and rarely E may progress to chronic hepatitis/cirrhosis/hepatocellular carcinoma.

## EBV/CMV Hepatitis

**Clinical Presentation:** Similar to acute viral hepatitis plus bilateral posterior cervical adenopathy and fatigue.

**Diagnostic Considerations:** EBV hepatitis is part of infectious mononucleosis and may be the presenting sign in adults. CMV hepatitis also may appear as a "mono-like" infection in normal hosts. In compromised hosts, hepatitis may be the primary manifestation of CMV infection. Diagnosis of EBV/CMV hepatitis can be made by serology (positive mono spot test, high EBV VCA IgM titer, high CMV IgM titer, CMV early antigen detection (via shell vial cultures) or molecular amplification techniques.

**Pitfalls:** In normal and immunocompromised hosts with unexplained aminotransferase (ALT/AST) elevations, consider CMV hepatitis and order appropriate tests.

**Treatment:** None effective in EBV hepatitis; CMV hepatitis in normal hosts may be treated with Valganciclovir 900 mg (PO) q12h × 12 days.

**Prognosis:** In normal hosts EBV and CMV hepatitis are usually self-limited. In immunocompromised hosts, the prognosis of CMV hepatitis is related to the degree of Immunosuppression and the rapidity of onset of treatment.

## Chronic Viral Hepatitis

**Clinical Presentation:** Often asymptomatic with persistently or intermittently elevated serum aminotransferases but in some aminotransferases are normal. Some present with signs and symptoms of chronic liver disease.

**Diagnostic Considerations:** Chronic hepatitis B is diagnosed by presence of HBsAg and HBV DNA. Chronic hepatitis C is diagnosed by positive tests for anti-HCV and HCV RNA. Signal cutoff (SCO) >1.0 = HCV infection. SCO < 1.0 = false + test. Most HCV infections have SCOs > 5-10. Chronic hepatitis D is diagnosed by positive tests for HBsAg and HDV RNA. Chronic hepatitis E is diagnosed by presence of anti-HEV and HEV RNA. Liver biopsy may be used to grade inflammation and stage fibrosis.

**Pitfalls:** Autoimmune hepatitis may present as an acute or chronic hepatitis but with elevated IgG levels, elevated ANAs, and anti-smooth muscle antibodies. For both HCV and HBV, rule out co-infection with HIV.

**Therapeutic Considerations:** In chronic hepatitis B (see p. 97) treat until HBV DNA becomes undetectable, ALT normalizes, and for HBeAg-positive patients, HBeAg seroconversion occurs (then continue for 6–12 additional months). For chronic hepatitis C therapy is based on genotype (see p. 98).

**Prognosis:** Sustained clearance of HCV RNA (measured 24 weeks after discontinuation of treatment) results in a cure in 99% of chronic hepatitis C patients. Sustained clearance of HBV DNA is linked with an improved prognosis in chronic hepatitis B.

## Intraabdominal or Pelvic Peritonitis/Abscess

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Mild/ moderate peritonitis | Entero-bacteriaceae B. fragilis | Moxifloxacin 400 mg (IV) q24h¥ **or** Cefoxitin 2 gm (IV) q6h¥ **or** Piperacillin/ tazobactam 3.375 gm (IV) q6h¥ | Ampicillin/ sulbactam 1.5 gm (IV) q6h¥ **or** Ceftazidime/ avibactam 2.5 gm (IV) q8h **plus** Metronidazole 500 mg (IV) q8h | Moxifloxacin 400 mg (PO) q24h¥ **or** Amoxicillin/ clavulanate 875/125 mg (PO) q12h¥ **or combination therapy with** Levofloxacin 500 mg (PO) q24h¥ **plus** Clindamycin 300 mg (PO) q8h¥ |
| Severe peritonitis‡ | Entero-bacteriaceae B. fragilis | Ertapenem 1 gm (IV) q24h¥ **or** Ceftazidime/ avibactam 2.5 gm (IV) q8h **plus** Metronidazole 1 gm (IV) q24h¥ **or** Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h¥ **or** Meropenem 1 gm (IV) q8h¥ | Ampicillin/ sulbactam 3 gm (IV) q6h¥ **or** Doripenem 1 gm (IV) q8h **or combination therapy with** Metronidazole 1 gm (IV) q24h¥ **plus either** Ceftriaxone 1 gm (IV) q24h¥ **or** Levofloxacin 500 mg (IV) q24h | Moxifloxacin 400 mg (PO) q24h¥ **or** Amoxicillin/ clavulanate 875/125 mg (PO) q12h¥ |
| | CRE | Ceftazidime/avibactam 2.5 gm (IV) q8h¥ **plus** Metronidazole 1 gm (IV) q24h¥ | | |

Duration of therapy represents total time IV, PO, or IV + PO.

¥ Duration of therapy as clinically indicated or for 5–7 days following corrective surgery.

## Intraabdominal or Pelvic Peritonitis/Abscess (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Spontaneous bacterial peritonitis (SBP)‡ | Entero-bacteriaceae<br>S. pneumoniae (children) | Ceftriaxone 1 gm (IV) q24h × 1–2 wks<br>**or**<br>Levofloxacin 500 mg (IV) × 1–2 weeks | Aztreonam 2 gm (IV) q8h × 1–2 weeks<br>**or**<br>Any aminoglycoside (IV) q24h × 1–2 wks | Quinolone¶ (PO) × 1–2 weeks<br>**or**<br>Amoxicillin/clavulanate 875/125 mg (PO) q12h × 1–2 weeks |
| Chronic TB peritonitis | M. tuberculosis | Not applicable | | Treat the same as pulmonary TB (see p. 53) |
| CAPD-associated peritonitis‡ | S. epidermidis (CoNS)<br>S. aureus (MSSA)<br>Entero-bacteriaceae<br>Non-ferment-ative GNBs | *Before culture results*<br>Vancomycin 1 gm (IV) initial dose*<br>**plus**<br>Gentamicin 5 mg/kg or 240 mg (IV) initial dose* | *After culture results*<br>*MSSA/Enterobacteriaceae*<br>Meropenem 1 gm (IV) initial dose*<br>*MRSA*<br>Vancomycin 1 gm (IV) initial dose*<br>**or**<br>Linezolid 600 mg (IV or PO) | |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus. Duration of therapy represents total time IV, PO, or IV + PO.

‡ Treat only IV or IV-to-PO switch.

* Follow with maintenance dosing × 2 weeks after culture results are available. For maintenance dosing, use renal failure (CrCl < 10 mL/min) and post-peritoneal dialysis dosing (see Drug Summaries).

### Intraabdominal or Pelvic Peritonitis/Abscess (Appendicitis/Diverticulitis/Septic Pelvic Thrombophlebitis)

**Clinical Presentation:** Spiking fevers with acute abdominal pain and peritoneal signs. In diverticulitis, the pain is localized over the involved segment of colon. Appendicitis ± perforation presents as RLQ pain/rebound tenderness or mass. Peri-diverticular abscess presents the same as intraabdominal/pelvic abscess, most commonly in the LLQ. Septic pelvic thrombophlebitis (SPT) presents as high spiking fevers unresponsive to antibiotic therapy following delivery/pelvic surgery.

**Diagnostic Considerations:** Diagnosis by CT/MRI scan of abdomen/pelvis.

**Pitfalls:** Tympany over liver suggests abdominal/visceral perforation. Pelvic peritonitis/abscess presents the same as intraabdominal abscess/peritonitis, but peritoneal signs are often absent.
**Therapeutic Considerations:** Patients with ischemic/inflammatory colitis should be treated the same as peritonitis, depending on severity. Obtain surgical consult for repair/lavage or abscess drainage. In SPT, fever rapidly falls when heparin is added to antibiotics.
**Prognosis:** Related to degree/duration of peritoneal spillage and rapidity/completeness of lavage. Prognosis for SPT is good if treated early and clots remain limited to pelvic veins.

## Spontaneous Bacterial Peritonitis (SBP)

**Clinical Presentation:** Acute or subacute onset of fever ± abdominal pain.
**Diagnostic Considerations:** Diagnosis by positive blood cultures of SBP pathogens. For patients with abdominal pain, ascites, and a negative CT/MRI, paracentesis ascitic fluid with > 500 WBCs and > 100 PMNs predicts a positive ascitic fluid culture and is diagnostic of SBP. Some degree of splenic dysfunction usually exists, predisposing to infection with encapsulated organisms.
**Pitfalls:** Do not overlook GI source of peritonitis (e.g, appendicitis, diverticulitis); obtain CT/MRI.
**Therapeutic Considerations:** B. fragilis/anaerobes are not common pathogens in SBP, and B. fragilis coverage is unnecessary.
**Prognosis:** Related to degree of hepatitic/splenic dysfunction.

## Chronic Tuberculous Peritonitis (Mycobacterium tuberculosis)

**Clinical Presentation:** Abdominal pain with fevers, weight loss, ascites over 1–3 months.
**Diagnostic Considerations:** "Doughy consistency" on abdominal palpation. Diagnosis by AFB on peritoneal biopsy/culture.
**Pitfalls:** Chest x-ray is normal in ~ 70%. Increased incidence in alcoholic cirrhosis.
**Therapeutic Considerations:** Treated the same as pulmonary TB.
**Prognosis:** Good if treated early.

## CAPD Associated Peritonitis

**Clinical Presentation:** Abdominal pain ± fever in a CAPD patient.
**Diagnostic Considerations:** Diagnosis by gram stain/culture and ↑ WBC count in peritoneal fluid. Lymphocytic predominance may suggest TB or fungi. Unlike SBP, there are not specific diagnostic criteria in peritoneal fluid.
**Pitfalls:** Fever is often absent.
**Therapeutic Considerations:** Treat with systemic antibiotics ± antibiotics in dialysate.
**Prognosis:** Good with early therapy and removal of peritoneal catheter.

# Empiric Therapy of Genitourinary Tract Infections

## Dysuria-Pyuria Syndrome (Acute Urethral Syndrome)

| Subset | Usual Pathogens | IV Therapy | PO Therapy |
|---|---|---|---|
| Acute urethral syndrome | S. saprophyticus<br>C. trachomatis<br>E. coli (< $10^5$ cfu/mL) | Not applicable | Doxycycline 100 mg (PO) q12h × 10 days<br>**or**<br>Quinolone (PO)* × 7 days |

* Ciprofloxacin 500 mg q12h or Levofloxacin 500 mg q24h.

**Clinical Presentation:** Dysuria, frequency, urgency, lower abdominal discomfort, fevers < 102°F.
**Diagnostic Considerations:** Diagnosis by symptoms of cystitis with pyuria and no growth or low concentration of E. coli (≤ $10^3$ colonies/mL) by urine culture. Clue to S. saprophyticus is alkaline urinary pH and RBCs in urine.
**Pitfalls:** Resembles "culture negative" cystitis.
**Therapeutic Considerations:** S. saprophyticus is susceptible to most antibiotics used to treat UTIs.
**Prognosis:** Excellent.

## **Cystitis** (see Color Atlas for Urine Gram stains)

| Subset | Usual Pathogens | Therapy |
|---|---|---|
| Bacterial | Enterobacteriaceae<br>E. faecalis (VSE)<br>S. agalactiae (group B streptococci)<br>S. saprophyticus | Amoxicillin 500 mg (PO) × q12h × 3 days<br>**or**<br>TMP–SMX 1 SS tablet (PO) × q12h × 3 days<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 3 days<br>**or**<br>Nitrofurantoin 100 mg (PO) q12h × 3 days |
| | MDR GNBs | Fosfomycin 3 gm (PO) q24h × 3 days |
| Fungal | C. albicans† | Fluconazole 200 mg (PO) × 1 dose, then 100 mg (PO) q24h × 4 days |
| | Fluconazole-resistant‡ Candida isolates or fluconazole-refractory disease | Amphotericin B 0.3 mg/kg (IV) × 1 dose |

† C. albicans cystitis (see p. 104)
‡ Fluconazole-resistant (see p. 104)

### Bacterial Cystitis

**Clinical Presentation:** Dysuria, frequency, urgency, lower abdominal discomfort, fevers < 102°F.
**Diagnostic Considerations:** Pyuria plus bacteriuria.
**Pitfalls:** Compromised hosts (chronic steroids, diabetes, SLE, cirrhosis, multiple myeloma) may require 3–5 days of therapy. A single dose of amoxicillin or TMP–SMX may be sufficient in acute uncomplicated cystitis in normal hosts.
**Therapeutic Considerations:** Pyridium 200 mg (PO) q8h after meals × 24–48h is useful to decrease dysuria (inform patients urine will turn orange).
**Prognosis:** Excellent in normal hosts.

### Candida Cystitis

**Diagnostic Considerations:** Marked pyuria, urine nitrate negative ± RBCs. Speciate if not C. albicans.
**Pitfalls:** Lack of response suggests renal candidiasis or a "fungus ball" in the renal collecting system.
**Therapeutic Considerations:** If fluconazole fails, use amphotericin. For chronic renal failure/dialysis patients with candiduria, use amphotericin B deoxycholate bladder irrigation (as for catheter-associated candiduria, below). Removal of devices and correction of anatomic abnormalities are critical to success.
**Prognosis:** Patients with impaired host defenses, abnormal collecting systems, cysts, renal disease or stones are prone to recurrent UTIs/urosepsis.

## Catheter Associated Bacteriuria (CAB)

| Subset | Usual Pathogens | Therapy |
|---|---|---|
| Catheter associated bacteriuria (CAB)†* | E. coli<br>E. faecalis (VSE) | Nitrofurantoin 100 mg (PO) q12h × 3 days<br>**or**<br>Amoxicillin 500 mg (PO) q12h × 3 days |
| | E. faecium (VRE) | Nitrofurantoin 100 mg (PO) q12h × 3 days<br>**or**<br>Fosomycin 3 gm (PO) q24h × 3 days†† |
| | MDR Klebsiella††<br>MDR Acinetobacter††<br>MDR P. aeruginosa†† | Nitrofurantoin 100 mg (PO) q12h × 3 days††<br>**or**<br>Fosomycin 3 gm (PO) q24h × 3 days††<br>**or**<br>Meropenem 1 gm (IV) q8h × 3 day††§<br>**or**<br>Doripenem 1 gm (IV) q8h × 3 days††§ |

VSE/VRE = vancomycin-sensitive/resistant enterococci, MDR = multidrug resistant

* **Remove/replace Foley catheter before initiating antibiotic therapy.**

† *No need to treat CAB in normal hosts, pre-emptive therapy suggested in compromised hosts*, e.g., cirrhosis, SLE, DM, myeloma, steroids, immunosuppressives, and those with renal insufficiency.

†† Longer courses of therapy may be needed in compromised hosts. If pyuria substantially decreased after 2 days of therapy, complete 3 days of therapy. If not, continue therapy for 7 days.

§ Only if oral therapy not possible.

## Catheter Associated Candiduria (CAC)

| Subset | Usual Pathogens | Therapy |
|---|---|---|
| Catheter associated candiduria (CAC)†* | C. albicans | Fluconazole 200 mg (PO) × 1 dose, then 100 mg (PO) q24h × 2 weeks |
| | Fluconazole-resistant C. albicans/non-albicans Candida | Amphotericin B 0.3–0.6 mg/kg q24h × 1–7 days<br>**or**<br>Flucytosine 25 mg/kg QID (PO) × 7–10 days<br>**or**<br>Amphotericin B bladder irrigation (continuous: 50 mg in 1 liter sterile water over 24h × 1–2 days; intermittent: 50 mg in 200–300 ml sterile water q6-8h × 1–2 days)§ |

§ Limited efficacy.

**Clinical Presentation:** Indwelling urinary (Foley) catheter with bacteriuria and pyuria; no symptoms.
**Diagnostic Considerations:** Pyuria plus bacteriuria/candiduria. Usually afebrile or temperature < 101°F.
**Pitfalls:** Bacteriuria/candiduria often represent colonization, not infection. Persistent candiduria after amphotericin B deoxycholate bladder irrigation suggests renal candidiasis.
**Therapeutic Considerations:** Avoid treating catheter-associated bacteriuria in normal hosts without GU tract abnormalities/disease. Compromised hosts (diabetes, SLE, chronic steroids, multiple myeloma, cirrhosis) may require therapy for duration of catheterization. If bacteriuria/candiduria does not clear with appropriate therapy, change the catheter. For chronic renal failure/dialysis patients with candiduria, use amphotericin B deoxycholate bladder irrigation. Efficacy of therapy of catheter-associated candiduria is limited and relapse is frequent unless the catheter can be replaced or (preferably) removed.
**Prognosis:** Excellent in normal hosts. Untreated bacteriuria/candiduria in compromised hosts may result in ascending infection (e.g., pyelonephritis) or bacteremia/candidemia.

## Epididymitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute<br>*Young males* | C. trachomatis | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 4 days | Levofloxacin 500 mg (IV) q24h × 7 days | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 7 days*<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 10 days<br>**or**<br>Ofloxacin 300 mg (PO) q12h × 10 days |
| *Elderly males* | P. aeruginosa | Cefepime 2 gm (IV) q8h × 10 days<br>**or**<br>Meropenem 1 gm (IV) q8h × 10 days | Ciprofloxacin 400 mg (IV) q8h × 10 days<br>**or**<br>Levofloxacin 750 mg (IV) q24h × 10 days | Ciprofloxacin 750 mg (PO) q12h × 10 days |
| Chronic | M. tuberculosis<br>Blastomyces dermatiditis | Treat the same as pulmonary TB (see p. 53) or pulmonary blastomycosis (see p. 267) | | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).

* Loading dose is not needed PO if given IV with the same drug.

### Acute Epididymitis (Chlamydia trachomatis/Pseudomonas aeruginosa)

**Clinical Presentation:** Acute unilateral testicular pain ± fever.
**Diagnostic Considerations:** Ultrasound to rule out torsion or tumor.
**Pitfalls:** Rule out torsion by absence of fever and ultrasound.
**Therapeutic Considerations:** Young males respond to treatment slowly over 1 week. Elderly males respond to anti-Pseudomonal therapy within 72 hours.
**Prognosis:** Excellent in young males. Related to health of host in elderly.

### Chronic Epididymitis (Mycobacterium tuberculosis/ Blastomyces dermatiditis)

**Clinical Presentation:** Chronic epididymoorchitis with epididymal nodules.
**Diagnostic Considerations:** Diagnosis by AFB on biopsy/culture of epididymis. TB epididymitis is always associated with renal TB. Blastomyces epididymitis is a manifestation of systemic infection.
**Pitfalls:** Vasculitis (e.g., polyarteritis nodosum) and lymphomas may present the same way.
**Therapeutic Considerations:** Treated the same as pulmonary TB/blastomycosis.
**Prognosis:** Good.

## **Acute Pyelonephritis** (see Color Atlas for Urine Gram stains)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute pyelonephritis<br><br>(Treat initially based on urine gram stain; see therapeutic considerations, below) | Entero-bacteriaceae | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (IV) q24h × 2 weeks | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Aztreonam 2 gm (IV) q8h × 2 weeks<br>**or**<br>Gentamicin 240 mg (IV) q24h × 2 weeks | Levofloxacin 500 mg (PO) q24h × 2 weeks<br>**or**<br>Amoxicillin 1 gm (PO) q8h × 2 weeks |
| | Enterococcus faecalis (VSE)§ | Ampicillin 1 gm (IV) q4h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks | Quinolone (IV) × 2 weeks | Amoxicillin 1 gm (PO) q8h × 2 weeks<br>**or**<br>Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 2 weeks |
| | Enterococcus faecium (VRE) | Linezolid 600 mg (IV) q12h × 2 weeks | Quinupristin/ dalfopristin 7.5 mg/ kg (IV) q8h × 2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg q12h × 2 weeks | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 2 weeks |
| | MDR GNB | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftolozane/ tazobactam 1.5 gm (IV) q8h × 2 weeks | Colistin 5 mg/kg (IV) q8h × 2 weeks | |
| | CRE | Ceftazidime/ avibactam 2.5 gm (IV) q8h × 2 weeks | Tigecycline 200 mg (IV) × 1 dose then 100 mg (IV) q24h × 2 weeks*<br>**or**<br>Colistin 5 mg/kg (IV) q8h × 2 weeks | |

VSE/VRE = vancomycin-sensitive/resistant enterococci.

* Depending on MICs, higher doses may be necessary LD: 400 mg (IV) × 1 dose, then MD: 200 mg (IV) q24h.

§ Treat vancomycin resistant E. faecalis as VRE.

## Chronic Pyelonephritis/Renal TB

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Chronic pyelonephritis | Entero-bacteriaceae | IV Therapy<br>Not applicable | Quinolone† (PO) × 4–6 weeks<br>**or**<br>TMP–SMX 1 DS tab (PO) q12h × 4–6 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4–6 weeks total | |
| Renal TB | M. tuberculosis | IV Therapy<br>Not applicable | Treated the same as pulmonary TB<br>(see p. 53) | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement (usually < 72 hours).

† Ciprofloxacin XR 1000 mg (PO) q24h or Ciprofloxacin 400 mg (IV) q12h or Levofloxacin 500 mg (IV or PO) q24h.

### Acute Bacterial Pyelonephritis (Enterobacteriaceae, E. faecalis/faecium)

**Clinical Presentation:** Unilateral CVA tenderness with fevers ≥ 102°F.

**Diagnostic Considerations:** Bacteriuria plus pyuria with unilateral CVA tenderness and temperature ≥ 102°F. Bacteremia usually accompanies acute pyelonephritis; obtain blood and urine cultures.

**Pitfalls:** Temperature decreases in 72 hours with or without antibiotic treatment. If temperature does not fall after 72 hours of antibiotic therapy, suspect renal/perinephric abscess.

**Therapeutic Considerations:** Initial treatment is based on the urinary gram stain: If gram-negative bacilli, treat as Enterobacteriaceae. If gram-positive cocci in chains (enterococcus), treat as E. faecalis; if enterococcus is subsequently identified as E. faecium, treat accordingly. Acute pyelonephritis is usually treated initially for 1–3 days IV, then switched to PO to complete 4 weeks of antibiotics to minimize progression to chronic pyelonephritis. Obtain a CT/MRI in persistently febrile patients after 72 hours of antibiotics to rule out renal calculi, obstruction, abscess, or xanthomatous pyelonephritis.

**Prognosis:** Excellent if first episode is adequately treated with antibiotics for 4 weeks.

### Chronic Bacterial Pyelonephritis (Enterobacteriaceae)

**Clinical Presentation:** Previous history of acute pyelonephritis with same symptoms as acute pyelonephritis but less CVA tenderness/fever.

**Diagnostic Considerations:** Diagnosis by CT/MRI showing changes of chronic pyelonephritis plus bacteriuria/pyuria. Urine cultures may be intermittently negative before treatment. Chronic pyelonephritis is bilateral pathologically, but unilateral clinically.

**Pitfalls:** Urine culture may be intermittently positive after treatment; repeat weekly × 4 to confirm urine remains culture-negative.

**Therapeutic Considerations:** Treat × 4–6 weeks. Impaired medullary vascular blood supply/renal anatomical distortion makes eradication of pathogen difficult.

**Prognosis:** Related to extent of renal damage.

**Renal TB (Mycobacterium tuberculosis)**

**Clinical Presentation:** Renal mass lesion with ureteral abnormalities (pipestem, corkscrew, or spiral ureters) microscopic hematuria/sterile pyuria. Painless unless complicated by ureteral obstruction.

**Diagnostic Considerations:** Combined upper/lower urinary tract abnormalities ± microscopic hematuria/urinary pH ≤ 5.5. Diagnosis by culture of TB from urine. Urine TB PCR is specific, but not very sensitive.

**Pitfalls:** Chest x-ray is normal in 50%, but most patients are PPD positive. Rule out other infectious/inflammatory causes of sterile pyuria (e.g., Trichomonas, interstitial nephritis).

**Therapeutic Considerations:** Treat the same as pulmonary TB.

**Prognosis:** Good if treated before renal parenchymal destruction/ureteral obstruction occur.

## Renal Abscess (Intrarenal/Perinephric)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Cortical<br><br>(Treat initially for MSSA; if later identified as MRSA, treat accordingly) | S. aureus | MSSA:<br>Nafcillin 2 gm (IV) q4h*<br>**or**<br>Ceftriaxone 1 gm (IV) q24h*<br>**or**<br>Clindamycin 600 mg (IV) q8h* | MSSA<br>Meropenem 1 gm (IV) q8h*<br>**or**<br>Ertapenem 1 gm (IV) q24h* | MSSA/MRSA<br>Linezolid 600 mg (PO) q12h*<br>**or**<br>Minocycline 100 mg (PO) q12h* |
| | | MRSA: Linezolid 600 mg (IV) q12h*<br>**or**<br>Minocycline 100 mg (IV) q12h* | MRSA<br>Vancomycin 1 gm (IV) q12h* | |
| Medullary | Entero-bacteriaceae | Quinolone (IV)†* | TMP–SMX 2.5 mg/kg (IV) q6h* | Quinolone (PO)†* |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

* Treat until renal abscess resolves completely or is no longer decreasing in size on CT/MRI.

† Levofloxacin 500 mg (IV/PO) q24h.

**Clinical Presentation:** Similar to pyelonephritis but fever remains elevated after 72 hours of antibiotics.

**Diagnostic Considerations:** Obtain CT/MRI to diagnose perinephric/intra-renal abscess and rule out mass lesion. Cortical abscesses are usually secondary to hematogenous/contiguous spread. Medullary abscesses are usually due to extension of intrarenal infection.

**Pitfalls:** Urine cultures may be negative with cortical abscesses.
**Therapeutic Considerations:** Most large abscesses need to be drained. Multiple small abscesses are managed medically. Obtain urology consult.
**Prognosis:** Related to degree of baseline renal dysfunction.

## Prostatitis/Prostatic Abscess

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute prostatitis/ acute prostatic abscess | Entero-bacteriaceae | Quinolone* (IV) × 2 weeks **or** Ceftriaxone 1 gm (IV) q24h × 2 weeks | TMP–SMX 2.5 mg/kg (IV) q6h × 2 weeks **or** Aztreonam 2 gm (IV) q8h × 2 weeks | Quinolone* (PO) × 2 weeks **or** Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q24h × 11 days **or** TMP–SMX 1 SS tablet (PO) q12h × 2 weeks |
| Chronic prostatitis | Entero-bacteriaceae | | Quinolone* (PO) × 1–3 months **or** TMP–SMX 1 DS tablet (PO) q12h × 1–3 months | |
| | MDR GNB | | Fosfomycin 3 gm (PO) q48h × 30 days ± Doxycycline 100 mg (PO) q24h × 1–3 months | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hours).
* Ciprofloxacin XR 1000 mg (PO) q24h or Ciprofloxacin 400 mg (IV) q12h or Levofloxacin 500 mg (IV or PO) q24h.

### Acute Prostatitis/Acute Prostatic Abscess (Enterobacteriaceae)

**Clinical Presentation:** Acute prostatitis presents as an acute febrile illness in males with dysuria and no CVA tenderness. Prostatic abscess presents with hectic/septic fevers without localizing signs.
**Diagnostic Considerations:** Acute prostatitis is diagnosed by bacteriuria, pyuria plus mucus threads, with exquisite prostate tenderness, and is seen primarily in young males. Positive urine culture is due to contamination of urine as it passes through infected prostate. Prostatic abscess is diagnosed by transrectal ultrasound or CT/MRI of prostate.

**Pitfalls:** Do not overlook acute prostatitis in males with bacteriuria without localizing signs, or prostatic abscess in patients with a history of prostatitis.
**Therapeutic Considerations:** Treat acute prostatitis for 2 full weeks to decrease progression to chronic prostatitis. Prostatic abscess is treated the same as acute prostatitis plus surgical drainage.
**Prognosis:** Excellent if treated early with full course of antibiotics (plus drainage for prostatic abscess).

### Chronic Prostatitis (Enterobacteriaceae/MDR GNB)

**Clinical Presentation:** Vague urinary symptoms (mild dysuria ± low back pain), history of acute prostatitis, and little or no fever.
**Diagnostic Considerations:** Diagnosis by bacteriuria plus pyuria with mucus threads ± mild prostate tenderness. Urine, semen, or prostate expressate are culture positive.
**Pitfalls:** Commonest cause of treatment failure is inadequate duration of therapy. Chronic prostatitis with prostatic calcifications (transrectal ultrasound) will not clear with antibiotics; transurethral resection of prostate (TURP) with removal of *all* calcifications curative.
**Therapeutic Considerations:** In sulfa-allergic patients, TMP alone may be used in place of TMP–SMX.
**Prognosis:** Excellent if treated × 1–3 months. Prostatic abscess is a rare but serious complication (may cause urosepsis).

## **Urosepsis** (see Color Atlas for Urine Gram stains)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Community acquired<br>(Treat initially based on urine gram stain) | Entero-bacteriaceae (ESBL–) | Ceftriaxone 1 gm (IV) q24h × 7 days*<br>**or**<br>Levofloxacin 500 mg (IV) q24h × 7 days* | Amikacin 1 gm (IV) q24h × 7 days*<br>**or**<br>Aztreonam 2 gm (IV) q8h × 7 days* | Levofloxacin 500 mg (PO) q24h × 7 days*<br>**or**<br>TMP–SMX 1 SS tablet (PO) q12h × 7 days* |
| | (ESBL +) | Meropenem 1 gm (IV) of q8h × 7 days* | Doripenem 1 gm (IV) of q8h × 7 days* | Fosfomycin 3 gm (PO) q 3 days × 7 days* |
| | E. faecalis (VSE)<br>Group B streptococci | Ampicillin 2 gm (IV) q4h × 7 days* | Meropenem 1 gm (IV) q8h × 7 days* | Amoxicillin 1 gm (PO) q8h × 7 days*<br>**or**<br>Levofloxacin 500 mg (PO) q24h × 7 days* |
| (No urine gram stain) | Entero-bacteriaceae<br>E. faecalis (VSE)<br>Group B streptococci | Meropenem 1 gm (IV) q8h × 7 days* | Piperacillin/ tazobactam 3.375 mg (IV) q6h × 7 days* | Levofloxacin 500 mg (PO) q24h × 7 days* |

* Longer duration needed if urologic/renal abnormalities present.

## **Urosepsis** (cont'd) (see Color Atlas of Urine Gram stains)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Related to urological procedure<br><br>(Treat intially for P. aeruginosa, etc; if later identified as non-aeruginosa Pseudomonas, treat accordingly) | P. aeruginosa<br>Enterobacter<br>Klebsiella<br>Serratia | Meropenem 1 gm (IV) q8h × 7 days<br>**or**<br>Levofloxacin 750 mg (IV) q24h × 7 days<br>**or**<br>Cefepime 2 gm (IV) q8h × 7 days | Doripenem 1 gm (IV) q8h × 7 days<br>**or**<br>Aztreonam 2 gm (IV) q8h × 7 days<br>**or**<br>Amikacin 1 gm (IV) q24h × 7 days<br>**or**<br>Ciprofloxacin 400 mg (IV) q8h × 7 days | Ciprofloxacin 750 mg (PO) q12h × 7 days<br>**or**<br>Levofloxacin 750 mg (PO) q24h × 7 days |
| | MDR GNB | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftolozane/ tazobactam 1.5 gm (IV) q8h × 2 weeks | Colistin 5 mg/kg (IV) q8h × 2 weeks | |
| | CRE | Ceftazidime/ avibactam 2.5 gm (IV) q8h × 2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose then 100 mg (IV) q24h × 2 weeks* | Colistin 5 mg/kg (IV) q8h × 2 weeks | |

* Depending on MICs, higher doses may be necessary LD: 400 mg (IV) × 1 dose, then MD: 200 mg (IV) q24h.

### Community-Acquired Urosepsis

**Clinical Presentation:** Sepsis from urinary tract source.

**Diagnostic Considerations:** Blood and urine cultures positive for same uropathogen. If patient does not have diabetes, SLE, cirrhosis, myeloma, steroids, pre-existing renal disease or obstruction, obtain CT/MRI of GU tract to rule out abscess/obstruction. Prostatic abscess is rarely a cause of urosepsis.

**Pitfalls:** Mixed gram-positive/negative urine cultures suggest specimen contamination or enterovesicular fistula.

**Therapeutic Considerations:** Empiric treatment is based on urine gram stain. If urine gram stain shows pyuria and gram-positive cocci, treat as group D enterococci (E. faecalis-VSE). If gram-negative bacilli, treat as Enterobacteriaceae. S. aureus/S. pneumoniae are not uropathogens.

**Prognosis:** Related to severity of underlying condition causing urosepsis and health of host.

### Urosepsis Following Urological Procedures

**Clinical Presentation:** Sepsis within 24 hours after GU procedure.

**Diagnostic Considerations:** Blood and urine cultures positive for same uropathogen. Use pre-procedural urine culture to identify uropathogen and guide therapy.

**Pitfalls:** If non-aeruginosa Pseudomonas in urine/blood, switch to TMP–SMX pending susceptibilities.

**Therapeutic Considerations:** Empiric P. aeruginosa monotherapy will cover most other uropathogens.

**Prognosis:** Related to severity of underlying condition causing urosepsis and health of host.

## Pelvic Inflammatory Disease (PID), Salpingitis, Tuboovarian Abscess, Endometritis/Endomyometritis, Septic Abortion

| Subset | Usual Pathogens | IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|
| Hospitalized patients† | B. fragilis<br>Entero-bacteriaceae<br>N. gonorrhoeae<br>C. trachomatis<br>C. sordelli§<br>(septic abortion) | **Monotherapy with**<br>Moxifloxacin 400 mg (IV) q24h × 2 weeks<br>**or combination therapy with**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days<br>**plus either**<br>Piperacillin/tazobactam 4.5 gm (IV) q8h × 2 weeks **or** Ertapenem 1 gm (IV) q24h × 3–10 days **or** Cefoxitin 2 gm (IV) q6h × 2 weeks **or** Cefotetan 2 gm (IV) q12h × 2 weeks<br>**Alternate combination therapy**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days **plus** Ampicillin/sulbactam 3 gm (IV) q6h × 2 weeks **or** Quinolone‡ (IV) q24h × 2 weeks **plus** Metronidazole 1 gm (IV) q24h × 2 weeks | **Monotherapy with**<br>Moxifloxacin 400 mg (PO) q24h × 2 weeks |
| Outpatients (mild PID only) | N. gonorrhoeae<br>C. trachomatis B. fragilis<br>Entero-bacteriaceae | Moxifloxacin 400 mg (PO) q24h × 2 weeks** **or** Doxycycline 100 mg (PO) q12h × 2 weeks | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† Treat only IV or IV-to-PO switch for salpingitis, tuboovarian abscess, endometritis, endomyometritis, septic abortion, or severe PID.

‡ Levofloxacin 500 mg (IV or PO) q24h or Ofloxacin 400 mg (IV or PO) q12h.

** Recent gonococcal resistance to quinolones requires careful follow-up during/after therapy.

§ Antibiotic therapy of septic abortion same as salpingitis/endometritis *plus* evacuation of uterine contents.

**Clinical Presentation:** PID/salpingitis presents with cervical motion/adnexal tenderness, lower quadrant abdominal pain, and fever. Endometritis/endomyometritis presents with uterine tenderness ± cervical discharge/fever. Endomyometritis is the most common postpartum infection.

**Diagnostic Considerations:** Unilateral lower abdominal pain in a female without a non-pelvic cause suggests PID/salpingitis.

**Pitfalls:** Obtain CT/MRI of abdomen/pelvis to confirm diagnosis and rule out other pathology or tuboovarian abscess.

**Therapeutic Considerations:** Tuboovarian abscess usually requires drainage/removal ± TAH/BSO, plus antibiotics (see p. 113) × 1–2 weeks after drainage/removal. Septic abortion is treated the same as endometritis/endomyometritis plus uterine evacuation.

**Prognosis:** Related to promptness of treatment/adequacy of drainage if tuboovarian abscess. Late complications of PID/salpingitis include tubal scarring/infertility.

## Empiric Therapy of Sexually Transmitted Diseases

### Urethritis/Cervicitis

| Subset | Usual Pathogens | IM Therapy | PO Therapy |
|---|---|---|---|
| Gonococcal (GC) | N. gonorrhoeae | Ceftriaxone 250 mg (IM) × 1 dose **plus either** Azithromycin 1–2 gm (PO) × 1 dose **or** Doxycycline 100 mg (PO) of q12h × days | Cefixime† 400 mg (PO) × 1 dose† **or** Cefpodoxime† 400 mg (PO) × 1 dose† **or** Azithromycin† 2 gm (PO) × 1 dose† |
| Non-gonococcal (NGU) | C. trachomatis U. urealyticum M. genitalium | Not applicable | Doxycycline 100 mg (PO) q12h × 7 days ‡ **or** Quinolone*† (PO) × 7 days **or** Azithromycin 1 gm (PO) × 1 dose **or** Erythromycin 500 mg (PO) q6h × 7 days |
| | Trichomonas vaginalis | Not applicable | Tinidazole 2 gm (PO) × 1 dose **or** Metronidazole 2 gm (PO) × 1 dose |

* Levofloxacin 500 mg q24h or Moxifloxacin 400 mg q24h or Ofloxacin 300 mg q12h.
† Increased resistance oral regimens should be considered alternate (second line) therapy and test of cure essential.
‡ (Doxycycline may be given as a 200 mg (PO) of q24h × 7 days.

#### Gonococcal Urethritis/Cervicitis (Neisseria gonorrhoeae)

**Clinical Presentation:** Purulent penile/cervical discharge with burning/dysuria 3–5 days after contact.
**Diagnostic Considerations:** Rapid diagnosis in males by Gram stain of urethral discharge showing gram-negative diplococci; urethral cultures also positive. In females, diagnosis requires identification of organism by culture or DNA probe, not Gram stain. Rapid diagnosis in males/females by DNA probe. Obtain throat/rectal culture for N. gonorrhoeae. Co-infections are common; obtain syphilis and HIV serologies.
**Pitfalls:** Gram stain of cervical discharge showing gram-negative diplococci is not diagnostic of N. gonorrhoeae; must confirm by culture or nucleic acid amplification. N. gonorrhoeae infections are asymptomatic in 10% of men and 70% of women.

**Therapeutic Considerations:** Failure to respond suggests re-infection or relapse. Treat all GC with ceftriaxone. Because of frequent coinfection with agents of NGU, add oral azithromycin. Because of increasing resistance, consider using azithromycin 2 gm for dual therapy in patients with GC.
**Prognosis:** Good even with disseminated infection.

### Non-Gonococcal Urethritis/Cervicitis (Chlamydia/Ureaplasma/Mycoplasma)

**Clinical Presentation:** Mucopurulent penile/cervical discharge ± dysuria ~ 1 week after contact.
**Diagnostic Considerations:** Diagnosis by positive chlamydial NAAT/Ureaplasma or Mycoplasma NAAT of urethral/cervical discharge. Evaluate urethral/cervical discharge to rule out N. gonorrhoeae. Co-infections are common; obtain syphilis and HIV serologies.
**Pitfalls:** C. trachomatis infections are asymptomatic in 25%.
**Therapeutic Considerations:** Failure to respond to doxycycline therapy suggests re-infection or Trichomonas/Ureaplasma/Mycoplasma infection. Failure to respond to azithromycin suggests trichomoniasis, or infection due to a resistant Mycoplasma (consider quinolone therapy).
**Prognosis:** Tubal scarring/infertility in chronic infection.

### Trichomonas Urethritis/Cervicitis (Trichomonas vaginalis)

**Clinical Presentation:** Frothy, pruritic vaginal discharge.
**Diagnostic Considerations:** Trichomonas by wet mount/culture on special media.
**Pitfalls:** Classic "strawberry cervix" is infrequently seen.
**Therapeutic Considerations:** Use week-long regimen if single dose fails. Resistance now recognized as a cause of treatment failure.
**Prognosis:** Excellent if partner is also treated.

## Vaginitis/Vaginosis

| Subset | Usual Pathogens | PO Therapy |
|---|---|---|
| Bacterial vaginosis/ vaginitis | Polymicrobial (Gardnerella vaginalis, Mobiluncus, Prevotella, M. hominis, etc.) | Tinidazole 1 gm (PO) × 5 days **or** 2 gm (PO) × 2 days **or** Clindamycin 300 mg (PO) q12h × 7 days **or** Metronidazole 500 mg (PO) q12h × 7 days |
| Candida vaginitis/balanitis | Candida | Fluconazole 150 mg (PO) × 1 dose† |

† Those failing to respond should be treated with Fluconazole 200 mg (PO) × 1 dose then 100 mg (PO) q24h × 1 week.

### Bacterial Vaginosis/Vaginitis

**Clinical Presentation:** Non-pruritic vaginal discharge with "fishy" odor.
**Diagnostic Considerations:** Diagnosis by "clue cells" in vaginal fluid wet mount. Vaginal pH ≥ 4.5.
**Pitfalls:** "Fishy" odor from smear of vaginal secretions intensified when 10% KOH solution is added (positive "whiff test").
**Therapeutic Considerations:** As an alternative to oral therapy, clindamycin cream 2% intravaginally qHS × 7 days (avoid in pregnancy) or metronidazole gel 0.075% 1 application intravaginally q12h × 5 days can be used.
**Prognosis:** Complications include premature rupture of membranes, premature delivery, increased risk of PID. Recurrences very common.

**Candida Vaginitis/Balanitis**

**Clinical Presentation:** Pruritic white plaques in vagina/erythema of glans penis.
**Diagnostic Considerations:** Diagnosis by gram stain/culture of whitish plaques.
**Pitfalls:** Rule out Trichomonas, which also presents with pruritus in females.
**Therapeutic Considerations:** Uncomplicated vaginitis (mild sporadic infections in healthy individuals) responds readily to single-dose therapy. Complicated vaginitis (severe, recurrent, or in difficult-to-control diabetes) often requires ≥ 7 days of therapy (daily topical therapy or 2 doses of fluconazole 150 mg given 72h apart). Non-albicans infections respond poorly to azoles. Topical boric acid (600 mg/d in a gelatin capsule × 14 days) is often effective in this setting.
**Prognosis:** Good with systemic therapy. Diabetics/uncircumcised males may need prolonged therapy.

## Genital Vesicles (Genital Herpes) (HSV-2/HSV-1)

| Subset | PO Therapy |
|---|---|
| Initial therapy | Acyclovir 200 mg (PO) 5×/day × 10 days **or** Famciclovir 500 mg (PO) q12h × 7–10 days **or** Valacyclovir 1 gm (PO) q12h × 3 days |
| Recurrent/ intermittent therapy (< 6 episodes/year) | Acyclovir 200 mg (PO) 5×/day × 5 days **or** Valacyclovir (normal host: 500 mg [PO] q24h × 5 days; HIV positive: 1 gm [PO] q12h × 7–10 days)** **or** Famciclovir (normal host: 125 mg [PO] q12h × 5 days **or** 1 gm [PO] q12h × 1 day*; HIV-positive: 500 mg [PO] q12h × 7 days) |
| Chronic suppressive therapy (> 6 episodes/year) | Acyclovir 400 mg (PO) q12h × 1 year **or** Valacyclovir (normal host: 1 gm [PO] q24h × 1 year; HIV-positive: 500 mg [PO] q12h × 1 year) **or** Famciclovir 250 mg (PO) q12h × 1 year |

* Patient initiated therapy to be started immediately when recurrence begins.
** Short-course therapy with Valaciclovir 500 mg (PO) q12h × 3 days or Acyclovir 800 mg (PO) q8h × 2 days also effective.

**Clinical Presentation:** Painful vesicles/ulcers on genitals with painful bilateral regional adenopathy ± low-grade fever.
**Diagnostic Considerations:** Diagnosis by clinical presentation may be misleading.
**Pitfalls:** 70% of newly acquired gential herpes is due to HSV-1. Elevated IgG HSV-2 titer indicates past exposure, not acute infection. HSV-2 IgM titers may be negative.
**Therapeutic Considerations:** If concomitant rectal herpes, increase acyclovir to 800 mg (PO) q8h × 7 days. For recurrent genital herpes, use acyclovir or valacyclovir (dose same as primary infection) for 7 days after each relapse. Recurrent episodes of HSV-2 are less painful than primary infection, and inguinal adenopathy is less prominent/painful.
**Prognosis:** HSV-2 tends to recur, especially during the first year. HSV-1 recurrences less frequent.

## Genital Ulcers

| Subset | Usual Pathogens | IM Therapy | PO Therapy |
|---|---|---|---|
| Primary syphilis | Treponema pallidum | Benzathine penicillin 2.4 mu (IM) × 1 dose | Doxycycline 100 mg (PO) q12h × 2 weeks **or** Azithromycin 2 gm (PO) × 1 dose** |
| Chancroid | Hemophilus ducreyi | Ceftriaxone 250 mg (IM) × 1 dose **or** Any 3rd generation cephalosporin 250–500 mg (IM) × 1 dose | Azithromycin 1 gm (PO) × 1 dose **or** Quinolone* (PO) × 3 days **or** Erythromycin base 500 mg (PO) q8h × 7 days |

* Ciprofloxacin 500 mg q12h or Levofloxacin 500 mg or Moxifloxacin 400 mg q24h.

** Resistance increasing (careful followup essential).

### Primary Syphilis (Treponema pallidum)

**Clinical Presentation:** Painless, indurated ulcers (chancres) with bilateral painless inguinal adenopathy. Syphilitic chancres are elevated, clean and indurated, but not undermined.
**Diagnostic Considerations:** Diagnosis by spirochetes on darkfield examination of ulcer exudate. Elevated non-treponemal (VDRL/RPR) titers after 1 week.
**Pitfalls:** Non-treponemal (VDRL/RPR) titers fall slowly within 1 year; failure to decline suggests treatment failure/HIV. Even after effective treatment some patients remain VDRL/RPR positive for life (serofast).
**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis. If treatment fails and VDRL/RPR titers do not decline, obtain HIV serology.
**Prognosis:** Good with early treatment.

### Chancroid (Hemophilus ducreyi)

**Clinical Presentation:** Ragged, undermined, painful ulcer(s) + painful unilateral inguinal adenopathy.
**Diagnostic Considerations:** Diagnosis by streptobacilli in "school of fish" configuration on gram-stained smear of ulcer exudate/culture of H. ducreyi/NAAT.
**Pitfalls:** Co-infection is common; obtain Syphilis and HIV serologies.
**Therapeutic Considerations:** In HIV, multiple dose regimens or azithromycin is preferred. Resistance to erythromycin/ciprofloxacin has been reported.
**Prognosis:** Good with early treatment.

## Suppurating Inguinal Adenopathy

| Subset | Pathogens | IV Therapy | PO Therapy |
|---|---|---|---|
| Lympho-granuloma venereum (LGV) | Chlamydia trachomatis ($L_{1-3}$ serotypes) | Not applicable | Doxycycline 100 mg (PO) q12h × 3 wks **or** Erythromycin base 500 mg (PO) q6h × 3 weeks |
| Granuloma inguinale (Donovanosis) | Klebsiella (Calymmato-bacterium) granulomatis | Not applicable | Azithromycin 1 gm (PO) q week until cured. Doxycycline 100 mg (PO) q12h until cured **or** Erythromycin 500 mg (PO) q6h until cured **or** TMP–SMX 1 DS (PO) q12h until cured **or** Ciprofloxacin 750 mg (PO) q12h until cured |

### Lymphogranuloma Venereum (Chlamydia trachomatis) LGV

**Clinical Presentation:** Unilateral inguinal adenopathy ± discharge/sinus tract.
**Diagnostic Consideration:** Diagnosis by very high Chlamydia trachomatis $L_{1-3}$ titers. Do not biopsy site (often does not heal and may form a fistula). May present as FUO.
**Pitfalls:** Initial papule not visible at clinical presentation. Biopsy shows granulomas; may be confused with perianal Crohn's disease.
**Therapeutic Considerations:** Rectal LGV may require additional courses of treatment.
**Prognosis:** Fibrotic perirectal/pelvic damage does not reverse with therapy.

### Granuloma Inguinale (Klebsiella [Calymmatobacterium] granulomatis) Donovanosis

**Clinical Presentation:** Pseudolymphadenopathy with painless inguinal ulcers.
**Diagnostic Considerations:** Donovan bodies ("puffed-wheat" appearance) in tissue biopsy.
**Pitfalls:** No true inguinal adenopathy, as opposed to LGV infection.
**Therapeutic Considerations:** Doxycycline or azithromycin preferred. Continue therapy until lesions are healed.
**Prognosis:** Good if treated early.

## Genital/Perianal Warts (Condylomata acuminata)

| Subset | Pathogens | Therapy |
|---|---|---|
| Genital/ perianal warts | Human papilloma virus (HPV) | Podophyllin 10–25% in tincture of benzoin or podofilox or imiquimod (patient applies) **or** surgical/laser removal/ cryotherapy with liquid nitrogen **or** cidofovir gel (1%) QHS × 5 days every other week for 6 cycles **or** trichloracetic acid (TCA)/bichloracetic acid (BCA) **or** intralesional interferon. Sinecatechins (15% ointment) q8h × 4 months |

**Clinical Presentation:** Single/multiple verrucous genital lesions ± pigmentation, without inguinal adenopathy.

**Diagnostic Considerations:** Diagnosis by clinical appearance. Genital warts are usually caused by HPV types 6, 11. Anogenital warts caused by HPV types 16,18,31,33,35 and others are associated with cervical neoplasia. Females with anogenital warts need serial cervical PAP smears to detect cervical dysplasia/neoplasia.
**Pitfalls:** Most HPV infections are asymptomatic.
**Therapeutic Considerations:** Cidofovir cures/halts HPV progression in 50% of cases.
**Prognosis:** Related to HPV serotypes with malignant potential (HPV types 16,18,31,33,35). Preventative (not therapeutic) vaccines now available.

## Syphilis

| Subset | Pathogen | IV/IM Therapy | PO Therapy |
|---|---|---|---|
| Primary, secondary, or early latent (duration < 1 year) syphilis | Treponema pallidum | Benzathine penicillin 2.4 mu (IM) × 1 dose | Doxycycline 100 mg (PO) q12h × 2 weeks **or** Azithromycin 2 gm (PO) × 1 dose* |
| Late latent (duration > 1 year) or tertiary syphilis | Treponema pallidum | Benzathine penicillin 2.4 mu (IM) weekly × 3 weeks | Doxycycline 100 mg (PO) q12h × 4 weeks |
| Neurosyphilis | Treponema pallidum | Penicillin G 3–4 mu (IV) q4h or continuous infusion × 10–14 days **or** Alternate: Procaine penicillin 2.4 mu (IM) q24h × 10–14 days plus probenecid 500 mg (PO) q6h × 10–14 days **or** Ceftriaxone 2 gm (IV) q24h × 10–14 days | Doxycycline 100 mg (PO) q12h × 4 weeks **or** Minocycline 100 mg (PO) q12h × 4 weeks |

* Resistance increasing (careful follow up essential).

Duration of therapy represents total time IV, IM, or PO. All stages of syphilis in HIV patients usually respond to therapeutic regimens recommended for normal hosts. Syphilis in pregnancy should be treated according to the stage of syphilis; penicillin-allergic pregnant patients should be desensitized and treated with penicillin.

### Primary Syphilis (Treponema pallidum)

**Clinical Presentation:** Painless, indurated ulcer(s) (chancre) with bilateral painless inguinal adenopathy.
**Diagnostic Considerations:** Diagnosis by spirochetes on darkfield or DFA examination of ulcer exudate. Reactive non-treponemal (VDRL/RPR) or treponemal (TPPA, others) test after 1 week. Patients with ↑ low titers of VDRL/RPR and – treponemal test may be BFP, e.g., SLE.
**Pitfalls:** VDRL/RPR titers fall slowly within 1 year; failure to decline suggests treatment failure.
**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis; if treatment fails and VDRL/RPR titers do not decline, obtain HIV serology. Some effectively treated patients remain VDRL/RPR positive in low titers eg 1:4 (serofast) for years.
**Prognosis:** Good with early treatment.

## Secondary Syphilis (Treponema pallidum)

**Clinical Presentation:** Facial/truncal macular, papular, papulosquamous, non-pruritic, non-tender, symmetrical rash which may involve the palms/soles. Usually accompanied by generalized adenopathy. Typically appears 4–10 weeks after primary chancre, although stages may overlap. Alopecia, condyloma lata, mucous patches, iritis/uveitis may be present. Renal involvement ranges from mild proteinuria to nephrotic syndrome. Without treatment, spontaneous resolution occurs after 3–12 weeks.
**Diagnostic Considerations:** Diagnosis by clinical findings and VDRL/RPR in high titers (≥ 1:64). After treatment, RPR/VDRL titers usually $\downarrow \times 4 < 6$ months.
**Pitfalls:** If only undiluted serum is tested, prozone phenomenon may render VDRL/RPR falsely negative.
**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis.
**Prognosis:** Excellent with early treatment.

## Latent Syphilis (Treponema pallidum)

**Clinical Presentation:** Patients are asymptomatic with elevated non-treponemal titers and reactive treponemal tests.
**Diagnostic Considerations:** Diagnosis by positive serology ± prior history, but no signs/symptoms of syphilis. Asymptomatic syphilis < 1 year in duration is termed "early" latent syphilis; asymptomatic syphilis > 1 year/unknown duration is termed "late" latent syphilis. Secondary syphilis may relapse in up to 25% of patients with early latent syphilis, but relapse is rare in late latent syphilis. Evaluate patients for neurosyphilis.
**Pitfalls:** Treponemal tests (FTA-ABS, MHA-TP, TPPA, others) usually remain positive for life, even after adequate treatment.
**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis. Repeat VDRL/RPR titers at 6, 12, and 24 months; therapeutic response is defined as a 4-fold reduction in RPR/VDRL titers (2 tube dilutions).
**Prognosis:** Excellent even if treated late.

## Tertiary Syphilis (Treponema pallidum)

**Clinical Presentation:** May present with aortitis, neurosyphilis, iritis, or gummata 5–30 years after initial infection.
**Diagnostic Considerations:** Diagnosis by history of syphilis plus positive serological tests with signs/symptoms of late syphilis.
**Pitfalls:** Treat for signs of neurosyphilis on clinical exam or LP, even if VDRL/RPR are non-reactive.
**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis.
**Prognosis:** Related to extent of end-organ damage.

## Neurosyphilis (Treponema pallidum)

**Clinical Presentation:** Patients are often asymptomatic, but may have ophthalmic/auditory symptoms, cranial nerve abnormalities, tabes dorsalis, paresis, psychosis, or signs of meningitis/dementia.
**Diagnostic Considerations:** Diagnosis by elevated CSF VDRL titers; no need to obtain CSF FTA-ABS titers. Diagnosis confirmed if CSF has pleocytosis (> 5 WBCs/hpf) or increased protein (> 50 mg/dL), and positive VDRL.
**Pitfalls:** Persistent CSF abnormalities suggest treatment failure. CSF VDRL (60% sensitive) may be negative in neurosyphilis.

**Therapeutic Considerations:** Parenteral penicillin is the preferred antibiotic for all stages of syphilis. CSF abnormalities should decrease in 6 months and return to normal after 2 years; repeat lumbar puncture 6 months after treatment. Failure rate with ceftriaxone is 20%.
**Prognosis:** Related to extent of end-organ damage.

# Empiric Therapy of Bone and Joint Infections

## Septic Arthritis/Bursitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute<br><br>(Treat initially based on gram stain of synovial fluid. If gram-positive cocci in clusters, treat initially for MRSA; if later identified as MSSA, treat accordingly) | S. aureus (MSSA) | Cefazolin<br>1 gm (IV) q8h × 3 weeks<br>**or**<br>Ceftriaxone<br>1 gm (IV) q24h × 3 weeks<br>**or**<br>Clindamycin<br>600 mg (IV) q8h × 3 weeks | Nafcillin<br>2 gm (IV) q4h × 3 weeks<br>**or**<br>Meropenem<br>1 gm (IV) q8h × 3 weeks<br>**or**<br>Ertapenem<br>1 gm (IV) q24h × 3 weeks | Cephalexin<br>1 gm (PO) q6h × 3 weeks<br>**or**<br>Clindamycin<br>300 mg (PO) q8h× 3 weeks<br>**or**<br>Quinolone* (PO) q24h × 3 weeks |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h × 3 weeks<br>**or**<br>Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 3 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 3 weeks | | Linezolid<br>600 mg (PO) q12h × 3 weeks<br>**or**<br>Minocycline<br>100 mg (PO) q12h × 3 weeks |
| | Group A,B,C,G streptococci | Ceftriaxone<br>1 gm (IV) q24h × 3 weeks<br>**or**<br>Clindamycin<br>600 mg (IV) q8h × 3 weeks | Cefazolin<br>1 gm (IV) q8h × 3 weeks<br>**or**<br>Quinolone* (IV) q24h × 3 weeks | Clindamycin 300 mg (PO) q8h × 3 weeks<br>**or**<br>Cephalexin<br>500 mg (PO) q6h × 3 weeks **or**<br>Quinolone* (PO) q24h × 3 weeks |

* Moxifloxacin 400 mg or Levofloxacin 500 mg.

## Septic Arthritis/Bursitis (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute (cont'd) | Entero-bacteriaceae | Ceftriaxone 1 gm (IV) q24h × 3 weeks **or** Cefepime 2 gm (IV) q12h × 3 weeks **or** Cefotaxime 2 gm (IV) q6h × 3 weeks **or** Ceftizoxime 2 gm (IV) q8h × 3 weeks | Aztreonam 2 gm (IV) q8h × 3 weeks **or** Respiratory quinolone‡ (IV) × 3 weeks | Respiratory quinolone‡ (PO) × 3 weeks |
| | P. aeruginosa | Meropenem 1 gm (IV) q8h × 3 weeks **or** Ciprofloxacin 400 mg (IV) q8h × 3 weeks | Aztreonam 2 gm (IV) q8h × 3 weeks **or** Cefepime 2 gm (IV) q8h × 3 weeks | Ciprofloxacin 750 mg (PO) q12h × 3 weeks **or** Levofloxacin 750 mg (PO) q24h x 3 weeks |
| | N. gonorrhea (PSNG/PPNG) | Ceftriaxone 1 gm (IV) q24h × 2 weeks **or** Ceftizoxime 2 gm (IV) q8h × 2 weeks | Levofloxacin 500 mg (IV) q24h × 2 weeks **or** Moxifloxacin 400 mg (IV) q24h × 2 weeks | Levofloxacin 500 mg (PO) q24h × 2 weeks **or** Moxifloxacin 400 mg (PO) q24h × 2 weeks |
| | Salmonella | Ceftriaxone 2 gm (IV) q24h × 2–3 weeks **or** Respiratory quinolone* (IV) × 2–3 weeks | Aztreonam 2 gm (IV) q8h × 2–3 weeks **or** TMP–SMX 2.5 mg/kg (IV) q6h × 2–3 weeks | Respiratory quinolone* (PO) × 2–3 weeks **or** TMP–SMX 1 DS tablet (PO) q12h × 2–3 weeks |

‡ Moxifloxacin 400 mg (IV/PO) q24h or Levofloxacin 500 mg (IV/PO) q24h.

† Loading dose is not needed PO if given IV with the same drug.

* Levofloxacin 500 mg (IV or PO) q24h or Moxifloxacin 400 mg (IV or PO) q24h.

## Septic Arthritis/Bursitis (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Secondary to animal bite wound | Pasteurella multocida<br>Streptobacillus moniliformis<br>Eikinella corrodens | Piperacillin/ tazobactam 3.375 gm (IV) q6h × 2 weeks<br>**or**<br>Ampicillin/ sulbactam 3 gm (IV) q6h × 2 weeks<br>**or**<br>Ticarcillin/ clavulanate 3.1 gm (IV) q6h × 2 weeks | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days | Amoxicillin/ clavulanic acid 875/125 mg (PO) q12h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days†<br>**or**<br>Moxifloxacin 400 mg (PO) q24h × 2 weeks |
| Fungal arthritis | Coccidioides immitis | Not applicable | Itraconazole 200 mg (PO) solution q12h × 12 months or until cured*<br>**or**<br>Fluconazole 800 mg (PO) q24h until cured* | |
| | Sporothrix schenckii | Not applicable | Itraconazole 200 mg (PO) q12h until cured* | |
| TB arthritis | M. tuberculosis | Not applicable | Treat the same as for pulmonary TB (p. 53) except treat for 6–9 months | |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus.* Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Itraconazole solution provides more reliable absorption than capsules.

### Acute Septic Arthritis/Bursitis

**Clinical Presentation:** Acute joint pain with fever. Septic joint unable to bear weight. Septic bursitis presents with pain on joint motion, but patient is able to bear weight.

**Diagnostic Considerations:** Diagnosis by demonstrating organisms in synovial fluid by stain/culture. In septic bursitis (knee most common), there is pain on joint flexion (although the joint can bear weight), and synovial fluid findings are negative for septic arthritis. Except for N. gonorrhoeae, polyarthritis is not usually due to bacterial pathogens. Post-infectious polyarthritis is usually viral in origin, most commonly due to parvovirus B19, rubella, or HBV.

**Pitfalls:** Reactive arthritis may follow C. jejuni, Salmonella, Shigella, Yersinia, N. gonorrheae C. trachomatis, or C. difficile infections. Synovial fluid cultures are negative. Reactive arthritis is usually asymmetrical and is monoarticular/oligoarticular.
**Therapeutic Considerations:** See specific pathogen, below. Treat septic bursitis as septic arthritis.

### ***Staphylococcus aureus* (MSSA/MRSA)**

**Diagnostic Considerations:** Painful hot joint; unable to bear weight. Diagnosis by synovial fluid pleocytosis and positive culture for joint pathogen. Examine synovial fluid to rule out gout (doubly birefringent crystals) and pseudogout (calcium pyrophosphate crystals). May occur in setting of endocarditis with septic emboli to joints; other manifestations of endocarditis are usually evident.
**Pitfalls:** Rule out causes of noninfectious arthritis (sarcoidosis, Whipple's disease, Ehlers-Danlos, etc.), which are less severe, but may mimic septic arthritis. In reactive arthritis following urethritis (C. trachomatis, Ureaplasma urealyticum, N. gonorrhoeae) or diarrhea (Shigella, Campylobacter, Yersinia, Salmonella), synovial fluid culture is negative, and synovial fluid WBCs counts are usually < 10,000/$mm^3$ with normal synovial fluid lactic acid and glucose. Do not overlook infective endocarditis in mono/polyarticular MSSA/MRSA septic arthritis without apparent source.
**Therapeutic Considerations:** For MRSA septic arthritis, vancomycin penetration into synovial fluid is poor; use linezolid instead. Immobilization of infected joint during therapy is helpful. Local installation of antibiotics into synovial fluid has no advantage over IV/PO antibiotics.
**Prognosis:** Treat as early as possible to minimize joint damage. Repeated aspiration/open drainage may be needed to preserve joint function.

### ***Group A, B, C, G Streptococci***

**Diagnostic Considerations:** Usually monoarticular. Not usually due to septic emboli from endocarditis.
**Prognosis:** Related to extent of joint damage and rapidity of antibiotic treatment.

### ***Enterobacteriaceae***

**Diagnostic Considerations:** Diagnosis by isolation of gram-negative bacilli from synovial fluid.
**Pitfalls:** Septic arthritis involving an unusual joint (e.g., sternoclavicular, sacral) should suggest IV drug abuse until proven otherwise.
**Therapeutic Considerations:** Joint aspiration is essential in suspected septic arthritis of the hip and may be needed for other joints; obtain orthopedic surgery consult. Local installation of antibiotics into joint fluid is of no proven value.
**Prognosis:** Related to extent of joint damage and rapidity of antibiotic treatment.

### ***Pseudomonas aeruginosa***

**Diagnostic Considerations** P. aeruginosa septic arthritis/osteomyelitis may occur after water contaminated puncture wound (e.g., nail puncture of heel through shoes). Sternoclavicular/sacroiliac joint involvement is common in IV drug abusers (IVDAs).
**Pitfalls:** Suspect IVDA in P. aeruginosa septic arthritis without a history of trauma.
**Therapeutic Considerations:** If ciprofloxacin is used, treat with 750 mg (not 500 mg) dose for P. aeruginosa septic arthritis/osteomyelitis.
**Prognosis:** Related to extent of joint damage and rapidity of antibiotic treatment.

***Neisseria gonorrhoeae***

**Diagnostic Considerations:** Gonococcal arthritis may present as a monoarticular arthritis, or multiple joints may be affected as part of gonococcal arthritis-dermatitis syndrome (disseminated gonococcal infection). Bacteremia with positive blood cultures occurs early during rash stage while synovial fluid cultures are negative. Joint involvement follows with typical findings of septic arthritis and synovial fluid cultures positive for N. gonorrhoeae; blood cultures are negative at this stage. Acute tenosynovitis is often a clue to gonococcal septic arthritis.
**Pitfalls:** Spectinomycin is ineffective against pharyngeal gonorrhea.
**Therapeutic Considerations:** Gonococcal arthritis-dermatitis syndrome is caused by very susceptible strains of N. gonorrhoeae. Cephalosporins also eliminate incubating syphilis.
**Prognosis:** Excellent with arthritis-dermatitis syndrome; worse with only monoarticular arthritis.

***Salmonella sp.***

**Diagnostic Considerations:** Occurs in sickle cell disease and hemoglobinopathies. Diagnosis by blood/joint cultures.
**Pitfalls:** S. aureus, not Salmonella, is the most common cause of septic arthritis in sickle cell disease.
**Prognosis:** Related to severity of infection and underlying health of host.

## Septic Arthritis Secondary to Animal Bite Wound

**Clinical Presentation:** Penetrating bite wound into joint space.
**Diagnostic Considerations:** Diagnosis by smear/culture of synovial fluid/blood cultures.
**Pitfalls:** May develop metastatic infection from bacteremia.
**Therapeutic Considerations:** Treat for at least 2 weeks of combined IV/PO therapy.
**Prognosis:** Related to severity of infection and underlying health of host.

## Chronic Septic Arthritis

**Clinical Presentation:** Subacute/chronic joint pain with decreased range of motion and little or no fever. Able to bear weight on joint.
**Diagnostic Considerations:** Diagnosis by smear/culture of synovial fluid/synovial biopsy.

***Coccidioides immitis***

**Diagnostic Considerations:** Must grow organisms from synovium/synovial fluid for diagnosis.
**Pitfalls:** Synovial fluid the same as in TB (lymphocytic pleocytosis, low glucose, increased protein).
**Therapeutic Considerations:** Oral therapy is preferred; same cure rates as amphotericin regimens. HIV patients need life-long suppressive therapy.
**Prognosis:** Related to severity of infection and underlying health of host.

***Sporothrix schenckii***

**Diagnostic Considerations:** Usually a monoarticular infection secondary to direct inoculation/trauma.
**Pitfalls:** Polyarticular arthritis suggests disseminated infection.
**Therapeutic Considerations:** SSKI is useful for lymphocutaneous sporotrichosis, not bone/joint involvement.

**Prognosis:** Excellent for localized disease (e.g., lymphocutaneous sporotrichosis). In disseminated disease, prognosis is related to host factors.

***Mycobacterium tuberculosis (TB)***

**Diagnostic Considerations:** Clue is subacute/chronic tenosynovitis over involved joint. Unlike other forms of septic arthritis, which are usually due to hematogenous spread, TB arthritis may complicate adjacent TB osteomyelitis. Synovial fluid findings include lymphocytic pleocytosis, low glucose, and increased protein.

**Pitfalls:** Send synovial biopsy for AFB smear/culture in unexplained chronic monoarticular arthritis.

**Therapeutic Considerations:** TB arthritis is usually treated for 6–9 months.

**Prognosis:** Related to severity of infection and underlying health of host.

## Lyme Disease*/Lyme Arthritis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Lyme disease | Borrelia burgdorferi | Ceftriaxone<br>1 gm (IV) q24h<br>× 2 weeks<br>**or**<br>Doxycycline<br>200 mg (IV) q12h × 3 days, then<br>100 mg (IV) q12h × 4 weeks | Ceftizoxime<br>2 gm (IV) q8h<br>× 2 weeks | Doxycycline<br>200 mg (PO) q12h × 3 days, then<br>100 mg (PO) q12h × 11 days‡<br>**or**<br>Amoxicillin<br>1 gm (PO) q8h<br>× 2 weeks |
| Lyme arthritis | | Ceftriaxone<br>1 gm (IV) q24h<br>× 4 weeks<br>**or**<br>Doxycycline<br>200 mg (IV) q12h × 3 days, then<br>100 mg (IV) q12h × 4 weeks | Ceftizoxime<br>2 gm (IV) q8h<br>× 4 weeks | Amoxicillin<br>1 gm (PO) q8h<br>× 4 weeks<br>**or**<br>Doxycycline<br>200 mg (PO) q12h × 3 days, then<br>100 mg (PO) q12h × 4 weeks |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* See p. 21 for Lyme neuroborreliosis and p. 78 for Lyme myocarditis.

† Doxycycline therapy × 10 days as effective as 2 weeks.

‡ For adult patients intolerant of Amoxicillin, Doxycycline, and Cefuroxime axetil, Azithromycin (500 mg orally per day for 7–10 days), Clarithromycin (500 mg orally twice per day for 14–21 days, if the patient is not pregnant), or Erythromycin (500 mg orally 4 times per day for 14–21 days) may be given. The recommended dosages of these agents for children are as follows: Azithromycin, 10 mg/kg per day (maximum of 500 mg per day); Clarithromycin, 7.5 mg/kg twice per day (maximum of 500 mg per dose); and Erythromycin, 12.5 mg/kg 4 times per day (maximum of 500 mg per dose).

## Lyme Disease

**Clinical Presentation:** Presents acutely with local or disseminated disease following bite of tick infected with Borrelia. Erythema migrans (annular lesion with central clearing) occurs in ~ 75% within 2 weeks of tick bite and may be associated with fever, headache, arthralgias/myalgias, meningismus. Other possible acute manifestations include aseptic meningitis, Bell's palsy, peripheral neuropathy, mild hepatitis, or heart block. Chronic disease may present with arthritis, peripheral neuropathy, or acrodermatitis chronica atrophicans (usually > 10 years after infection).

**Diagnostic Considerations:** Diagnosis by clinical presentation plus elevated IgM Lyme titers. If the IgM ELISA Lyme titer is borderline or suspected to be a false-positive, obtain an IgM Western blot to confirm the diagnosis. False negative early IgM titers are common. IgM cross-reactivity common with EBV, CMV. After ruling out EBV/CMV, retest for Lyme disease IgM and IgG by ELISA/immunoblot 4 weeks later (false + IgM titers revert to negative). IgM titers may take 4–6 weeks to increase after tick bite.

**Pitfalls:** Rash is not always seen, and tick bite often goes unnoticed (tick often spontaneously falls off after 1–2 days of feeding). Do not overlook Lyme disease in patients with sudden unexplained heart block in areas where Ixodes ticks are endemic.

**Therapeutic Considerations:** B. burgdorferi is highly susceptible to all beta-lactams. For Bell's palsy or neuroborreliosis, minocycline (100 mg PO q12h × 2 weeks) may be preferred to doxycycline. Highest failure rates with macrolide therapy. Symptoms may persist for 1 year or more after adequate therapy. No rationale to re-treat persistent symptoms.

**Prognosis:** Excellent in normal hosts.

## Lyme Arthritis

**Clinical Presentation:** Acute Lyme arthritis presents with joint pain, decreased range of motion, ability to bear weight on joint, and little or no fever. Chronic Lyme arthritis resembles rheumatoid arthritis.

**Diagnostic Considerations:** Usually affects children and large weight-bearing joints (e.g., knee). Acute Lyme arthritis is diagnosed by clinical presentation plus elevated IgM Lyme titer. Chronic Lyme arthritis is suggested by rheumatoid arthritis-like presentation with negative ANA and rheumatoid factor, and positive IgG Lyme titer and synovial fluid PCR.

**Pitfalls:** Acute Lyme arthritis joint is red but not hot, in contrast to septic arthritis. In chronic Lyme arthritis, a negative IgG Lyme titer essentially rules out chronic Lyme arthritis, but an elevated IgG Lyme titer indicates only past exposure to B. burgdorferi and is not diagnostic of Lyme arthritis. Joint fluid in chronic Lyme disease is usually negative by culture, but positive by PCR; synovial fluid PCR, however, does not differentiate active from prior infection.

**Therapeutic Considerations:** IgG Lyme titers remain elevated for life, and do not decrease with treatment. Joint symptoms often persist for months/years after effective antibiotic therapy due to autoimmune joint inflammation; treat with anti-inflammatory drugs, not repeat antibiotic courses. Oral therapy as effective as IV therapy.

**Prognosis:** Good in normal hosts. Chronic/refractory arthritis may develop in genetically predisposed patients with DRW 2/4 HLA types.

## Infected Joint Prosthesis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Staphylococcal<br>(Treat initially for MSSA; if later identified as MRSA/CoNS, treat accordingly) | S. epidermidis (CoNS) | Linezolid 600 mg (IV) q12h*<br>**or**<br>Vancomycin 1 gm (IV) q12h* | Cefotaxime 2 gm (IV) q6h*†<br>**or**<br>Ceftizoxime 2 gm (IV) q8h*† | Linezolid 600 mg (PO) q12h* |
| | S. aureus (MSSA) | Nafcillin 2 gm (IV) q4h*<br>**or**<br>Cefazolin 1 gm (IV) q8h*<br>**or**<br>Ceftriaxone 1 gm (IV) q24h*† | Meropenem 1 gm (IV) q8h*<br>**or**<br>Clindamycin 600 mg (IV) q8h* | Clindamycin 300 mg (PO) q8h*<br>**or**<br>Linezolid 600 mg (PO) q12h*<br>**or**<br>Cephalexin 1 gm (PO) q6h* |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h*<br>**or**<br>Vancomycin 1 gm (IV) q12h*<br>**or**<br>Minocycline 100 mg (IV) q12h*<br>**or**<br>Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h* | | Linezolid 600 mg (PO) q12h*<br>**or**<br>Minocycline 100 mg (PO) q12h* |

*MRSA/MSSA = methicillin-resistant/sensitive S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis.* Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Treat for 1 week after joint prosthesis is replaced.

† Only if MSSE strain susceptible.

**Clinical Presentation:** Pain in area of prosthesis with joint loosening/instability ± low-grade fevers.

**Diagnostic Considerations:** Infected prosthesis is suggested by prosthetic loosening/lucent areas adjacent to prosthesis on plain films ± positive blood cultures. Diagnosis confirmed by bone scan. Use joint aspiration to identify organism.

**Pitfalls:** An elevated ESR with prosthetic loosening suggests prosthetic joint infection. Mechanical loosening without infection is comon many years after joint replacement, but ESR is normal.

**Therapeutic Considerations:** Infected prosthetic joints usually must be removed for cure. Replacement prosthesis may be inserted anytime after infected prosthesis is removed. To prevent infection of new joint prosthesis, extensive debridement of old infected material is important. *If replacement of*

*infected joint prosthesis is not possible,* **chronic suppressive therapy** may be used with oral antibiotics e.g., minocycline 100 mg (PO) q12h. TMP–SMX 5 mg/kg (PO) q6h may be successful in long-term suppression/cure in total hip replacement (treat × 6 months) or total knee replacement (treat × 9 months) due to susceptible strains of MSSA/MSSE; adding rifampin 300 mg (PO) q12h may be helpful.
**Prognosis:** Related to adequate debridement of infected material when prosthetic joint is removed.

## Osteomyelitis

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Acute<br><br>(Treat initially for MSSA; if later identified as MRSA or Entero-bacteriaceae, treat accordingly) | S. aureus (MSSA) | Cefazolin 1 gm (IV) q8h × 4–6 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 4–6 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 4–6 weeks | Cefotaxime 2 gm (IV) q6h × 4–6 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 4–6 weeks | Clindamycin 300 mg (PO) q8h × 4–6 weeks<br>**or**<br>Cephalexin 1 gm (PO) q6h × 4–6 weeks<br>**or**<br>Respiratory quinolone‡ (PO) q24h × 4–6 weeks |
| | S. aureus (MRSA) | Linezolid 600 mg (IV) q12h × 4–6 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 4–6 weeks<br>**or**<br>Vancomycin 2 gm (IV) q12h × 4–6 weeks<br>**or**<br>Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 4–6 weeks | | Linezolid 600 mg (PO) q12h × 4–6 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 4–6 weeks |
| | Entero-bacteriaceae | Ceftriaxone 1 gm (IV) q24h × 4–6 wks<br>**or**<br>Quinolone† (IV) × 4–6 weeks<br>**or**<br>Tigecycline 100 mg (IV) × 1 dose, then 50 mg (IV) q12h × 4–6 weeks | Cefotaxime 2 gm (IV) q6h × 4–6 wks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 4–6 wks | Quinolone† (PO) × 4–6 weeks |

## **Osteomyelitis** (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Chronic<br>*Diabetes mellitus/ Peripheral vascular disease* | Group A, B streptococci<br>S. aureus (MSSA)<br>E. coli<br>P. mirabilis K. pneumoniae<br>B. fragilis | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2–4 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h*<br>**or**<br>Piperacillin/ tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Ertapenem 1 gm (IV) q24h* | Moxifloxacin 400 mg (IV) q24h*<br>**or**<br>Ceftizoxime 2 gm (IV) q8h*<br>**or**<br>Ampicillin/ sulbactam 3 gm (IV) q6h*<br>**or**<br>**combination therapy with**<br>Ceftriaxone 1 gm (IV) q24h***plus**<br>Metronidazole 1 gm (IV) q24h* | Clindamycin 300 mg (PO) q8h*<br>**plus**<br>Levofloxacin 500 mg (PO) q24h*<br>**or monotherapy with**<br>Moxifloxacin 400 mg (PO) q24h* |
| | Above pathogens/ S. aureus (MRSA) | Same as above<br>**plus either**<br>Minocycline 100 mg (IV) q12h × 2–4 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 4–6 weeks<br>**or**<br>**monotheraphy with**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2–4 weeks | Minocycline 100 mg (IV) q12h × 2–4 weeks<br>**plus either**<br>Levofloxacin 500 mg (IV) q24h<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2–4 weeks | Minocycline 100 mg (PO) q12h × 2–4 weeks<br>**plus**<br>Quinolone† (PO) q24h × 2–4 weeks |
| | Above pathogens/ B. fragilis (foul discharge) | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2–4 weeks | Moxifloxacin 400 mg (IV) q24h × 2–4 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2–4 weeks | Moxifloxacin 400 mg (PO) q24h × 2–4 weeks |

## **Osteomyelitis** (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Chronic (cont'd) | Brucella | Streptomycin 1 gm (IM) q24h until cured **plus** Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h until cured | Gentamicin 5 mg/kg (IV) q24h until cured **plus** Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h until cured | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h until cured† **plus** Rifampin 600 mg (PO) q24h until cured |
| TB osteomyelitis | M. tuberculosis | Treat the same as pulmonary TB (p. 53), but extend treatment to 6–9 months | | |

MSSA/MRSA = methicillin-sensitive/resistant S. aureus. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

* Treat for 1 week after adequate debridement or amputation.

† Moxifloxacin 400 mg or Levofloxacin 500 mg.

### Acute Osteomyelitis

**Clinical Presentation:** Tenderness over infected bone. Fever and positive blood cultures common.
**Diagnostic Considerations:** Diagnosis by elevated ESR with positive bone scan. Bone biopsy is not needed for diagnosis. Bone scan is positive for acute osteomyelitis in first 24 hours.
**Pitfalls:** Earliest sign on plain films is soft tissue swelling; bony changes evident after 2 weeks.
**Therapeutic Considerations:** Treat 4–6 weeks with antibiotics. Debridement is not necessary for cure.
**Prognosis:** Related to adequacy/promptness of treatment.

### Chronic Osteomyelitis

#### *Diabetes Mellitus*

**Clinical Presentation:** Afebrile or low-grade fever with normal WBC counts and deep penetrating ulcers ± draining sinus tracts.
**Diagnostic Considerations:** Diagnosis by elevated ESR and bone changes on plain films. Bone scan is not needed for diagnosis. Bone biopsy is preferred method of demonstrating organisms, since blood cultures are usually negative and cultures from ulcers/sinus tracts are unreliable.
**Pitfalls:** P. aeruginosa is a common colonizer and frequently cultured from deep ulcers/sinus tracts, but is not a pathogen in chronic osteomyelitis in diabetics.
**Therapeutic Considerations:** Surgical debridement is needed for cure; antibiotics alone are ineffective. Revascularization procedures usually do not help, since diabetes is a microvascular disease. Do not culture penetrating foot ulcers/draining sinus tracts; culture results reflect superficial flora. Bone biopsy during debridement is the best way to identify pathogen; if biopsy not possible, treat empirically.
**Prognosis:** Related to adequacy of blood supply/surgical debridement.

***Non-Diabetics with Peripheral Vascular Disease (PVD)***

**Clinical Presentation:** Absent or low-grade fever with normal WBC counts ± wet/dry digital gangrene.
**Diagnostic Considerations:** Diagnosis by clinical appearance of dusky/cold foot ± wet/dry gangrene. Chronic osteomyelitis secondary to PVD/open fracture is often polymicrobial.
**Pitfalls:** Wet gangrene usually requires surgical debridement/antibiotic therapy; dry gangrene may not.
**Therapeutic Considerations:** Surgical debridement needed for cure. Antibiotics alone are ineffective. Revascularization procedure may help treat infection by improving local blood supply.
**Prognosis:** Related to degree of vascular compromise.

**Brucella Osteomyelitis (Brucella sp.)**

**Diagnostic Considerations:** May be evidence of brucellosis elsewhere (epididymoorchitis). Suspect in patients with a history of animal/raw milk/cheese exposure. Serologic diagnosis by serum SAT, ELISA, or PCR.
**Pitfalls:** Brucella has predilection for vertebra, sacroiliac joints. Erosions of anterior vertebra adjacent to disc space typical vs. TB with diffuse vertebral destruction.
**Therapeutic Considerations:** May require 6 weeks of antibiotic therapy.
**Prognosis:** Joint destruction usually permanent.

**TB Osteomyelitis (Mycobacterium tuberculosis)**

**Clinical Presentation:** Presents similarly to chronic bacterial osteomyelitis. Vertebral TB (Pott's disease) affects disk spaces early and presents with chronic back/neck pain ± inguinal/paraspinal mass.
**Diagnostic Considerations:** Diagnosis by AFB on biopsy/culture of infected bone. T-spot PPD–positive.
**Pitfalls:** Chest x-ray is normal in 50%. May be confused with cancer, brucella osteomyelitis or chronic bacterial osteomyelitis.
**Therapeutic Considerations:** Treated the same as TB arthritis.
**Prognosis:** Good for non-vertebral TB/vertebral (if treated before paraparesis/paraplegia).

## Empiric Therapy of Skin and Soft Tissue Infections

### Cellulitis, Erysipelas, Mastitis (uSSSIs)

| Subset | Usual Pathogens | Preferred IV Therapy | | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Above-the-waist | Group A, B streptococci | Ceftriaxone 1–2 gm (IV) q24h × 2 weeks<br>**or**<br>Cefazolin 1 gm (IV) q8h × 2 weeks | Quinolone* (IV) of q24h × 2 weeks<br>**or**<br>Clindamycin 600 mg (IV) q8h × 2 weeks | Cephalexin 500 mg (PO) q6h × 2 weeks<br>**or**<br>Clindamycin 300 mg (PO) q6h × 2 weeks<br>**or**<br>Quinolone* (PO) q24h × 2 weeks |

## Cellulitis, Erysipelas, Mastitis (uSSSIs) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Below-the-waist<br><br>(Treat initially for MSSA; if later identified as MRSA, treat accordingly) | Group A, B streptococci<br>P. mirabilis<br>K. pneumoniae<br>E. coli | Cefazolin 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks | Quinolone* (IV) q24h × 2 weeks | Cephalexin 500 mg (PO) q6h × 2 weeks<br>**or**<br>Quinolone* (PO) q24h × 2 weeks |

uSSSIs = uncomplicated skin skin structure infections.
MRSA/MSSA = methicillin-resistant/sensitive S. aureus. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.
* Moxifloxacin 400 mg or Levofloxacin 500 mg.

**Clinical Presentation:** Cellulitis presents as warm, painful, flat, non-pruritic skin erythema without discharge. Erysipelas resembles cellulitis but is raised and sharply demarcated. Mastitis presents as cellulitis of the breast cellulitis caused by groups A, B, C or G streptococci. Aspiration of streptococcal cellutitis is serous/serosanguinous fluid not purulent (as with MSSA/MRSA abscesses). MSSA/MRSA causes cutaneous abscesses, not cellutitis. MSSA/MRSA abscesses raised, warm, and tender ± bullae. No regional adenopathy or lymphangitis.
**Diagnostic Considerations:** Diagnosis by clinical appearance ± culture of pathogen from aspirated skin lesion(s). Group B streptococci are important pathogens in diabetics. Lower extremity cellulitis tends to recur. Chronic lymphedema or edema of an extremity predisposes to recurrent/persistent cellulitis.
**Pitfalls:** Streptococcal cellulitis often accompanied by lymphangitis and regional adenopathy; fever/chills common.
**Therapeutic Considerations:** Lower extremity cellulitis requires ~ 1 week of antibiotics to improve. Patients with peripheral vascular disease, chronic venous stasis, alcoholic cirrhosis, and diabetes take 1–2 weeks longer to improve and often require 3–4 weeks of treatment. Treat mastitis as cellulitis above-the-waist, and drain surgically if an abscess is present.
**Prognosis:** Related to degree of micro (DM) and or macrovascular (PVD) insufficiency.

## Complicated Skin/Skin Structure Infections (cSSSIs)

| Subset | Usual Pathogens | Preferred IV Therapy | | IV-to-PO Switch |
|---|---|---|---|---|
| Mixed aerobic-anaerobic deep soft tissue infection | Entero-bacteriaceae<br>Group A streptococci<br>S. aureus (MSSA)<br>Anaerobic streptococci<br>Fusobacterium | Piperacillin/ tazobactam 3.375 gm (IV) q6h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks | Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Doripenem 1 gm (IV) q8h<br>**or**<br>Moxifloxacin 400 mg (IV) q24h × 2 weeks | Moxifloxacin 400 mg (PO) q24h × 2 weeks<br>**or combination therapy with**<br>Levofloxacin 500 mg (PO) q24h × 2 weeks<br>**plus**<br>Clindamycin 300 mg (PO) q8h × 2 weeks |
| Clostridial myonecrosis (gas gangrene) | Clostridium sp. | Preferred IV<br>Penicillin G 10 mu (IV) q4h × 2 weeks<br>**or**<br>Clindamycin 600 mg (IV) q8h × 2 weeks | Alternate IV<br>Piperacillin 4 gm (IV) q8h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks | Not applicable |
| Necrotizing fasciitis/ synergistic gangrene/ Fournier's gangrene | Group A streptococci<br>Entero-bacteriaceae<br>Anaerobic streptococci<br>S. aureus(MSSA) | Piperacillin/ tazobactam 3.375 gm (IV) q6h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks | Clindamycin 600 mg (IV) q8h × 2 weeks<br>**plus**<br>Levofloxacin 500 mg (IV) q24h × 2 weeks | Clindamycin 300 mg (PO) q8h × 2 weeks<br>**plus**<br>Levofloxacin 500 mg (PO) q24h × 2 weeks |
| Phegmon, abscesses | MRSA/MSSA | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks<br>**or**<br>Daptomycin 6 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks<br>**or**<br>Tedizolid 200 mg (IV) q24h × 6 days, then 200 mg (PO) q24h × 6 days<br>**or**<br>Telavancin 10 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Dalbavancin 1 gm (IV) × 1 dose, then 500 mg (IV) 7 days later | | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |

cSSSIs = complicated skin skin structure infections.

*CA-MRSA = community-acquired methicillin-resistant S. aureus (see p. 15), MSSA = methicillin-sensitive S. aureus.* Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

## Complicated Skin/Skin Structure Tissue Infections (cSSSIs) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | IV-to-PO Switch |
|---|---|---|---|
| Pyomyositis/ necrotizing abscesses | Community-acquired MRSA (CA-MRSA)§ | Daptomycin 6 mg/kg (IV) q24h × 2 weeks **or** Linezolid 600 mg (IV) q12h × 2 weeks | Linezolid 600 mg (PO) q12h × 2 weeks **or** Minocycline 100 mg (PO) q12h × 2 weeks |

CA-MRSA = community-acquired methicillin-resistant S. aureus (see p. 15), MSSA = methicillin-sensitive S. aureus.

§ CA-MRSA PVL-positive strains (see p. 15).

### Mixed Aerobic/Anaerobic Deep Soft Tissue Infection

**Clinical Presentation:** Local pain/tenderness ± gross gas deep in soft tissues and usually high fevers. More common in diabetics.

**Diagnostic Considerations:** Diagnosed clinically. Bacteriologic diagnosis by gram stain/culture of aspirated fluid. Patients usually have high fevers. Wound discharge is foul when present.

**Pitfalls:** Gross crepitance/prominent gas in soft tissues on x-ray suggests a mixed aerobic/anaerobic necrotizing infection, not gas gangrene. Gas gangrene extremely rare in diabetics.

**Therapeutic Considerations:** Prompt empiric therapy and surgical debridement may be lifesaving.

**Prognosis:** Related to severity of infection, adequacy of debridement, and underlying health of host.

### Gas Gangrene (Clostridial Myonecrosis)

**Clinical Presentation:** Fulminant infection of muscle with little or n fever. Infected area is extremely painful, indurated, and discolored with or without bullae.

**Diagnostic Considerations:** Diagnosis is clinical. Aspiration of infected muscle shows few PMNs and gram-positive bacilli without spores (C. perfringens only). Gas gangrene is not accompanied by high fever. Patients are often apprehensive with relative bradycardia ± diarrhea. Wound discharge, if present, is sweetish and not foul. Rapidly progressive hemolytic anemia is characteristic.

**Pitfalls:** Gas gangrene (clostridial myonecrosis) has little visible gas on plain film x-rays; abundant gas should suggest a mixed aerobic/anaerobic infection, not gas gangrene. Gas gangrene extremely rare in diabetics.

**Therapeutic Considerations:** Surgical debridement is life saving and the only way to control infection.

**Prognosis:** Related to speed/extent of surgical debridement. Progression/death may occur in hours.

### Necrotizing Fasciitis/Synergistic Gangrene

**Clinical Presentation:** Acutely ill patient with high fevers and extreme local pain without gas in tissues. If scrotum involved (± abdominal wall involvement), the diagnosis is Fournier's gangrene.

**Diagnostic Considerations:** Diagnosis by CT/MRI of involved extremity showing infection confined to one or more muscle compartments/fascial planes. Patients are febrile and ill. Gas is not present on exam or x-rays. May be polymicrobial or due to a single organism. Foul smelling exudate from infected soft tissues indicates anaerobes are present.

**Pitfalls:** Extreme pain in patients with deep soft tissue infections should suggest a compartment syndrome/necrotizing fasciitis. No hemolytic anemia, diarrhea, or bullae as with gas gangrene.

**Therapeutic Considerations:** Control/cure of infection requires surgical, debridement of dead tissue, and antimicrobial therapy. Clindamycin may be added for its anti-exotoxin effects if pathogen group A streptococci.

**Prognosis:** Related to rapidity/extent of surgical debridement.

## Phegmon, Abscesses

**Clinical Presentation:** MSSA/MRSA infection often accompanied by bullae. A phegmon is a pre-abscess before abscess wall formation. MSSA/MRSA abscesses are clinically indistinguishable from other abscesses, but remain the most common pathogens in cSSSI abscesses.

**Diagnostic Considerations:** Diagnosis of cellulitis and abscesses is clinical. Demonstration of fascitis, phegmons, of abscesses are by imaging studies by CT/MRI.

**Pitfalls:** Bullae with cellulitis should suggest MSSA/MRSA (not group A streptococci). Bullae in DM/bullous diseases are not accompanied by fever/cellulitis.

**Therapeutic Considerations:** Cellulitis and phegmons may be treated with antibiotic therapy alone. Fasciitis and abscesses usually require debridement (fascitis) or drainage (abscesses).

**Prognosis:** Good if treated appropriately/early.

## Pyomyositis/Necrotizing Abscesses (CA-MRSA)

**Clinical Presentation:** Abrupt onset of severe/deep muscle infection ± large abscesses should suggest community-acquired MRSA (CA-MRSA).

**Diagnostic Considerations:** The diagnosis of CA-MRSA is made on the basis of the distinctively fulminant/severe clinical presentation and by culturing MRSA from muscle/abscess. If available, test isolate for SCC *mec* IV ± Panton-Valentine leukocidin (PVL) gene.

**Pitfalls:** CA-MRSA susceptible to clindamycin, TMP–SMX, and doxycycline.

**Therapeutic Considerations:** Prompt/complete incision and drainage of abscesses and early use of anti-CA-MRSA drugs may be life-saving. Antibiotics effective against CA-MRSA (TMP–SMX, clindamycin, doxycycline) are ineffective against CO-MRSA/HA-MRSA; antibiotics effective against CO-MRSA/HA-MRSA are also effective against CA-MRSA (see p. 15). Use minocycline instead of doxycycline for CA-MRSA/CO-MRSA. Doxycycline resistance with CA-MRSA of concern. Minocycline more effective than doxycycline, TMP-SMX or clindamycin for CA-MRSA.

**Prognosis:** Related to presence of PVL gene CA-MRSA. CA-MRSA PVL negative infections are similar in severity to MSSA infections.

## Skin Ulcers

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Decubitus ulcers (*above the waist)* | Group A streptococci<br>E. coli,<br>P. mirabilis<br>K. pneumoniae<br>S. aureus (MSSA) | Cefazolin 1 gm (IV) q8h*<br>**or**<br>Ceftriaxone 1 gm (IV) q24h* | Cefotaxime 2 gm (IV) q6h*<br>**or**<br>Ceftizoxime 2 gm (IV) q8h* | Cephalexin 500 mg (PO) q6h* |
| *(sacral ulcers/ ulcers below the waist) stage III/ IV ulcers =* ***chronic osteomyelitis*** | B. fragilis<br>Group A streptococci<br>E. coli<br>P. mirabilis<br>K. pneumoniae<br>S. aureus (MSSA)<br>S. aureus (MRSA)†<br>(*not P. aeruginosa*§) | Tigecycline 100 mg (IV) × 1 dose, then 50 mg (IV) q12h*<br>**or**<br>Ertapenem 1 gm (IV) q24h*<br>**or**<br>Piperacillin/ tazobactam 3.375 gm (IV) q6h*<br>**or**<br>Meropenem 1 gm (IV) q8h* | Moxifloxacin 400 mg (IV) q24h*<br>**or**<br>**combination therapy with**<br>Clindamycin 600 mg (IV) q6h*<br>**plus**<br>Levofloxacin 500 mg (IV) q24h* | Moxifloxacin 400 mg (PO) q24h*<br>**or**<br>**combination therapy with**<br>Clindamycin 300 mg (PO) q8h*<br>**plus**<br>Levofloxacin 500 mg (PO) q24h* |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

* Treat Stages I/II (superficial) decubitus ulcers with local care. If no underlying chronic osteomyelitis, treat Stages III/IV (deep) decubitus ulcers with antibiotics and adequate *bone* debridement.

† MRSA: Tigecycline 100 mg (IV) × 1 dose then 50 mg (IV) q12h* alone or one of above non-MRSA antibiotics *plus* [Daptomycin 4 mg/kg (IV) q24h* or Linezolid 600 mg (IV) q12h*] or Vancomycin 1 gm (IV) q12h* or Minocycline 100 mg (IV) q12h*. PO therapy or IV-to-PO switch if MRSA: Linezolid 600 mg (PO) q12h* or Minocycline 100 mg (PO) q12h* *plus* one of above antibiotics.

§ Deep penetrating ulcers (stage III/IV) in diabetics represent underlying *chronic osteomyelitis* and are *not due to P. aeruginosa*. However, P. aeruginosa (a water associated organism) can be cultured from > 90% of deep diabetic foot ulcers and represents superficial colonization (from moist socks, moist dressings, whirlpool baths, etc.)

## Skin Ulcers (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Diabetic foot ulcers (deep/ complicated)<br><br>(Treat initially for MSSA; if later identified as Group A streptococci, MRSA, etc., treat accordingly) | S. aureus (MRSA) | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h†<br>**or**<br>Vancomycin 1 gm (IV) q12h†<br>**or**<br>Daptomycin 4 mg/kg (IV) q24h†<br>**or**<br>Linezolid 600 mg (IV) q12h†<br>**or**<br>Minocycline 100 mg (IV) q12h† | Telavancin 10 mg/kg (IV) q24h†<br>**or**<br>Tedizolid 200 mg (IV) q24h × 6 days, then 200 mg (PO) × 6 days<br>**or**<br>Dalbavancin 1 gm (IV) × 1 dose, then 500 mg (IV) 7 days later | Linezolid 600 mg (PO) q12h†<br>**or**<br>Minocycline 100 mg (PO) q12h† |
| | S. aureus (MSSA)<br>Group A, B streptococci<br>E. coli<br>P. mirabilis<br>K. pneumoniae<br>B. fragilis | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h†<br>**or**<br>Ertapenem 1 gm (IV) q24h†<br>**or**<br>Piperacillin/tazobactam 3.375 gm (IV) q6h†<br>**or**<br>Moxifloxacin 400 mg (IV) q24h† | Cefoperazone 2 gm (IV) q12h†<br>**or**<br>Doripenem 1 gm (IV) q8h†<br>**or**<br>Ampicillin/sulbactam 3 gm (IV) q6h†<br>**or combination therapy with**<br>Ceftriaxone 1 gm (IV) q24h†<br>**or**<br>Levofloxacin 500 mg (IV) q24h†<br>**plus either**<br>Metronidazole 1 gm (IV) q24h†<br>**or**<br>Clindamycin 600 mg (IV) q8h† | Moxifloxacin 400 mg (PO) q24h†<br>**or combination therapy with**<br>Minocycline 100 mg (PO) q12h†<br>**plus**<br>Levofloxacin 500 mg (PO) q24h† |

† Treat × 1 week after adequate debridement/amputation.

## Skin Ulcers (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Ischemic foot ulcers | S. aureus (MRSA) | Treat the same as for deep/complicated diabetic foot ulcers, above | | |
| (Treat initially for MSSA; if later identified as Gp. A strep, MRSA, etc., treat accordingly) | Group A streptococci<br>E. coli<br>S. aureus (MSSA) | Cefazolin 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks | Quinolone* (IV) q24h × 2 weeks | Quinolone* (PO) q24h × 2 weeks |
| | Any pathogen(s) above **plus** S. aureus (MRSA) | IV Therapy: MRSA drug **plus** a non-MRSA drug (see diabetic foot ulcers) PO Therapy or IV-to-PO Switch: MRSA drug **plus** a non-MRSA drug (see diabetic foot ulcers) | | |

*MSSA = methicillin-sensitive S. aureus.* Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

* Levofloxacin 750 mg or Moxifloxacin 400 mg.

### Decubitus Ulcers

**Clinical Presentation:** Painless ulcers with variable depth and infectious exudate ± fevers ≤ 102°F.

**Diagnostic Considerations:** Diagnosis by clinical appearance. Obtain ESR/bone scan to rule out underlying osteomyelitis with deep (Stage III/IV) decubitus ulcers.

**Pitfalls:** Superficial decubitus ulcers do not require systemic antibiotics.

**Therapeutic Considerations:** Deep decubitus ulcers require antibiotics and debridement, superficial ulcers do not. Coverage for B. fragilis is needed for deep perianal decubitus ulcers. Good nursing care is important in preventing/limiting extension of decubitus ulcers.

**Prognosis:** Related to fecal contamination of ulcer and bone involvement (e.g., osteomyelitis).

### Diabetic Foot Ulcers/Chronic Osteomyelitis

**Clinical Presentation:** Ulcers/sinus tracts on bottom of foot/between toes; usually painless. Fevers ≤ 102°F and a foul smelling exudate are common.

**Diagnostic Considerations:** In diabetics, deep, penetrating, chronic foot ulcers/draining sinus tracts are diagnostic of chronic osteomyelitis. ESR ≥ 100 mm/hr in a diabetic with a foot ulcer/sinus tract is diagnostic of chronic osteomyelitis. Foot films confirm chronic osteomyelitis. Bone scan is needed only in acute osteomyelitis.

**Pitfalls:** Do not rely on culture results of deep ulcers/sinus tracts to choose antibiotic coverage, since cultures reflect skin colonization, not bone pathogens. Treat empirically.

**Therapeutic Considerations:** B. fragilis coverage is required in deep penetrating diabetic foot ulcers/fetid foot infection. P. aeruginosa is often cultured from diabetic foot ulcers/sinus tracts, but represents colonization, not infection. P. aeruginosa is a "water" organism that colonizes feet from moist socks/dressings, irrigant solutions, or whirlpool baths. Surgical debridement is essential for cure of chronic osteomyelitis in diabetics. Treat superficial diabetic foot ulcers the same as cellulitis in non-diabetics (see p. 132).

**Prognosis:** Related to adequacy of debridement of infected bone.

**Ischemic Foot Ulcers**

**Clinical Presentation:** Ulcers often clean/dry ± digital gangrene. No fevers/exudate.

**Diagnostic Considerations:** Diagnosis by clinical appearance/location in a patient with peripheral vascular disease. Ischemic foot ulcers most commonly affect the toes, medial malleoli, dorsum of foot, or lower leg.

**Pitfalls:** In contrast to ulcers in diabetics, ischemic ulcers due to peripheral vascular disease usually do not involve the plantar surface of the foot.

**Therapeutic Considerations:** Dry gangrene should not be treated with antibiotics unless accompanied by signs of systemic infection. Wet gangrene should be treated as a mixed aerobic/anaerobic infection. Both dry/wet gangrene may require debridement for cure/control. Do not rely on ulcer cultures to guide treatment; treat empirically if necessary. Evaluate for revascularization.

**Prognosis:** Related to degree of vascular insufficiency.

## Skin Abscesses/Infected Cysts (Skin Pustules, Skin Boils, Furunculosis) (uSSSIs/cSSSIs)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| **cSSSIs** (Deep/ multiple skin abscesses)<br><br>(Treat initially for MSSA; if later identified as MRSA, treat accordingly) | S. aureus (MRSA) | Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks<br>**or**<br>Daptomycin 4 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Minocycline 100 mg (IV) q12h × 2 weeks<br>**or**<br>Ceftaroline 600 mg (IV) of q12h × 2 weeks<br>**or**<br>Vancomycin 1 mg (IV) q12h × 2 weeks<br>**or**<br>Tedizolid 200 mg (IV) q24h × 6 days, then 200 mg (PO) × 6 days<br>**or**<br>Dalbavancin 1 gm (IV) × 1 dose, then 500 mg (IV) 7 days later<br>**or**<br>Telavancin 10 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Oritavancin 1200 mg (IV) × 1 dose | | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |
| | S. aureus (MSSA) | Cefazolin 1 gm (IV) q8h × 2 weeks<br>**or**<br>Nafcillin 2 gm (IV) q4h × 2 weeks | Clindamycin 600 mg (IV) q8h × 2 weeks<br>**or**<br>Ceftriaxone 1gm (IV) q24h × 2 weeks | Cephalexin 500 mg (PO) q6h × 2 weeks<br>**or**<br>Clindamycin 300 mg (PO) q8h × 2 weeks |

uSSSIs = uncomplicated skin skin structure infections; cSSSIs = complicated skin skin structure infections.
*MRSA/MSSA = methicillin-resistant/sensitive S. aureus.*

## Skin Abscesses/Infected Cysts (Skin Pustules, Skin Boils, Furunculosis) (cSSSIs/uSSSIs) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| **uSSSIs** *Infected pilonidal cysts* | Group A streptococci<br>E. coli<br>P. mirabilis<br>K. pneumoniae<br>S. aureus (MSSA) | Cefazolin 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks | Levofloxacin 500 mg (IV) q24h × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (IV) q24h × 2 weeks<br>**or**<br>Ceftizoxime 2 gm (IV) q8h × 2 weeks | Levofloxacin 500 mg (PO) q24h × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (PO) q24h × 2 weeks |
| *Hydradenitis suppurativa* | S. aureus (MSSA) | Not applicable | TMP–SMX 1 SS tablet (PO) q12h × 2–4 weeks<br>**or**<br>Clindamycin 300 mg (PO) q8h × 2–4 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2–4 weeks | |
| | S. aureus (MRSA) | Not applicable | Minocycline 100 mg (PO) q12h × 2–4 weeks | |

uSSSIs = uncomplicated SSSIs.
cSSSIs = complicated SSSIs.
*MRSA/MSSA = methicillin-resistant/sensitive S. aureus*. Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

### Skin Abscesses

**Clinical Presentation:** Warm painful nodules ± bullae, low-grade fever ± systemic symptoms, no lymphangitis. Skin boils/furunculosis present as acute, chronic, or recurrent skin pustules, and remain localized without lymphangitis.

**Diagnostic Considerations:** Specific pathogen diagnosed by gram stain of abscess. Recurring S. aureus abscesses are not uncommon and should be drained. Blood cultures are rarely positive. Suspect Job's syndrome if recurring abscesses with peripheral eosinophilia. Skin boils/furunculosis are diagnosed by clinical appearance (skin pustules).

**Pitfalls:** Recurring S. aureus skin infections may occur on immune basis but immunologic studies are usually negative.

**Therapeutic Considerations:** Repeated aspiration of abscesses may be necessary. Surgical drainage is required if antibiotics fail. Treat boils/furunculosis as in hydradenitis suppurativa.

**Prognosis:** Excellent if treated early.

### Infected Pilonidal Cysts

**Clinical Presentation:** Chronic drainage from pilonidal cysts.

**Diagnostic Considerations:** Diagnosis by clinical appearance. Deep/systemic infection is rare.
**Pitfalls:** Culture of exudate is usually unhelpful.
**Therapeutic Considerations:** Surgical debridement is often necessary.
**Prognosis:** Good with adequate excision.

### Hydradenitis Suppurativa

**Clinical Presentation:** Chronic, indurated, painful, raised axillary/groin lesions ± drainage/sinus tracts.
**Diagnostic Considerations:** Diagnosis by clinical appearance/location of lesions. Infections are often bilateral and tend to recur.
**Pitfalls:** Surgical debridement is usually not necessary unless deep/extensive infection.
**Therapeutic Considerations:** Most anti-S. aureus antibiotics have poor penetration and usually fail.
**Prognosis:** Good with recommended antibiotics. Surgery, if necessary, is curative.

## Skin Vesicles (Non-Genital)

| Subset | Pathogen | Therapy |
|---|---|---|
| Herpes simplex | Herpes simplex virus (HSV) | Acyclovir 400 mg (PO) q8h × 10 days **or** Valacyclovir 1 gm (PO) q12h × 7–10 days **or** Famciclovir 250 mg (PO) q8h × 10 days |
| Chickenpox | Varicella zoster virus (VZV) | Acyclovir 800 mg (PO) q6h × 5 days **or** Valacyclovir 1 gm (PO) q8h × 5 days **or** Famciclovir 500 mg (PO) q8h × 5 days |
| Herpes zoster *Dermatomal zoster (shingles)* | Varicella zoster virus (VZV) | Acyclovir 800 mg (PO) 5x/day × 7–10 days **or** Valacyclovir 1 gm (PO) q8h × 7–10 days **or** Famciclovir 500 mg (PO) q8h × 7–10 days |
| *Disseminated zoster* | | IV therapy: Acyclovir 10 mg/kg (IV) q8h × 7–10 days<br>PO therapy: Valacyclovir 1 gm (PO) q8h × 7–10 days **or** Famciclovir 500 mg (PO) q8h × 7–10 days |
| Herpes whitlow | HSV-1 | Acyclovir 400 mg (PO) q8h × 7–10 days **or** Valacyclovir 1 gm (PO) q12h × 7–10 days **or** Famciclovir 250 mg (PO) q8h × 7–10 days |

### Herpes Simplex (HSV)

**Clinical Presentation:** Painful, sometimes pruritic vesicles that form pustules or painful erythematous ulcers. Associated with fever, myalgias.
**Diagnostic Considerations:** Diagnosis by clinical appearance and demonstration of HSV by culture of vesicle fluid/vesicle base. May be severe in HIV.
**Pitfalls:** Painful vesicular lesions surrounded by prominent induration distinguishes HSV from insect bites (pruritic) and cellulitis (no induration).

**Therapeutic Considerations:** Topical acyclovir ointment may be useful early when vesicles erupt, but is ineffective after vesicles stop erupting. For severe/refractory cases, use acyclovir 5 mg/kg (IV) q8h × 2–7 days, then if improvement, switch to acyclovir 400 mg (PO) q8h to complete 10-day course.
**Prognosis:** Related to extent of tissue involvement/degree of cellular immunity dysfunction.

## Chickenpox (VZV)

**Clinical Presentation:** Abrupt appearance of discrete/diffuse pruritic vesicles. Appear in successive crops over 3 days, then no more new lesions. Patients do not appear toxic.
**Diagnostic Considerations:** Chickenpox lesions are central and typically concentrated on the trunk, although vesicles may also occur in the mouth, GI or GU tract. Vesicles are seen at different stages of development, and are superficial with the classic "dew drop on a rose petal" appearance. Tzanck test is positive in chickenpox (negative in smallpox).
**Pitfalls:** Vesicles are not deep/umbilicated like smallpox. Smallpox patients are sick/toxic, and vesicles are at the same stage of development in each anatomical area. Vesicles begin and are concentrated on the face with smallpox.
**Therapeutic Considerations:** Begin therapy as early as possible before appearance of successive crops of vesicles appear. Treat VZV pneumonia early with acyclovir.
**Prognosis:** Children do better than adults. Worst prognosis in smokers/pregnancy (may develop chickenpox/VZV pneumonia).

## Herpes Zoster (VZV)

**Clinical Presentation:** Painful, vesicular eruption in dermatomal distribution. Pain may be difficult to diagnose. Risk of disseminated VZV with steroids or statins.
**Diagnostic Considerations:** Diagnosis by appearance/positive Tzanck test of vesicle base scrapings.
**Pitfalls:** Begin therapy within 2 days of vesicle eruption.
**Therapeutic Considerations:** Higher doses of acyclovir are required for VZV than HSV. See p. 343 for disseminated VZV, ophthalmic nerve/visceral involvement, or acyclovir-resistant strains.
**Prognosis:** Good if treated early. Some develop painful post-herpetic neuralgia of involved dermatomes.

## Herpes Whitlow

**Clinical Presentation:** Multiple vesicopustular lesions on fingers and hands. Lymphangitis, adenopathy, fever/chills are usually present, suggesting a bacterial infection.
**Diagnostic Considerations:** Common in healthcare workers giving patients oral care/suctioning.
**Pitfalls:** No need for antibiotics even though lesions appear infected with "pus."
**Therapeutic Considerations:** Never incise/drain herpes whitlow; surgical incision will flare/prolong the infection.
**Prognosis:** Excellent, unless incision/drainage has been performed.

## **Wound Infections** (for rabies, see pp. 362, 374–375)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Animal bite wounds† | Group A streptococci<br>P. multocida<br>Capnocytophaga canimorsus (DF2)<br>S. aureus (MSSA) | Ampicillin/sulbactam 3 gm (IV) q6h × 2 weeks<br>**or**<br>Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks | Ertapenem 1 gm (IV) q24h × 2 weeks<br>**or**<br>Piperacillin/tazobactam 3.375 gm (IV) q6h × 2 weeks | Amoxicillin/clavulanic acid 500/125 mg (PO) q8h or 875/125 mg (PO) q12h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days |
| Human bite wounds | Oral anaerobes<br>Group A streptococci<br>E. corrodens<br>S. aureus (MSSA) | Same as for animal bite wounds, above | Same as for animal bite wounds, above | Same as for animal bite wounds, above |
| Cat scratch disease (CSD) | Bartonella henselae (invasive disease) | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 4–8 weeks<br>**or**<br>Azithromycin 500 mg (IV) q24h × 4–8 weeks | Chloramphenicol 500 mg (IV) q6h × 4–8 weeks<br>**or**<br>Erythromycin 500 mg (IV) q6h × 4–8 weeks | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4–8 weeks*<br>**or**<br>Azithromycin 250 mg (PO) q24h × 4–8 weeks<br>**or**<br>Quinolone‡ (PO) × 4–8 weeks |
| | B. henselae (lymphadenopathy only) | PO therapy: Azithromycin 500 mg (PO) × 1 dose, then 250 mg (PO) × 4 days | | |

*MSSA = methicillin-sensitive S. aureus.* Duration of therapy represents total time IV, PO, or IV + PO.

* Loading dose is not needed PO if given IV with the same drug.

‡ Ciprofloxacin 400 mg (IV) or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h or Moxifloxacin 400 mg (IV or PO) q24h.

† Rabies (see p. 362)

## **Wound Infections** (cont'd) (for rabies, see pp. 362, 374–375)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| Burn wounds (severe)† | Group A streptococci<br>S. aureus (MSSA)<br>Enterobacter<br>P. aeruginosa | Doripenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Meropenem 1 gm (IV) q8h × 2 weeks | Cefepime 2 gm (IV) q8h × 2 weeks<br>**or**<br>Cefoperazone 2 gm (IV) q12h × 2 weeks | Not applicable |
| Freshwater-exposed wounds | Aeromonas hydrophilia | Quinolone‡ (IV) × 2 weeks<br>**or**<br>TMP–SMX 2.5 mg/kg (IV) q6h × 2 weeks | Ceftriaxone 1 gm (IV) q24h × 2 weeks<br>**or**<br>Aztreonam 2 gm (IV) q8h × 2 weeks<br>**or**<br>Gentamicin 240 mg (IV) q24h × 2 weeks | Quinolone‡ (PO) × 2 weeks<br>**or**<br>TMP–SMX 1 SS tablet (PO) q12h × 2 weeks |
| Saltwater-exposed wounds | Vibrio vulnificus<br>Vibrio sp. | Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days<br>**or**<br>Quinolone‡ (IV) × 2 weeks | Ceftriaxone 2 gm (IV) q12h × 2 weeks<br>**or**<br>Chloramphenicol 500 mg (IV) q6h × 2 weeks | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days*<br>**or**<br>Quinolone‡ (PO) × 2 weeks |

*MSSA = methicillin-sensitive S. aureus.* Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

† Treat only IV or IV-to-PO switch.

‡ Ciprofloxacin 400 mg (IV) or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h or Moxifloxacin 400 mg (IV or PO) q24h.

### **Animal Bite Wounds** (for rabies, see p. 362)

**Clinical Presentation:** Cellulitis surrounding bite wound.

**Diagnostic Considerations:** Diagnosis by culture of bite wound exudate. Deep bites may also cause tendinitis/osteomyelitis, and severe bites may result in systemic infection with bacteremia.

**Pitfalls:** Avoid erythromycin in penicillin-allergic patients (ineffective against P. multocida).

**Therapeutic Considerations:** For facial/hand bites, consult a plastic surgeon.

**Prognosis:** Related to adequacy of debridement and early antibiotic therapy.

### **Human Bite Wounds**

**Clinical Presentation:** Cellulitis surrounding bite wound.

**Diagnostic Considerations:** Diagnosis by culture of bite wound exudate. Infection often extends to involve tendon/bone.
**Pitfalls:** Compared to animal bites, human bites are more likely to contain anaerobes, S. aureus, and Group A streptococci.
**Therapeutic Considerations:** Avoid primary closure of human bite wounds.
**Prognosis:** Related to adequacy of debridement and early antibiotic therapy.

## Cat Scratch Disease (Bartonella henselae)

**Clinical Presentation:** Subacute presentation of obscure febrile illness associated with cat bite/contact. Usually accompanied by adenopathy.
**Diagnostic Considerations:** Diagnosis by wound culture/serology for Bartonella. Cat scratch fever/disease may follow a cat scratch, but a lick from a kitten contaminating an inapparent micro-laceration is more common. May present as an FUO. Culture of exudate/node is unlikely to be positive, but silver stain of biopsy material shows organisms.
**Pitfalls:** Rule out lymphoma, which may present in similar fashion. Titers may cross react with C. burnetii (Q fever).
**Therapeutic Considerations:** For invasive disease, treat until symptoms/signs resolve. For lymphadenopathy, oral azithromycin decreases the size of nodes but may not reduce fever/systemic symptoms. Bartonella are sensitive in vitro to cephalosporins and TMP–SMX, but these antibiotics are ineffective in vivo.
**Prognosis:** Related to health of host.

## Burn Wounds

**Clinical Presentation:** Severe (3rd/4th degree) burns ± drainage.
**Diagnostic Considerations:** Semi-quantitative bacterial counts help differentiate colonization (low counts) from infection (high counts). Burn wounds quickly become colonized.
**Pitfalls:** Treat only infected 3rd/4th degree burn wounds with systemic antibiotics.
**Therapeutic Considerations:** Meticulous local care/eschar removal/surgical debridement is key in preventing and controlling infection.
**Prognosis:** Related to severity of burns and adequacy of eschar debridement.

## Freshwater-Exposed Wounds (Aeromonas hydrophilia)

**Clinical Presentation:** Fulminant wound infection with fever and diarrhea.
**Diagnostic Considerations:** Diagnosis by stool/wound/blood culture.
**Pitfalls:** Suspect A. hydrophilia in wound infection with fresh water exposure followed by diarrhea.
**Therapeutic Considerations:** Surgical debridement of devitalized tissue may be necessary.
**Prognosis:** Related to severity of infection and health of host.

## Saltwater-Exposed Wounds (Vibrio vulnificus/Vibrio sp.)

**Clinical Presentation:** Fulminant wound infection with fever, painful hemorrhagic bullae, diarrhea.
**Diagnostic Considerations:** Diagnosis by stool/wound/blood culture. Vibrio vulnificus is a fulminant, life-threatening infection that may be accompanied by hypotension.
**Pitfalls:** Suspect V. vulnificus in acutely ill patients with fever, diarrhea, and bullous lesions after saltwater exposure.
**Therapeutic Considerations:** Surgical debridement of devitalized tissue may be necessary.
**Prognosis:** Related to extent of infection and health of host.

## Superficial Fungal Infections of Skin and Nails

| Subset | Usual Pathogens | Topical Therapy | PO Therapy |
|---|---|---|---|
| Mucocutaneous (local/non-disseminated) candidiasis | C. albicans | Clotrimazole 1% cream twice daily × 2 weeks | Fluconazole 400 mg (PO) × 1 dose, then 200 mg (PO) q24h × 2 weeks |
| Tinea corporis (body ringworm) | Trichophyton rubrum<br>Epidermophyton floccosum<br>Microsporum canis<br>Trichophyton mentagrophytes | Clotrimazole 1% cream twice daily × 4–8 weeks<br>**or**<br>Miconazole 2% cream twice daily × 2 weeks<br>**or**<br>Econazole 1% cream twice daily × 2 weeks | Terbinafine 250 mg (PO) q24h × 4 weeks<br>**or**<br>Ketoconazole 200 mg (PO) q24h × 4 weeks<br>**or**<br>Fluconazole 200 mg (PO) weekly × 4 weeks |
| Tinea capitis (scalp ringworm) | Same as Tinea corporis, above | Selenium sulfide shampoo daily × 2–4 weeks | Same as Tinea corporis (see above) |
| Tinea cruris (jock itch) | T. cruris | Same as Tinea corporis, above | Same as Tinea corporis (see above) |
| Tinea pedis (athlete's foot) | Same as Tinea corporis, above | Same as Tinea corporis, above | Terbinafine 250 mg (PO) q24h × 2 weeks<br>**or**<br>Ketoconazole 200 mg (PO) q24h × 4 weeks<br>**or**<br>Itraconazole 200 mg (PO) q24h × 4 weeks* |
| Tinea versicolor (pityriasis) | Malasezzia furfur (Pityrosporum orbiculare) | Clotrimazole cream (1%) or miconazole cream (2%) or ketoconazole cream (2%) daily × 7 days | Ketoconazole 200 mg (PO) q24h × 7 days<br>**or**<br>Itraconazole 200 mg (PO) q24h × 7 days*<br>**or**<br>Fluconazole 400 mg (PO) × 1 dose |

* Itraconazole solution provides more reliable absorption than Itraconazole capsules.

## Superficial Fungal Infections of Skin and Nails (cont'd)

| Subset | Usual Pathogens | Topical Therapy | PO Therapy |
|---|---|---|---|
| Onychomycosis (nail infection) | Epidermophyton floccosum<br>Trichophyton mentagrophytes<br>Trichophyton rubrum<br>C. albicans | Not applicable | Fluconazole 200 mg (PO) q24h *pulse dosed, i.e.,* 1 week per month × 3 months (fingernail infection) or 6 months (toenail infection)<br>**or**<br>Itraconazole 200 mg (PO) q24h* *pulse dosed, i.e.,* 1 week per month × 2 months (fingernail infection) or 3 months (toenail infection)<br>**or**<br>Terbinafine 250 mg (PO) q24h × 6 weeks (fingernail infection) or 12 weeks (toenail infection) |

* Itraconazole solution provides more reliable absorption than itraconazole capsules.

### Mucocutaneous (Local/Non-disseminated) Candidiasis

**Clinical Presentation:** Primary cutaneous findings include an erythematous rash with satellite lesions, which may be papular, pustular, or ulcerated. Lesions can be limited or widespread over parts of body. Chronic mucocutaneous candidiasis manifests as recurrent candidal infections of skin, nails, or mucous mebranes.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. In HIV, Candida is very common on skin/mucous membranes.
**Pitfalls:** Do not confuse with the isolated, multinodular lesions of disseminated disease, which may resemble ecthyma gangrenosa or purpura fulminans.
**Therapeutic Considerations:** Diabetics and other compromised hosts may require prolonged therapy. In contrast to local disease, nodular cutaneous candidiasis represents disseminated disease (p. 290).
**Prognosis:** Related to extent of disease/host defense status.

### Tinea Corporis (Body Ringworm)

**Clinical Presentation:** Annular pruritic lesions on trunk/face with central clearing.
**Diagnostic Considerations:** Diagnosis by clinical appearance/skin scraping.
**Pitfalls:** Do not confuse with erythema migrans, which is not pruritic.
**Therapeutic Considerations:** If topical therapy fails, treat with oral antifungals.
**Prognosis:** Excellent.

### Tinea Capitis (Scalp Ringworm)

**Clinical Presentation:** Itchy, annular scalp lesions.
**Diagnostic Considerations:** Scalp lesions fluoresce with ultraviolet light. Culture hair shafts.
**Pitfalls:** T. capitis is associated with localized areas of alopecia.
**Therapeutic Considerations:** Selenium sulfide shampoo may be used first for 2–4 weeks. Treat shampoo Failures with oral ketoconazole, terbinafine, or fluconazole.
**Prognosis:** Excellent.

### Tinea Cruris (Jock Itch)

**Clinical Presentation:** Groin, inguinal, perineal, or buttock lesions that are pruritic and serpiginous with scaling borders/central clearing.
**Diagnostic Considerations:** Diagnosis by clinical appearance/culture.
**Pitfalls:** Usually spares penis/scrotum, unlike Candida.
**Therapeutic Considerations:** In addition to therapy, it is important to keep area dry.
**Prognosis:** Excellent.

### Tinea Pedis (Athlete's Foot)

**Clinical Presentation:** Painful cracks/fissures between toes.
**Diagnostic Considerations:** Diagnosis by clinical appearance/skin scraping.
**Pitfalls:** Must keep feet dry or relapse/reinfection may occur.
**Therapeutic Considerations:** In addition to therapy, it is important to keep area dry.
**Prognosis:** Excellent.

### Tinea Versicolor (Pityriasis)

**Clinical Presentation:** Oval hypo- or hyperpigmented scaly lesions that coalesce into large confluent areas typically on upper trunk; chronic/relapsing.
**Diagnostic Considerations:** Diagnosis by clinical appearance and culture of affected skin lesions.
**Pitfalls:** M. furfur also causes seborrheic dermatitis, but seborrheic lesions are typically on the face/scalp.
**Therapeutic Considerations:** If topical therapy fails, treat with oral antifungals. Treat non-scalp seborrheic dermatitis with ketoconazole cream (2%) daily until cured.
**Prognosis:** Excellent.

### Dermatophyte Nail Infections

**Clinical Presentation:** Chronically thickened, discolored nails.
**Diagnostic Considerations:** Diagnosis by culture of nail clippings.
**Pitfalls:** Nail clipping cultures often contaminated by bacterial/fungal colonizers. Green nail discoloration suggests P. aeruginosa, not a fungal nail infection; treat with ciprofloxacin 500 mg (PO) q12h × 2–3 weeks.
**Therapeutic Considerations:** Lengthy therapy is required. However, terbinafine and itraconazole remain bound to nail tissue for months following dosing and thus therapy with these compounds is not continued until clearance of the nail bed.
**Prognosis:** Excellent if infection is totally eradicated from nail bed. New nail growth takes months.

## Skin Infestations

| Subset | Usual Pathogens | Therapy |
|---|---|---|
| Scabies | Sarcoptes scabiei | Treat whole body with Permethrin cream 5% (Elimite); leave on for 8–10 hours **or** Ivermectin 18 mg (three 6-mg pills) (PO) × 1 dose |
| Head lice | Pediculus humanus var. capitis | Shampoo with Permethrin 5% (Elimite) or 1% (NIX) cream × 10 minutes |
| Body lice | Pediculus humanus var. corporis | Body lice removed by shower. Removed clothes should be washed in hot water or sealed in bags for 1 month, or treated with DDT powder 10% or malathion powder 1% |
| Pubic lice (crabs) | Phthirus pubis | Permethrin 5% (Elimite) or 1% (NIX) cream × 10 minutes to affected areas |

### Scabies (Sarcoptes scabiei)

**Clinical Presentation:** Punctate, serpiginous, intensely pruritic black spots in webbed spaces of hands/feet and creases of elbows/knees.
**Diagnostic Considerations:** Diagnosis by visualization of skin tracts/burrows. Incubation period up to 6 weeks after contact. Spread by scratching from one part of body to another.
**Pitfalls:** Mites are not visible, only their skin tracks, but mites may be scraped out of tracts for diagnosis.
**Therapeutic Considerations:** Permethrin cream is usually effective. If itching persists after treatment, do not retreat (itching is secondary to hypersensitivity reaction of eggs in skin burrows). Treat close contacts. Vacuum bedding/furniture.
**Prognosis:** Norwegian scabies is very difficult to eradicate.

### Head Lice (Pediculus humanus var. capitis)

**Clinical Presentation:** White spots may be seen on hair shafts of head/neck, but not eyebrows.
**Diagnostic Considerations:** Nits on hair are unhatched lice eggs, seen as white dots attached to hair shaft. May survive away from body × 2 days.
**Pitfalls:** May need to retreat in 7 days to kill any lice that hatched from surviving nits.
**Therapeutic Considerations:** Shampoo with Permethrin 5% (Elimite) or 1% (NIX) cream kills lice/nits. Clothes and non-washables should be tied off in plastic bags × 2 weeks to kill lice. Alternately, wash and dry clothes/bed linens; heat from dryer/iron kills lice.
**Prognosis:** Related to thoroughness of therapy.

### Body Lice (Pediculus humanus var. corporis)

**Clinical Presentation:** Intense generalized pruritus.
**Diagnostic Considerations:** Smaller than head lice and more difficult to see. May survive away from body × 1 week.
**Pitfalls:** Body lice live in clothes; leave only for a blood meal, then return to clothing.
**Therapeutic Considerations:** Can survive in seams of clothing × 1 week.
**Prognosis:** Good if clothes are also treated.

**Pubic Lice (Phthirus pubis) Crabs**

**Clinical Presentation:** Genital pruritus.
**Diagnostic Considerations:** Seen on groin, eyelashes, axilla. May survive away from body × 1 day.
**Pitfalls:** Smaller than head lice, but easily seen.
**Therapeutic Considerations:** Treat partners. Wash, dry, and iron clothes; heat from dryer/iron kills lice. Non-washables may be placed in a sealed bag × 7 days.
**Prognosis:** Good if clothes are also treated.

## Ischiorectal/Perirectal Abscess

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Ischiorectal/ perirectal abscess | Enterobacteriaceae B. fragilis | Treat the same as mild/severe peritonitis (p. 100) ± surgical drainage depending on abscess size/severity |

**Clinical Presentation:** Presents in normal hosts with perirectal pain, pain on defecation, leukocytosis, erythema/tenderness over abscess ± fever/chills. In febrile neutropenia, there is only tenderness.
**Diagnostic Considerations:** Diagnosis by erythema/tenderness over abscess or by CT/MRI.
**Pitfalls:** Do not confuse with perirectal regional enteritis (Crohn's disease) in normal hosts, or with ecthyma gangrenosum in febrile neutropenics.
**Therapeutic Considerations:** Antibiotic therapy may be adequate for mild cases. Large abscesses require drainage plus antibiotics × 1–2 weeks post-drainage. With febrile neutropenia, use an antibiotic that is active against both P. aeruginosa and B. fragilis e.g., meropenem.
**Prognosis:** Good with early drainage/therapy.

# Sepsis/Septic Shock

## Sepsis/Septic Shock

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Unknown source | Entero-bacteriaceae<br>B. fragilis<br>E. faecalis (VSE)† | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Piperacillin/ tazobactam 3.375 gm (IV) q6h × 2 weeks<br>**or**<br>Moxifloxacin 400 mg (IV) q24h × 2 weeks | Quinolone* (IV) × 2 weeks<br>**plus either**<br>Metronidazole 1 gm (IV) q24h × 2 weeks<br>**or**<br>Clindamycin 600 mg (IV) q8h × 2 weeks | Moxifloxacin 400 mg (PO) q24h × 2 weeks |

*VSE/VRE = vancomycin-sensitive/resistant enterococci.* Duration of therapy represents total time IV or IV + PO.
* Ciprofloxacin 400 mg (IV) q12h or Levofloxacin 500 mg (IV or PO) q24h.
† Treat initially for E. faecalis (VSE); if later identified as E. faecium (VRE), treat accordingly (urosepsis see pp. 154–155).

## Sepsis/Septic Shock (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Lung source<br>*Community-acquired pneumonia*§ | S. pneumoniae<br>H. influenzae<br>K. pneumoniae** | Respiratory quinolone‡ (IV) q24h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks | Any 2nd generation cephalosporin (IV) × 2 weeks | Respiratory quinolone‡ (PO) q24h × 2 weeks<br>**or**<br>Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days |
| | Influenza A (ILI **with** rapidly cavitating <72 hours multiple pulmonary infiltrates) | MSSA/MRSA | (see pp. 62–63) | (see p. 52) |
| *Nosocomial pneumonia* | P. aeruginosa<br>K. pneumoniae<br>E. coli<br>S. marcescens (*not* MSSA/MRSA) | Same as ventilator-associated pneumonia (see p. 68) | | |
| CVC source***<br>*Bacteremia*<br>(Treat initially for MSSA; if later identified as MRSA, etc., treat accordingly) | S. epidermidis (CoNS)<br>S. aureus (MSSA)<br>Klebsiella<br>Enterobacter<br>Serratia | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Cefepime 2 gm (IV) q12h × 2 wks | Ceftriaxone 1 gm (IV) q24h × 2 wks<br>**or**<br>Respiratory quinolone* (IV) q24h × 2 wks | Respiratory quinolone* (PO) q24h × 2 weeks<br>**or**<br>Cephalexin 500 mg (PO) q6h × 2 weeks |
| | S. aureus (MRSA) | Daptomycin 6 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks | | Linezolid 600 mg (PO) q12h × 2 weeks |

ILI = Influenza like illness.

*MRSA/MSSA = methicillin resistant/sensitive S. aureus.* Duration of therapy represents total time IV or IV + PO.

* Moxifloxacin 400 mg or Levofloxacin 500 mg.

** In alcoholics only

*** If clinically possible, remove CVC as soon as possible.

† Patients with ILI/influenza A (human/swine) presenting with *simultaneous* MSSA/MRSA CAP often present in shock.

‡ Levofloxacin 750 mg (IV) q24h or Moxifloxacin 400 mg (IV) q24h.

§ *Uncomplicated by cardiopulmonary decompensation/failure, CAP does not present with hypotension/shock in normal hosts. Hyposplenia/asplenia should be suspected if CAP presents with hypotension/shock in patients with good cardiopulmonary function.*

## **Sepsis/Septic Shock** (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| | | Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 2 weeks **or** Vancomycin 1 gm (IV) q12h × 2 weeks | | Minocycline 100 mg (PO) q12h × 2 weeks |
| *Candidemia* (disseminated/ invasive)<br><br>Unless species is known, empiric therapy as for non-albicans/ possibly fluconazole-resistant Candida is preferred if recent prior azole therapy, severe illness, neutropenia or high risk for infection with C. glabrata or C. krusei | Candida albicans (or other fluconazole-susceptible species)¶ | If less critically ill, not neutropenic, and no recent azole exposure: fluconazole is usual first choice alternates an echinocandin may be used. In critically ill, neutropenia or recent azole exposure: an echinocandin is preferred. **or** Micafungin 100 mg (IV) q24h × 2 weeks† **or** Caspofungin 70 mg (IV) × 1 dose, then 50 mg (IV) q24h × 2 weeks† Fluconazole 800 mg (IV) × 1, then 400 mg (IV) q24h × 2 weeks† **or** Lipid-associated formulation of amphotericin B (p. 525) (IV) q24h × 2 weeks† **or** Amphotericin B deoxycholate 0.7 mg/kg (IV) q24h × 2 weeks† **or** Voriconazole (see "usual dose," p. 714) **or** Anidulafungin 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks† | | Fluconazole 400 mg (PO) q24h × 2 weeks† **or** Voriconazole (see "usual dose," p. 714) |
| | Non-albicans Candida¶ (possibly fluconazole-resistant) | Choices are as for C. albicans (see above), but Fluconazole should *not* be used and an echinocandin is preferred. Micafungin 100 mg (IV) q24h × 2 weeks† **or** Caspofungin (see C. albicans, above) Use an Amphotericin or Voriconazole if additional mould coverage is desired **or** Lipid amphotericin B (p. 525) (IV) q24h† **or** Amphotericin B deoxycholate (see C. albicans, above) × 2 weeks† **or** Voriconazole (see "usual dose," p. 714) × 2 weeks¶† **or** Itraconazole (see C. albicans, above) **or** Anidulafungin 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks† | | Voriconazole (see "usual dose," p. 714) × 2 weeks¶† |

¶ Best agent depends on infecting species. Fluconazole-susceptibility varies predictably by species. (See Fluconazole Drug Summary) also, see Amphotericin B (deoxycholate and lipid-associated formulations) Drug Summaries.

† Treat candidemia for 2 weeks after negative blood cultures.

## **Sepsis/Septic Shock** (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Intra-abdominal/ pelvic source | Entero-bacteriaceae B. fragilis | Ertapenem 1 gm (IV) q24h × 2 weeks **or** Tigecycline 200 mg (IV) × 1 dose, then 100 mg (IV) q24h × 2 weeks **or** Meropenem 1 gm (IV) q8h × 2 weeks **or** Piperacillin/ tazobactam 3.375 gm (IV) q6h × 2 weeks | **Combination therapy with either** Ceftriaxone 1 gm (IV) q24h × 2 weeks **or** Levofloxacin 500 mg (IV) q24h × 2 weeks **plus** Metronidazole 1 gm (IV) q24h × 2 weeks | Moxifloxacin 400 mg (PO) q24h × 2 weeks **or combination therapy with** Levofloxacin 500 mg (PO) q24h × 2 weeks **plus** Clindamycin 300 mg (PO) q8h × 2 weeks |
| Urosepsis (*community-acquired*) | Entero-bacteriaceae E. faecalis (VSE) | Levofloxacin 500 mg (IV) q24h × 1–2 weeks **or** Piperacillin/ tazobactam 3.375 gm (IV) q6h × 1–2 weeks | Meropenem 1 gm (IV) q8h × 1–2 weeks **or** Levofloxacin 500 mg (IV) q24h | Levofloxacin 500 mg (PO) q24h × 1–2 weeks |
| | E. faecium (VRE) | Daptomycin 6 mg/ kg (IV) q24h × 1–2 weeks **or** Linezolid 600 mg (IV) q12h × 1–2 weeks | Quinupristin/ dalfopristin 7.5 mg/kg (IV) q8h × 1–2 weeks | Linezolid 600 mg (PO) q12h × 1–2 weeks **or** Minocycline 100 mg (PO) q12h × 1–2 weeks |
| (*nosocomial*) | P. aeruginosa Entero-bacteriaceae | Meropenem 1 gm (IV) q8h × 1–2 weeks **or** Doripenem 1 gm (IV) q8h × 1–2 weeks **or** Levofloxacin 750 mg (IV) q24h × 1–2 weeks | Aztreonam 2 gm (IV) q8h × 1–2 weeks **or** Cefepime 2 gm (IV) q12h × 1–2 weeks | Levofloxacin 750 mg (PO) q24h × 1–2 weeks |
| | CRE | Ceftazidime/ avibactam 2.5 gm (IV) q 8 h × 1–2 weeks | Colistin 5 mg/kg (IV) q8h × 1–2 weeks | |

## **Sepsis/Septic Shock** (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Urosepsis (*group D enterococci)* | E. faecalis (VSE) | Ampicillin 2 gm (IV) q4h × 1–2 weeks **or** Piperacillin/tazobactam 3.375 gm (IV) q6h × 1–2 weeks **or combination therapy with** Vancomycin 1 gm (IV) q12h × 1–2 weeks **plus** Gentamicin 240 mg (IV) q24h × 1 week | | Amoxicillin 1 gm (PO) q8h × 1–2 weeks **or** Levofloxacin 500 mg (PO) q24h × 1–2 weeks |
| | E. faecium (VRE) | Linezolid 600 mg (IV) q12h × 1–2 weeks **or** Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 1–2 weeks | | Linezolid 600 mg (PO) q12h × 1–2 weeks **or** Minocycline 100 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4–11 days |
| Overwhelming sepsis with purpura (asplenia or hyposplenia) | S. pneumoniae H. influenzae N. meningitidis | Ceftriaxone 2 gm (IV) q24h × 2 weeks **or** Levofloxacin 500 mg (IV) q24h × 2 weeks | Cefepime 2 gm (IV) q12h × 2 weeks **or** Cefotaxime 2 gm (IV) q6h × 2 weeks | Levofloxacin 500 mg (PO) q24h × 2 weeks **or** Amoxicillin 1 gm (PO) q8h × 2 weeks |
| Steroids (high chronic dose) | Aspergillus | Treat as Aspergillus pneumonia (see p. 55) | | |
| Miliary TB | M. tuberculosis | Treat as pulmonary TB (see p. 53) plus steroids × 1–2 wks | | |
| Miliary BCG (disseminated BCG) | Bacille Calmette-Guérin (BCG) | Treat with INH plus RIF × 9 months; EMB, until susceptibilities known; may add steroids e.g., prednisolone 40 mg q24h × 1–2 weeks | | |
| Septic shock | Gram-negative or gram-positive bacteria | Meropenem 1 gm (IV) q8h × 1-2 weeks* | | |

Duration of therapy represents total time IV or IV + PO.

* Plus surgical decompression/drainage if needed.

## Sepsis (Unknown Source)

**Clinical Presentation:** Abrupt onset of high spiking fevers, rigors ± hypotension.

**Diagnostic Considerations:** Diagnosis suggested by high-grade bacteremia (2/4–4/4 positive blood cultures) with unexplained hypotension. Rule out pseudosepsis (GI bleed, myocardial infarction, pulmonary embolism, acute pancreatitis, adrenal insufficiency, etc.). Sepsis usually occurs from a GI, GU, or IV source, so coverage is directed against GI and GU pathogens if IV line infection is unlikely.

**Pitfalls:** Most cases of fever/hypotension are *not* due to sepsis. Before the label of "sepsis" is applied to febrile/hypotensive patients, first consider treatable/reversible mimics (see p. 151).

**Therapeutic Considerations:** Resuscitate shock patients initially with rapid adequate volume replacement, followed by pressors, if needed. Do not give pressors before volume replacement or hypotension may continue/worsen. Use normal saline, plasma expanders, or blood for volume replacement, not $D_5W$. If patient is persistently hypotensive despite volume replacement, consider relative adrenal insufficiency: Obtain a serum cortisol level, then give cortisone 100 mg (IV) q6h × 24–72h; blood pressure will rise promptly if relative adrenal insufficiency is the cause of volume-unresponsive hypotension. Do not add/change antibiotics if patient is persistently hypotensive/febrile; look for GI bleed, myocardial infarction, pulmonary embolism, pancreatitis, undrained abscess, adrenal insufficiency, or IV line infection. Drain abscesses as soon as possible. Remove IV lines if the entry site is red or a central line has been in place for ≥ 7 days and there is no other explanation for fever/hypotension. Early antibiotic therapy/surgical drainage of abscesses, debridement of necrotic tissue eg. necrotizing fasciitis or relief of obstruction is critical.

**Prognosis:** Related to severity of septic process and underlying cardiopulmonary/immune status.

## Sepsis (Lung Source)

**Clinical Presentation:** Normal hosts with community-acquired pneumonia (CAP) do not present with sepsis. CAP with sepsis suggests the presence of impaired immunity/hyposplenic function (see "sepsis in hyposplenia/asplenia," p. 157). Nosocomial pneumonia uncommonly presents as (or is complicated by) sepsis with otherwise unexplained hypotension.

**Diagnostic Considerations:** Impaired splenic function may be inferred by finding Howell-Jolly bodies (small, round, pinkish or bluish inclusion bodies in red blood cells) in the peripheral blood smear. The number of Howell-Jolly bodies is proportional to the degree of splenic dysfunction.

**Pitfalls:** CAP with hypotension/sepsis should suggest hyposplenic function, impaired immunity, or an alternate diagnosis that can mimic CAP/shock. Be sure to exclude acute MI, acute heart failure/COPD, PE/infarction, overzealous diuretic therapy, concomitant GI bleed, and acute pancreatitis.

**Therapeutic Considerations:** Patients with malignancies, myeloma, or SLE are predisposed to CAP, which is not usually severe or associated with shock. Be sure patients with CAP receiving steroids at less than "stress doses" do not have hypotension/shock from relative adrenal insufficiency. In patients with SLE, try to distinguish between lupus pneumonitis and CAP; SLE pneumonitis usually occurs as part of a SLE flare, CAP usually does not.

**Prognosis:** Related to underlying cardiopulmonary/immune status. Early treatment is important.

## Sepsis (Central Venous Catheter [CVC] Source)

**Clinical Presentation:** Temperature ≥ 102°F ± IV site erythema.

**Diagnostic Considerations:** Diagnosis by semi-quantitative catheter tip culture with ≥ 15 colonies plus blood cultures with same pathogen. If no other explanation for fever and line has been in place ≥ 7 days, remove CVC and obtain semi-quantitative catheter tip culture. Suppurative thrombophlebitis presents with hectic/septic fevers and pus at IV site ± palpable venous cord.

**Pitfalls:** Temperature ≥ 102°F with CVC infection, in contrast to phlebitis (temperature ≤ 102°F). Acute bacterial endocarditis (ABE) may complicate intracardiac or CVC (not peripheral) infection.
**Therapeutic Considerations:** Line removal is usually curative, but antibiotic therapy is usually given for 1 week after CVC removal for gram-negative bacilli or 2 weeks after CVC removal for S. aureus (MSSA/MRSA). Antifungal therapy is also usually given for 2 weeks after CVC removal for candidemia. Dilated ophthalmoscopy by an ophthalmologist is important to exclude candidal endophthalmitis following candidemia.
**Prognosis:** Good if CVC is removed before endocarditis/metastatic spread.

## Sepsis (Intra-abdominal/Pelvic Source)

**Clinical Presentation:** Fever, peritonitis ± hypotension. Usually a history of an intra-abdominal disorder that predisposes to sepsis (e.g., diverticulosis, gallbladder disease, recent intra-abdominal/pelvic surgery). Signs and symptoms are referable to the abdomen/pelvis.
**Diagnostic Considerations:** Clinical presentation plus imaging studies (e.g., abdominal/pelvic CT or MRI to demonstrate pathology) are diagnostic.
**Pitfalls:** Elderly patients may have little/no fever and may not have rebound tenderness. Be sure to exclude intra-abdominal mimics of sepsis (e.g., GI bleed, pancreatitis).
**Therapeutic Considerations:** Empiric coverage should be directed against aerobic gram-negative bacilli plus B. fragilis. Anti-enterococcal coverage is not essential. Antibiotic therapy is ineffective unless ruptured viscus is repaired, obstruction is relieved, abscesses are drained.
**Prognosis:** Related to rapidity/adequacy of abscess drainage and repair/lavage of ruptured organs. The preoperative health of the host is also important.

## Sepsis (Urinary Source)

**Clinical Presentation:** Fever/hypotension in a patient with diabetes mellitus, SLE, myeloma, pre-existing renal disease, stone disease, or partial/total urinary tract obstruction.
**Diagnostic Considerations:** Urine gram stain determines initial empiric coverage. Pyuria is also present. Diagnosis confirmed by culturing the same isolate from urine and blood.
**Pitfalls:** Pyuria without bacteriuria and bacteremia due to same pathogens is not diagnostic of urosepsis. Urosepsis does not occur in normal hosts; look for host defect (e.g., diabetes, renal disease).
**Therapeutic Considerations:** If stones/obstruction are not present, urosepsis resolves rapidly with appropriate therapy. Delayed/no response suggests infected/obstructed stent, stone, partial/total urinary tract obstruction, or renal abscess.
**Prognosis:** Good if stone/stent removed, obstruction relieved, abscess drained. Fatalities rare with urosepsis.

## Sepsis (Hyposplenia/Asplenia)

**Clinical Presentation:** Presents as overwhelming septicemia/shock with petechiae.
**Diagnostic Considerations:** Diagnosis by gram stain of buffy coat of blood or by blood cultures. Organism may be stained/cultured from aspirated petechiae. Howell-Jolly bodies in the peripheral smear are a clue to decreased splenic function. Conditions associated with hyposplenism include sickle cell trait/disease, cirrhosis, rheumatoid arthritis, SLE, systemic necrotizing vasculitis, amyloidosis, celiac disease, chronic active hepatitis, Fanconi's syndrome, IgA deficiency, intestinal lymphangiectasia, intravenous gammaglobulin therapy, myeloproliferative disorders, non-Hodgkin's lymphoma, regional enteritis, ulcerative colitis, Sezary syndrome, splenic infarcts/malignancies, steroid therapy, systemic mastocytosis, thyroiditis, infiltrative diseases of spleen, mechanical compression of splenic artery/spleen, Waldenstrom's macroglobulinemia, hyposplenism of old age, congenital absence of spleen.
**Pitfalls:** Suspect hyposplenia/asplenia in unexplained overwhelming infection.

**Therapeutic Considerations:** In spite of early aggressive antibiotic therapy and supportive care, patients often die within hours from overwhelming infection, especially due to S. pneumoniae.
**Prognosis:** Related to degree of splenic dysfunction.

### Sepsis (Chronic High Dose Steroids)

**Clinical Presentation:** Subacute onset of fever with disseminated infection (Candida, Aspergillus) in multiple organs.
**Diagnostic Considerations:** Diagnosis by positive blood cultures for fungi or demonstration of invasive fungal infection from tissue biopsy specimens. Sepsis is most commonly due to fungemia.
**Pitfalls:** Obtain blood cultures to diagnose fungemias and rule out bacteremias (uncommon).
**Therapeutic Considerations:** Empirical approach is the same as for invasive candidiasis (p. 153) or invasive *aspergillosis* (p. 159 and p. 164). Therapy focused solely on candidiasis (e.g., fluconazole alone) should be used only if *aspergillosis* seems unlikely following careful review of the epidemiologic and clinical presentation.
**Prognosis:** Related to degree of immunosuppression.

### Miliary (Disseminated) TB (Mycobacterium tuberculosis)

**Clinical Presentation:** Unexplained, prolonged fevers without localizing signs.
**Diagnostic Considerations:** Diagnosis by AFB on biopsy/culture of liver or bone marrow.
**Pitfalls:** Chest x-ray is negative early in 1/3. Subtle miliary (2 mm) infiltrates on chest x-ray 1–4 weeks).
**Therapeutic Considerations:** Treated the same as pulmonary TB ± steroids initially.
**Prognosis:** Death within weeks without treatment.

### Miliary (Disseminated) BCG (Bacille Calmette-Guérin)

**Clinical Presentation:** Fever, circulatory collapse, DIC days to weeks after intravesicular BCG.
**Diagnostic Considerations:** Usually occurs in compromised hosts (e.g., transplants, active TB, congenital/acquired immunodeficiencies [e.g., HIV], leukemias/lymphomas). Rare in normal hosts.
**Pitfalls:** Avoid intravesicular BCG immediately after traumatic catheterization, bladder biopsy, TURP.
**Therapeutic Considerations:** Treat with 4 anti-TB drugs plus steroids. Do not repeat BCG therapy.
**Prognosis:** Good with early treatment.

## Febrile Neutropenia

## Febrile Neutropenia

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | IV-to-PO Switch |
|---|---|---|---|---|
| Febrile leukopenia ***< 7 days*** | P. aeruginosa Entero-bacteriaceae (*not* MSSA/MRSA)[¶] | Meropenem 1 gm (IV) q8h* **or** Levofloxacin 750 mg (IV) q24h* | Cefepime 2 gm (IV) q8h* **or** Doripenem 1 gm (IV) q8h* | Levofloxacin 750 mg (PO) q24h* |

## Febrile Neutropenia (cont'd)

| | | | | |
|---|---|---|---|---|
| ***> 7 days*** | C. albicans<br>Non-albicans Candida<br>Aspergillus | Micafungin 100 mg (IV) q24h* **or** Voriconazole (see "usual dose," p. 714)* **or** Caspofungin 70 mg (IV) × 1 dose, then 50 mg (IV) q24h* **or** Lipid-associated formulation of amphotericin B (IV) (p. 525) q24h* | Amphotericin B deoxycholate 1.5 mg/kg (IV) q24h until 1–2 gm given | Itraconazole 200 mg (PO) q12h* **or** Voriconazole (see "usual dose," p. 714)* |
| | MSSA (2° to CVC)† | Same as above (have good GNB and MSSA activity) | Same as above (have good GNB and MSSA activity) | Linezolid 600 mg (PO) q12h **or** Minocycline§ 100 mg (PO) q12h |
| | MRSA (2° to CVC)† | Meropenem 1 gm (IV) q8h* **or** Levofloxacin 750 mg (IV) q24h* **plus** Daptomycin§ 6 mg/kg (IV) q24h **or** Vancomycin§ 1 gm (IV) q12h | Cefepime 2 gm (IV) q8h* **or** Doripenem 1 gm (IV) q8h* **plus either** Linezolid 600 mg (IV) q12h **or** Quinupristin/dalfopristin§ 7.5 mg/kg (IV) q8h | Linezolid 600 mg (PO) q12h **or** Minocycline§ 100 mg (PO) q12h |

*MSSA = methicillin-sensitive S. aureus.* Duration of therapy represents total time IV or IV + PO.

* Treat until neutropenia resolves.

† If clinically possible, remove CVC.

§ Treat for 2 weeks post--CVC removal.

¶ Neutropenia, per se, does not predispose to MSSA/MRSA bacteremias. MSSA/MRSA bacteremias in febrile neutropenia are 2° to CVC associated infection, *not* neutropenia.

**Clinical Presentation:** Incidence of infection rises as PMN counts fall below 1000/mm$^3$.

**Diagnostic Considerations:** Febrile neutropenia < 7 days ± positive blood cultures. After blood cultures are drawn, anti-P. aeruginosa coverage should be initiated. Do not overlook ischiorectal or perirectal abscess as sources of fever.

**Pitfalls:** Suspect fungemia if abrupt rise in temperature occurs after 7 days of appropriate anti-P. aeruginosa antibiotic therapy. Fungemias usually do not occur in first 7 days of neutropenia. Viridans streptococci (S. mitis) may present with bacteremia, shock, ARDs, and rash in febrile neutropenia.

**Therapeutic Considerations:** If a patient is neutropenic for > 2 weeks and develops RUQ/LUQ pain/increased alkaline phosphatase, suspect hepatosplenic candidiasis; confirm diagnosis with abdominal CT/MRI showing mass lesions in liver/spleen and treat as systemic/invasive candidiasis (p. 79). S. aureus is not a common pathogen in neutropenic compromised hosts without central IV lines, and B. fragilis/anaerobes are not usual pathogens in febrile neutropenia. If IV line infection/perirectal abscess are ruled out, consider tumor fever or drug fever before changing antibiotic therapy.
**Prognosis:** Related to degree and duration of neutropenia.

## Transplant Infections

## Transplant Infections

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| **BACTEREMIA OR CANDIDEMIA** | | | | |
| ***Bacteremia*** *Post-**BMT*** *(leukopenic pre-engraftment)* ***< 7 days*** | P. aeruginosa<br>Entero-bacteriaceae<br>S. aureus (MSSA)<br>Viridans streptococci<br>E. faecalis (VSE) | Meropenem 1 gm (IV) q8h*<br>**or**<br>Piperacillin 4 gm (IV) q6h* | Quinolone† (IV) q24h*<br>**plus either**<br>Aztreonam 2 gm (IV) q8h*<br>**or**<br>Amikacin 1 gm (IV) q24h* | Quinolone† (PO) q24h*<br>**or**<br>Ciprofloxacin 750 mg (PO) q12h* |
| | S. aureus (Co-MRSA/HA-MRSA) | Daptomycin 6 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks<br>**or**<br>Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 2 weeks<br>**or**<br>Vancomycin 1 gm (IV) q12h × 2 weeks | | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |
| | E. faecium (VRE) | Linezolid 600 mg (IV) q12h × 1–2 weeks | Daptomycin 6 mg/kg (IV) q24h × 1–2 weeks | Linezolid 600 mg (PO) q12h × 1–2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 1–2 weeks |

*BMT/SOT = bone marrow/solid organ transplant, CO/HA-MRSA = community-onset/hospital-acquired methicillin-resistant S. aureus (see p. 14), MSSA = Methicillin-sensitive S. aureus.*

† Levofloxacin 750 mg or Moxifloxacin 400 mg.

* Treat until neutropenia resolves.

## Transplant Infections (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy | Alternate IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|---|
| ***Candidemia*** *Post-**BMT** (leukopenic pre-engraftment)* ***> 7 days*** | C. albicans<br>Non-albicans Candida | Micafungin 100 mg (IV) q24h Ambisome (L-Amb) 3–5 mg/kg (IV) q24h*<br>**or**<br>Caspofungin 70 mg (IV) × 1 dose, then 50 mg (IV) q24h*<br>**or**<br>Voriconazole (see "usual dose," p. 714)¶<br>**or**<br>Anidulafungin 200 mg (IV) × 1 dose, then 100 mg (IV) q24h | Itraconazole 200 mg (IV) q12h × 2 days, then 200 mg (IV) q24h*¶<br>**or**<br>Amphotericin B deoxycholate 0.6–1.5 mg/kg (IV) q24h until 1–2 gm given (significant toxicity likely—alternate therapy preferred) | Itraconazole 200 mg (PO) q12h*¶<br>**or**<br>Voriconazole (see "usual dose," p. 714)*¶<br>**or**<br>Fluconazole 800 mg (PO) × 1, then 400 mg (PO) q24h*‡ |
| ***Bacteremia*** *Post-**SOT*** (Treat initially for MSSA; if later identified as MRSA, treat accordingly) | S. aureus (MSSA)<br>Enterobacteriaceae | Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks | Quinolone† (IV) q24h × 2 weeks<br>**or**<br>Cefepime 2 gm (IV) q12h × 2 weeks | Quinolone† (PO) q24h × 2 weeks<br>**or**<br>Cephalexin 500 mg (PO) q6h × 2 weeks |
| | S. aureus (CO-MRSA/HA-MRSA) | Linezolid 600 mg (IV) q12h × 2 weeks<br>**or**<br>Daptomycin 6 mg/kg (IV) q24h × 2 weeks<br>**or**<br>Vancomycin 1 gm (IV) q12h × 2 weeks<br>**or**<br>Quinupristin/dalfopristin 7.5 mg/kg (IV) q8h × 2 weeks | | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |

*BMT/SOT = bone marrow/solid organ transplant, CO/HA-MRSA = community-onset/hospital-acquired methicillin-resistant S. aureus (see p. 14), MSSA = methicillin-sensitive S. aureus.*

† Levofloxacin 750 mg or Moxifloxacin 400 mg.

* Treat until neutropenia resolves.

‡ Loading dose is not needed PO if given IV with the same drug.

¶ Significant drug interactions are possible with usual immunosuppressive agents (e.g., sirolinus, cyclosporine, tacrolimus).
Review all concomitant medications for potential interactions. *Voriconazole contraindicated in patients with sirolinus.*

## Transplant Infections (cont'd)

| | | Viremia |
|---|---|---|
| CMV | Ganciclovir 5 mg/kg (IV) q12h until clinical/virologic response (not < 2 weeks)<br>**or**<br>Valganciclovir 900 mg (PO) q12h until clinical/virologic response (not < 2 weeks) | Follow therapy with 1-3 months of CMV prophylaxis (see p. 368) or frequent clinical/virologic followup. Risk of CMV disease greatest 3-6 months post-organ transplant in D+/R- patients during the period of maximum immuno-suppression. Coinfection with HHV-6/7 may increase risk of CMV disease. Risk also high where ALG is used for induction therapy to treat organ rejection. Also, CMV disease risk higher in lung, pancreas and intestine transplants (kidney, liver have lower risk).<br>Lowest risk of CMV disease in D-/R- transplants (should be given leukodepleted blood products and CMV negative blood). Consider IVIG† in patients with CMV pneumonia or consider CMVIG†† in patients with CMV pneumonia or severe CMV infection. |
| HHV-6 | Ganciclovir: 5 mg/kg (IV) q12h until viremia/infection clears.<br>**or**<br>Foscarnet 90 mg/kg (IV) q12h until viremia/infection clears.<br>**or**<br>Cidofovir 5 mg/kg (IV) q week × 2, then q other week* until viremia/infection clears. | *Reduction of immunosuppression remains the mainstay of treatment.*<br>HHV-6-A may be gangcyclovir resistant. HHV-6-B variants susceptible to Ganciclovir and Foscarnet<br><br>Treatment recommended for HHV-6 CNS disease with Ganciclovir, Foscarnet or a combination of both. |
| BK virus | Cidofovir 0.25 –1 mg/kg (IV) q2 weeks*<br>**or** | *Reduction of immunosuppression remains the mainstay of treatment*. Treatment indicated for BKV viremia/BKV nephropathy. *No treatment necessary for asymptomatic BKV infection*. BV viremia predicts presence of BK nephropathy which precedes viruria. "Decoy cells" in urine indicate BK viruria. BK viruria is common and preceeds viremia and invasive infection. ALG: antilymphoayte globulin (thymoglobulin). |

* IVIG: 500 mg/kg (IV) q48h.

†† CMVIG:

**Renal Transplants:** 150 mg/kg (IV) within 72 hours post-transplant, then 100 mg/kg (IV) at weeks 2, 4, 6, 8, then 50 mg/kg (IV) at weeks 12 and 16.

**Non-Renal Transplants:** 150 mg/kg (IV) given within 72 hours post-transplant, then 150 mg/kg (IV) at weeks 2, 4, 6, 8, then 100 mg/kg (IV) at weeks 12 and 16 after transplant.

## **Transplant Infections** (cont'd)

| | | |
|---|---|---|
| **Viremia (cont'd)** | | |
| | Leflunomide (given as mycophenolate replacement)<br>**Loading Dose:** 100 mg (PO) q24h × 5 days, then<br>**Maintenance Dose:** 40 mg (PO) q24h until viremia/ infection clears. | Measure leflunomide trough levels to ensure therapeutic concentrations (50–100 mcg/ml). |
| EBV/PTLD | Rituximab<br>**or**<br>Chemotherapy/ surgery | *Reduction or discontinuation of immunosuppression remains the mainstay of treatment of PTLD* (spontaneous regression in ¼ – ½ of cases). |
| RSV | Ribavirin 20 mg/ mL (aerosol) for 12–18 hours q24h × 3–7 days. | *Reduction of immunosuppression remains the mainstay of treatment.* Palivizumab may prevent progression from upper to lower RTI. IVIG may be added in severe cases. |
| Adenovirus | Ribavirin<br>**Loading Dose:** 30 mg/kg (IV), then<br>**Maintenance Dose:** 16 mg/kg (IV) q6h × 4 days, then 8 mg/kg (IV) q8h until viremia/ infection clears.<br>**or**<br>Cidofovir 5 mg/kg (IV) q 1–2 weeks (with saline hydration and probenecid) until viremia/ infection clears.[§] | *Reduction of immunosuppression remains the mainstay of treatment.*<br>Oral ribavirin may be effective, but outcomes are variable and may be adenovirus-serotype specific. |

§ Probenecid 2 gm (PO) 3 hours prior to cidofovir, 1 gm at 2 hours and 8 hours after completion of infusion. Patient should receive 1 liter normal saline (IV) prior to each infusion of cidofovir; a second liter may be administered over 1-3 hours at the start of cidofovir infusion or immediately following infusion.

* With hydration/probenecid (see Cidofovir Drug Summary).

## **Transplant Infections** (cont'd)

| | | | | |
|---|---|---|---|---|
| **CNS INFECTIONS** | | | | |
| Encephalitis/ meningitis | CMV<br>HHV-6 | Ganciclovir 5 mg/kg (IV) q12h × 2–4 weeks or until resolution of symptoms and viremia<br>IVIG or CMVIG may be beneficial in severe cases<br>Valganciclovir 900 mg (PO) q24h × 3 months. After successful treatment, a course of 2° prophylaxis is recommended | | |
| | CMV (ganciclovir-resistant CMV: MIC ≥ 3 mcg/mL) or UL 54 or UL 97 mutations | Cidofovir 5 mg/kg (IV) of 1–2 weeks with saline plus probenecid (see p. 163)<br>**or**<br>Foscarnet 60 mg/kg (IV) q8h × 2 weeks<br>**or**<br>Foscarnet plus Ganciclovir (see above)<br>**or**<br>Cidofovir (see above) may be used in severe cases | | |
| | Listeria, HSV, C. neoformans, M. tuberculosis treated the same as in normal/other compromised hosts (see pp. 25–26) | | | |
| Brain abscess/ mass lesions | Aspergillus | Voriconazole (see "usual dose," p. 714) until cured¶ | Ambisome (L-Amb) 5 mg/kg (IV) q24h until cured<br>**or**<br>Amphotericin B 1.5 mg/kg (IV) q24h until cured | Voriconazole (see "usual dose," p. 714) until cured¶ |
| | Nocardia | TMP–SMX 5 mg/kg (IV) q6h<br>**or**<br>Minocycline 200 mg (IV) q12h until clinical improvement, then (PO) therapy for at least 9–12 months or until cured | Linezolid 600 mg (IV) q12h until clinical improvement, then (PO) therapy for at least 9–12 months or until cured<br>**or**<br>Meropenem 2 gm (IV) q8h for at least 9–12 months or until cured | TMP–SMX 2 DS (PO) q8h<br>**or**<br>Minocycline 200 mg (PO) q12h<br>**or**<br>Linezolid 600 mg (PO) q12h for at least 9–12 months or until cured |
| | T. gondii | Preferred Therapy<br>Sulfadiazine 1–1.5 gm (PO) q6h + Pyrimethamine 200 mg (PO) × 1 dose then 50 mg (PO) q6h + folinic acid 10 mg (PO) q24h × 6–8 weeks until CT/MRI clinical response. | | |

¶ Significant drug interactions are possible with usual immunosuppressive agents (e.g., sirolimus, cyclosporine tacrolimus). Review all concomitant medications for potential interactions. *Voriconazole contraindicated in patients on sirolimus.*

## Transplant Infections (cont'd)

| | | |
|---|---|---|
| **CNS INFECTIONS (cont'd)** | | |
| | | Follow with sulfadiazine 1 gm (PO) q12h + Pyrimethamine 50 mg (PO) q24h + folinic acid 10 mg (PO) q24h until cured<br>Alternate Therapy<br>Clindamycin 600 mg (IV or PO) q6h + Pyrimethamine 200 mg (PO) × 1 dose then 50 mg (PO) q6h + folinic acid 10 mg (PO) q24h × 6–8 weeks until CT/MRI clinical response. Follow with Sulfadiazine 1 gm (PO) q12h + Pyrimethamine 50 mg (PO) q24h + folinic acid 10 mg (PO) q24h until cured |
| | C. neoformans | Treat the same as in chronic meningitis (see p. 21) |
| **PNEUMONIAS** | | |
| Focal/ segmental/ nodular infiltrates<br>*Acute* | Legionella sp. | Treat the same as in normal hosts (see p. 56–57) |
| | L. micdadei | Treat the same as in normal hosts (see p. 56–57)<br>Alternate Therapy<br>TMP-SMX (see p. 55) |
| *Subacute* | Aspergillus | Preferred Therapy<br>Voriconazole (see "usual dose," p. 714) until cured*¶<br>**or**<br>Isavuconazole 200 mg (IV) q8h × 48 hours, then 200 mg (IV/PO) q24h until cured<br>**or**<br>Lipid amphotericin (p. 525) (IV) q24h until cured<br>Alternate Therapy<br>Itraconazole 200 mg (IV) q12h × 2 days, then 200 mg (IV) q24h × 1–2 weeks, then 200 mg (PO) solution q12h until cured¶ |
| | M. tuberculosis<br>C. neoformans<br>Nocardia | For TB (see p. 53). For C. neoformans (see p. 269).<br>For Nocardia (see p. 268). |
| Diffuse infiltrates | S. stercoralis (hyperinfection syndrome) | Preferred Therapy<br>Ivermectin 200 mcg/kg (PO) q24h until cured<br>Alternate Therapy<br>Thiabendazole 25–50 mg/kg (PO) q12h (max. 3 gm/day) until cured |

Duration of therapy represents total time PO, IV, or IV + PO. Most patients on IV therapy able to take PO medications should be switched to PO therapy after clinical improvement.

* If < 40 kg, use 100 mg (PO) maintenance dose.

¶ Significant drug interactions are possible with usual immunosuppressive agents (e.g., sirolimus, cyclosporine, tacrolimus). Review all concomitant medications for potential interactions. *Voriconazole contraindicated in patients on sirolimus.*

## Transplant Infections (cont'd)

| | | |
|---|---|---|
| **PNEUMONIAS (cont'd)** | | |
| | PCP/RSV | Treat the same as in other compromised hosts (see p. 325) |
| | CMV, HHV-6 | Treat the same as CMV (see p. 55), HHV-6 (see p. 164) |
| **HEPATITIS** | | |
| Viral hepatitis | CMV | Treat the same as for CMV pneumonia (see p. 55) |
| | HBV, HCV | Treat the same as in normal hosts (see pp. 97–98) |

### Bacteremia/Candidemia (Bacteremia)

**Clinical Presentation:** Fever and shaking chills ± localizing signs. If localizing signs are present, the organ involved indicates the origin of the bacteremia (e.g., urinary tract findings suggest urosepsis).
**Diagnostic Considerations:** Diagnosis is clinical and is confirmed by positive blood cultures.
**Pitfalls:** 3/4 or 4/4 positive blood cultures indicates bacteremia. Even 1/4 positive blood cultures of an unusual pathogen may be clinically significant in BMT/SOT. The significance of 1/4 blood cultures with coagulase-negative staphylococci is less clear. S. epidermidis bacteremia is usually IV-line related, but in some compromised hosts, it may be pathogenic without an IV line focus.
**Therapeutic Considerations:** In SOT, coverage should be directed against S. aureus and Enterobacteriaceae. Anti-P. aeruginosa coverage is usually not needed since these patients are not neutropenic. If the source of infection is a central IV line, the line should be removed. In pre-engraftment BMT, coverage should be directed against P. aeruginosa until leukopenia resolves. Continued fever after 1 week of appropriate antibiotic therapy suggests the presence of candidemia, or another invasive fungal infection.
**Prognosis:** Good with early antibiotic therapy and, if appropriate, IV line removal.

### Bacteremia/Candidemia (Candidemia)

**Clinical Presentation:** Fever and shaking chills ± localizing signs. If localizing signs are present, the organ involved indicates the origin of the fungemia (e.g., reddened central IV line site suggests IV line-related fungemia).
**Diagnostic Considerations:** Candida and Fusarium are the most common fungi associated with fungemia in BMT/SOT.
**Pitfalls:** Do not assume that all Candida are C. albicans. Non-albicans Candida are more common in SOT patients. Empiric therapy should be directed against non-albicans Candida pending speciation, which will also cover C. albicans (including fluconazole-resistant strains). Because mortality/morbidity associated with candidemia exceeds that of bacteremia, empiric therapy should be started as soon as candidemia is suspected. Aspergillus, common after BMT/SOT, rarely grows in blood cultures.
**Prognosis:** Related to underlying immune status and promptness of empiric antifungal therapy, and if appropriate, CVC removal.

### CNS Infections (Encephalitis/Meningitis)

**Clinical Presentation:** Typical encephalitis/meningitis presentation (fever, headache, ± stiff neck, change in mental status).

**Diagnostic Considerations:** CSF usually reveals a lymphocytic predominance with a normal or normal CSF lactic acid and low glucose. The diagnosis of HSV, CMV, HHV-6 encephalitis can be made by CSF PCR.
**Pitfalls:** Patients with Listeria encephalitis often have a negative CSF Gram stain, but Listeria nearly always grows on CSF culture. HSV and listeria encephalitis typically have RBCs in the CSF. Head CT/MRI rules out CNS mass lesions. Nuchal rigidity may be absent in meningitis.
**Therapeutic Considerations:** CMV encephalitis is rare but treatable, resulting in clinical/radiological improvement. However, neurological deficits usually remain. CMV retinitis, common in HIV (p. 327), is unusual in BMT/SOT.
**Prognosis:** Related to underlying immune status and promptness of therapy.

## CNS Infections (Brain Abscess/Mass Lesions)

**Clinical Presentation:** BMT/SOT patients with brain abscesses/mass lesions present with seizures/cranial nerve abnormalities. Mental status is clear, in contrast to patients with encephalitis, and nuchal rigidity is absent, in contrast to most patients with meningitis.
**Diagnostic Considerations:** Head CT/MRI is the preferred diagnostic modality, and brain biopsy is the definitive diagnostic method. CSF analysis is not usually helpful in mass lesions, with the exception of infection due to M. tuberculosis or C. neoformans. With C. neoformans, the CSF cryptococcal antigen test is positive, and the CSF India ink preparation may be positive. With M. tuberculosis, acid fast smear of the CSF is sometimes positive, but culture has a higher yield and PCR is the preferred diagnostic modality.
**Pitfalls:** Patients with brain abscesses/mass lesions should have a head CT/MRI before lumbar puncture. To avoid herniation during lumbar puncture when a mass lesion is present, lumbar puncture should be performed by an experienced operator, and a minimal amount of CSF should be withdrawn.
**Therapeutic Considerations:** M. tuberculosis and C. neoformans are readily treatable. Be sure to use antimicrobial therapy that penetrates into CSF/brain. If TMP, TMP–SMX, or minocycline cannot be used for CNS Nocardia, linezolid or meropenem (meningeal doses) may be useful.
**Prognosis:** Related to underlying immune status and promptness of therapy.

## Pneumonias (Focal, Segmental, or Nodular Pulmonary Infiltrates)

**Clinical Presentation:** Acute or subacute community-acquired pneumonia (CAP) with respiratory symptoms and fever.
**Diagnostic Considerations:** BMT/SOT patients with focal/segmental infiltrates are most commonly infected with the usual CAP pathogens affecting normal hosts (e.g., S. pneumoniae, H. influenzae, Legionella). The clinical presentation of CAP in organ transplants is indistinguishable from that in normal hosts. However, BMT/SOT patients presenting subacutely with focal/segmental infiltrates are usually infected with pulmonary pathogens with a slower clinical onset (e.g., Nocardia, Aspergillus). L. micdadei common in BMT/SOT, and may cavitate. Empiric therapy will not cover all possible pathogens; tissue biopsy is necessary for definitive diagnosis and specific therapy. Preferred diagnostic modalities include transbronchial lung biopsy, percutaneous thin needle biopsy, or open lung biopsy, not BAL which may be negative in tissue invasive infections, e.g., Aspergillus.
**Pitfalls:** Patients presenting with subacute onset of CAP have a different pathogen distribution than those presenting with acute CAP. PCP/CMV does not present with focal/segmental infiltrates. Unlike other Legionella sp., L. micdadei partially acid fast, and susceptible to TMP-SMX (as well as doxycycline and quinolones).
**Therapeutic Considerations:** BMT/SOT patients with acute onset of CAP are treated with the same antibiotics used to treat CAP in normal hosts. Empiric coverage is directed against both typical and atypical

bacterial pathogens. If no improvement in clinical status after 72 hours, proceed to transbronchial biopsy or lung biopsy to identify nonbacterial pathogens (e.g., Nocardia, Aspergillus). Nocardia reinfection may require 6–12 months of therapy.

**Prognosis:** Best with acute focal/segmental infiltrates. Not as good with subacute or chronic focal/segmental infiltrates.

## Pneumonias (Diffuse Pulmonary Infiltrates)

**Clinical Presentation:** Insidious onset of interstitial pneumonia usually accompanied by low-grade fevers. Focal/segmental infiltrates are absent.

**Diagnostic Considerations:** Bilateral diffuse infiltrates, which can be minimal or extensive, fall into two clinical categories: those with and without hypoxemia/↑ A-a gradient. Diffuse pulmonary infiltrates without hypoxemia suggest a noninfectious etiology (e.g., CHF, pulmonary drug reaction, pulmonary hemorrhage). The differential diagnosis of diffuse pulmonary infiltrates with hypoxemia includes PCP, CMV, HSV, RSV, HHV-6, VZV. Quantitative PCR testing of BAL fluid for CMV, VZV, RSV, HHV-6 may be diagnostically helpful. For interstitial infiltrates with hypoxemia, the chest x-ray may be only minimally abnormal, but chest CT scans are more revealing. CMV/PCP may require tissue biopsy for definitive diagnosis. A very highly elevated LDH suggests PCP. PCP = β 1,3 D-glucan +, aspergillus galactomannan –. Transbronchial biopsy is preferable, but BAL may be used. The incidence of CMV pneumonia is highest in lung transplants and BMTs.

**Pitfalls:** Because infections in BMT/SOT are sequential, many patients with PCP pneumonia may have underlying CMV or HHV-6. In BMT, CMV found alone on lung biopsy suggests it is the primary pathogen. Serological tests are helpful for CMV (↑ CMV IgM); ↑ CMV viral loads reflective of peripheral WBC reactivation, not pneumonia. CMV pneumonia diagnosed by demonstrations CMV CPEs (intracellular inclusions) on lung BAL/biopsy. Candida pneumonia does not exist as a separate entity but only rarely as part of disseminated/invasive candidiasis.

**Therapeutic Considerations:** Among the subacute diffuse pneumonias, PCP is readily treatable. Initiate treatment for CMV pneumonia with ganciclovir IV; after clinical improvement, complete therapy with valganciclovir (PO) until cured. If after treatment, there is an ↑ in CMV antigen levels or quantitative PCR, treat pre-emptively to prevent CMV pneumonia with valganciclovir 900 mg (PO) q24h until CMV antigen levels return to previous levels or quantitative PCR becomes undetectable.

**Prognosis:** Related to underlying immune status, promptness of therapy, and general health of host.

## Hepatitis (Viral)

**Clinical Presentation:** Fever with ↑ SGOT/SGPT ± RUQ pain.

**Diagnostic Considerations:** Because CMV is of such critical importance in BMT/SOT, CMV testing should always be done in organ transplants with ↑ SGOT/SGPT. Liver biopsy with immunohisto chemical staining is diagnostic; quantitative PCR may be helpful. Prior to SOT, HIV, HBV, HCV testing should be performed on donor and recipient. Other viruses causing acute viral hepatitis post-transplant include EBV, HHV-6, VZV, adenovirus, and influenza. Viral hepatitis is usually accompanied by some degree of leukopenia. A few atypical lymphocytes may be present, and serum transaminases may be mildly or markedly elevated. CMV viremia is the commonest manifestation of CMV infection in BMT/SOT patients. CMV has a predilection for infecting the organ transplanted, and CMV hepatitis is particularly common in liver transplants. Anicteric hepatitis is more common than icteric hepatitis.

**Pitfalls:** The diagnosis of active CMV hepatitis in organ transplant patients is critical because it is an immunomodulating virus, adding to the net immunosuppressive effect of immunosuppressive therapy. Do not rely on CMV IgM/IgG titers for diagnosis.

**Therapeutic Considerations:** CMV should be treated aggressively to minimize its potentiating immunoregulatory defects, which may predispose to non-viral opportunistic pathogens and ↑ risk of chronic rejection in SOT. CMV antigen levels or quantitative PCR increase before CMV infection. Therefore, when CMV antigen levels or quantitative PCR increase, begin early pre-emptive therapy with valganciclovir 900 mg (PO) q12h until CMV antigen levels or quantitative PCR return to previous levels. There is no treatment for EBV.

**Prognosis:** Treated early, CMV responds well to therapy. CMV is associated with chronic allograft rejection in SOT recipient so that prevention or early diagnosis/therapy are critical.

## Toxin-Mediated Infectious Diseases

## Toxin-Mediated Infectious Diseases

| Subset | Usual Pathogens | IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|
| Toxic shock syndrome (TSS)*<br><br>(Treat initially for MRSA; if later identified as MSSA, treat accordingly) | S. aureus (MRSA) | Preferred IV Therapy<br>Vancomycin 1 gm (IV) q12h × 2 weeks<br>**or**<br>Linezolid 600 mg (IV) q12h × 2 weeks<br>Alternate IV Therapy<br>Minocycline 100 mg (IV) q12h × 2 weeks<br>**or**<br>Daptomycin 6 mg/kg (IV) q24h × 2 weeks | Linezolid 600 mg (PO) q12h × 2 weeks<br>**or**<br>Minocycline 100 mg (PO) q12h × 2 weeks |
| | S. aureus (MSSA) | Preferred IV Therapy<br>Cefazolin 1 gm (IV) q8h × 2 weeks<br>Alternate IV Therapy<br>Nafcillin 2 gm (IV) q4h × 2 weeks<br>**or**<br>Clindamycin 600 mg (IV) q8h × 2 weeks | Cephalexin 500 mg (PO) q6h × 2 weeks<br>**or**<br>Clindamycin 300 mg (PO) q6h × 2 weeks |
| | Clostridium sordelli | Preferred IV Therapy<br>Penicillin G 10 mu (IV) q4h × 2 weeks<br>**or**<br>Clindamycin 600 mg (IV) q8h × 2 weeks<br>**or**<br>Piperacillin 4 gm (IV) q8h × 2 weeks<br>Alternate IV Therapy<br>Meropenem 1 gm (IV) q8h × 2 weeks<br>**or**<br>Ertapenem 1 gm (IV) q24h × 2 weeks | Not applicable |

*MRSA/MSSA = methicillin-resistant/sensitive S. aureus.* Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Treat only IV or IV-to-PO switch.

## Toxin-Mediated Infectious Diseases (cont'd)

| Subset | Usual Pathogens | IV Therapy | PO Therapy or IV-to-PO Switch |
|---|---|---|---|
| Botulism (food, infant, wound) | Clostridium botulinum | Preferred Therapy<br>2 vials of type-specific trivalent (types A,B,E) or polyvalent (types A,B,C,D,E) antitoxin (IV) | Alternate Therapy<br>Amoxicillin 1 gm (PO) q8h × 7 days (wound botulism only) |
| Tetanus | Clostridium tetani | Preferred Therapy Tetanus immune globulin (TIG)<br>3,000–6,000 units (IM) (50% into deltoid, 50% into wound site)<br>**plus either**<br>Penicillin G 4 mu (IV) q4h × 10 days<br>**or**<br>Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) × 7 days | Alternate Therapy<br>Tetanus antitoxin 1,500–3,000 units (IM/IV)<br>**plus**<br>Metronidazole 1 gm (IV) q12h × 10 days |
| Diphtheria (pharyngeal, nasal, wound, myocarditis) | Coryne-bacterium diphtheriae C. ulcerans | Diphtheria antitoxin (IV) over 1 hour (pharyngeal diphtheria = 40,000 units; nasopharyngeal diphtheria = 60,000 units; systemic diphtheria or diphtheria > 3 days duration = 100,000 units)<br>**plus either**<br>Penicillin G 1 mu (IV) q4h × 14 days<br>**or**<br>Erythromycin 500 mg (IV) q6h × 14 days | Diphtheria antitoxin (IV) over 1 hour (pharyngeal diphtheria = 40,000 units; nasopharyngeal diphtheria = 60,000 units; systemic diphtheria or diphtheria > 3 days duration = 100,000 units)<br>**plus**<br>Procaine penicillin 600,000 units (IM) q24h × 14 days |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

### Toxic Shock Syndrome (S. aureus)

**Clinical Presentation:** Scarlatiniform rash ± hypotension. Spectrum ranges from minimal infection to multiorgan system failure/shock. ↑ CPK common.

**Diagnostic Considerations:** Diagnosis by clinical presentation with mucous membrane, renal, liver, and skin involvement/culture of TSS-1 toxin-producing strain of S. aureus from mouth, nares, vagina, or wound.

**Pitfalls:** Toxic shock syndrome wound discharge is clear, not purulent.

**Therapeutic Considerations:** Remove source of toxin production if possible (e.g., remove tampon, drain collections). Clindamycin may be added for its anti-toxin effect.

**Prognosis:** Good in early/mild form. Poor in late/multisystem disease form.

## Toxic Shock Syndrome (C. sordelli)

**Clinical Presentation:** Resembles clostridial myonecrosis (gas gangrene) with soft tissue necrotizing infection are local edema. Hypotension with acute onset of nausea/vomiting and weakness characteristic. Associated with IVDA (black tar heroin), trauma, parturition, abortion, cadaver graft surgery. Hemoconcentration with leukocytosis typical; leukemoid reactions common with WBC counts > 50k/$mm^3$.

**Diagnostic Considerations:** Clinical diagnosis. Culture of C. sordelli from necrotic soft tissue.

**Pitfalls:** Gas gangrene like clinical presentation but with hemoconcentration not hemolytic anemia. Nausea/vomiting instead of diarrhea as with gas gangrene. Shock with no/low fever and ↑ WBC should suggest the diagnosis. Muscle involvement (clostridial myonecrosis) and bullae typical of gas gangrene not a feature of C. sordelli TSS.

**Therapeutic Considerations:** Early/adequate debridement critical. Anti-anerobic antibiotics and supportive measures important.

**Prognosis:** Like gas gangrene, prognosis related to early diagnosis and early/adequate surgical debridement.

## Botulism (Clostridium botulinum)

**Clinical Presentation:** Descending symmetrical paralysis beginning with cranial nerve involvement, induced by botulinum toxin. Onset begins with blurry vision, followed rapidly by ocular muscle paralysis, difficulty speaking, and inability to swallow. Respiratory paralysis may occur in severe cases. Mental status is unaffected. Usual incubation period is 10–12 hours. Incubation is shortest for Type E strain (hours), longest for Type A strain (up to 10 days), and is inversely proportional to the quantity of toxin consumed (food botulism). Wound botulism (Types A or B) may follow C. botulinum entry into IV drug abuser injection site, surgical or traumatic wounds. Infant (< 1 year) botulism (most commonly Type A or B) is acquired from C. botulinum containing honey. Patients with botulism are afebrile, and have profuse vomiting without diarrhea.

**Diagnostic Considerations:** Detection of botulinum toxin from stool, serum, or food (especially home canned foods with neutral or near neutral pH [~ 7] or smoked fish [Type E]) is diagnostic of food botulism. Wound botulism is diagnosed by culturing C. botulinum from the wound or by detecting botulinum toxin in the serum.

**Pitfalls:** Clinical diagnosis based on descending paralysis with cranial nerve involvement in an afebrile patient must be differentiated from Guillain-Barre (fever, ascending paralysis, sensory component) and polio (fever, pure ascending motor paralysis). Do not diagnose botulism in the absence of ocular/pharyngeal paralysis.

**Therapeutic Considerations:** Antitoxin neutralizes only unbound toxin, and does not reverse toxin-induced paralysis. Botulism is a toxin-mediated infection and antibiotic therapy (wound botulism) is adjunctive. Guanidine has been used with variable effect. Ventilator support is needed for respiratory paralysis. Bioterrorist botulism presents clinically and is treated the same as naturally-acquired botulism.

**Prognosis:** Good if treated early, before respiratory paralysis.

## Tetanus (Clostridium tetani)

**Clinical Presentation:** Begins with jaw stiffness/difficulty chewing induced by C. tetani toxin (tetanospasmin). Trismus rapidly follows with masseter muscle spasm, followed by spasm of the abdominal/back muscles. Rigidity and convulsions may occur. Patients are afebrile unless there is hypothalamic involvement (central fever), in which case fevers may exceed 106°F. Usual incubation period is 3–21 days.

**Diagnostic Considerations:** Diagnosis suggested by muscle spasms/rigidity in a patient with trismus.

**Pitfalls:** In rabies, muscle spasms are localized and usually involve the face/neck, rather than primary involvement of the extremities, as in tetanus.

**Therapeutic Considerations:** Tetanus is self-limited with intensive supportive care. Sedation is important, and avoidance of all stimuli is mandatory to reduce the risk of convulsions. Avoid unnecessary handling/movement of patient. Antitoxin is effective only in neutralizing unbound toxin. Tracheostomy/respiratory support can be lifesaving in severe cases.

**Prognosis:** Good if not complicated by spinal fractures, aspiration pneumonia, or CNS involvement (hyperpyrexia, hyper/hypotension).

## Diphtheria (Corynebacterium diphtheriae/Corynebacterium ulcerans)

**Clinical Presentation:** Within 1 week following insidious onset of sore throat without fever, pharyngeal patches coalesce to form a gray diphtheric membrane (surrounded by a red border), which is adherent/bleeds easily when removed. Membrane begins unilaterally; may extend to the soft palate, uvula and contralateral posterior pharynx; are accompanied by prominent bilateral anterior adenopathy; become necrotic (green/black); and have a foul odor (fetor oris). Submandibular edema ("bull neck") and hoarseness (laryngeal stridor) precede respiratory obstruction/death. Cutaneous diphtheria may follow C. diphtheriae contaminated wounds (traumatic, surgical) or insect/human bites, and is characterized by a leathery eschar (cutaneous membrane) covering a deep punched out ulcer. Serosanguineous discharge is typical of nasal diphtheria (membrane in nares). Diphtheric myocarditis may complicate any form of diphtheria (most commonly follows pharyngeal form), and usually occurs in the second week, but may occur up to 8 weeks after infection begins. Diphtheric polyneuritis is a common complication. Cardiac/neurologic complications are due to elaboration of a potent toxin.

**Diagnostic Considerations:** Diagnosis is suggested by unilateral membranous pharyngitis/palatal paralysis, absence of fever, and relative tachycardia. Diagnosis is confirmed by culture of C. diphtheriae from nares, membrane, or wound.

**Pitfalls:** Differentiated from Arcanobacterium (Corynebacterium) haemolyticum (which also forms a pharyngeal membrane) by culture and absence of scarlatiniform rash with C. diphtheriae. C.ulcerans has the same clinical features as C. diphtheriae.

**Therapeutic Considerations:** Antibiotic therapy treats the infection and stops additional toxin production. Antitoxin is effective against unbound toxin, but will not reverse toxin-mediated myocarditis/neuropathy. Serum sickness is common 2 weeks after antitoxin. Respiratory/cardiac support may be lifesaving. C.ulcerans is treated the same as C. diptheriae.

**Prognosis:** Poor with airway obstruction or myocarditis. Myocarditis may occur despite early treatment.

# Bioterrorist Agents

## Bioterrorist Agents in Adults¶

| Subset | Pathogen | IV/IM Therapy | IV-to-PO Switch |
|---|---|---|---|
| Anthrax *Inhalation, oropharyngeal, gastrointestinal* | Bacillus anthracis | Quinolone* (IV) × 2 weeks **or** Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11 days‡ **or** Penicillin G 4 MU (IV) q4h ± Clindamycin 600 mg (IV) q8h × 2 weeks | Quinolone* (PO) × 2 weeks **or** Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11 days (loading dose not needed PO if given IV). Duration of IV + PO therapy = 60 days |
| *Cutaneous* | | Treat severe cases with same (PO) antibiotics as for inhalation anthrax | |
| *Meningitis* | | If penicillin susceptible, treat with Penicillin G 4 MU (IV) q24h **or** Meropenem 2 gm (IV) q8h for at least 2 weeks or markedly improved and complete 60–100 days of therapy as described in the inhalation, oropharyngeal or gastrointestinal forms, in addition to quinolones or doxycycline. Consider adjunctive steroid therapy. Penicillin should NOT be used as a single agent. Not susceptible to cephalosporins or TMP–SMX. | |
| Tularemia pneumonia | Francisella tularensis | Streptomycin 1 gm (IM) q12h × 10 days **or** Gentamicin 5 mg/kg (IM or IV) q24h × 10 days **or** Doxycycline 200 mg (IV) q12h × 3 days, then 100 mg (IV) q12h × 11–18 days‡ **or** Chloramphenicol 500 mg (IV) q6h × 14 days **or** Quinolone* (IV) × 10 days<br>If meningitis: add Chloramphenicol | Doxycycline 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 11–18 days<br>**or**<br>Quinolone* (PO) × 10 days<br>If meningitis: add Chloramphenicol |

Duration of therapy represents total treatment time.

‡ Patients who remain critically ill after Doxycycline 200 mg (IV) q12h × 3 days should continue receiving 200 mg (IV) q12h for the full course of therapy. For patients who have improved after 3 days, the dose may be decreased to 100 mg (IV or PO) q12h to complete the course of therapy. Total duration of IV + PO therapy = 60 days.

* Ciprofloxacin 400 mg (IV) q12h or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h.

¶ Additional information can be obtained at www.bt.cdc.gov. For post-exposure prophylaxis, see p. 358.

## Bioterrorist Agents in Adults¶ (cont'd)

| Subset | Pathogen | IV/IM Therapy | IV-to-PO Switch |
|---|---|---|---|
| Pneumonic plague | Yersinia pestis | Treat the same as tularemic pneumonia (see p. 176) | |
| Botulism | Clostridium botulinum | Contrary to the package insert, administer 50 mg/kg up to 1 vial of type-specific trivalent (types A,B,E) or polyvalent (types A,B,C,D,E) antitoxin (IV) after skin testing. Antitoxin administration is not repeated (circulating antitoxin's half-life = 5–8 days). Treatment with 1 vial resulted in adverse effects in < 1%; treatment with 2–4 times present dose resulted in hypersensitivity reactions in 9%. Antibiotics do not neutralize toxin | |
| Smallpox | Variola virus | Smallpox vaccine ≤ 4 days after exposure. Cidofovir 5 mg/kg (IV) × 1 dose may be protective for up to 6 days post-exposure. | |
| Ebola | Ebola virus | No specific therapy. Supportive therapy can be life saving | |

Duration of therapy represents total treatment time.

* Ciprofloxacin 400 mg (IV) q12h or 500 mg (PO) q12h or Levofloxacin 500 mg (IV or PO) q24h.

¶ Additional information can be obtained at www.bt.cdc.gov. For post-exposure prophylaxis, see p. 358.

‡ Patients who remain critically ill after Doxycycline 200 mg (IV) q12h × 3 days should continue receiving 200 mg (IV) q12h for the full course of therapy. For patients who have improved after 3 days, the dose may be decreased to 100 mg (IV or PO) q12h to complete the course of therapy. Total duration of IV + PO therapy = 60 days.

### Anthrax (B. anthracis)

**Clinical Presentation:** Bioterrorist anthrax usually presents as cutaneous or inhalational anthrax. Cutaneous anthrax has the same clinical presentation as naturally-acquired anthrax: Lesions begin as painless, sometimes mildly pruritic papules, usually on the upper extremities, neck, or face, and evolve into a vesicular lesion which may be surrounded by satellite lesions. A "gelatinous halo" surrounds the vesicle as it evolves into an ulcer, and a black eschar eventually develops over the ulcer. Inhalational anthrax is a biphasic illness. Initially, there is a viral illness-like prodrome with fever, chills, and myalgias with chest discomfort 3–5 days after inhaling anthrax spores. Bacteremia is common. Patients often improve somewhat over the next 1–2 days, only to rapidly deteriorate and become critically ill with high fevers, dyspnea, cyanosis, crushing substernal chest pain, and shock. Oropharyngeal anthrax presents with fever, soft tissue edema, painful cervical adenopathy. Lesions in oropharynx ulcerate in ~ 2 weeks. GI anthrax presents with fever, malaise ± syncope, followed in 24 hours by mild nausea/vomiting, severe abdominal pain, and then ascites, ↑ abdominal pain, flushed face, and shock.

**Diagnostic Considerations:** Cutaneous anthrax is a clinical diagnosis suggested by the lack of pain relative to the size of the lesion. A presumptive microbiologic diagnosis is made by finding gram-positive bacilli in the fluid from the gelatinous halo surrounding the ulcer or from under

the eschar. Blood cultures may reveal B. anthracis. Definitive diagnosis depends on identifying B. anthracis from culture of the skin lesions or blood cultures. Inhalation anthrax is suspected in patients with fevers, chest pain, and mediastinal widening accompanied by bilateral pleural effusions on chest x-ray. If chest x-ray findings are equivocal, then a chest CT/MRI is recommended to demonstrate mediastinal lymph node enlargement. Inhalational anthrax presents as a hemorrhagic mediastinitis, not community-acquired pneumonia. The diagnosis is clinical but supported by Gram stain of hemorrhagic pleural fluid demonstrating gram-positive bacilli. Patients with inhalational anthrax often have positive blood cultures and may have associated anthrax meningitis. If meningitis is present, the CSF is hemorrhagic and CSF Gram stain shows gram-positive bacilli, which, when cultured, is B. anthracis.

**Pitfalls:** Cutaneous anthrax is most often initially confused with ringworm or a brown recluse spider bite. Subacute/chronic lesions may initially resemble ringworm, but the skin lesion in ringworm has an annular configuration, is painless, and is accompanied by prominent pruritus, particularly at the edges of the lesion. Patients with ringworm have no fever or systemic symptoms. Brown recluse spider bites produce extremely painful lesions with irregular edges, which eventually develop a necrotic center followed by eschar formation. The lesions of the brown recluse spider bite are irregular, not accompanied by fever, and intensely painful. In contrast, cutaneous anthrax lesions are painless, round, and are not primarily pruritic in nature. Be alert to the possibility of smallpox following outbreaks of other bioterrorist agents such as anthrax, as the genome of smallpox is easily modified and can be incorporated into bacteria.

**Therapeutic Considerations:** B. anthracis is highly susceptible to nearly all antibiotics; in the U.S. bioterrorist experience, no strains were resistant to antibiotics. Traditionally, penicillin has been used to treat natural anthrax, but because of concern for resistant bioterrorist strains, doxycycline or quinolones are preferred. Because meningitis is frequently associated with inhalational anthrax, penicillin in (IV) meningeal doses may be added as a second or third antibiotic to quinolones or doxycycline. For meningeal anthrax use penicillin G or meropenem in meningeal doses. Clindamycin is active against B. anthracis and has been used in combination therapy because of its potential anti-exotoxin activity. Some patients seemed to respond somewhat better when clindamycin 600 mg (IV) q8h or 300 mg (PO) q8h plus rifampin 300 mg (PO) q12h is added to either a quinolone or doxycycline. Corticosteroids should be considered for severe mediastinal edema or meningitis. Depending upon antimicrobial susceptibility testing, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin or clarithromycin may be added if the need arises. Prolonged therapy of 100 days with or without anthrax vaccine has been recommended by some authors. Three doses of anthrax vaccine (BioThraxT, formerly AVA - anthrax vaccine absorbed) have been recommended by the ACIP and the John Hopkins Working Group on Civilian Bio-Defense with antimicrobials for prophylaxis after aerosolized exposure, but as it is not licensed, it must be administered under an IND application. Some B. anthracis strains produce cephalosporinase and inducible beta-lactamase that make penicillins drugs less suitable for initial therapy. In general, the organism is resistant to trimethoprim-sulfamethoxazole.

**Prognosis:** Prognosis of cutaneous anthrax is uniformly good. With inhalational anthrax, prognosis is related to the inhaled dose of the organism, underlying host status, and rapidity of initiating antimicrobial therapy. Inhalational anthrax remains a highly lethal infectious disease, but with early intervention/supportive care, some patients survive. Patients with associated anthrax meningitis have a poor prognosis.

## Tularemic Pneumonia (F. tularensis)

**Clinical Presentation:** Fever, chills, myalgias, headache, dyspnea and a nonproductive cough may occur, but encephalopathy is absent. Chest x-ray resembles other causes of community-acquired pneumonia, but tularemic pneumonia is usually accompanied by hilar adenopathy and pleural effusion, which is serosanguineous or frankly bloody. Cavitation sometimes occurs. Relative bradycardia is not present and serum transaminases are not elevated.

**Diagnostic Considerations:** Tularemic pneumonia can resemble other atypical pneumonias, but in a patient presenting with community-acquired pneumonia, the presence of hilar adenopathy with pleural effusions should suggest the diagnosis. F. tularensis may be seen in the Gram stain of the sputum or bloody pleural effusion fluid as a small, bipolar staining, gram-negative bacillus. Diagnosis is confirmed serologically or by culture of the organism from respiratory fluid/blood.

**Pitfalls:** Gram-negative bacilli in the sputum may resemble Y. pestis but are not bipolar staining. Chest x-ray may resemble inhalational anthrax (hilar adenopathy/mediastinal widening). Both tularemic pneumonia and inhalational anthrax may be accompanied by bloody pleural effusions. In contrast to inhalational anthrax (which may be accompanied by anthrax meningitis), CNS involvement is not a feature of tularemic pneumonia.

**Therapeutic Considerations:** Streptomycin is the antibiotic traditionally used to treat tularemia. Gentamicin may be substituted for streptomycin if it is not available. Doxycycline, chloramphenicol, or a quinolone are also effective.

**Prognosis:** Depends on inoculum size and health of host. Mortality rates for severe untreated infection can be as high as 30%, although early treatment is associated with mortality rates < 1%.

## Pneumonic Plague (Y. pestis)

**Clinical Presentation:** Bioterrorist plague presents as pneumonic plague and has the potential for person-to-person spread. After an incubation period of 1–4 days, the patient presents with acute onset of fever, chills, headache, myalgias and dizziness, followed by pulmonary manifestations including cough, chest pain, dyspnea. Hemoptysis may occur, and increasing respiratory distress and circulatory collapse are common. Compared to community-acquired pneumonia, patients presenting with plague pneumonia are critically ill. Sputum is pink and frothy and contains abundant bipolar staining gram-negative bacilli. Chest x-ray is not diagnostic.

**Diagnostic Considerations:** Yersinia pestis may be demonstrated in sputum Gram stain (bipolar staining gram-negative bacilli) and may be recovered from blood cultures. Laboratory confirmation requires isolation of Y. pestis from body fluid or tissue culture. Consider the diagnosis in any critically ill patient with pneumonia and bipolar staining gram-negative bacilli in the sputum.

**Pitfalls:** Plague pneumonia can resemble tularemic pneumonia, but there are several distinguishing features. Unlike plague, tularemic pneumonia is usually associated with hilar enlargement and pleural effusion. Although gram-negative bacilli may be present in the sputum of patients with tularemia, the organisms are not bipolar staining.

**Therapeutic Considerations:** Streptomycin is the preferred drug for pneumonic plague. Doxycycline or a quinolone is also effective.

**Prognosis:** Depends on inoculum size, health of the host, and the rapidity of treatment. Left untreated, mortality rates exceed 50%. ARDS, DIC, and other manifestations of gram-negative sepsis are more common when treatment is delayed.

**Botulism (C. botulinum)** (see p. 171)

## Smallpox

**Clinical Presentation:** After an incubation period of 1–12 days, typical smallpox is heralded by high fever, headache, and gastrointestinal complaints (vomiting, colicky pain). No rash is present at this time. After 1–2 days, the fever decreases to near normal level, and macules begin to appear on the head, usually at the hairline. Macules progress to papules, then vesicles, then finally pustules. The rash begins on the face/head and rapidly spreads to the extremities with relative sparing of the trunk. The mucous membranes of the oropharynx and upper/lower airways are also affected early. Lesions initially are umbilicated, then later lose their umbilication. The fully formed smallpox pustule is located deep in the dermis. The appearance of the pustules is accompanied by recrudescence of fever. Hemorrhagic smallpox is a fulminant form of smallpox that begins with petechial lesions in a "swimming trunk" distribution and results in widespread hemorrhage into the skin and mucous membranes. Patients look toxemic and have high fevers with no other signs of smallpox; death from toxemia often occurs before the typical rash appears.

**Diagnostic Considerations:** Smallpox is most likely to be confused with chickenpox or drug eruptions. Patients with chickenpox are less toxemic and the lesion distribution is different from smallpox. Chickenpox lesions occur in crops for the first 72 hours, then stop. The lesions of chickenpox are superficial, not deep in the dermis like smallpox, and chickenpox vesicles are predominantly centripetal rather than centrifugal. The chickenpox vesicle has been described as a "dewdrop on a rose petal" because of its fragility and superficial location on the skin. If there is any doubt, a Tzanck test should be performed by unroofing the vesicle, scraping cells from the base of the vesicle, and staining the cells. A positive Tzanck test indicates chickenpox, not smallpox. Alternatively, a monoclonal VZV test can be performed on vesicle base cells. Drug eruptions are not accompanied by toxemia and are usually accompanied by relative bradycardia if fever is present.

**Pitfalls:** Smallpox is easily missed before the rash and is difficult to diagnose. Look for the combination of high fever/headache with gastrointestinal symptoms (e.g., abdominal pain) that precedes the rash. GI complaints may be confused with appendicitis. A petechial rash in a swimming trunk distribution does not occur with any other infectious disease and should immediately suggest smallpox. Recently human monkeypox has occurred in the Western Hemisphere after transmission via imported African rodent pets. After an incubation period of 7–19 days, patients develop fever, headache, and malaise. Skin lesions appear on head, trunk, and extremities (including palms/soles). Rash begins like smallpox as macules, then papules, and finally umbilicated vesicles. Some exudative pharyngitis/tonsillitis with cervical adenopathy may be present. Encephalitis is very rare. Laboratory results are nonspecific. Unlike smallpox, human monkeypox patients are not toxic, have pharyngitis/tonsillitis with cervical adenopathy, and have focal hemorrhage into some lesions (in hemorrhagic smallpox, hemorrhages are extensive/widespread). Patients immunized against smallpox are unlikely to acquire human monkeypox.

**Therapeutic Considerations:** Smallpox vaccination should be initiated as soon as the diagnosis is suspected. Smallpox vaccine may be given at full strength or in a 1:5 dilution, which is also protective. Cidofovir may prove useful but dose for smallpox is not established.

**Prognosis:** Variable in typical smallpox, with deep, permanent scarring, especially on the face. Hemorrhagic smallpox is highly lethal.

## Ebola/Lassa Fever

**Clinical Presentation:** After an incubation period of 3–9 days, abrupt onset of high fevers, severe headache/myalgias followed by diarrhea, extreme malaise. Hemorrhagic phenomenon–GI, renal, vaginal, conjunctival bleeding-occur at 5–7 days. Patients rapidly become critically ill. Fever is biphasic. Patients usually have leukopenia, thrombocytopenia, and hepatic/renal dysfunction. Conjunctival suffusion is also an early finding in half the cases. If a patient is not a traveler from an endemic area (e.g., Africa), suspect bioterrorist Ebola/Lassa fever. Lassa fever differs from Ebola in having prominent head/neck edema. CNS finding (oculogyric crisis, seizures, deafness) are characteristic of Lassa fever.

**Diagnostic Considerations:** Ebola is a hemorrhagic fever clinically indistinguishable from Yellow fever and other African hemorrhagic fevers (e.g., Lassa fever, Marburg virus disease). Presumptive diagnosis is clinical; definitive diagnosis is confirmed by specific virologic/serologic studies.

**Pitfalls:** Patients with Ebola may complain initially of a sore throat and dry cough, with or without chest pain. Diarrhea/abdominal pain is not uncommon. The rash is maculopapular before it becomes hemorrhagic. Failure to consider the diagnosis may occur early when sore throat/GI symptoms are prominent (i.e., before hemorrhagic manifestations appear).

**Therapeutic Considerations:** There is no effective therapy available for Ebola infection. Supportive therapy can be life saving.

**Prognosis:** Varies with severity of infection and health of the host.

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# Chapter 3
# Antibiotic Susceptibility Profiles and Initial Therapy of Isolates Pending Susceptibility Results

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If isolate is a pathogen (P), in the appropriate body site, pathogens should be treated. Pathogens isolated from body sites not causing infections *at the site cultured* should ordinarily not be treated, e.g., S. pneumoniae from urine or a wound. Non-pathogens (NP), colonizers (C), or skin contaminants (C*) ordinarily should not be "covered" or treated.

**Table 3.1. Antibiotic Susceptibility Profiles (Penicillins, Macrolides, Tetracyclines, and Others)**

| | Penicillins | | | | | | | Anti-Pseudomonal Penicillins | | | | Macrolides | | | | Tetra-Cyclines | | | Miscellaneous | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Penicillin G (IV) | Penicillin V (PO) | Ampicillin (IV/PO) | Ampicillin/Sulbactam (IV) | Amoxicillin (PO) | Amoxicillin/ Clavulanate (PO) | Nafcillin (IV) | Ticarcillin (IV) | Ticarcillin/ Clavulanate (IV) | Piperacillin (IV) | Piperacillin/ Tazobactam (IV) | Erythromycin (IV/PO) | Clarithromycin (PO) | Azithromycin (IV/PO) | Telithromycin (PO) | Tetracycline (IV/PO) | Doxycycline (IV/PO) | Minocycline (IV/PO) | Clindamycin (IV/PO) | Metronidazole (IV/PO) | Rifampin (PO) | TMP-SMX (IV/PO) | Chloramphenicol (IV/PO) |
| **Aerobic Gram Positive Cocci (Clusters)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Staphylococcus aureus* (MSSA) | 0 | 0 | 1 | 2 | 0 | 2 | 3 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 2 | 1 | 2 |
| *Staphylococcus aureus* (HA/CO-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2[†] | 1 | 2[†] | 0 | 2 | 3[†] | 0 |
| S. aureus (CA-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 2 | 1 | 2 | 0 | 0 | 2 | 0 |
| S. *epidermidis* (CoNS) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 2 | 2 | 0 |
| **Aerobic Gram Positive Cocci (Chains)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Enterococcus faecalis* (VSE) | 0 | 0 | 1 | 2 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| *Enterococcus faecium* (VRE)[††] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | 3 |
| Streptococci (Groups A, B, C, F, G) | 1 | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Streptococcus (bovis) galloyticus | 1 | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Viridans streptococci (S. mitior, milleri, mitis, mutans, oralis, sanguis, parasanguis, salivarius)* | 1 | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 |
| **Aerobic Gram Positive Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Streptococcus pneumoniae (PSSP)* | 1 | 1 | 3* | 2 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 3* | 3* | 3* | 2 | 3* | 1 | 2 | 1 | 0 | 3* | 3* | 3 |
| *Streptococcus pneumoniae (PRSP)* | 1 | 0 | 0* | 2 | 1 | 2 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 3 |
| *Streptococcus pneumoniae (MDRSP)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 3 | 3 | 0 | 3 | 0 | 3 |
| **Aerobic Gram Negative Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Neisseria gonorrhoeae* | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 2 | 0 | 2 | 3 | 0 | 2 | 0 | 3* | 2 | 2 | 0 | 0 | 2 | 0 | 3 |
| *Neisseria meningitidis* | 1 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 2 | 0 | 2 |
| **Aerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacillus anthracis* | 2 | 3 | 2 | 3 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 2 | 1 | 0 | 2 | 0 | 2 | 0 | 2 |
| *Corynebacterium diphtheriae* | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience. * = May be effective initially but as a "high resistance" antibiotic potential, resistance may develop during/after therapy. † = Preferably use another CA-MRSA antibiotic, e.g., minocycline. †† = Same for vancomycin resistant E. faecalis.

**Table 3.1. Antibiotic Susceptibility Profiles (Penicillins, Macrolides, Tetracyclines, and Others)** (cont'd)

| | Penicillins | | | | | | | Anti-Pseudomonal Penicillins | | | | Macrolides | | | | Tetra-Cyclines | | | Miscellaneous | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Penicillin G (IV) | Penicillin V (PO) | Ampicillin (IV/PO) | Ampicillin/Sulbactam (IV) | Amoxicillin (PO) | Amoxicillin/ Clavulanate (PO) | Nafcillin (IV) | Ticarcillin (IV) | Ticarcillin/ Clavulanate (IV) | Piperacillin (IV) | Piperacillin/ Tazobactam (IV) | Erythromycin (IV/PO) | Clarithromycin (PO) | Azithromycin (IV/PO) | Telithromycin (PO) | Tetracycline (IV/PO) | Doxycycline (IV/PO) | Minocycline (IV/PO) | Clindamycin (IV/PO) | Metronidazole (IV/PO) | Rifampin (PO)[§] | TMP-SMX (IV/PO) | Chloramphenicol (IV/PO) |
| *Corynebacterium jeikeium (JK)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| *Listeria monocytogenes* | 2 | 2 | 1 | 2 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 2 | 1 | 1 |
| *Nocardia* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 2 | 0 | 0 | 0 | 1 | 0 |
| **Aerobic Gram-Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Acinetobacter sp.* | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 3 | 3 | 0 |
| *Aeromonas hydrophila* | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 2 | 2 |
| *Bordetella sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 0 | 0 | 3 | 2 | 3 |
| *Brucella sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 3 | 0 | 0 | 3 | 3 | 3 |
| *Burkholderia (Pseudomonas) cepacia* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 3 | 3 |
| *Citrobacter sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| *Enterobacter sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Escherichia coli* | 0 | 0 | 3* | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 3 | 2 |
| *Francisella tularensis* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 | 3 | 3 |
| *Haemophilus sp.* | 0 | 0 | 3* | 2 | 2 | 2 | 0 | 3 | 2 | 3 | 2 | 0 | 3 | 3 | 2 | 3* | 1 | 3 | 0 | 0 | 3 | 3 | 2 |
| *Klebsiella sp.* | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| *Moraxella catarrhalis* | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 3 | 2 | 3 | 2 | 0 | 0 | 3 | 2 | 3 | 1 | 3 | 0 | 0 | 0 | 3* | 3 |
| *Morganella sp.* | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3* | 3 |
| *P. aeruginosa* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Proteus sp.* | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3* | 3 |
| *Providencia sp.* | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3* | 3 |
| *Salmonella sp.* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 3 | 0 | 3* | 2 | 0 | 0 | 0 | 0 | 3 | 2 |
| *Serratia marcescens* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 |
| *Shigella sp.* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 0 | 0 | 3 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 3* | 2 |
| *Stenotrophomonas (Pseudomonas) maltophilia* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 2 | 3 |
| *Vibrio vulnificus* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | 3 |
| *Yersinia enterocolitica* | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 3 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| **Anaerobic Gram Positive Cocci (chains)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Peptostreptococcus* | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 0 | 3 | 2 | 2 | 2 | 2 | 0 | 0 | 2 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience. * = May be effective initially but as a "high resistance" antibiotic potential, resistance may develop during/after therapy.

[§] = Always use in combination with another antibiotic.

**Table 3.1. Antibiotic Susceptibility Profiles (Penicillins, Macrolides, Tetracyclines, and Others)** (cont'd)

| | Penicillins | | | | | | | Anti-Pseudomonal Penicillins | | | | Macrolides | | | | Tetra-Cyclines | | | Miscellaneous | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Penicillin G (IV) | Penicillin V (PO) | Ampicillin (IV/PO) | Ampicillin/Sulbactam (IV) | Amoxicillin (PO) | Amoxicillin/ Clavulanate (PO) | Nafcillin (IV) | Ticarcillin (IV) | Ticarcillin/ Clavulanate (IV) | Piperacillin (IV) | Piperacillin/ Tazobactam (IV) | Erythromycin (IV/PO) | Clarithromycin (PO) | Azithromycin (IV/PO) | Telithromycin (PO) | Tetracycline (IV/PO) | Doxycycline (IV/PO) | Minocycline (IV/PO) | Clindamycin (IV/PO) | Metronidazole (IV/PO) | Rifampin (PO)§ | TMP-SMX (IV/PO) | Chloramphenicol (IV/PO) |
| **Anaerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Actinomyces sp.* | 1 | 1 | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 |
| **Anaerobic Gram Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacteroides fragilis group (B. distasonis, ovatus, thetaiotaomicron, vulgatus)* | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 0 | 3 | 2 | 2 | 1 | 1 | 0 | 0 | 2 |
| *Prevotella sp.* | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 0 | 0 | 2 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience. § = Always use in combination with another antibiotic.

**Table 3.2. Antibiotic Susceptibility Profiles (Cephalosporins)**

| | CEPHALOSPORINS | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st GC (IV) | 1st GCs (PO) | | 2nd GCs (IV) | | | 2nd GCs (PO) | | | | 3rd GCs (IV) | | | 3rd GCs (PO) | | | | | Anti-Pseudomonal Cephalosporins (IV) | | | | | Anti-MRSA (IV) |
| **ORGANISMS** | Cefazolin (IV) | Cefadroxil (PO) | Cephalexin (PO) | Cefoxitin (IV) | Cefuroxime (IV) | Cefotetan (IV) | Cefaclor (PO) | Loracarbef (PO) | Cefprozil (PO) | Cefuroxime axetil (PO) | Cefotaxime (IV) | Ceftizoxime (IV) | Ceftriaxone (IV) | Cefixime (PO) | Ceftibuten (PO) | Cefpodoxime (PO) | Cefdinir (PO) | Cefditoren (PO) | Cefoperazone (IV) | Ceftazidime (IV) | Ceftazidime/ Avibactam (IV) | Ceftolozane/ Tazobactam (IV) | Cefepime (IV) | Ceftaroline fosamil (IV) |
| **Aerobic Gram Positive Cocci (Clusters)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Staphylococcus aureus* (MSSA) | 1 | 2 | 1 | 2 | 2 | 3 | 3 | 0 | 3 | 2 | 2 | 2 | 2 | 0 | 0 | 2 | 2 | 0 | 2 | 3 | 3 | 3 | 2 | 2 |
| *Staphylococcus aureus* (HA/CO-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *S. aureus* (CA-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| *S. epidermidis* (CoNS) | 3 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 3 | 3 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance potential" (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience.

**Table 3.2. Antibiotic Susceptibility Profiles (Cephalosporins)** (cont'd)

| | CEPHALOSPORINS | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st GC (IV) | 1st GCs (PO) | | 2nd GCs (IV) | | | 2nd GCs (PO) | | | | 3rd GCs (IV) | | | 3rd GCs (PO) | | | | | Anti-Pseudomonal Cephalosporins (IV) | | | | | Anti-MRSA (IV) |
| **ORGANISMS** | Cefazolin (IV) | Cefadroxil (PO) | Cephalexin (PO) | Cefoxitin (IV) | Cefuroxime (IV) | Cefotetan (IV) | Cefaclor (PO) | Loracarbef (PO) | Cefprozil (PO) | Cefuroxime axetil (PO) | Cefotaxime (IV) | Ceftizoxime (IV) | Ceftriaxone (IV) | Cefixime (PO) | Ceftibuten (PO) | Cefpodoxime (PO) | Cefdinir (PO) | Cefditoren (PO) | Cefoperazone (IV) | Ceftazidime (IV) | Ceftazidine/ Avibactam (IV) | Ceftolozame/ Tazobactam (IV) | Cefepime (IV) | Ceftaroline fosamil (IV) |
| **Aerobic Gram Positive Cocci (Chains)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Enterococcus faecalis* (VSE) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| *Enterococcus faecium* (VRE) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Streptococci (groups A, B, C, E, G) | 1 | | 1 | 2 | 2 | 2 | 2 | | 1 | 2 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 2† |
| Streptococcus (bovis) galloyticus | 1 | | 1 | 2 | 2 | 2 | 2 | | 2 | 2 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 0 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Viridans streptococci (S. mitior, milleri, mitis, mutans, oralis, sanguis, par sanguis, salivarius)* | 1 | | 1 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 0 |
| **Aerobic Gram Positive Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Streptococcus pneumoniae (PSSP)* | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 3 | 0 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 3 | 2 |
| *Streptococcus pneumoniae (PRSP)* | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 3 | 2 | 3 | 3 | 3 | 3 | 2 |
| *Streptococcus pneumoniae (MDRSP)* | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 0 | 2 | 2 | 3 | 2 | 3 | 3 | 3 | 3 | 2 |
| **Aerobic Gram Negative Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Neisseria gonorrhoeae* | 2 | 0 | 0 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 0 |
| *Neisseria meningitidis* | 3 | 0 | 0 | 3 | 2 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 1 | 3 | 3 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 2 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance potential" (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience.

† Group A & B only.

**Table 3.2. Antibiotic Susceptibility Profiles (Cephalosporins)** (cont'd)

| | CEPHALOSPORINS | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st GC (IV) | 1st GCs (PO) | | 2nd GCs (IV) | | | 2nd GCs (PO) | | | | 3rd GCs (IV) | | | 3rd GCs (PO) | | | | | Anti-Pseudomonal Cephalosporins (IV) | | | | | Anti-MRSA (IV) |
| **ORGANISMS** | Cefazolin (IV) | Cefadroxil (PO) | Cephalexin (PO) | Cefoxitin (IV) | Cefuroxime (IV) | Cefotetan (IV) | Cefaclor (PO) | Loracarbef (PO) | Cefprozil (PO) | Cefuroxime axetil (PO) | Cefotaxime (IV) | Ceftizoxime (IV) | Ceftriaxone (IV) | Cefixime (PO) | Ceftibuten (PO) | Cefpodoxime (PO) | Cefdinir (PO) | Cefditoren (PO) | Cefoperazone (IV) | Ceftazidime (IV) | Ceftazidime/ Avibactam (IV) | Ceftolozane/ Tazobactam (IV) | Cefepime (IV) | Ceftaroline fosamil (IV) |
| **Aerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacillus anthracis* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Corynebacterium diphtheriae* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Corynebacterium jeikeium (JK)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Listeria monocytogenes* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Nocardia sp.* | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Aerobic Gram-Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Acinetobacter sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 0 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Aeromonas hydrophila* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 3 | 3 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 2 | 0 |
| *Bordetella pertussis* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Brucella sp.* | 3 | 0 | 0 | 2 | 2 | 2 | 0 | 3 | 3 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 |
| *Burkholderia (Pseudomonas) cepacia* | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 3 | 0 |
| *Campylobacter sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Citrobacter sp.* | 0 | 0 | 0 | 2 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 0 |
| *Enterobacter sp.* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 1 | 1 | 1 | 0 |
| *Escherichia coli* | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 3 |
| *Francisella tularensis* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Haemophilus sp.* | 3 | 1 | 1 | 2 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2[†] |
| *Klebsiella sp.* | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 1 | 0 |
| *Moraxella catarrhalis* | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |
| *Morganella sp.* | 3 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 | 2 | 2 | 2 | 0 |
| *P. aeruginosa* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 1 | 1 | 1 | 0 |
| *Providencie sp.* | 3 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 | 2 | 2 | 2 | 0 |
| *Proteus sp.* | 3 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 3 | 2 | 2 | 2 | 0 |
| *Salmonella sp.* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 2 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance potential" (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience.
[†] H. influenzae only.

**Table 3.2. Antibiotic Susceptibility Profiles (Cephalosporins)** (cont'd)

| | CEPHALOSPORINS | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st GC (IV) | 1st GCs (PO) | | 2nd GCs (IV) | | | 2nd GCs (PO) | | | | 3rd GCs (IV) | | | 3rd GCs (PO) | | | | | Anti-Pseudomonal Cephalosporins (IV) | | | | | Anti-MRSA (IV) |
| **ORGANISMS** | Cefazolin (IV) | Cefadroxil (PO) | Cephalexin (PO) | Cefoxitin (IV) | Cefuroxime (IV) | Cefotetan (IV) | Cefaclor (PO) | Loracarbef (PO) | Cefprozil (PO) | Cefuroxime axetil (PO) | Cefotaxime (IV) | Ceftizoxime (IV) | Ceftriaxone (IV) | Cefixime (PO) | Ceftibuten (PO) | Cefpodoxime (PO) | Cefdinir (PO) | Cefditoren (PO) | Cefoperazone (IV) | Ceftazidime (IV) | Ceftazidime/ Avibactam (IV) | Ceftolozane/ Tazobactam (IV) | Cefepime (IV) | Ceftaroline fosamil (IV) |
| *Serratia marcescens* | 0 | 0 | 0 | 3 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 0 | 3 | 1 | 3 | 2 | 2 | 1 | 0 |
| *Shigella sp.* | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 3 | 3 | 2 | 0 |
| *Stenotrophomonas (Pseudomonas) maltophilia* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 |
| *Vibrio vulnificus* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| *Yersinia enterocolitica* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 0 | 2 | 3 | 0 | 0 | 2 | 0 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Anaerobic Gram Positive Cocci (chains)** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Peptostreptococcus* | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 2 | 0 |
| **Anaerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Actinomyces sp.* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| **Anaerobic Gram Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacteroides fragilis group (B distasonis, ovatus, thetaiotaomicron, vulgatus)* | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 3† | 3† | 0 | 0 |
| *Prevotella sp.* | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 3 | 3 | 2 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance potential" (see Chapter 11 Drug Summaries for antibiotic dosing details).

2 = Alternate choice—With many attributes of a preferred antibiotic.

3 = Acceptable, but preferably select an alternate antibiotic.

0 = No activity or no data or limited experience.

†For intra-abdominal/pelvic infections, add metronidazole.

**Table 3.3. Antibiotic Susceptibility Profiles (Aminoglycosides, Fluoroquinolones, Carbapenems, and Others)**

| | Amino-Glycosides | | | Fluoro-Quinolones | | | Miscellaneous | | | | | | | | | | | | Carbapenems | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Gentamicin (IV) | Tobramycin (IV) | Amikacin (IV) | Ciprofloxacin (IV/PO) | Levofloxacin (IV/PO) | Moxifloxacin (IV/PO) | Colistin (IV) Polymyxin B (IV) | Aztreonam (IV) | Tigecycline (IV) | Vancomycin (IV) | Q/D* (IV) | Linezolid (IV/PO) | Tedizolid (IV/PO) | Daptomycin (IV) | Oritavancin (IV) | Telavancin (IV) | Dalbavancin (IV) | Nitrofurantoin † (PO) | Fosfomycin † (PO) | Imipenem (IV) | Meropenem (IV) | Ertapenem (IV) | Doripenem (IV) |
| **Aerobic Gram Positive Cocci (Clusters)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Staphylococcus aureus* (MSSA) | 2 | 3 | 3 | 3* | 2 | 2 | 0 | 0 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Staphylococcus aureus* (HA/CO-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| *S. aureus* (CA-MRSA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| *S. epidermidis* (CoNS) | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 3 | 3 | 3 | 3 |
| **Aerobic Gram Positive Cocci (Chains)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Enterococcus faecalis* (VSE) | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 1 | 2 | 0 | 1 | 1 | 2 | 3 | 3 | 3 | 1 | 2 | 2 | 2 | 0 | 3 |
| *Enterococcus faecium* (VRE) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 2 | 3 | 3 | 3 | 1 | 3 | 0 | 0 | 0 | 3 |
| Streptococci (groups A, B, C, E, G) | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | 2 |
| Streptococcus (bovis) galloyticus | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 0 | 0 | 2 | 2 | 0 | 2 |

* Q/D: Quinupristin/Dalfopristin

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Viridans streptococci (S. mitior, milleri, mitis, mutans, oralis, sanguis, parasanguis, salivarius)* | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 0 | 2 | 2 | 0 | 2 |
| **Aerobic Gram Positive Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Streptococcus pneumoniae (PSSP)* | 0 | 0 | 0 | 3* | 1 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Streptococcus pneumoniae (PRSP)* | 0 | 0 | 0 | 3* | 1 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Streptococcus pneumoniae (MDRSP)* | 0 | 0 | 0 | 3* | 1 | 1 | 0 | 0 | 1 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 0 | 0 | 2 | 2 | 2 | 2 |
| **Aerobic Gram Negative Cocci (Pairs)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Neisseria gonorrhoeae* | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 3 |
| *Neisseria meningitidis* | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 2 |
| **Aerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacillus anthracis* | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Corynebacterium diphtheriae* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Corynebacterium jeikeium (JK)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience. * = May be effective initially but as a "high resistance" antibiotic potential, resistance may develop during/after therapy.

**Table 3.3. Antibiotic Susceptibility Profiles (Aminoglycosides, Fluoroquinolones, Carbapenems, and Others)** (cont'd)

| | Amino-Glycosides | | | Fluoro-Quinolones | | | Miscellaneous | | | | | | | | | | | | Carbapenems | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Gentamicin (IV) | Tobramycin (IV) | Amikacin (IV) | Ciprofloxacin (IV/PO) | Levofloxacin (IV/PO) | Moxifloxacin (IV/PO) | Colistin (IV) Polymyxin B (IV) | Aztreonam (IV) | Tigecycline (IV) | Vancomycin (IV) | Q/D* (IV) | Linezolid (IV/PO) | Tedizolid (IV/PO) | Daptomycin (IV) | Oritavancin (IV) | Telavancin (IV) | Dalbavancin | Nitrofurantoin† (PO) | Fosfomycin† (PO) | Imipenem (IV) | Meropenem (IV) | Ertapenem (IV) | Doripenem (IV) |
| *Listeria monocytogenes* | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 |
| *Nocardia* | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 |
| **Aerobic Gram-Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Acinetobacter sp.* | 1 | 2 | 2 | 3* | 2 | 3 | 2 | 1 | 2* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2* | 1 | 0 | 1 |
| *Aeromonas hydrophila* | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 0 |
| *Bordetella sp.* | 0 | 0 | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 0 |
| *Brucella sp.* | 2 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Burkholderia (Pseudomonas) cepacia* | 0 | 0 | 0 | 3* | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 3 | 0 |
| *Campylobacter sp.* | 3 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 3 |
| *Citrobacter sp.* | 1 | 1 | 2 | 3 | 2 | 3 | 3 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 1 | 1 |
| *Enterobacter sp.* | 1 | 1 | 1 | 2* | 2 | 2 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 1 | 1 | 1 | 1 |
| *Escherichia coli* | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 2 |
| *Francisella tularensis* | 1 | 3 | 0 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

* Q/D: Quinupristin/Dalfopristin

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Haemophilus sp.* | 3 | 3 | 3 | 2 | 2 | 2 | 3 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Klebsiella sp.* | 2 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 1 | 1 |
| *Moraxella catarrhalis* | 3 | 3 | 3 | 2 | 2 | 2 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Morganella sp.* | 2 | 2 | 1 | 3 | 2 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 2 |
| *P. aeruginosa* | 3 | 3 | 1 | 1* | 1 | 0 | 1 | 1* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2* | 1 | 0 | 1 |
| *Proteus sp.* | 2 | 2 | 1 | 3 | 2 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 |
| *Providencia sp.* | 2 | 2 | 1 | 3 | 2 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 |
| *Salmonella sp.* | 0 | 0 | 0 | 1 | 1 | 1 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Serratia marcescens* | 3 | 2 | 3 | 1* | 1 | 2 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 2 |
| *Shigella sp.* | 3 | 3 | 3 | 1 | 1 | 1 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| *Stenotrophomonas (Pseudomonas) maltophilia* | 0 | 0 | 0 | 3 | 2 | 2 | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Vibrio vulnificus* | 0 | 0 | 0 | 3 | 3 | 3 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Yersinia enterocolitica* | 2 | 2 | 2 | 2 | 2 | 2 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Anaerobic** Gram Positive Cocci (chains)** | | | | | | | | | | | | | | | | | | | | | | | |
| *Peptostreptococcus* | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 2 | 3 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 2 |
| **Anaerobic Gram Positive Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Actinomyces sp.* | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 3 | | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details). 2 = Alternate choice—With many attributes of a preferred antibiotic. 3 = Acceptable, but preferably select an alternate antibiotic. 0 = No activity or no data or limited experience. * = May be effective initially but as a "high resistance" antibiotic potential, resistance may develop during/after therapy.

**Table 3.3. Antibiotic Susceptibility Profiles (Aminoglycosides, Fluoroquinolones, Carbapenems, and Others)** (cont'd)

| | Amino-Glycosides | | | Fluoro-Quinolones | | | Miscellaneous | | | | | | | | | | | | Carbapenems | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ORGANISMS** | Gentamicin (IV) | Tobramycin (IV) | Amikacin (IV) | Ciprofloxacin (IV/PO) | Levofloxacin (IV/PO) | Moxifloxacin (IV/PO) | Colistin (IV) Polymyxin B (IV) | Aztreonam (IV) | Tigecycline (IV) | Vancomycin (IV) | Q/D* (IV) | Linezolid (IV/PO) | Tedizolid (IV/PO) | Daptomycin (IV) | Oritavancin (IV) | Telavancin (IV) | Dalvabancin (IV) | Nitrofurantoin† (PO) | Fosfomycin† (PO) | Imipenem (IV) | Meropenem (IV) | Ertapenem (IV) | Doripenem (IV) |
| **Anaerobic Gram Negative Bacilli** | | | | | | | | | | | | | | | | | | | | | | | |
| *Bacteroides fragilis group (B distasonis, ovatus, thetaiotaomicron, vulgatus)* | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 3 | 0 | | 0 | | 0 | | 0 | 0 | 1 | 1 | 1 | 1 |
| *Prevotella sp.* | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | | 0 | | 0 | | 0 | 0 | 2 | 2 | 2 | 2 |

1 = Preferred antibiotic—High degree of activity against the isolate and likely to be clinically effective, most strains susceptible, has a favorable PK/PD characteristics, has a good safety profile, and has a "low resistance" potential (see Chapter 11 Drug Summaries for antibiotic dosing details).

2 = Alternate choice—With many attributes of a preferred antibiotic.

3 = Acceptable, but preferably select an alternate antibiotic.

0 = No activity or no data or limited experience.

* Q/D: Quinupristin/Dalfopristin

† = For lower tract infections (UTIs)/catheter associated bacteriuria (CAB) only.

# Gram Stain Characteristics of Isolates
(by Morphology, Arrangement, Oxygen Requirements)

## AEROBIC ISOLATES

**SPIROCHETES**



*** Oxidase negative.** **† Catalase positive.** **§ Non-lactose fermenter.** **(α) = α (alpha) hemolysis on BAP.** **(β) = β (beta) hemolysis on BAP.** **(γ) = γ (gamma) hemolysis on BAP.** **(m) = motile.** **(v) = Gram variable bacilli.**

## CAPNOPHILIC ISOLATES+

**GRAM-NEGATIVE BACILLI**



**+ Capnophilic organisms grow best under increased $CO_2$ tension.** **(m) = motile.**

## ANAEROBIC ISOLATES

**GRAM-POSITIVE COCCI (CHAINS)**



**GRAM-POSITIVE BACILLI**

**++ Microaerophilic organisms. Grow best under decreased $O_2$ concentration.**
*** Oxidase negative. (m) = motile.**
**† Catalase positive. (v) = Gram variable bacilli.**

**YEASTS/FUNGI**



## Alphabetical Index of Isolates

**Table 3.4. Key Factors in Antibiotic Selection (Isolate Known)**

- **Select an antibiotic with a high degree of activity against the known pathogen** (*not colonizer*).
- **Dose appropriate for the target tissue to assure therapeutic/effective concentrations at site of infection**. If necessary, adjust dose ↑ for tissue targets that require higher doses, e.g., bacterial meningitis, endocarditis, etc., or ↓ dose for sites with antibiotic concentrations that are above serum concentrations, e.g., skin, urine, etc.
- **Select an empiric antibiotic with a "low resistance" potential** avoid, if possible, antibiotics with a "high resistance" potential (also with a high degree of activity against the presumed pathogen). Select a "low resistance" potential antibiotic for the same/different class with a high degree of activity.
- **Select antibiotic with a good safety profile** and minimal potential for drug-drug interactions.
- **Select antibiotic that is relatively cost effective** (first take into account the above principles).

**Table 3.5. Antibiotic Selection Based on Resistance Potential**

- Antibiotic resistance may be classified as natural (P. aeruginosa is naturally resistant to chloramphenicol, i.e., not in its spectrum). Acquired resistance may be relative or high level resistance (gentamicin resistant P. aeruginosa with extremely high MIC cannot be overcome by increased dosing). In contrast, relative resistance, e.g., meropenem relative resistance to P. aeruginosa may be overcome, if antibiotic concentrations can be achieved with normal/high dosing that exceed the MIC of the organism at the site of infection.
- There are many mechanisms of antibiotic resistance, but mechanisms do not explain differences in resistance potential within antibiotic classes. Mechanism of resistance does not explain why ciprofloxacin is responsible for nearly all fluoroquinolone resistance to S. pneumoniae and P. aeruginosa. Similarly, among the five 3rd GC, only ceftazidime has been associated with P. aeruginosa resistance problems.
- Clinically, antibiotics may be considered in terms of resistance potential, i.e., high, moderate, or low. "High resistance potential" antibiotics cause resistance even with minimal use, but with widespread use can cause (non-clonal) resistance problems when used in high volume or over time. While an occasional mutation may result sporadic resistance with any antibiotic, resistance to "low resistance potential" antibiotics is not related to antibiotic class, volume or duration of use. After decades of extensive worldwide use with "low resistance potential" antibiotics, there are no widespread resistance problems with "low resistance potential" antibiotics, e.g., nitrofurantoin, amikacin, ceftriaxone, doxycycline.
- If possible, always try to preferentially select a "low resistance potential" antibiotic with the appropriate spectrum and PK/PD characteristics for the pathogen/body site being treated. For each resistant problem pathogen in each antibiotic class, there are usually "low resistance potential" antibiotics alternatives within the class. In addition, other "low resistance potential" antibiotics may be found in different antibiotic classes. Try to use "low resistance potential" antibiotics in place of "high resistance potential" antibiotics, e.g., TMP-SMX (S. pneumoniae and MSSA resistance), tetracycline (S. pneumoniae and MSSA resistance), gentamicin (P. aeruginosa resistance), ceftazidime (S. pneumoniae and P. aeruginosa resistance), imipenem (P. aeruginosa resistance).

**Table 3.6. Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing**

| GRAM-POSITIVE COCCI (CLUSTERS) | | | |
|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Therapy** | **Comments** |
| Staphylococcus aureus (MSSA/MRSA) | • CSF = C*, P (CNS shunts)<br>• Blood = C*, P (from soft tissue/bone infection, abscess, IV line infection, ABE, PVE)<br>• Sputum = C, P (S. aureus pneumonia is rare; usually only after viral influenza)<br>• Urine = C, P (S. aureus in urine is usually due to skin contamination or rarely overwhelming S. aureus bacteremia)<br>• Stool = C, P (enterocolitis)<br>• Wound = C, P (cellulitis, abscess) | MSSA: Nafcillin (IV), Cefazolin (IV), Clindamycin (IV/PO), a "respiratory quinolone" (IV/PO), Minocycline (IV/PO), Daptomycin (IV), any carbapenem (IV), Linezolid (IV/PO), Tigecycline (IV), Telavancin (IV)<br><br>Hospital-acquired MRSA (HA-MRSA)/ Community-onset MRSA (CO-MRSA): Daptomycin (IV), Linezolid (IV/PO), Tigecycline (IV), Vancomycin (IV), Minocycline (IV/PO), Quinupristin/dalfopristin (IV), Telavancin (IV)<br><br>Community acquired MRSA (CA-MRSA): Doxycycline*, TMP–SMX, Clindamycin<br><br>VISA/VRSA: Linezolid (IV/PO), Daptomycin (IV), Telavancin (IV) | MSSA: For oral treatment, 1st generation cephalosporins are better than oral anti-staphylococcal penicillins (e.g., dicloxacillin)<br>MRSA: *in-vitro susceptibility testing is unreliable*; treat MRSA infections empirically. Most effective drugs for MRSA are vancomycin, linezolid, ceftaroline fosamil (ABSSSI only), quinupristin/dalfopristin, minocycline, daptomycin, tigecycline. ***Preferentially use minocycline instead of doxycycline for MSSA/MRSA.***<br>Community-acquired MRSA (CA-MRSA) SCC *mec* IV, V CA-MRSA has different susceptibilities than HA-MRSA/CO-MRSA (see p. 14). CA-MRSA strains with Panton-Valentin Leukocidin PVL+ gene cause two distinct clinical syndromes: severe necrotizing pneumonia (with viral influenza) and severe necrotizing fasciitis/pyomyositis. **CA-MRSA is usually susceptible to doxycycline *in vitro,* but minocycline more effective *in vivo* than doxycycline,** TMP–SMX, clindamycin. *Drugs effective against HA-MRSA/CO-MRSA are also effective against CA-MRSA. However, drugs effective against CA-MRSA are may not be effective against HA-MRSA/CO-MRSA*<br>MSSA/MRSA: Noncontinuous low-grade blood culture positivity indicates skin contamination during venipuncture. Continuous high-grade blood culture positivity (3/4 or 4/4) indicates intravascular infection or abscess |

| | | | |
|---|---|---|---|
| | | | VISA/VRSA: MICs for vancomycin sensitive (VSSA), heteroresistant vancomycin intermediate (hVISA), intermediate (VISA), and resistant (VRSA) S. aureus are < 4 mcg/mL, < 4 mcg/mL (with subpopulations > 4 mcg/mL), 8–16 mcg/mL, and ≥ 32 mcg/mL, respectively. |
| Staphylococcus epidermidis (MSSE/MRSE) or coagulase-negative staphylococci (CoNS)<br>Staphylococcus lugdunensis | • CSF = C*, P (CNS shunts)<br>• Blood = C*, P (from IV lines, infected implants, prosthetic valve endocarditis [PVE], rarely from native valve subacute bacterial endocarditis [SBE])<br>• Sputum = C<br>• Urine = C (may be reported as S. saprophyticus; request novobiocin sensitivity to differentiate S. epidermidis from other coagulase-negative staphylococci)<br>• Stool = NP<br>• Wound = C, P (infected foreign body drainage) | MSSE: Linezolid (IV/PO), Daptomycin (IV), Vancomycin (IV), Telavancin (IV), any carbapenem (IV), a "respiratory quinolone" (IV/PO), Minocycline (IV/PO)<br><br>MRSE: Linezolid (IV/PO), Daptomycin (IV), Vancomycin (IV), Quinupristin/dalfopristin (IV), Minocycline (IV/PO) | Usually non-pathogenic in absence of prosthetic/implant materials. Common cause of PVE; rare cause of native valve SBE. Treat foreign body-related infection until foreign body is removed.<br><br>S. lugdunensis is a CoNS but is often misidentified as S. aureus since it produces "clumping factor" which gives a 1 rapid short tube coagulase test (long tube test —) although a CoNS resembles S. aureus in terms of invasiveness/virulence. Unlike S. aureus, S. lugdensis is pan-sensitive to antibiotics which is another clue the isolate is not S. aureus. S. lugdensis bacteremia associated with community acquired (not nosocomial) SBE. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

* Minocycline (IV/PO) preferred.

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| Isolate | Isolate Significance | Preferred Therapy | Alternate Therapy | Comments |
|---|---|---|---|---|
| **GRAM-POSITIVE COCCI (CLUSTERS)** | | | | |
| Staphylococcus saprophyticus (coagulase-negative staphylococci) | • CSF = NP<br>• Blood = NP<br>• Sputum = NP<br>• Urine = P (cystitis, pyelo)<br>• Stool = NP<br>• Wound = NP | Preferred therapy<br>Amoxicillin (PO)<br>TMP–SMX (PO)<br>Nitrofurantoin (PO)<br>Alternate therapy<br>Any quinolone (PO)<br>Any 1st generation cephalosporin (PO) | | S. saprophyticus UTI is associated with a urinary "fishy odor," alkaline urine pH, and microscopic hematuria. Novobiocin sensitivity differentiates coagulase-negative staphylococci (sensitive) from S. saprophyticus (resistant). |
| **GRAM-POSITIVE COCCI (CHAINS)** | | | | |
| Enterococcus faecalis (VSE) | • CSF = NP (except from S. stercoralis hyperinfection or V-P shunt infection)<br>• Blood = C*, P (from GI/GU source, SBE)<br>• Sputum = NP<br>• Urine = C, P (cystitis, pyelonephritis)<br>• Stool = NP<br>• Wound = C, P (cellulitis) | Non-SBE<br>Ampicillin (IV)<br>Amoxicillin (PO)<br>Meropenem (IV)<br>Piperacillin (IV)<br>Linezolid (IV/PO)<br>Tigecycline (IV)<br>Daptomycin (IV)<br>SBE<br>Gentamicin + ampicillin (IV) or vancomycin (IV)<br>Meropenem (IV)<br>Piperacillin (IV)<br>Linezolid (IV/PO) | Non-SBE<br>Cefoperazone (IV)<br>Chloramphenicol (IV)<br>Levofloxacin (IV/PO)<br>Moxifloxacin (IV/PO)<br>Nitrofurantoin (PO) (UTIs only)<br>SBE<br>Any quinolone (IV/PO)<br>Cefoperazone (IV) | Sensitive to ampicillin, not penicillin. Cause of intermediate (severity between ABE and SBE) endocarditis, hepatobiliary infections, and UTIs. Enterococci (E. faecalis, E. faecium) are the only cause of SBE (below the waist) from GI/GU sources. Permissive pathogen (i.e., usually does not cause infection alone) in the abdomen/pelvis (except in gallbladder or urinary bladder/kidneys). Cefoperazone is the only cephalosporin with anti-E. faecalis (VSE) activity (MIC ~ 32 mcg/mL). Quinupristin/dalfopristin is not active against E. faecalis (VSE).<br>Treat vancomycin resistant E. faecalis as VRE (see E. faecium VRE p. 211). |

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| Enterococcus faecium (VRE) | • CSF = NP (except from S. stercoralis hyperinfection or V-P shunt infection)<br>• Blood = C*, P (from GI/GU source, SBE)<br>• Sputum = C<br>• Urine = C, P (cystitis, pyelo)<br>• Stool = NP<br>• Wound = C, P (cellulitis) | Non-SBE<br>Linezolid (IV/PO), quinupristin/dalfopristin (IV), doxycycline (IV/PO), tigecycline (IV), chloramphenicol (IV/PO), nitrofurantoin (PO) (UTIs only)<br><br>SBE<br>Linezolid (IV/PO)<br>Quinupristin/dalfopristin (IV) | | Same spectrum of infection as E. faecalis. Colonization common; infection uncommon. Fecal carriage is intermittent but prolonged. In vitro sensitivity = in vivo efficacy. Increased prevalence of E. faecalis (VRE) related to vancomycin IV (not PO) use. Nitrofurantoin preferred for VRE lower UTIs/catheter-associated bacteriuria. |
| Group A streptococci | • CSF = C*, P (rare cause of ABM)<br>• Blood = P (from skin/soft tissue infection)<br>• Sputum = P (rare cause of CAP)<br>• Urine = NP<br>• Stool = NP<br>• Wound = C, P (cellulitis)<br>• Throat = C, P (pharynx is colonized with Group A streptococci in ~ 30% of patients with EBV mono) | Amoxicillin (PO)<br>Any β-lactam (IV/PO) | Penicillin (PO)<br>Clindamycin (IV/PO) | For Group A streptococcal pharyngitis, amoxicillin is preferred over penicillin. Clindamycin is best for elimination of carrier states, and for penicillin-allergic patients with streptococcal pharyngitis. Any β-lactam is equally effective against Group A streptococci. Nafcillin is the most active anti-staphylococcal penicillin against Group A streptococci. Erythromycin is no longer reliable against Group A streptococci due to increasing resistance. Doxycycline has little/no activity against Group A streptococci. |
| Group B streptococci (S. agalactiae) | • CSF = P<br>• Blood = P (from IV line/urine source, SBE) | Non-SBE, non-CNS<br>Clindamycin (IV/PO) | Non-SBE, non-CNS<br>Vancomycin (IV)<br>Amoxicillin (PO) | Cause of UTIs and IV line infections in diabetics and the elderly. Cause of neonatal meningitis. Infection is uncommon in the general population. Rarely a cause of SBE in |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-POSITIVE COCCI (CHAINS) | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Sputum = NP<br>• Urine = P (CAB, UTIs, especially in diabetics, elderly)<br>• Stool = NP<br>• Wound = C, P (diabetic foot infections) | Any 1st, 2nd, 3rd generation cephalosporin (IV/PO)<br><br>SBE<br>Ceftriaxone (IV)<br>Penicillin (IV)<br>Vancomycin (IV)<br><br>CNS<br>Ceftriaxone (IV)<br>Penicillin (IV) | SBE<br>Meropenem (IV)<br>Ertapenem (IV)<br>Linezolid (IV/PO)<br><br>CNS<br>Chloramphenicol (IV)<br>Linezolid (IV/PO) | Non-pregnant adults. On gram stain, GBS appear larger/rounder than S. pneumoniae. Colonies of GBS on BAP have a "sheen" (vs. S. pneumoniae). Aminoglycosides and tetracyclines are ineffective. |
| Group C, F, G streptococci | • CSF = P (meningitis)<br>• Blood = P (from skin/soft tissue infection, SBE)<br>• Sputum = P (rare cause of CAP)<br>• Throat = C (especially with viral pharyngitis), P (pharyngitis in medical personnel)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (cellulitis) | Ceftriaxone (IV)<br>Penicillin (IV)<br>Ampicillin (IV)<br>Clindamycin (IV/PO) | Vancomycin (IV)<br>Amoxicillin (PO)<br>Any 1st, 2nd, 3rd generation cephalosporin (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Group C, G streptococci may cause pharyngitis, wound infections, and rarely SBE. Group G streptococci associated with malignancies. Common pharyngeal colonizers in medical personnel. |

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| **GRAM-POSITIVE COCCI (CHAINS)** | | | | |
| Streptococcus (bovis) gallolyticus | • Blood = P (SBE from GI source)<br>• Urine = NP | Ceftriaxone (IV)<br>Ampicillin (IV)<br>Clindamycin (IV/PO) | Vancomycin (IV)<br>Amoxicillin (PO)<br>Any cephalosporin (IV) | Associated with GI malignancies. Non-enterococcal Group D streptococci (e.g., S. bovis) are sensitive to penicillin. |
| S. anginosus (S. milleri) group (S. intermedius, S. anginosus, S. constellatus) | • CNS = P<br>• Blood = P<br>• Wound = P (head/neck abscesses) | Ceftriaxone (IV)<br>Vancomycin (IV) | Amoxicillin (PO)<br>Any cephalosporin (PO) | S. anginosus (S. milleri) group (S. intermedius, S. anginosus, S. constellatus) prone to invasive disease, bacteremia and abscess formation. |
| Viridans streptococci (S. mitior, mitis, mutans, oralis, sanguis, parasanguis, salivarius) | • CSF = NP (aseptic meningitis with SBE)<br>• Blood = C*, P (1° bacteremia, SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Ceftriaxone (IV)<br>Penicillin (IV) | Amoxicillin (PO)<br>Any 1st, 2nd, 3rd generation cephalosporin (IV/PO)<br>Meropenem (IV)<br>Ertapenem (IV)<br>Vancomycin (IV) | Low-grade blood culture positivity (1/4) indicates contamination during venipuncture. Continuous/high-grade blood culture positivity (3/4 or 4/4) indicates SBE until proven otherwise. |
| **GRAM-POSITIVE COCCI (PAIRS)** | | | | |
| Leuconostoc | • CSF = NP<br>• Blood = P (PVE)<br>• Sputum = NP<br>• Urine = P (UTIs)<br>• Stool = NP<br>• Wound = NP | Penicillin (IV)<br>Ampicillin (IV)<br>Clindamycin (IV/PO) | Amoxicillin (PO)<br>Erythromycin (IV)<br>Minocycline (IV/PO)<br>Clarithromycin XL (PO) | Coccobacillary forms resemble streptococci/enterococci. Cause of infection in compromised hosts. Rare cause of IV line infection. Usually vancomycin-resistant. |
| Streptococcus pneumoniae | • CSF = P (ABM)<br>• Blood = P (from respiratory tract source)<br>• Sputum = C, P<br>• Urine = NP<br>• Stool = NP | Multidrug Resistant S. pneumoniae (MDRSP)<br>A "respiratory quinolone" (IV/PO); telithromycin (PO); ertapenem (IV); meropenem (IV); cefepime (IV); linezolid (IV/PO); vancomycin (IV) | | Penicillin-resistant S. pneumoniae (PRSP) are still sensitive to full-dose/high-dose β-lactams. If possible, avoid macrolides, as > 30% of S. pneumoniae are macrolide resistant (MRSP). (~ 20–25% are naturally resistant and 10–15% acquire macrolide resistance). |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO.* *See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| Isolate | Isolate Significance | Preferred Therapy | Alternate Therapy | Comments |
|---|---|---|---|---|
| **GRAM-POSITIVE COCCI (PARIS)** | | | | |
| | • Wound = P (cellulitis only in SLE) | Sensitive or relatively PCN-resistant<br>Doxycycline (IV/PO); any cephalosporin (IV/PO); clindamycin (IV/PO); amoxicillin/clavulanic acid (PO) | | |
| **GRAM-NEGATIVE COCCI (PARIS)** | | | | |
| Neisseria gonorrhoeae (GC) | • CSF = NP<br>• Blood = P (from pharyngitis, proctitis, ABE)<br>• Sputum = NP<br>• Urine = P (urethritis)<br>• Stool = NP<br>• Wound = NP<br>• Rectal discharge = P (GC proctitis) | Penicillin-sensitive N. gonorrhoeae (PSNG)<br>Ceftriaxone (IV/IM) Any quinolone (IV/PO)<br>PRNG<br>Ceftriaxone (IV/IM) | Penicillin-sensitive N. gonorrhoeae (PSNG)<br>Penicillin (IV/IM)<br>Amoxicillin (PO)<br>Doxycycline (IV/PO)<br>PPNG<br>Spectinomycin (IM)<br>Any quinolone (PO)<br>Any 1st, 2nd, 3rd gen. cephalosporin (IV/IM) | Cause of "culture negative" right-sided ABE. May be cultured from synovial fluid/blood in disseminated GC infection (arthritis-dermatitis syndrome). Spectinomycin is ineffective against pharyngeal GC/incubating syphilis. PRNG are tetracycline-resistant (TRNG). GC strains from Hawaii/California have increased quinolone resistance; use cefixime or ceftriaxone for such strains. Treat possible Chlamydia trachomatis co-infection and sexual partners. |
| Neisseria meningitidis | • CSF = P (ABM)<br>• Blood = P (acute/chronic meningococcemia)<br>• Sputum = C, P (only in closed populations, e.g., military recruits) | Penicillin (IV)<br>Ampicillin (IV)<br>Any 3rd generation cephalosporin (IV) | Chloramphenicol (IV)<br>Cefepime (IV)<br>Meropenem (IV) | In ABM, do not decrease meningeal dose of β-lactam antibiotics as patient improves, since CSF penetration/concentration decreases as meningeal inflammation decreases. Chloramphenicol is an excellent choice for penicillin-allergic patients. Preferred meningococcal prophylaxis is an oral quinolone (single dose). |

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| | • Urine C, P (urethritis rarely)<br>• Stool = NP<br>• Wound = NP | | | |
| **GRAM-POSITIVE BACILLI** | | | | |
| Arcanobacterium (Corynebacterium) haemolyticum | • CSF = NP<br>• Blood = NP<br>• Sputum = P (oropharyngeal secretions)<br>• Urine = NP<br>• Stool/Wound = NP | Doxycycline (PO) | Erythromycin (PO)<br>Azithromycin (PO)<br>Any 1st, 2nd, 3rd generation cephalosporin (PO)<br>Clarithromycin XL (PO) | Causes membranous pharyngitis with scarlet fever-like rash. Differentiate from C. diphtheriae by culture. Penicillin and ampicillin are less effective than erythromycin or doxycycline. |
| Bacillus anthracis (naturally acquired) (For potential bioterrorist anthrax, see p. 173) | • CSF = P (ABM)<br>• Blood = P (septicemia; isolation required; dangerous)<br>• Sputum = P (mediastinitis; anthrax pneumonia rare)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (ulcer; isolation required; dangerous) | Penicillin (IV)<br>Doxycycline (IV/PO)<br>Any quinolone (IV/PO) | Amoxicillin (PO)<br>Ampicillin (IV) | Doxycycline may be used for therapy/outbreak prophylaxis. Streptobacillary configuration in blood. Causes hemorrhagic meningitis, wound infections, and bacteremia. Quinolones are effective. Alert microbiology laboratory of potentially biohazardous specimens. |
| Bacillus cereus, subtilis, megaterium | • CSF = NP<br>• Blood = C*, P (leukopenic compromised hosts) | Vancomycin (IV)<br>Clindamycin (IV/PO) | Meropenem (IV)<br>Any quinolone (IV/PO) | Soil organisms not commonly pathogenic for humans. Suspect pseudoinfection if isolated from clinical specimens. Look for soil/dust contamination of blood culture tube top/ |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-POSITIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | | | apparatus. Rare pathogen in leukopenic compromised hosts. |
| Corynebacterium diphtheriae | • CSF = NP<br>• Blood = NP<br>• Sputum = P (oropharyngeal secretions)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (wound diphtheria) | Penicillin (IV)<br>Erythromycin (IV)<br>Clindamycin (IV/PO) | Doxycycline (IV/PO)<br>Clarithromycin XL (PO)<br>Rifampin (PO) | Administer diphtheria antitoxin as soon as possible (p. 170). Antibiotic therapy is adjunctive, since diphtheria is a toxin-mediated disease. Patients may die unexpectedly from toxin-induced myocarditis during recovery. |
| Corynebacterium jeikeium (JK) | • CSF = C*, P (CSF shunts)<br>• Blood = C*, P (from IV lines)<br>• Sputum = NP<br>• Urine/Stool = NP<br>• Wound = C | Vancomycin (IV)<br>Linezolid (IV/PO) | Quinupristin/ dalfopristin (IV) | Cause of IV line/foreign body infections. In-vitro testing is not always reliable. Highly resistant to most anti-gram positive antibiotics. |
| Erysipelothrix rhusiopathiae | • CSF = NP<br>• Blood = P (from SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (chronic erysipelas-like skin lesions) | Penicillin (IV)<br>Ampicillin (IV) | Any 3rd generation cephalosporin (IV)<br>Any quinolone (IV/PO) | Cause of "culture-negative" SBE. Susceptible to clindamycin but resistant to vancomycin. |

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| Listeria monocytogenes | • CSF = P (ABM)<br>• Blood = P (1° bacteremia, SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Ampicillin (IV)<br>Amoxicillin (PO)<br>Chloramphenicol (IV)<br><br>CNS<br>Ampicillin (IV)<br>TMP–SMX (IV/PO)<br>Chloramphenicol (IV/PO)<br><br>SBE<br>Ampicillin (IV) | Doxycycline (IV/PO)<br>Erythromycin (IV)<br>Meropenem (IV)<br><br>CNS<br>Meropenem (IV) (Meningeal dosed)<br>Linezolied (IV/PO)<br><br>SBE<br>Meropenem (IV)<br>Linezolied (IV/PO) | Listeria ABM is common in T-cell deficiencies (e.g., lymphoma, steroids, HIV). Causes SBE in normal hosts, and is the commonest cause of bacteremia in non-neutropenic cancer patients. 3rd generation cephalosporins are ineffective against Listeria. |
| Nocardia asteroides, brasiliensis | • CSF = P (brain abscess)<br>• Blood = P (from lung/soft tissue source)<br>• Sputum = P (pneumonia, lung abscess)<br>• Urine/Stool = NP<br>• Wound = P (skin lesions from direct inoculation or dissemination) | TMP–SMX (IV/PO)<br>Minocycline (IV/PO) | Imipenem (IV) plus either amikacin (IV) or any 3rd generation cephalosporin (IV) | Branched, filamentous, beady hyphae are typical, but coccobacillary and bacillary forms are also common. Nocardia are gram-positive, aerobic, and acid fast. Linezolid is active against Nocardia and may be effective if other agents cannot be used. Quinolones and macrolides are usually ineffective. |
| Rhodococcus equi | • CSF = NP<br>• Blood = P (from<br>• pneumonia, lung abscess)<br>• Sputum = P (pneumonia with abscess/cavitation) | Any quinolone (IV/PO)<br>Vancomycin (IV) | Erythromycin (IV)<br>Imipenem (IV)<br>Meropenem (IV)<br>Doxycycline (IV/PO)<br>TMP–SMX (IV/PO) | Causes TB-like community-acquired pneumonia in AIDS patients. Filamentous bacteria break into bacilli/cocci. Aminoglycosides and β-lactams are relatively ineffective. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| Isolate | Isolate Significance | Preferred Therapy | Alternate Therapy | Comments |
|---|---|---|---|---|
| **GRAM-POSITIVE BACILLI** | | | | |
| | • Urine = NP<br>• Stool = NP<br>• Wound = NP | | | |
| **GRAM-NEGATIVE BACILLI** | | | | |
| Acinetobacter baumannii, lwoffi, calcoaceticus, haemolyticus | • CSF = C*, P (ABM)<br>• Blood = P (from IV line, lung, or urine source)<br>• Sputum = C, P (VAP)<br>• Urine = C, P (CAB)<br>• Stool = NP<br>• Wound = C (common), P (rare) | Any carbapenem (IV)<br>Ampicillin/ sulbactam (IV)<br>Colistin<br>Polymyxin B<br>Minocycline (IV/PO) | Any 3rd generation cephalosporin (IV) (except ceftazidime)<br>Cefepime (IV)<br>Fosfomycin (PO) | Colonization common; infection uncommon. If possible, avoid treating Acinetobacter colonization in respiratory secretions or urine (CAB). Occurs in outbreaks of ventilator-associated pneumonia. Test susceptibility to each carbapenem (may be susceptible to one but not others). Use meropenem for MDR susceptible isolates. For meropenem resistant MDR isolates, use colistin, polymyxin B, tigacycline, minocycline, or doripenem. |
| Aeromonas hydrophila | • CSF = NP<br>• Blood = P (from wound, urine, or GI source)<br>• Sputum = NP<br>• Urine = C, P (CAB)<br>• Stool = P (diarrhea)<br>• Wound = P (cellulitis) | Gentamicin (IV)<br>TMP–SMX (IV/PO)<br>Any quinolone (IV/PO) | Doxycycline (IV/PO)<br>Any 3rd generation cephalosporin (IV/PO)<br>Any carbapenem (IV)<br>Aztreonam (IV) | Cause of wound infection, septic arthritis, diarrhea, and necrotizing soft tissue infection resembling gas gangrene. |
| Aggregatibacter (Actinobacillus) actinomycetem-comitans | • CSF = NP<br>• Blood = P (from abscess, SBE)<br>• Sputum = NP<br>• Urine/Stool = NP | Any quinolone (IV/PO)<br>Any 3rd generation cephalosporin (IV/PO) | Penicillin (IV) + gentamicin (IV)<br>TMP–SMX (IV/PO) | Cause of "culture-negative" SBE. One of the HACEK organisms. Found with Actinomyces in abscesses. Resistant to erythromycin and clindamycin. |

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| | • Wound = P (from abscess, draining fistulous tract) | | | |
| Alcaligenes (Achromobacter) xylosoxidans | • CSF = P (rarely ABM)<br>• Blood = P (from urine)<br>• Sputum = NP<br>• Urine = P (CAB)<br>• Stool = NP<br>• Wound = P (cellulitis rare) | Imipenem (IV)<br>Meropenem (IV)<br>Any 3rd generation cephalosporin (IV/PO) | Any quinolone (IV/PO)<br>Cefepime (IV)<br>Aztreonam (IV) | Water-borne pathogen resembling Acinetobacter microbiologically. Resistant to aminoglycosides and 1st, 2nd generation cephalosporins. |
| Bartonella henselae, quintana, bacilliformis | • CSF = NP<br>• Blood = P (from skin source, SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (skin lesions) | Doxycycline (IV/PO)<br>Azithromycin (PO) | Clarithromycin XL (PO)<br>Any quinolone (IV/PO)<br>Any aminoglycoside (IV) | B. henselae (bacteremia, endocarditis, peliosis hepatis, bacillary angiomatosis); B. quintana (relapsing, trench fever, bacillary angiomatosis); B. bacilliformis (Oroyo fever, Carrion's disease). May present as FUO. Titers may cross react with C. burnetii (Q fever). TMP–SMX and cephalosporins are ineffective. |
| Bordetella pertussis, parapertussis | • CSF = NP<br>• Blood = P (from respiratory tract source)<br>• Sputum = C, P (pertussis)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Erythromycin (IV)<br>Clarithromycin XL (PO)<br>Azithromycin (IV/PO) | Any quinolone (IV/PO)<br>TMP–SMX (IV/PO)<br>Doxycycline (IV/PO) | Causes pertussis in children and incompletely/non-immunized adults. Macrolides remain the preferred therapy. Resistant to penicillins, cephalosporins, and aminoglycosides. |
| Brucella abortus, canis, suis, melitensis | • CSF = P (meningitis)<br>• Blood = P (from abscess, SBE) | Doxycycline (IV/PO) + gentamicin (IV) | TMP–SMX (IV/PO) + gentamicin (IV) | Causes prolonged relapsing infection. Zoonotic cause of brucellosis/Malta fever. Resistant to penicillins. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Sputum = NP<br>• Urine = P (pyelonephritis)<br>• Stool/Wound = NP | Doxycycline + streptomycin (IM) | Doxycycline (IV/PO) + rifampin (PO)<br>Any quinolone (IV/PO) + rifampin (PO) | |
| Burkholderia (Pseudomonas) cepacia | • CSF = NP<br>• Blood = P (usually from IV line/urinary tract infection)<br>• Sputum = C (not a cause of VAP)<br>• Urine = C<br>• Stool = NP<br>• Wound = NP | TMP–SMX (IV/PO)<br>Minocycline (IV/PO) | A "respiratory quinolone" (IV/PO)<br>Chloramphenicol (IV/PO) | Rare cause of urosepsis following urologic instrumentation. Common water-borne colonizer in intensive care units. Opportunistic pathogen in cystic fibrosis/bronchiectasis. Resistant to aminoglycosides, colistin, and polymyxin B. |
| Burkholderia (Pseudomonas) pseudomallei | • CSF = NP<br>• Blood = P (from septicemic melioidosis)<br>• Sputum = P (chronic cavitary pneumonia)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Imipenem (IV)<br>Meropenem (IV)<br>Ceftazidime (IV)<br>Doxycycline (IV/PO) | Chloramphenicol (IV)<br>TMP–SMX (IV/PO)<br>Amoxicillin/clavulanic acid (PO) | Acute (septicemia)/chronic (cavitary CAP/abscesses) melioidosis endemic in S.E. Asia. Chronic melioidosis resembles reactivation TB, but has lower lobe distribution. Prolonged latency until reactivation years later. Slow response to effective therapy (1–2 weeks). Prolonged therapy needed to prevent relapse (≥ 3 months). Oxidase positive. Resistant to penicillin, aminoglycosides, colistin. |
| Campylobacter fetus | • CSF = P (ABM)<br>• Blood = P (from vascular source) | Gentamicin (IV)<br>Imipenem (IV)<br>Meropenem (IV) | Chloramphenicol (IV)<br>Ampicillin (IV) | Causes invasive infection with spread to CNS. CNS infection may be treated with meningeal doses of chloramphenicol, ampicillin, |

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| | • Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | | Any 3rd generation cephalosporin (IV) | or a 3rd generation cephalosporin. Resistant to erythromycin. |
| Campylobacter jejuni | • CSF = NP<br>• Blood = P (from GI source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (diarrhea)<br>• Wound = NP | Any quinolone (IV/PO)<br>Erythromycin (PO)<br>Doxycycline (IV/PO) | Azithromycin (PO)<br>Clarithromycin XL (PO) | Commonest cause of acute bacterial diarrhea. Resistant to TMP–SMX. |
| Cardiobacterium hominis | • CSF = NP<br>• Blood = P (from SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Penicillin (IV) + gentamicin (IV)<br>Ampicillin (IV) + gentamicin (IV) | Any 3rd generation cephalosporin (IV) + gentamicin (IV) | Pleomorphic bacillus with bulbous ends. Often appears in clusters resembling rosettes. Indole positive. Cause of "culture-negative" SBE (one of the HACEK organisms). Rare cause of abdominal abscess. Grows best with $CO_2$ enhancement. Resistant to macrolides and clindamycin. |
| Chromobacterium violaceum | • CSF = NP<br>• Blood = P (from wound infection)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (drainage from deep soft tissue infection) | Gentamicin (IV)<br>Doxycycline (IV/PO) | Chloramphenicol (IV) | Cause of cutaneous lesions primarily in tropical/subtropical climates. Often mistaken for Vibrio or Alcaligenes. Resistant to β-lactams. |
| Chryseobacterium (Flavobacterium) meningosepticum | • CSF = P (ABM)<br>• Blood = P (from IV line infection, PVE)<br>• Sputum = NP | CNS<br>TMP–SMX (IV/PO) | CNS<br>Chloramphenicol (IV) | Rare cause of ABM in newborns and PVE in adults. Only unencapsulated Flavobacterium species. Clindamycin, clarithromycin, and vancomycin are useful only in non-CNS |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
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| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Urine = C, P (from urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (cellulitis) | Non-CNS<br>Vancomycin (IV) + rifampin (PO)<br>Any quinolone (IV/PO) | Non-CNS<br>Clarithromycin XL (PO) + rifampin (PO)<br>Clindamycin (IV/PO) | infections. Resistant to aztreonam and carbapenems. |
| Citrobacter diversus, freundii, koseri | • CSF = C*, P (from NS procedure)<br>• Blood = C*, P (from IV line/urinary tract infection)<br>• Sputum = C (not pneumonia)<br>• Urine = C, P (from urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (rarely in compromised hosts) | Any carbapenem (IV)<br>Cefepime (IV)<br>Any quinolone (IV/PO) | Aztreonam (IV)<br>Piperacillin (IV)<br>Any 3rd generation cephalosporin (IV) | Common wound/urine colonizer. Rare pathogen in normal hosts. Often aminoglycoside resistant. (C. freundii is usually more resistant than C. koseri). |
| Edwardsiella tarda | • CSF = NP<br>• Blood = P (from liver abscess)<br>• Sputum/Urine = NP<br>• Stool = P<br>• Wound C, P (wound infection) | Ampicillin (IV)<br>Amoxicillin (PO)<br>Any quinolone (IV/PO) | Doxycycline (IV/PO)<br>Any 3rd generation cephalosporin (IV/PO) | Cause of bacteremia, usually from liver abscess or wound source. |

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| Enterobacter agglomerans, aerogenes, cloacae | • CSF = C*, P (from NS procedure)<br>• Blood = C*, P (from IV line/urinary tract infection)<br>• Sputum = C (not a cause of pneumonia)<br>• Urine = C, P (post-urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (rarely in compromised hosts) | Any carbapenem (IV) | Any quinolone (IV/PO)<br>Aztreonam (IV)<br>Piperacillin (IV)<br>Cefepime (IV) | Not a cause of community-acquired or nosocomial pneumonia. Common colonizer of respiratory secretions and wound/urine specimens. Antibiotic resistance to E. cloacae > E. aerogenes > E. agglomerans. Treatment of Enterobacter colonizers with ceftazidime or ciprofloxacin may result in MDR/ESBL Enterobacter sp.<br><br>CRE usually susceptible only to tigacycline, colistin, polymyxin B, ceftazidime/avibactam, fosfomycin. |
| Escherichia coli | • CSF = P (ABM)<br>• Blood = P (from GI/GU source)<br>• Sputum = P (rarely CAP from urinary source, VAP)<br>• Urine = C, P (CAB, cystitis, pyelonephritis)<br>• Stool = C, P<br>• (diarrhea)<br>• Wound = P (cellulitis) | Any 1st, 2nd, 3rd generation cephalosporin (IV/PO)<br>Amoxicillin (PO)<br>Any quinolone (IV/PO)<br>Ceftriaxone (IV)<br>Nitrofurantoin (PO) (UTIs only) | Aztreonam (IV)<br>Gentamicin (IV)<br>TMP–SMX (IV/PO) | Common pathogen, usually from GI/GU source. Many strains are resistant to ampicillin and some to 1st generation cephalosporins. ESBL-producing E. coli may be treated with a carbepenem.<br><br>CRE usually susceptible only to tigacycline, colistin, polymyxin B, ceftazidime/avibactam, fosfomycin. |
| Francisella tularensis | • CSF = NP<br>• Blood = P (isolation dangerous)<br>• Sputum = P (tularemic pneumonia; isolation dangerous) | Doxycycline (IV/PO)<br>Gentamicin (IV/IM)<br>Streptomycin (IM) | Chloramphenicol (IV/PO)<br>Any quinolone (IV/PO) | Six clinical tularemia syndromes. Alert microbiology laboratory of potentially biohazardous specimens. Do not culture. Resistant to penicillins and cephalosporins. Bioterrorist tularemia is treated the same as naturally-acquired tularemia. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Urine/Stool = NP<br>• Wound = P (isolation dangerous) | | | |
| Hafnia alvei | • CSF = C, P (from NS procedure)<br>• Blood = C*, P (from IV line/urinary tract infection)<br>• Sputum = C (not pneumonia)<br>• Urine = C, P (post-urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (rarely in compromised hosts) | Cefepime (IV)<br>Any quinolone (IV/PO)<br>Aztreonam (IV) | Piperacillin (IV)<br>Imipenem (IV)<br>Meropenem (IV) | Formerly Enterobacter hafniae. Uncommon nosocomial pathogen. Rarely pathogenic in normal hosts. Cause of UTIs in compromised hosts. |
| Helicobacter (Campylobacter) pylori | • CSF = NP<br>• Blood = NP<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (from upper GI tract biopsy specimens, not stool)<br>• Wound = NP | Omeprazole (PO) + clarithromycin XL (PO)<br>Omeprazole (PO) + amoxicillin (PO)<br>Metronidazole (PO) + amoxicillin (PO) + bismuth subsalicylate (PO) | Doxycycline (PO) + metronidazole (PO) + bismuth subsalicylate (PO) | Optimal therapy awaits definition. Treat until cured. Some strains of resistant H. pylori may respond to treatment with a quinolone. TMP–SMX is ineffective. |

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| Haemophilus influenzae, parainfluenzae, aphrophilus, paraphrophilus | • CSF = P (ABM)<br>• Blood = P (from respiratory tract or cardiac source)<br>• Sputum = C, P (CAP)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P | For all Haemophilus species<br>Any 2nd, 3rd generation cephalosporin (IV/PO)<br>Any quinolone (IV/PO)<br>Doxycycline (IV/PO) | For all Haemophilus species<br>Chloramphenicol (IV)<br>TMP–SMX (IV/PO)<br>Azithromycin (PO)<br>Aztreonam (IV)<br>Ampicillin-resistant H. influenzae<br>Meropenem (IV)<br>Imipenem (IV)<br>Ertapenem (IV)<br>Cefepime (IV)<br>Aztreonam (IV) | 1st generation cephalosporins, erythromycin, and clarithromycin have limited anti-H. influenzae activity; doxycycline and azithromycin are better. Hemophilus species are common colonizers of the respiratory tract. Rarely a cause of "culture-negative" SBE (H. parainfluenzae/aphrophilus are HACEK organisms). H. influenzae and H. parainfluenzae (pathogens) may be differentiated from the throat commensals H. hemolyticus and H. parahemolyticus (non-pathogens) by hemolysis on sheep agar. |
| Kingella (Moraxella) kingae | • CSF = NP<br>• Blood = P (from skeletal or cardiac source)<br>• Sputum = C<br>• Urine = NP<br>• Stool/wound = NP | Ampicillin (IV) + any aminoglycoside (IV) | Any 3rd generation (IV) cephalosporin + any aminoglycoside (IV)<br>Imipenem (IV)<br>Meropenem (IV)<br>Any quinolone (IV/PO) | Common colonizer of respiratory tract, but rarely a respiratory pathogen. Causes septic arthritis/osteomyelitis in children and endocarditis in adults (one of HACEK organisms). Oxidase positive. Growth enhanced with $CO_2$. |
| Klebsiella pneumoniae, oxytoca | • CSF = P (ABM)<br>• Blood = P (from respiratory, GI, GU source) | Tigecycline (IV)<br>Any carbapenem (IV) | Any 3rd generation cephalosporin (IV, PO) except ceftazidine<br>Any quinolone (IV/PO) | TMP–SMX may be ineffective in systemic infection. Anti-pseudomonal penicillins have limited anti-Klebsiella activity. Klebsiella usually susceptible to carbapenems. CRE usually susceptible only to tigecycline, colistin, polymyxin B, ceftazidime/avibactam, fosfomycin. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Sputum = C, P (CAP/VAP)<br>• Urine = C (CAB), P<br>• Stool = NP<br>• Wound = C, P | | Aztreonam (IV)<br>Cefepime (IV) | NDM-1 metallo β-lactamase strains are carbapenem resistant and usually susceptible only to colistin, tigacycline. |
| Klebsiella ozaenae, rhinoscleromatis | • CSF = NP<br>• Blood = NP<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (rhinoscleromatis lesions) | Any quinolone (PO) | TMP–SMX (PO) + rifampin (PO) | Skin infection usually requires prolonged treatment for cure (weeks-to-months). |
| Legionella sp. | • CSF = NP<br>• Blood = NP<br>• Sputum = P (CAP or VAP)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Any quinolone (IV/PO)<br>Doxycycline (IV/PO)<br>Tigacycline (IV)<br>Azithromycin (IV/PO) | Clarithromycin XL (PO)<br>Erythromycin (IV)<br>Telithromycin (PO) | Anti-Legionella activity: quinolones > doxycycline > erythromycin. Erythromycin failures are not uncommon. Rarely a cause of culture-negative SBE/PVE. |
| Leptospira interrogans | • CSF = P (ABM)<br>• Blood = P (1° bacteremia)<br>• Sputum = NP<br>• Urine = P (excreted in urine)<br>• Stool = NP<br>• Wound = NP | Doxycycline (IV/PO) Penicillin G (IV)<br>Any 3rd generation cephalosporin (IV/PO) | Amoxicillin (PO) | Blood/urine cultures may be positive during initial/bacteremic phase, but are negative during immune phase. Relapse is common. Resistant to chloramphenicol. |

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| Moraxella (Branhamella) catarrhalis | • CSF = NP<br>• Blood = P (rarely from CAP)<br>• Sputum = C, P (CAP)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Any 2nd, 3rd generation cephalosporin (IV/PO)<br>Any quinolone (IV/PO)<br>Telithromycin (PO)<br>Doxycycline (IV/PO) | Azithromycin (PO)<br>Clarithromycin XL (PO)<br>TMP–SMX (IV/PO)<br>Amoxicillin/ clavulanic acid (PO) | Almost all strains are β-lactamase positive and resistant to penicillin/ampicillin. β-lactamase-resistant β-lactams are effective. Resembles Acinetobacter on sputum gram stain. |
| Morganella morganii | • CSF = NP<br>• Blood = P (from GU source)<br>• Sputum = NP<br>• Urine = P (CAB, cystitis, pyelonephritis)<br>• Stool = NP<br>• Wound = P (cellulitis rare) | Any quinolone (IV/PO)<br>Any 3rd generation cephalosporin (IV)<br>Any carbapenem (IV) | Any aminoglycoside (IV)<br>Aztreonam (IV)<br>Cefepime (IV) | Common uropathogen. Causes bacteremia with urosepsis. Rare cause of wound infections. |
| Ochrobactrum anthropi (CDC group Vd) | • CSF = NP<br>• Blood = P (from IV line infections)<br>• Sputum = C<br>• Urine = C<br>• Stool/Wound = C | Any quinolone (IV/PO)<br>TMP–SMX (IV/PO) | Any aminoglycoside (IV)<br>Imipenem (IV)<br>Meropenem (IV) | Pathogen in compromised hosts. Oxidase and catalase positive. Resistant to β-lactams. |
| Pasteurella multocida | • CSF = P (ABM)<br>• Blood = P (from respiratory source, bite wound/abscess)<br>• Sputum = C, P (CAP, bronchiectasis) | Amoxicillin (PO)<br>Doxycycline (IV/PO)<br>Penicillin G (IV) | Ampicillin/ sulbactam (IV)<br>Piperacillin (IV)<br>Any quinolone (IV/PO) | Common cause of infection following dog/ cat bites. Many antibiotics are effective, but erythromycin is ineffective. Resembles Hemophilus sp. on sputum gram stain. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | • Urine = C, P (pyelonephritis)<br>• Stool = NP<br>• Wound = P (human/animal bites) | | | |
| Plesiomonas shigelloides | • CSF = NP<br>• Blood = P (from GU source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (diarrhea)<br>• Wound = NP | Any quinolone (PO)<br>TMP–SMX (PO) | Doxycycline (PO)<br>Aztreonam (PO) | Infrequent cause of diarrhea, less commonly dysentery. Oxidase positive. β-lactamase strains are increasing. Resistant to penicillins. |
| Proteus mirabilis, vulgaris | • CSF = NP<br>• Blood = P (from urinary source)<br>• Sputum = C<br>• Urine = C, P (from urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (wound infection) | P. mirabilis, indole (–)<br>Ampicillin (IV)<br>Any 1st, 2nd, 3rd gen. cephalosporin (IV/PO)<br>P. vulgaris, indole (+)<br>Any 3rd generation cephalosporin (IV/PO)<br>Cefepime (IV)<br>Any quinolone (IV/PO) | P. mirabilis, indole (–)<br>TMP–SMX (IV/PO)<br>Amoxicillin (PO)<br>P. vulgaris, indole (+)<br>Aztreonam (IV) Any carbapenem (IV)<br>Any aminoglycoside (IV) | Usually a uropathogen. Most antibiotics are effective against P. mirabilis (indole-negative); P. penneri (indole-negative P. vulgaris) is resistant to ceftriaxone. Indole-positive Proteus sp. require potent antibiotics to treat non-UTIs. P. penneri (indole-negative P. vulgaris) resistant to 3rd gen. cephalosporins; use cefepime, carbapenem, or quinolone. |

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| Providencia alcalifaciens, rettgeri, stuartii | • CSF = NP<br>• Blood = C*, P (from GU source)<br>• Sputum/Stool = NP<br>• Urine = C, P<br>• Wound = C, P (rare) | Any quinolone (IV/PO)<br>Any 3rd generation cephalosporin (IV/PO)<br>Cefepime (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Any aminoglycoside (IV)<br>Aztreonam (IV)<br>Piperacillin (IV)<br>Imipenem (IV) | Almost always a uropathogen. Formerly classified as indole-positive Proteus. |
| Pseudomonas aeruginosa | • CSF = NP<br>• Blood = P (from respiratory, GU source)<br>• Sputum = C (usually), P (rarely indicates VAP)<br>• Urine = C, P (from urologic instrumentation)<br>• Stool = NP<br>• Wound = C (almost always) | Monotherapy<br>Meropenem (IV)<br>Cefepime (IV)<br>Combination therapy<br>either meropenem (IV) or cefepime (IV) *plus* amikacin | Doripenem (IV)<br>Colistin (IV)<br>Polymyxin B (IV)<br>Amikacin (IV)<br>Aztreonam (IV) | Colonization common; infection uncommon.<br>If possible, avoid treating P. aeruginosa in respiratory secretions in ventilated patients (unless tracheobronchitis) or urine cultures (CAB).<br>For serious systemic P. aeruginosa infection, double-drug therapy preferred. All double anti-P. aeruginosa regimens are equally effective.<br>Individual differences in activity (MICs) are unimportant if combination therapy is used.<br>If MDR P. aeruginosa meropenem susceptible, treat with meropenem. If MDR P. aeruginosa meropenem resistant, treat with colistin, polymyxin B, or doripenem. |
| Pseudomonas (Chryseomonas) luteola (CDC group Ve-1) | • CSF = NP<br>• Blood = P (from IV line infection)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Imipenem (IV)<br>Meropenem (IV)<br>Cefepime (IV) | Piperacillin/tazobactam (IV)<br>Aztreonam (IV) | Opportunistic pathogen primarily in compromised hosts. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
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| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Pseudomonas (Flavimonas) oryzihabitans (CDC group Ve-2) | • CSF = P (NS procedures)<br>• Blood = P (from IV line infection)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (rare) | Imipenem (IV)<br>Meropenem (IV)<br>Cefepime (IV) | Any 3rd generation cephalosporin (IV)<br>Piperacillin (IV)<br>Aztreonam (IV) | Rare cause of central IV line infections in compromised hosts (usually in febrile neutropenics). Rare cause of peritonitis in CAPD patients. Oxidase negative, unlike other Pseudomonas species. |
| Salmonella typhi, non-typhi | • CSF = NP<br>• Blood = P (from GI source)<br>• Sputum = NP<br>• Urine = P (only with enteric fever)<br>• Stool = C (carrier), P (gastroenteritis, enteric fever)<br>• Wound = NP | Any quinolone (IV/PO)<br>Any 3rd generation cephalosporin (IV) | Chloramphenicol (IV)<br>TMP–SMX (IV/PO)<br>Doxycycline (IV/PO) | Carrier state is best eliminated by a quinolone or TMP–SMX. If drug therapy fails to eliminate carrier state, look for hepatic/bladder calculi for persistent focus. Many strains are resistant to ampicillin/amoxicillin. |
| Serratia marcescens | • CSF = P (from NS procedures)<br>• Blood = P (from IV line or urinary source)<br>• Sputum = C, P (rarely in VAP)<br>• Urine = C, P (post-urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (rare) | Any 3rd generation cephalosporin (IV/PO) (except ceftazidime)<br>Any quinolone (IV/PO)<br>Cefepime (IV) | Any carbapenem (IV)<br>Gentamicin (IV)<br>Aztreonam (IV)<br>Piperacillin (IV) | Enterobacteriaceae. Associated with water sources. Common colonizer of respiratory secretions/urine in ICU. Serratia nosocomial pneumonia and PVE are rare. Cause of septic arthritis, osteomyelitis, and SBE (IV drug abusers). Among the aminoglycosides, gentamicin has the greatest anti-Serratia activity. |

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| Shigella boydii, sonnei, flexneri, dysenteriae | • CSF = NP<br>• Blood = P (from GI source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (Shigella dysentery)<br>• Wound = NP | Any quinolone (IV/PO) | TMP–SMX (IV/PO)<br>Azithromycin (IV/PO) | No carrier state. Severity of dysentery varies with the species: S. dysenteriae (most severe) > S. flexneri > S. sonnei/boydii (least severe). |
| Steno-trophomonas (Pseudomonas, Xanthomonas) maltophilia | • CSF = C, P (from NS procedures)<br>• Blood = C*, P (from IV line infection, GU source)<br>• Sputum = C (not VAP)<br>• Urine = C, P (from urologic instrumentation)<br>• Stool = NP<br>• Wound = C, P (rarely in compromised hosts) | TMP–SMX (IV/PO)<br>Minocycline (IV/PO) | Cefepime (IV)<br>Any respiratory quinolone (IV/PO) | Potential pulmonary pathogen only in bronchiectasis/cystic fibrosis. Resistant to aminoglycosides and carbapenems. Although usually carbapenem resistant, ~60% of strains demonstrate synergy with meropenem + levofloxacin. Susceptible to chloramphenicol, rifampin, colistin, polymyxin B. |
| Streptobacillus moniliformis | • CSF = P (brain abscess)<br>• Blood = P (from wound)<br>• Sputum = P (lung abscess)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (from rat bite) | Penicillin (IV)<br>Ampicillin (IV)<br>Amoxicillin (PO) | Oxycycline (IV/PO)<br>Erythromycin (IV)<br>Clindamycin (IV/PO) | Cause of Haverhill fever and rat-bite fever, with abrupt onset of severe headache/arthralgias after bite wound has healed. No regional adenopathy. Morbilliform/petechial rash. Arthritis in 50%. May cause SBE. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
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| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Vibrio cholerae | • CSF = NP<br>• Blood = P (from GI source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (cholera)<br>• Wound = NP | Doxycycline (IV/PO)<br>Any quinolone (IV/PO) | TMP–SMX (IV/PO) | No carrier state. Treat for 3 days. Single-dose therapy is often effective. Resistant to ampicillin. |
| Vibrio parahaemolyticus | • CSF = NP<br>• Blood = P (from GI source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (diarrhea)<br>• Wound = P | Doxycycline (IV/PO) | Any quinolone (IV/PO) | Most cases of gastroenteritis caused by V. parahaemolyticus are self-limited and require no treatment. |
| Vibrio vulnificus, alginolyticus | • CSF = NP<br>• Blood = P (from GI/ wound source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = P (diarrhea)<br>• Wound = P (water-contaminated wound raw oysters, other shell fish ingestion) | Doxycycline (IV/PO)<br>Any quinolone (IV/PO) | Piperacillin (IV)<br>Ampicillin/ sulbactam (IV) | Causes necrotizing soft tissue infection resembling gas gangrene. Patients are critically ill with fever, bullous lesions, diarrhea, and hypotension. Treat wound infection, bacteremia. Aminoglycoside susceptibilities are unpredictable. |
| Yersinia enterocolitica | • CSF = NP<br>• Blood = P (from GI source) | Any quinolone (IV/PO) | TMP–SMX (IV/PO)<br>Any 3rd generation cephalosporin (IV/PO) | Cause of diarrhea with abdominal pain. If pain in is right lower quadrant, may be mistaken for acute appendicitis. |

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|---|---|---|---|---|
| | • Sputum = NP<br>• Urine = NP<br>• Stool = P (diarrhea)<br>• Wound = NP | Gentamicin (IV)<br>Doxycycline (IV/PO) | | |
| Yersinia pestis | • CSF = NP<br>• Blood = P (septicemic plague; isolation required; dangerous)<br>• Sputum = P (pneumonic plague; isolation required; dangerous)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (lymph nodes, lymph node drainage; bubonic plague; isolation required; dangerous) | Doxycycline (IV/PO)<br>Streptomycin (IM)<br>Gentamicin (IV/IM)<br>Any quinolone (IV/PO) | Chloramphenicol (IV/PO) | Cause of bubonic, septicemic, and pneumonic plague. Doxycycline or any quinolone may be used for prophylaxis. Alert microbiology laboratory of potentially biohazardous specimens. Do not culture. Bioterrorist plague is treated the same as naturally-acquired plague. |
| **SPIROCHETES** | | | | |
| Borrelia burgdorferi | • CSF = P (neuroborreliosis)<br>• Blood = P (rarely isolated; requires special media)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (rarely isolated from erythema migrans lesions) | Doxycycline (PO)<br>Amoxicillin (PO) | Any cephalosporin (PO)<br>Azithromycin (PO)<br>Erythromycin (PO) | Cause of Lyme disease. β-lactams and doxycycline are effective. Erythromycin least effective for erythema migrans. Minocycline may be preferred to doxycycline for neuroborreliosis. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.6. Usual Clinical Significance of AEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| SPIROCHETES | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Borrelia recurrentis | • CSF = P (ABM)<br>• Blood = P (1° bacteremia)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Doxycycline (IV/PO)<br>Azithromycin (IV/PO) | Erythromycin (IV)<br>Penicillin (IV)<br>Ampicillin (IV)<br>Any 1st, 2nd, 3rd generation cephalosporin (IV/PO) | Cause of relapsing fever. May be recovered from septic metastatic foci. Septic emboli may cause sacroiliitis, SBE, myositis, orchitis, or osteomyelitis. |
| Spirillum minus | • CSF = NP<br>• Blood = P (from wound source, SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (from rat bite) | Penicillin (IV)<br>Amoxicillin (PO) | Doxycycline (IV/PO)<br>Any quinolone (IV/PO) | Cause of rat-bite fever. Bite wound heals promptly, but 1–4 weeks later becomes painful, purple and swollen, and progresses to ulceration and eschar formation. Painful regional adenopathy. Central maculopapular rash is common (rarely urticarial). Arthralgias/arthritis is rare compared to rat-bite fever from Streptobacillus moniliformis. Rarely causes SBE. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO.* *See p. xi for all other abbreviations.*

**Table 3.7. Clinical Significance of CAPNOPHILIC Isolates Pending Susceptibility Testing**

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Capnocytophaga canimorsus/ cynodegni (DF-2 like) | • CSF = NP<br>• Blood = P (from GI source, bite wound)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (from dog/cat bite) | Ampicillin/ sulbactam (IV)<br>Piperacillin/ tazobactam (IV)<br>Imipenem (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Clindamycin (IV/PO)<br>Any quinolone (IV/PO)<br>Doxycycline (IV/PO) | Associated with animal bites or cancer. May cause fatal septicemia in cirrhotics/asplenics. Resistant to aminoglycosides, metronidazole, TMP–SMX, and aztreonam. |
| Capnocytophaga ochraceus (DF-1) | • CSF = NP<br>• Blood = P (from GI, wound, abscess source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P | Ampicillin/ sulbactam (IV)<br>Piperacillin/ tazobactam (IV)<br>Imipenem (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Clindamycin (IV/PO)<br>Any quinolone (IV/PO)<br>Doxycycline (IV/PO) | Thin, spindle-shaped bacilli resemble Fusobacteria morphologically."Gliding motility" seen in hanging drop preparations. Cause of septicemia, abscesses, and wound infections. Resistant to aminoglycosides, metronidazole, TMP–SMX, and aztreonam. |
| Eikenella corrodens | • CSF = NP<br>• Blood = P (SBE in IV drug abusers)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (IV drug abusers) | Penicillin (IV)<br>Ampicillin (IV)<br>Imipenem (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Piperacillin (IV)<br>Ampicillin/ sulbactam (IV)<br>Doxycycline (IV/PO)<br>Amoxicillin (PO) | Cause of "culture-negative" SBE (one of the HACEK organisms). Resistant to clindamycin and metronidazole. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.8. Usual Clinical Significance of ANAEROBIC Isolates Pending Susceptibility Testing**

| GRAM-POSITIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Peptococcus | • CSF = P (brain abscess)<br>• Blood = P (from GI/pelvic source)<br>• Sputum = C, P (aspiration pneumonia, lung abscess)<br>• Urine/Stool = NP<br>• Wound = P (rarely a sole pathogen) | Penicillin (IV)<br>Ampicillin (IV)<br>Amoxicillin (PO)<br>Clindamycin (IV/PO) | Chloramphenicol (IV)<br>Erythromycin (IV)<br>Any carbapenem (IV)<br>Moxifloxacin (IV/PO) | Normal flora of mouth, GI tract, and pelvis. Associated with mixed aerobic/anaerobic dental, abdominal, and pelvic infections, especially abscesses. |
| Peptostreptococcus | • CSF = P (brain abscess)<br>• Blood = P (GI/pelvic source)<br>• Sputum = C, P (aspiration pneumonia, lung abscess)<br>• Urine/Stool = NP<br>• Wound = P (rarely a sole pathogen) | Penicillin (IV)<br>Ampicillin (IV)<br>Amoxicillin (PO)<br>Clindamycin (IV/PO) | Chloramphenicol (IV)<br>Erythromycin (IV)<br>Any carbapenem (IV)<br>Moxifloxacin (IV/PO) | Normal flora of mouth, GI tract, and pelvis. Associated with mixed aerobic/anaerobic dental, abdominal, and pelvic infections, especially abscesses. |
| **GRAM-POSITIVE BACILLI** | | | | |
| Actinomyces israelii, odontolyticus | • CSF = P (brain abscess)<br>• Blood = NP | Amoxicillin (PO)<br>Doxycycline (PO) | Erythromycin (PO)<br>Clindamycin (PO) | Anaerobic and non-acid fast. Usually presents as cervical, facial, thoracic, or abdominal masses/fistulas. Prolonged |

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|---|---|---|---|---|
| | • Sputum = C, P (lung abscess)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (fistulas/ underlying abscess) | | | (6–12 month) treatment is needed for cure. Unlike Nocardia, Actinomyces rarely causes CNS infections. May be cultured from polymicrobial brain abscess of pulmonary origin. Quinolones, aminoglycosides, metronidazole, and TMP–SMX have little activity. |
| Arachnia propionica | • CSF = P (brain abscess)<br>• Blood = P (from dental, GI, lung source)<br>• Sputum = C, P (lung abscess)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Clindamycin (IV/PO)<br>Ampicillin (IV) + gentamicin (IV) | Erythromycin (IV) | Polymicrobial pathogen in dental, lung, and brain abscesses. |
| Bifidobacterium sp. | • CSF = P (brain abscess)<br>• Blood = NP<br>• Sputum = C, P (lung abscess)<br>• Urine/Stool = NP<br>• Wound = NP | Clindamycin (IV/PO)<br>Ampicillin (IV) + gentamicin (IV) | Erythromycin (IV) | Usually part of polymicrobial infection. |
| Clostridium botulinum | • CSF = NP<br>• Blood = NP<br>• Sputum = NP<br>• Urine/Stool = NP<br>• Wound = P (wound botulism) | Penicillin (IV) | Clindamycin (IV/PO)<br>Imipenem (IV)<br>Meropenem (IV) | Give trivalent equine antitoxin (p. 170) as soon as possible. Antibiotic therapy is adjunctive. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.8. Usual Clinical Significance of ANAEROBIC Isolates Pending Susceptibility Testing** (Cont'd)

| GRAM-POSITIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Clostridium difficile | • CSF = NP<br>• Blood = P (rarely from GI source)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = C (normal fecal flora), P (antibiotic-associated diarrhea/colitis)<br>• Wound = NP | C. difficile diarrhea<br>Vancomycin (PO)<br>Nitazoxanide (PO)<br>C. difficile colitis<br>Metronidazole (IV/PO)<br>Nitazoxanide (PO) | C. difficile diarrhea<br>Metronidazole (PO)<br>C. difficile colitis<br>Tigacycline (IV) | **C. difficile diarrhea** PO vancomycin preferred. *PO vancomycin more reliably effective than PO metronidazole.* Nitazoxanide also highly effective. PO metronidazole, not PO vancomycin, increases prevalence of VRE. **C. difficile colitis**, use IV or PO metronidazole (IV vancomycin ineffective). Nitazoxanide (PO) or tigacycline (IV) also highly effective. Diagnose C. difficile diarrhea by stool C. difficile toxin assay/PCR. Diagnose C. difficile colitis by C. difficile + toxin assay/PCR plus colitis on abdominal CT scan/colonoscopy. |
| Clostridium perfringens, septicum, novyi | • CSF = NP<br>• Blood = P (from GI source/malignancy)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (gas gangrene) | Penicillin (IV)<br>Piperacillin/tazobactam (IV)<br>Meropenem (IV)<br>Ertapenem (IV) | Clindamycin (IV)<br>Chloramphenicol (IV)<br>Imipenem (IV) | Usual cause of myonecrosis (gas gangrene). Surgical debridement is crucial; antibiotic therapy is adjunctive. Also causes emphysematous cholecystitis/cystitis. Does not form spores in blood cultures as does C. sordelli. |
| Clostridium tetani | • CSF = NP<br>• Blood = NP | Penicillin (IV)<br>Clindamycin (IV) | Imipenem (IV)<br>Meropenem (IV) | Prompt administration of tetanus immune globulin is crucial (p. 170). Antibiotic therapy is adjunctive. |

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|---|---|---|---|---|
| | • Sputum = NP<br>• Urine/Stool = NP<br>• Wound = P (wound tetanus) | | | |
| Eubacterium sp. | • CSF = P (brain abscess)<br>• Blood = P (from dental, GI, GU, lung source)<br>• Sputum = P (lung abscess)<br>• Urine/Stool = NP<br>• Wound = NP | Clindamycin (IV/PO)<br>Ampicillin (IV) + gentamicin (IV) | Erythromycin (IV) | Pathogen in lung/pelvic/brain abscesses, and chronic periodontal disease. Eubacterium bacteremias are associated with malignancies. |
| Lactobacillus sp. | • CSF = P (ABM)<br>• Blood = P (1° bacteremia, SBE, or from endometritis)<br>• Sputum = NP<br>• Urine = P (rare)<br>• Stool = NP<br>• Wound = NP | Ampicillin (IV) + gentamicin (IV)<br>Clindamycin (IV/PO) | Erythromycin (IV) | Uncommon pathogen in normal/compromised hosts. Rare cause of SBE. Variably resistant to cephalosporins and quinolones. Some clindamycin-resistant strains. Resistant to metronidazole and vancomycin. |
| Propionibacterium acnes | • CSF = C*, P (meningitis from NS shunts)<br>• Blood = C*, P (from IV line infection, SBE)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = C | Penicillin (IV)<br>Clindamycin (IV/PO) | Doxycycline (IV/PO) | Common skin colonizer/blood culture contaminant. Rarely causes prosthetic joint infection, endocarditis, or CNS shunt infection. Resistant to metronidazole. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.8. Usual Clinical Significance of ANAEROBIC Isolates Pending Susceptibility Testing** (cont'd)

| GRAM-NEGATIVE BACILLI | | | | |
|---|---|---|---|---|
| **Isolate** | **Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Bacteroides fragilis group (B. distasonis, ovatus, thetaiotaomicron, vulgatus) | • CSF = P (meningitis from Strongyloides hyperinfection)<br>• Blood = P (from GI/pelvic source)<br>• Sputum = NP<br>• Urine = NP, P (only from colonic fistula)<br>• Stool = NP<br>• Wound = NP | Tigecycline (IV)<br>Piperacillin/tazobactam (IV)<br>Any carbapenem (IV) | Moxifloxacin (IV/PO)<br>Ampicillin/sulbactam (IV)<br>Clindamycin (IV/PO) *or combination of* Metronidazole (IV/PO) *plus either* ceftriaxone (IV) or levofloxacin (IV/PO) | Major anaerobe below the diaphragm. Usually part of polymicrobial lower intra-abdominal and pelvic infections. Cefotetan is less effective against B. fragilis DOT strains (B. distasonis, B. ovatus, B. thetaiotaomicron). Resistant to penicillin. |
| Fusobacterium nucleatum | • CSF = P (brain abscess)<br>• Blood = P (from lung, GI source)<br>• Sputum = P (aspiration pneumonia, lung abscess)<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (rarely) | Clindamycin (IV/PO)<br>Piperacillin/tazobactam (IV)<br>Ampicillin/sulbactam (IV) | Chloramphenicol (IV)<br>Metronidazole (IV/PO) | Mouth flora associated with dental infections and anaerobic lung infections. F. nucleatum is associated with jugular vein septic phlebitis and GI cancer. Resembles Capnophagia sp. on sputum gram stain. |
| Prevotella (Bacteroides) bivia | • CSF = NP<br>• Blood = P (from dental, lung, pelvic source)<br>• Sputum = P (lung abscess) | Penicillin (IV/PO)<br>Any β-lactam (IV/PO) | Any quinolone (IV/PO)<br>Doxycycline (IV/PO)<br>Clindamycin (IV/PO) | Cause of dental, oropharyngeal, and female genital tract infections. |

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|---|---|---|---|---|
| | • Urine = NP<br>• Stool = NP<br>• Wound = NP | | | |
| Prevotella (Bacteroides) melaninogenicus, intermedius | • CSF = P (brain abscess)<br>• Blood = P (from oral/pulmonary source)<br>• Sputum = P (from aspiration pneumonia, lung abscess)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP | Aspiration pneumonia/lung abscess<br>Any β-lactam (IV/PO)<br>Any quinolone (IV/PO)<br><br>Brain abscess<br>Penicillin (IV) | Aspiration pneumonia/lung abscess<br>Doxycycline (IV/PO)<br><br>Brain abscess<br>Chloramphenicol (IV) | Predominant anaerobic flora of mouth. Known as "oral pigmented" Bacteroides (e.g., B. melanogenicus). Antibiotics used to treat community-acquired pneumonia are effective against oral anaerobes (e.g., Prevotella) in aspiration pneumonia; does not require anti-B. fragilis coverage with clindamycin, metronidazole, or moxifloxacin. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

**Table 3.9. Clinical Significance of YEAST/FUNGI Pending Susceptibility Testing**

| YEAST/FUNGI | | | | |
|---|---|---|---|---|
| **Isolate** | ****Usual Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| Aspergillus species | • CSF = P (only from disseminated infection)<br>• Blood = C, P (1° fungemia or from pulmonary source)<br>• Sputum = C, P (pneumonia)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP, P (rarely, but possible with extensive wounds, e.g., burns) | See p. 55:<br>Voriconazole (IV/PO)<br>Amphotericin B lipid formulation (IV) | See p. 55:<br>Posaconazole (PO);<br>Amphotericin B deoxycholate (IV) | A. fumigatus is the usual cause of invasive aspergillosis. Growth of Aspergillus sp. from a specimen can represent airborne contamination. Aspergillus pneumonia and disseminated aspergillosis are not uncommon in patients on chronic steroids or immunosuppressives (esp. organ transplants). Recovery of Aspergillus from sputum or BAL is not diagnostic of Aspergillus pneumonia. Definative Dx is by lung biopsy demonstrating vessel/tissue invasion. β 1,3 D-glucan (BG)+, aspergillus galactomannan (AG)+. |
| Candida albicans | • CSF = P (only from disseminated infection)<br>• Blood = P (1° candidemia or from IV line infection)<br>• Sputum = C, P (only from disseminated infection) | Fluconazole (IV/PO)<br>Micafungin (IV)<br>Caspofungin (IV)<br>Anidulafungin (IV)<br>Posaconazole (PO) | Amphotericin B deoxycholate (IV/PO)<br>Amphotericin B lipid formulation (IV)<br>Itraconazole (IV/PO)<br>Voriconazole (IV/PO) | Common colonizer of GI/GU tracts. Colonization common in diabetics, alcoholics, patients receiving steroids/antibiotics. Commonest cause of fungemia in hospitalized patients. Candidemia secondary to central IV lines should always be treated as possible disseminated disease even though this is not invariably the case. Repeated blood cultures and careful follow-up (including |

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| | • Urine = C, P (from cystitis, pyelonephritis)<br>• Stool = C (source of candiduria)<br>• Wound = NP | | | ophthalmoscopy) should be undertaken to exclude possible occult dissemination following even a single positive blood culture. Primary candidal pneumonia is rare. |
| Candida non-albicans | • CSF = P (only from disseminated infection)<br>• Blood = P (1° candidemia or from IV line infection)<br>• Sputum = NP<br>• Urine = C (indwelling catheters), P (from cystitis, pyelonephritis)<br>• Stool = C (source of candiduria)<br>• Wound = NP | Micafungin (IV)<br>Caspofungin (IV)<br>Anidulafungin (IV)<br>Posaconazole (PO)<br>Voriconazole (IV/PO) | Fluconazole (IV/PO)<br>Amphotericin B deoxycholate (IV/PO)<br>Amphotericin B lipid formulation (IV)<br>Itraconazole (IV/PO) | Non-albicans Candida cause the same spectrum of invasive disease as C. albicans. Fluconazole-susceptibility varies predictably by species. C. glabrata (usually) and C. krusei (almost always) are resistant to fluconazole. C. lusitaniae is often resistant to amphotericin B (deoxycholate and lipid-associated formulations). Other species are generally susceptible to all agents. |
| Cryptococcus neoformans | • CSF = P (meningitis, brain abscess)<br>• Blood = P (from pulmonary source)<br>• Sputum = P (pneumonia)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP* | CNS<br>Amphotericin B deoxycholate (IV) ± flucytosine (PO)<br><br>Non-CNS<br>Amphotericin B deoxycholate (IV) | CNS<br>Fluconazole (IV/PO)<br><br>Non-CNS<br>Itraconazole (IV/PO)<br>Fluconazole (IV/PO) | C. neoformans meningitis may occur with or without dissemination. Cryptococcal pneumonia frequently disseminates to CNS. C. neoformans in blood cultures occurs in compromised hosts (e.g., HIV) and indicates disseminated infection. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*
* Cutaneous cryptococcus represents disseminated infection. ** Fungi can produce disseminated infections that involve essentially any organ. Isolation of a fungus from any normal sterile site should be cause for a careful review of the patient's epidemiology, risk factors, and clinical presentation.

**Table 3.9. Usual Clinical Significance of YEAST/FUNGI Pending Susceptibility Testing** (cont'd)

| YEAST/FUNGI | | | | |
|---|---|---|---|---|
| **Isolate** | ****Usual Isolate Significance** | **Preferred Therapy** | **Alternate Therapy** | **Comments** |
| | | Amphotericin B lipid formulation (IV) | | |
| Histoplasma capsulatum | • CSF = P (from disseminated infection, pneumonia)<br>• Blood = P (1° fungemia, rarely SBE)<br>• Sputum = P (pneumonia, mediastinitis)<br>• Urine = P<br>• Stool = P<br>• Wound = P | Itraconazole (IV/PO)<br>Amphotericin B deoxycholate (IV) | Fluconazole (IV/PO)<br>Amphotericin B lipid formulation (IV) | Histoplasma recovered from CSF/blood cultures indicates dissemination. Disseminated (reactivated latent) histoplasmosis is most common in compromised hosts (e.g., HIV). Itraconazole is ineffective for meningeal histoplasmosis, but is preferred for chronic suppressive therapy. |
| Malassezia furfur | • CSF = NP<br>• Blood = P (from IV line infection)<br>• Sputum = NP<br>• Urine = NP<br>• Stool = NP<br>• Wound = P (eosinophilic folliculitis) | Itraconazole (IV/PO)<br>Ketoconazole (PO) | Fluconazole (IV/PO) | M. furfur IV line infections are associated with IV lipid hyperalimentation emulsions. Fungemia usually resolves with IV line removal. Morphology in blood is blunt buds on a broad base yeast. M. furfur requires long chain fatty acids for growth (overlay agar with thin layer of olive oil, Tween 80, or oleic acid). |

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| Penicillium marneffei | • CSF = NP<br>• Blood = P (usually from dissemination)<br>• Sputum = P (pneumonia)<br>• Urine = NP<br>• Stool = NP<br>• Wound = NP* | Amphotericin B deoxycholate (IV)<br>Itraconazole (IV/PO) | Amphotericin B lipid formulation (IV) | Histoplasma-like yeast forms seen in lymph nodes, liver, skin, bone marrow, blood. Characteristic red pigment diffuses into agar. Closely resembles histoplasmosis yeast forms (H. capsulatum has narrow based budding yeast forms, but P. marneffei has transverse septa). Skin lesions indicate dissemination. May resemble molluscum contagiosum. Hepatosplenomegaly is common. |

*C = colonizer; C* = skin contaminant; NP = non-pathogen at site; P = pathogen at site; (IV/PO) = IV or PO. See p. xi for all other abbreviations.*

* Cutaneous lesions represents disseminated infection.

** Fungi can produce disseminated infections that involve essentially any organ. Isolation of a fungus from any normal sterile site should be cause for a careful review of the patient's epidemiology, risk factors, and clinical presentation.

**Table 3.10. Technique for Gram Stain and Giemsa Stain**

**GRAM STAIN**

**Clinical applications:** CSF, sputum, urine

**Technique:**

1. Place specimen on slide.
2. Heat fix smear on slide by passing it quickly over a flame.
3. Place crystal violet solution on slide for 20 seconds.
4. Wash gently with water.
5. Apply Gram iodine solution to slide for 20 seconds.
6. Decolorize the slide quickly in solution of acetone/ethanol.
7. Wash slide gently with water.
8. Counterstain slide with safranin for 10 seconds.
9. Wash gently with water; air dry or blot dry with bibulous paper.

**Interpretation:** Gram-negative organisms stain red; gram-positive organisms stain blue. B fragilis stains weakly pink. Fungi stain deep blue. For interpretation of Gram stain findings in CSF, urine, sputum, and feces see Tables 3.6–3.9.

**GIEMSA STAIN**

**Clinical applications:** Blood buffy coat, bone marrow

**Technique:**

1. Place specimen on slide.
2. Fix smear by placing slide in 100% methanol for 1 minute.
3. Drain methanol off slide.
4. Flood slide with Giemsa stain (freshly diluted 1:10 with distilled water) for 5 minutes.
5. Wash slide gently with water; air dry.

**Interpretation:** Fungi/parasites stain light/dark blue.

**Table 3.11. Clinical Use of CSF Gram Stain, WBC Type, Glucose (see Color Atlas of CSF Gram stains)**

| Gram Stain | Organism/Condition | |
|---|---|---|
| Gram-positive bacilli | Pseudomeningitis (Bacillus, Corynebacteria) | Listeria |
| Gram-negative bacilli | H. influenzae (small, encapsulated, pleomorphic) | Non-enteric/enteric aerobic bacilli (larger, unencapsulated) |
| Gram-positive cocci | Gp A, B, D, streptococci (pairs/chains)<br>S. pneumoniae (pairs) | S. aureus (pairs/clusters)<br>S. epidermidis (pairs/clusters) |
| Gram-negative diplococci | Neisseria meningitidis | |

**Table 3.11. Clinical Use of CSF Gram Stain, WBC Type, Glucose** (cont'd)

| Gram Stain | Organism/Condition | |
|---|---|---|
| Mixed organisms (polymicrobial) | Pseudomeningitis<br>Anaerobic organisms (brain abscess with meningeal leak) | Neonatal meningitis Meningitis 2° to penetrating head trauma |
| **WBC Type/Glucose** | **Organism/Condition** | |
| Purulent CSF, no organisms | Neisseria meningitidis | Listeria |
| Clear CSF, no organisms | Viral meningitis<br>Viral encephalitis<br>TB/fungal meningitis<br>Sarcoidosis meningitis<br>Meningeal carcinomatosis<br>Brain abscess<br>Parameningeal infection<br>Septic emboli 2° to SBE<br>SLE cerebritis<br>Lyme's disease | Lymphocytic choriomeningitis (LCM)<br>Drug induced aseptic meningitis<br>Listeria<br>HIV<br>Syphilis<br>Leptospirosis<br>Bacterial meningitis (very early/ partially-treated)<br>Meningitis (leukopenic host)<br>Rocky Mountain Spotted Fever |
| Cloudy CSF, no WBCs | S. pneumoniae | |
| Predominantly PMNs, decreased glucose | Bacterial meningitis (partially-treated)<br>Listeria<br>HSV-1/2 encephalitis<br>TB (early/beginning therapy)<br>Sarcoidosis | Parameningeal infection<br>Septic emboli 2° to SBE<br>Amebic meningoencephalitis<br>Syphilis (early)<br>Posterior-fossa syndrome |
| Predominantly lymphocytes, normal glucose | Bacterial meningitis (partially-treated)<br>Sarcoidosis<br>Lyme's disease<br>HIV<br>Leptospirosis<br>Rocky Mountain Spotted Fever | Viral meningitis<br>Viral encephalitis<br>Parameningeal infection<br>TB/fungal meningitis<br>Parasitic meningitis<br>Meningeal carcinomatosis |
| Predominantly lymphocytes, decreased glucose | Bacterial meningitis (partially-treated)<br>TB/fungal meningitis<br>Sarcoidosis<br>Lymphocytic choriomeningitis (LCM)<br>Mumps | Enteroviral meningitis<br>Listeria<br>Leptospirosis<br>Syphilis<br>Meningeal carcinomatosis |
| Red blood cells | Traumatic tap<br>CNS bleed/tumor<br>Listeria<br>Leptospirosis<br>Herpes (HSV-1) encephalitis | TB meningitis<br>Amebic (Naegeleria) meningoencephalitis<br>Anthrax |

**Table 3.12. Clinical Use of the Sputum Gram Stain (see Color Atlas of Sputum Gram stains)**

| Gram Stain | Organism | Comments |
|---|---|---|
| Gram-positive diplococci | S. pneumoniae | Lancet-shaped encapsulated diplococci (not streptococci) |
| Gram-positive cocci (grape-like clusters) | S. aureus | Clusters predominant. Short chains or pairs may also be present |
| Gram-positive cocci (short chains or pairs) | Group A streptococci | Virulence inversely proportional to length of streptococci. Clusters not present |
| Gram-positive beaded/ filamentous branching organisms | Nocardia | Coccobacillary forms common |
| Gram-negative cocco-bacillary organisms | H. influenzae | Pleomorphic may be encapsulated. Gram negative cocci/bacilli. Lightly stained |
| Gram-negative bacilli | Klebsiella<br>P. aeruginosa | Plump and encapsulated<br>Thin and often arranged in end-to-end pairs |
| Gram-negative diplococci | Moraxella (Branhamella) catarrhalis<br>Neisseria meningitidis | Kidney bean-shaped diplococci |

**Table 3.13. Clinical Use of the Urine Gram Stain (see Color Atlas of Urine Gram stains)**

| Gram Stain | Organism | Comments |
|---|---|---|
| Gram-positive cocci (clusters)* | S. aureus<br>S. epidermidis<br>S. saprophyticus | Skin flora contaminant<br>Skin flora contaminant<br>Uropathogen |
| Gram-positive cocci (chains) | Group B streptococci<br>Group D streptococci<br>E. faecalis<br>E. faecium | Uropathogen<br>Uropathogen<br>May represent colonization or infection<br>May represent colonization or infection |
| Gram-negative bacilli* | Coliform bacilli | Uropathogen; may represent colonization or infection |
| Gram-negative diplococci* | N. gonorrhoeae<br>N. meningitidis | Gonococcal urethritis<br>Rare cause of urethritis |

* Staphylococci (except S. saprophyticus), S. pneumoniae, and B. fragilis are *not* uropathogens.

**Table 3.14. Clinical Use of the Fecal Gram Stain**

| Gram Stain | Possible Organisms | |
|---|---|---|
| Fecal leukocytes present | Enteropathogenic E. coli (EPEC)<br>Enteroinvasive E. coil (EIEC)<br>Shigella<br>Yersinia<br>Campylobacter<br>Salmonella<br>Vibrio parahaemolyticus<br>Vibrio vulnificus | Aeromonas hydrophila<br>Chlamydia trachomatis<br>Plesiomonas shigelloides<br>Neisseria gonorrhoeae (proctitis)<br>Herpes simplex virus (HSV-1)<br>*Noninfectious:* Ulcerative colitis |
| No fecal leukocytes | Enterovirus<br>Rotavirus<br>Coronavirus<br>Enterotoxigenic E. coli (ETEC)<br>S. aureus<br>Clostridium perfringens<br>Adenovirus | Norwalk virus<br>Vibrio cholerae<br>Bacillus cereus (food poisoning)<br>Giardia lamblia<br>Isospora belli<br>Cryptosporidia<br>Strongyloides stercoralis |
| Fecal leukocytes variable | Clostridium difficile<br>Enterohemorrhagic E. coli (EHEC) | Cytomegalovirus (CMV)<br>Herpes simplex virus (HSV-1) |
| Red blood cells present | Shigella<br>Salmonella<br>Campylobacter<br>EPEC<br>EHEC<br>Enteroinvasive E. coli (EIEC)<br>Enterohemorrhagic E. coli (EHEC) | Clostridium difficile<br>Cytomegalovirus (CMV)<br>Yersinia<br>Plesiomonas shigelloides<br>*Noninfectious:* Ulcerative colitis |

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Chapter 4

# Parasites, Fungi, Unusual Organisms*

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# Parasites, Fungi, Unusual Organisms in Blood

## Microfilaria in Blood

| Subset | Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Filariasis | Brugia malayi | Doxycycline 100 mg (PO) of q12h × 6 weeks **plus**<br>Diethylcarbamazine:<br>day 1: 50 mg (PO)<br>day 2: 50 mg (PO) q8h<br>day 3: 100 mg (PO) q8h<br>days 4–14: 2 mg/kg (PO) q8h | Ivermectin 200 mcg/kg (PO) × 1 dose ± albendazole 400 mg (PO) × 1 dose |
| | Wuchereria bancrofti | Doxycycline 100 mg (PO) q12h × 6 weeks **plus**<br>Albendazole 400 mg (PO) × 1 dose<br>**plus**<br>Diethylcarbamazine:<br>day 1: 50 mg (PO)<br>day 2: 50 mg (PO) q8h<br>day 3: 100 mg (PO) q8h<br>days 4–14: 2 mg/kg (PO) q8h | Ivermectin 400 mcg/kg (PO) × 1 dose. |

### Brugia malayi

**Clinical Presentation:** May present as an obscure febrile illness, chronic lymphedema, lymphangitis, or cutaneous abscess. "Filarial fevers" usually last 1 week and spontaneously remit.

**Diagnostic Considerations:** Diagnosis by demonstrating microfilaria on Giemsa's stained thick blood smear or by using the concentration method; yield is increased by passing blood through a Millipore filter before staining. Several smears should be taken over 24 hours. Adult worms may be detected in scrotal lymphatics by ultrasound. Common infection in Southeast Asia (primarily China, Korea, India, Indonesia, Malaysia, Philippines, Sri Lanka). Most species have nocturnal periodicity (microfilaria in blood at night). Eosinophilia is most common during periods of acute inflammation.

**Pitfalls:** Genital manifestations—scrotal edema, epididymitis, orchitis, hydrocele—are frequent with W. bancrofti, but rare with B. malayi.

**Prognosis:** Related to state of health and extent of lymphatic obstruction. No satisfactory treatment is available. Single-dose ivermectin is effective treatment for microfilaremia, but does not kill the adult worm (although diethylcarbamazine kills some). If no microfilaria in blood, full-dose diethylcarbamazine (2 mg/kg q8h) can be started on day one. Antihistamines or corticosteroids may decrease allergic reactions from disintegration of microfilaria.

### Wuchereria bancrofti

**Clinical Presentation:** May present as an obscure febrile illness, chronic lymphedema, lymphangitis, or cutaneous abscess. Genital (scrotal) lymphatic edema, groin lesions, epididymitis, orchitis, hydroceles are characteristic. Chyluria may occur. "Filarial fevers" usually last 1 week and spontaneously remit. Lymphedema worsened by cellulitis associated with Tinea pedis infections.

**Diagnostic Considerations:** Diagnosis by demonstrating microfilaria on Giemsa's stained thick blood smear or by using the concentration method; yield is increased by passing blood through a Millipore filter before staining. Several smears should to be taken over 24 hours. W. bancrofti is the most common

human filarial infection, particularly in Asia (China, India, Indonesia, Japan, Malaysia, Philippines), Southeast Asia, Sri Lanka, Tropical Africa, Central/South America, and Pacific Islands. Most species have nocturnal periodicity (microfilaria in blood at night). Eosinophilia is common.

**Pitfalls:** Differentiate from "hanging groins" of Loa Loa, which usually do not involve the scrotum.

**Prognosis:** Related to state of health and extent of lymphatic obstruction. No satisfactory treatment is available. Single-dose ivermectin is effective treatment for microfilaremia, but does not kill the adult worm (although diethylcarbamazine kills some). If no microfilaria in blood, full-dose diethylcarbamazine (2 mg/kg q8h) can be started on day one. Antihistamines or corticosteroids decrease allergic reactions from disintegration of microfilaria. Wolbachia bacteria are endosymbionts in W. bancrofti filariasis. Treatment with doxycycline effective against Wolbachia which are important in microfilarial reproduction.

## Trypanosomes in Blood

| Subset | Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Chagas' disease (American trypanosomiasis) | Trypanosoma brucei cruzi | Nifurtimox 2–3 mg/kg/day (PO) q6h × 30–90 days | Benznidazole 2.5–3.5 mg/kg (PO) q12h × 60 days |
| Loa Loa (Loiasis) | L. loa | Diethylcarbamazine 2 mg/kg (PO) q8h × 3 weeks | Albendazole 200 mg (PO) q12h × 3 weeks |
| Sleeping sickness *West African (Gambian) trypanosomiasis* | Trypanosoma brucei gambiense | Early disease<br>Pentamidine 4 mg/kg (IM) q24h × 7 days | |
| | | Late disease<br>Melarsoprol 2.2 mg/kg (IV) q24h × 10 days<br>**plus**<br>Nifurtimox 15 mg/kg (PO) q8h × 10 days<br>**or**<br>Eflornithine 100 mg/kg (PO) q6h × 10 days | |
| *East African (Rhodesian) trypanosomiasis* | Trypanosoma brucei rhodesiense | Early disease<br>Suramin test dose of 4–5 mg/kg (IV) day 1, then five injections of 20 mg/kg (IV) q 7 days (max. dose 1 gm/injection day 3, 10, 17, 24, 31) max. dose 1 gm/injection | |
| | | Late disease<br>Melarsoprol 3 series of 1.8, 2.16, 2.52 mg/kg (IV) q24h; 3 series of 2.52, 2.88, 3.25 mg/kg (IV) q24h; 3 series of 3.6, 3.6, 3.6 mg/kg (IV) q24h; the series given at intervals of 7 days | |

## Chagas' Disease (Trypanosoma brucei cruzi) American Trypanosomiasis

**Clinical Presentation:** Presents acutely after bite of infected reduviid bug with unilateral painless edema of the palpebrae/periocular tissues (Romaña's sign), or as an indurated area of erythema and swelling with local lymph node involvement (chagoma). Fever, malaise, and edema of the face and lower extremities may follow. Generalized lymphadenopathy and hepatosplenomegaly occur. Patients with chronic disease may develop cardiac involvement (cardiomyopathy with arrhythmias, heart block, heart failure, thromboembolism), GI involvement (megaesophagus, megaduodenum, megacolon) or CNS involvment in HIV/immunosuppressed.

**Diagnostic Considerations:** Common in Central and South America. Acquired from infected reduviid bug, which infests mud/clay parts of primitive dwellings. Transmitted by blood transfusion (~10%), organ transplants, and congenitally. Diagnosis in acute disease by detecting trypanosomes in wet prep of anti-coagulated blood or stained buffy coat smears. Amastigote forms present intracellularly in monocytes/histiocytes in Giemsa-stained smears, bone marrow or lymph node aspirates, or by xenodiagnosis. Screening test ELISA IFA; confirmatory test RIPA (radioimmuno precipitation assay).

**Pitfalls:** Do not overlook the diagnosis in patients from endemic areas with unexplained heart block ± apical ventricular aneurysms. May be transmitted by blood transfusion/organ transplantation.

**Prognosis:** Related to extent of cardiac GI, or CNS involvement.

## Sleeping Sickness (T. brucei gambiense/rhodesiense) West African (Chronic)/East African (Acute) Trypanosomiasis

**Clinical Presentation:** Sleeping sickness from T. brucei gambiense is milder than sleeping sickness from T. brucei rhodesiense, which is usually a fulminant infection. A few days to weeks after bite of tsetse fly, patients progress through several clinical stages:

- *Chancre stage*: Trypanosomal chancre occurs at bite site and lasts several weeks.
- *Blood/lymphatic stage*: Blood parasitemia is associated with intermittent high fevers, headaches and insomnia, followed by generalized adenopathy. Posterior cervical lymph node enlargement (Winterbottom's sign) is particularly prominent with T. brucei gambiense. Hepatosplenomegaly and transient edema/pruritus/irregular circinate rash are common. Myocarditis (tachycardia unrelated to fevers) occurs early (before CNS involvement) and is responsible for acute deaths from T. brucei rhodesiense.
- *CNS stage*: Occurs acutely with East African trypanosomiasis or chronically with West African trypanosomiasis after non-specific symptoms, and is characterized by increasing lethargy, somnolence (sleeping sickness), and many subtle CNS findings. Coma and death ensue without treatment. With melarsoprol, use prednisolone 1 mg/kg (PO) q24h (start steroid 1 day prior to first dose and continue to last dose)**.**

**Diagnostic Considerations:** Diagnosis by demonstrating trypanosomes in blood, chancre, or lymph nodes aspirates by Giemsa-stained thin and thick preparations, light microscopy, or buffy coat concentrates with acridine orange. CSF determines early vs. late stage disease (> 20 WBCs/$mm^3$).

**Pitfalls:** Do not miss other causes of prominent bilateral posterior cervical lymph node enlargement, e.g., lymphoma, EBV. Serum arginase a biomarker for effective therapy.

**Prognosis:** Related to extent of cardiac/CNS involvement. Relapse may occur.

## Loa Loa (Loiasis)

**Clinical Presentation:** Cutaneous swellings (Calabar swellings) with pruritus. Adults may be visible when migrations under the conjuctiva or under the skin. Disappear in 3 days. Calabar swellings are painless and appear on the extremeties. Eosinophilia prominent.

**Diagnostic Considerations:** Demonstrates of microfilariae in blood (at noon) or by demonstration of L. loa in skin/eye. Immunodiagnosis unhelpful.
**Pitfalls:** Calabar swellings occur one at time and may last for hours/days.
**Prognosis:** Poorest with CNS involvement.

## Spirochetes in Blood

| Subset | Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Relapsing fever<br>*Louse-borne (LBRF)*<br>*Tick-borne (TBRF)* | Borrelia recurrentis<br>> 15 Borrelia species (U.S. B. hermsi; Africa: B. duttonii; Africa/Middle East: B. crocidurae) | LBRF<br>Erythromycin 500 mg (IV or PO) q6h × 7 days<br><br>TBRF<br>Doxycycline 200 mg (PO) × 3 days, then 100 mg (PO) q12h × 7 days | TBRF with CNS involvement<br>Penicillin G 2 mu (IV) q4h × 2 weeks<br>**or**<br>Ceftriaxone 1 gm (IV) q12h × 2 weeks<br>**or**<br>Cefotaxime 3 gm (IV) q6h × 2 weeks |
| Rat bite fever | Spirillum minus | Penicillin G 4 mu (IV) q4h × 2 weeks<br>**or**<br>Ceftriaxone 1 g (IV) q24h × 2 weeks<br>**or**<br>Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) q12h × 11 days | Amoxicillin 1 gm (PO) q8h × 2 weeks<br>**or**<br>Erythromycin 500 mg (IV or PO) q6h × 2 weeks<br>**or**<br>Chloramphenicol 500 mg (IV) q6h × 2 weeks |

### Relapsing Fever, Louse-Borne (LBRF) / Tick-Borne (TBRF)

**Clinical Presentation:** Abrupt onset of "flu-like" illness with high fever, rigors, headache, myalgias, arthralgias, tachycardia, dry cough, abdominal pain after exposure to infected louse or tick. Truncal petechial rash and conjunctival suffusion are common. Hepatosplenomegaly/DIC may occur. Bleeding or rash at bite site. Complications more common in LBRF. Fevers last ~ 1 week, remit for a week, and usually relapse only once in LBRF, but several times in TBRF. Relapses usually last 2–3 days. Fevers are often higher in TBRF.
**Diagnostic Considerations:** Borreliae seen in Wright/Giemsa-stained blood smears. LBRF is endemic in South American Andes, Central and East Africa, and is associated with crowded, unhygienic conditions. Soft ticks (Ornithodoros) TBRF main vector. Bite at night, patients do not recall tick bite. TBRF is seen throughout the world, and is endemic in Western U.S., British Columbia, Mexico, Central/South America, Mediterranean, Central Asia, and Africa. With TBRF, meningismus ± facial nerve palsy common with B. duttoni rare with B. hermsii.
**Pitfalls:** Spirochetes are most likely to be seen during febrile periods. Blood smears may be negative if not obtained during fever.
**Prognosis:** Good if treated early. Usually no permanent sequelae.

**Rat Bite Fever (Spirillum minus)**

**Clinical Presentation:** Infection develops 1–4 weeks following bite of a rat. Healed rat bite becomes red, painful, swollen and ulcerated, with regional lymphangitis/adenopathy. Recurrent fevers occurs in 2–4 day fever cycles. Fevers are usually accompanied by chills, headache, photophobia, nausea, vomiting. Rash on palms/soles develops in > 50%. Arthritis, myalgias, and SBE are rare.

**Diagnostic Considerations:** Spirochetes are seen in Wright/Giemsa-stained blood smears. Differential diagnosis includes Borrelia, malaria, and lymphoma. VDRL is positive.

**Pitfalls:** May be confused with syphilis, due to rash on palms/soles and false-positive syphilis serology in 50%. SBE occurs with Streptobacillus moniliformis, not S. minus (unless there is preexisting valvular disease). Bite wound ulcerates in S. minus, not Streptobacillus moniliformis.

**Prognosis:** Patients with arthritis have a protracted course.

## Intracellular Inclusion Bodies in Blood

| Subset | Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Babesiosis | Babesia microti | Azithromycin 500 mg (PO) × 1, then 250 mg (PO) q24h × 7 days **plus** Atovaquone (suspension) 750 mg (PO) q12h × 7 days | Clindamycin 600 mg (PO) q8h × 7 days **plus** Quinine 650 mg (PO) q8h × 7 days |
| Ehrlichiosis/ anaplasmosis | | Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) q12h × 1–2 weeks total | Any once-daily quinolone (IV or PO) × 1–2 weeks **or** Rifampin 300 mg (PO) q12h × 1–2 weeks* **or** Chloramphenicol 500 mg (IV or PO) q6h × 1–2 weeks* |
| *Human monocytic ehrlichiosis (HME)* | Ehrlichia chaffeensis, ewubguum | | |
| *Human granulocytic anaplasmosis (HGA)* | Anaplasma (Ehrlichia) phagocytophilium | | |
| **Severe Malaria** (Usually P. falciparum) | **Quinidine gluconate *plus* either doxycycline or clindamycin** 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 24h. An alternative regimen is 15 mg base/kg (= 24 mg salt/kg) loading dose infused over 4 hours, followed by 7.5 mg base/kg (= 12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose. Once parasitemia <1%; and patient can take oral medications, complete therapy with oral quinine or an oral regimen. (see below chloroquine-sensitive or resistant). **Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or south America.** | | |

* May be used in pregnancy.

## Intracellular Inclusion Bodies in Blood (cont'd)

| Subset | Therapy |
|---|---|
| | **or**<br>**Quinine** 20 mg (salt)/kg (IV) over 4 hours (in $D_5W$), then 10 mg (salt)/kg (IV) over 2 hours q8h until able to take oral meds; complete 7 days total therapy with **doxycycline** or **oral regimen** (*see below* chloroquine-sensitive or resistant).<br>**or**<br>**Artemether-lumefantrine** 3.2 mg/kg (IM) × 1 dose, then 1.6 mg/kg (IM) q24h until able to take oral meds; complete 7 days total therapy with **doxycycline** or **oral regimen** (*see below* chloroquine-sensitive or resistant).<br>**or**<br>**Artesunate** 2.4 mg/kg (IV) initially and at 12, 24, and 48 hours, then q24h until able to take oral meds; complete 7 days total therapy with **doxycycline** or **oral regimen** (*see below* chloroquine-sensitive or resistant). |
| **Uncomplicated Malaria** (P. falciparum, P. malariae, P. knowlesi or unidentified species) | ***Chloroquine-sensitive***<br>**Chloroquine phosphate** 600 mg base (= 1000 mg salt) (PO) immediately, followed by 300 mg base (= 500 mg salt) (PO) at 6,24, and 48 hours. Total dose = 1500 mg base (= 2500 mg salt).<br>**or**<br>**Hydroxychloroquine** 620 mg base (= 800 mg salt) (PO) loading dose, then 310 mg base (= 400 mg salt) (PO) at 6, 24, and 48 hours. |
| P. vivax and P. ovale | ***Plus*** **primaquine phosphate** 30 mg base (PO) q24h × 2 weeks.<br><br>***Chloroquine-resistant***<br>**Quinine sulfate** 625 mg base (= 625 mg salt) (PO) q8h × 7 days *plus* **doxycycline** 200 mg (PO) q12h × 3 days, then 100 mg (PO) q12h × 4 days.<br>**or**<br>**Atovaquone/proguanil** (250/100 gm PO tab) 4 tablets as single dose or 4 tablets (PO) q12h × 3 days.<br>**or**<br>**Artesunate** 4 mg/kg (PO) × 3 days *plus* **Mefloquine** 684 mg base (= 750 mg salt) (PO) as initial dose followed by 456 mg base (= 500 mg salt) (PO) given 6–12 hours after initial dose. Total dose = 1250 mg salt.<br>**or**<br>**Artemether/lumefantrine** 4 tabs = 1 dose (20/120 mg tablets) give initial dose, followed by second dose 8h later, then 1 dose (PO) q12h for the following 2 days.<br><br>**or**<br>**Dihydroartemisinin** 40 mg plus piperaquine 320 mg (PO) q24h × 3 days. |

**For CDC guidelines for malaria in US** (see p. 721).

## Babesiosis (Babesia microti)

**Clinical Presentation:** "Malarial-like illness" with malaise, fever, relative bradycardia, shaking chills, myalgias, arthralgias, headache, abdominal pain, and splenomegaly. Laboratory abnormalities include anemia, atypical lymphocytes, relative lymphopenia, thrombocytopenia, mildly elevated LFTs, highly elevated ↑ ESR, ↑ ferritin, and ↑ LDH. Transmitted by infected Ixodes ticks.

**Diagnostic and Considerations:** Characteristic four merozoites (often pear shaped) arranged in "Maltese cross" formation (tetrads). Serology diagnostic of acute infection. Hyposplenic patients may have profound hemolytic anemia and life-threatening infection.

**Pitfalls:** Co-infection with Lyme disease may occur. No serological cross-reactivity between Babesia and Borrelia (Lyme disease). Merozoites only may be confused with P. falciparum malaria. Extra-RBC forms and vacuolated RBCs distinguish babesiosis from malaria. Travel history is important. Doxycycline ineffective.

**Prognosis:** May be more severe with Lyme disease co-infection. Severe/fatal if ↓/absent splenic function. Exchange transfusions may be life saving.

## Ehrlichiosis (HME)/Anaplasmosis (HGA)

**Clinical Presentation:** Acute febrile illness with chills, headache, malaise, myalgias, leukopenia, relative lymphopenia, atypical lymphocytes, thrombocytopenia, ↑ LFTs, ↓ ESR, ↑ ferritin. No vasculitis. Resembles Rocky Mountain spotted fever (RMSF), but without rash.

**Diagnostic Considerations:** Characteristic "morula" (spherical, basophilic, mulberry-shaped, cytoplasmic inclusion bodies) may be seen in peripheral blood neutrophils in HGA. PCR from blood is 86% sensitive and highly specific for early diagnosis. Obtain acute and convalescent IFA serology. HGA vector is Ixodes ticks clinical co-infection with B. burgdorferi (Lyme Disease) is rare, but may occur. Main HME vector Ambylomma americanum (lone star tick).

**Pitfalls:** No morula with HME. Rash uncommon in HME and rare in HGA. E. chaffeensis (HME) titers will not be elevated with A. phagocytophilium (HGA) and vice versa. PCR/blood smears positive early. Seropositivity increases over time.

**Prognosis:** Good if treated early. Delayed response/more severe with Lyme co-infection disease.

## Malaria (Plasmodium ovale/vivax/falciparum/malariae/knowlesi)

**Clinical Presentation:** Presents acutely with fever/chills, severe headaches, cough, nausea/vomiting, diarrhea, abdominal/back pain. Typical "malarial paroxysm" consists of chills, fever and profuse sweating, followed by extreme prostration. There are a paucity of physical findings, but most have tender hepatomegaly/splenomegaly and relative bradycardia. ↑ T. bilirubin, thrombocytopenia, atypical lymphocytes, and ↑ LFTs are common.

**Diagnostic Considerations:** Diagnosis by visualizing Plasmodium on thick/thin Giemsa or Wright-stained smears.

**Pitfalls:** Be wary of diagnosing malaria without headache. Dengue most closely resembles malaria. On abdominal US, dengue patients have gallbladder wall thickening/splenomegaly but not hepatomegaly vs.malaria patients which have a normal gallbladder, splenomegaly/heptomegaly. If no atypical lymphocytes on smear (auto cell counters are insensitive to atypical lymphocytes), question the diagnosis of malaria. P. knowlesi (monkey malaria emerging cause of human malaria. Resembles P. malariae (microscopically) but may be severe resembing P. falciparum (clinically). Treat P. knowlesi as chloroquine sensitive (P. vivax, P. ovale, P. malariae) malaria.

**Prognosis:** Related to species degree of parasitemia P. falciparum with high-grade parasitemia is most severe, and may be complicated by coma, hypoglycemia, renal failure, or non-cardiogenic pulmonary edema. If parasitemia exceeds 15%, consider exchange transfusions.

**Fungi/Mycobacterium in Blood**

See histoplasmosis (p. 341), Mycobacterium tuberculosis (treat as pulmonary TB, p. 326), Mycobacterium avium-intracellulare (p. 321, 342).

## Parasites, Fungi, Unusual Organisms in CSF/Brain

### Cysts/Mass Lesions in CSF/Brain

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Cerebral nocardiosis | Nocardia sp. | Preferred IV Therapy: TMP–SMX (TMP 5 mg/kg, SMX 15 mg/kg) (IV) q6h until clinical improvement, then (PO) therapy<br><br>Alternate IV PO Therapy: Minocycline or Doxycycline 100 mg (IV) q12h until clinical improvement, then (PO) therapy | Preferred PO Therapy TMP–SMX 1 DS tablet (PO) q12h × 6 months<br><br>Alternate PO Therapy Minocycline 100 mg (PO) q12h × 6 months<br>**or**<br>Doxycycline 100 mg (PO) q12h × 6 months |
| Cryptococcal meningitis/ cryptococcomas | Cryptococcus neoformans | See p. 22 | |
| Cerebral amebiasis | Entamoeba histolytica | Metronidazole 750 mg (PO) q8h × 10 days<br>**or**<br>Tinidazole 800 mg (PO) q8h × 5 days | |
| Primary amebic meningo-encephalitis | Naegleria fowleri | See p. 21 | |
| Granulomatous amebic encephalitis | Acanthamoeba | See p. 22 | |
| Cerebral echinococcosis (hydatid cyst disease) | Echinococcus granulosus or multilocularis | Surgical resection plus Albendazole 400 mg* (PO) q12h until cured | Surgical resection plus Mebendazole 50 mg/kg (PO) q24h until cured |
| Cerebral gnathostomiasis | Gnathostoma spinigerum | Surgical resection | Albendazole 400 mg (PO) q12h × 3 weeks **or** Ivermectin 200 mcg/kg/d × 2 days |
| Cerebral coenurosis | Taenia multiceps | Surgical resection | |

## Cysts/Mass Lesions in CSF/Brain (cont'd)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Neurocysticercosis | Taenia solium | Albendazole 400 mg* (PO) q12h × 2 weeks | Praziquantel 33 mg/kg (PO) q8h × 1day, then 15 mg/kg (PO) q8h × 2–4 weeks ± cimetidine 400 mg (PO) q8h (to ↑ praziquantel levels) |
| Cerebral paragonimiasis (lung fluke) | Paragonimus westermani | Praziquantel 25 mg/kg (PO) q8h × 2 days | Bithionol 50 mg/kg (PO) q48h × 2 weeks **or** Tridabendazole 10 mg/kg (PO) q24h × 2 days |
| Cerebral toxoplasmosis | Toxoplasma gondii | See pp. 331–332 | |
| Chagas' disease (American trypanosomiasis) | Trypanosoma brucei cruzi | Nifurtimox 2 mg/kg (PO) q6h × 4 months | Benznidazole 3.5 mg/kg (PO) q12h × 2 months |

* If < 60 kg, give albendazole 7.5 mg/kg.

### Cerebral Nocardiosis

**Clinical Presentation:** CNS mass lesion resembling brain tumor/abscess. Symptoms are highly variable, and result from local effects of granulomas/abscesses in CNS. Up to 40% of patients with systemic nocardiosis have associated mass lesions in CNS.

**Diagnostic Considerations:** Diagnosis by demonstrating Nocardia (gram positive, delicate, beaded, branching filaments) in brain biopsy specimens. Notify laboratory for modified acid fast specimen staining/aerobic cultures if suspect Nocardia. Nocardia are weakly acid-fast and aerobic.

**Pitfalls:** Usually not limited to brain. Look for Nocardia in skin, lungs or liver. Use in-vitro susceptibility data to guide therapy for refractory cases. IV regimens are recommended for critically ill patients. HIV patients require life-long suppression with TMP–SMX.

**Prognosis:** Related to health of host, degree of immunosuppression, and extent of lesions.

### Cerebral Amebiasis (Entamoeba histolytica)

**Clinical Presentation:** Rare cause of brain abscess. Onset is frequently abrupt with rapid progression. Suspect in patients with a history of amebiasis and altered mental status/focal neurologic signs. If present, meningeal involvement resembles acute bacterial meningitis. CT/MRI shows focal lesions.

**Diagnostic Considerations:** Diagnosis by demonstrating E. histolytica trophozoites in wet preps or by trichrome stain from aspirated brain lesions under CT guidance. Worldwide distribution. Mass lesions may be single or multiple, and more commonly involve the left hemisphere. Most patients have concomitant liver ± lung abscesses.

**Pitfalls:** Trophozoites/cysts in stool are not diagnostic of CNS disease. E. histolytica serology is often positive, but is nonspecific. E. histolytica trophozoites are not present in CSF.

**Prognosis:** Related to size/location of CNS lesions.

**Primary Amebic Meningoencephalitis (Naegleria fowleri)** (see p. 23)

**Granulomatous Amebic Encephalitis (Acanthamoeba)** (see p. 23)

**Cerebral Echinococcosis (Echinococcus granulosus) Hydatid Cyst Disease**

**Clinical Presentation:** Most cysts are asymptomatic. Mass lesions may cause seizures, cranial nerve abnormalities, other focal neurologic symptoms.

**Diagnostic Considerations:** CT/MRI typically shows a single large cyst without edema or enhancement. Multiple cysts are rare. Diagnosis by demonstrating protoscolices in "hydatid sand" in cysts. Usually associated with liver/lung hydatid cysts.

**Pitfalls:** E. granulosus serology lacks specificity.

**Prognosis:** Related to size/location of CNS cysts. CSF eosinophilia is not a feature of CNS involvement. Treatment consists of surgical removal of total cyst after instilling cysticidal agent (hypertonic saline, iodophor, ethanol) into cyst plus albendazole.

**Cerebral Echinococcosis (Echinococcus multilocularis) Hydatid Cyst Disease**

**Clinical Presentation:** Frequently associated with hydatid bone cysts (may cause spinal cord compression), liver/lung cysts. Peripheral eosinophilia occurs in 50%, but eosinophils are not seen in the CSF.

**Diagnostic Considerations:** E. multilocularis ELISA is sensitive and specific.

**Pitfalls:** Praziquantel is ineffective for CNS hydatid cyst disease. Imaging studies suggest carcinoma/sarcoma. Diagnosis is frequently not made until brain biopsy.

**Prognosis:** If treatment is effective, improvement of CNS lesions is evident in 8 weeks. Brain/bone cysts are difficult to cure.

**Cerebral Gnathostomiasis (Gnathostoma spinigerum)**

**Clinical Presentation:** Nausea, vomiting, increased salivation, skin flushing, pruritus, urticaria, and upper abdominal pain 1–6 days after exposure. Cerebral form presents as eosinophilic meningitis with radiculomyeloencephalitis, with headache and severe sharp/shooting pains in extremities often followed by paraplegia and coma. Any cranial nerve may be involved. The most characteristic feature is changing/migratory neurological findings. Intense peripheral eosinophilia occurs in 90% of patients. CSF has eosinophilic pleocytosis and may have RBCs.

**Diagnostic Considerations:** In cases with ocular involvement, the worm may be seen in the anterior chamber of eye. Specific Gnathostoma serology of CSF is helpful in establishing the diagnosis. Acquired from infected cat/dog feces. Most cases occur in Southeast Asia also Central/South America (Mexico, Peru) and most recently in Africa (Botswana). Few other CNS infections have both RBCs and eosinophils in the CSF.

**Pitfalls:** Do not miss associated eye involvement or characteristic episodic non-pitting subcutaneous edema.

**Prognosis:** Related to invasion of medulla/brainstem.

**Cerebral Coenurosis (Taenia multiceps)**

**Clinical Presentation:** CNS mass lesion with seizures/cranial nerve abnormalities, often presenting as a posterior-fossa syndrome. Common sites of CNS involvement include paraventricular and basal subarachnoid spaces. Eosinophils not in CSF.

**Diagnostic Considerations:** Diagnosis by demonstrating protoscolices in brain cyst specimens. Worldwide distribution. Transmitted via dog feces.
**Pitfalls:** Do not miss associated ocular lesions, which mimic intraocular neoplasms/granulomas.
**Prognosis:** Related to size/extent of CNS lesions.

### Neurocysticercosis (Taenia solium)

**Clinical Presentation:** Chronic eosinophilic meningitis/mass lesions with seizures. Hydrocephalus is common. Spinal involvement may result in paraplegia. Cerebral cysts are usually multiple.
**Diagnostic Considerations:** CT/MRI shows multiple enhancing and non-enhancing unilocular cysts. Diagnosis by specific T. solium serology of serum/CSF or excision of cyst. Neurocysticercosis is the most common CNS parasite. Worldwide in distribution; most common in Eastern Europe, Asia, Latin America.
**Pitfalls:** Cranial nerve abnormalities are uncommon.
**Prognosis:** Related to extent/location of CNS lesions. Adjunctive therapy includes corticosteroids, antiepileptics, and shunt for hydrocephalus.

### Cerebral Paragonimiasis (Paragonimus westermani) Lung Fluke

**Clinical Presentation:** Can resemble epilepsy, cerebral tumors, or brain embolism. Primary focus of infection is pulmonary, with pleuritic chest pain, cough, and night sweats. CNS findings are a manifestation of extrapulmonary (ectopic) organ involvement.
**Diagnostic Considerations:** Diagnosis by demonstrating operculated eggs in sputum, pleural fluid, or feces. Multiple sputum samples are needed to demonstrate P. westermani eggs. Charcot-Leyden crystals are seen in sputum. Endemic in Far East, India, Africa, and Central/South America.
**Pitfalls:** Extrapulmonary (ectopic) organ involvement (cerebral, subcutaneous, abdominal) is common. Up to 20% of patients have normal chest x-rays.
**Prognosis:** Related to size/location of CNS cysts and extent of lung involvement.

### Cerebral Toxoplasmosis (T. gondii) (see pp. 331–332)

### Cerebral Cryptococcosis (C. neoformans) (see pp. 329–330)

### Chagas' Disease (Trypanosoma brucei cruzi) American Trypanosomiasis

**Clinical Presentation:** Acute unilateral periorbital cellulitis (Romaña's sign) or regional adenopathy and edema of extremity at site of infected reduviid bug (Chagoma). Chronic disease manifests as myocarditis/heart block or megaesophagus, megaduodenum, megacolon. Hepatosplenomegaly is common. Overt CNS signs are frequently absent. CNS Chagas' disease typically have hypodense ring enhancing lesions with surrounding edema on head CT/MRI scans. If meningoencephalitis develops, the prognosis is very poor. In immunosuppressed patients (especially AIDS), recrudescence of disease occurs with development of T. brucei cruzi brain abscesses.
**Diagnostic Considerations:** Diagnosis in acute disease by demonstrating trypanosomes in wet prep of anticoagulated blood or stained buffy coat smears. Amastigote forms present intracellularly in monocytes/histiocytes in Giemsa-stained smear of bone marrow/lymph node aspirate, or by xenodiagnosis. Serology (mostly used for chronic disease) has limited value in endemic areas due to lack of specificity, but is useful in non-endemic areas. Common in Central/South America. Acquired from infected reduviid bugs, which infest mud/clay/stone parts of primitive dwellings. Infection in humans occurs in areas containing reduviids that defecate during or immediately after a blood meal.

**Diagnostic Considerations:** Screening test ELISA IFA; confirmatory test RIPA (radioimmuno precipitation assay).
**Pitfalls:** Do not overlook diagnosis in persons from endemic areas with unexplained heart block. For children ages 11–16 years, use nifurtimox 3.5 mg/kg (PO) q6h × 3 months. For children < 11 years, use nifurtimox 5 mg/kg (PO) q6h × 3 months.
**Prognosis:** Related to extent of GI cardiac or CNS involvement. The addition of gamma interferon to nifurtimox × 20 days may shorten the acute phase of the disease.

# Parasites, Fungi, Unusual Organisms in Lungs

## Pulmonary Cystic Lesions/Masses

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Alveolar echinococcosis | Echinococcus multilocularis | Operable cases<br>Wide surgical resection plus Albendazole 400 mg* (PO) q12h or Mebendazole 50 mg/kg (PO) q24h until cured | Inoperable cases: Albendazole 400 mg* (PO) q12h × 1 month, then repeat therapy after 2 weeks × 3 cycles (i.e., 4 total months of albendazole) |
| Pulmonary amebiasis | Entamoeba histolytica | Metronidazole 750 mg (PO) q8h × 10 days | Tinidazole 800 mg (PO) q8h × 5 days |
| Pulmonary paragonimiasis (lung fluke) | Paragonimus westermani | Praziquantel 25 mg/kg (PO) q8h × 2 days | Bithionol 50 mg/kg (PO) q48h × 4 weeks<br>**or**<br>Tridabendazole 10 mg/kg (PO) q24h × 2 days |

* If < 60 kg, give albendazole 7.5 mg/kg.

### Alveolar Echinococcosis (Echinococcus multilocularis)

**Clinical Presentation:** Slowly growing cysts remain asymptomatic for 5–20 years, until space-occupying effect elicits symptoms. Rupture/leak into bronchial tree can cause cough, chest pain, and hemoptysis.
**Diagnostic Considerations:** Diagnosis is suggested by typical "Swiss cheese calcification" findings on chest x-ray, and confirmed by specific E. multilocularis serology (which does not cross react with E. granulosus). Most common in Northern forest areas of Europe, Asia, North America, and Arctic. Acquired by ingestion of viable parasite eggs in food. Tapeworm-infected canines/cats or wild rodents are common vectors. Less common than infection with E. granulosus.
**Pitfalls:** Do not confuse central cavitary lesions with squamous cell carcinoma.
**Prognosis:** Related to size/location of cysts.

### Pulmonary Amebiasis (Entamoeba histolytica)

**Clinical Presentation:** Cough, pelvic pain, fever, and right lung/pleural mass mimicking pneumonia or lung abscess. Bronchopleural fistulas may occur. Sputum has "liver-like" taste if cyst ruptures into bronchus. Bacterial co-infection is rare. Amebic lung lesions are associated with hepatic liver abscesses, and invariably involve the right lobe of lung/diaphragm.

**Diagnostic Considerations:** Diagnosis by aspiration of lungs cysts, which may be massive. Amebic serology is sensitive and specific. Worldwide distribution. Acquired by ingesting amebic cysts. Key to diagnosis is concomitant liver involvement; liver abscess presents years after initial diarrheal episode.
**Pitfalls:** Lung involvement is rarely the sole manifestation of amebic infection, and is usually due to direct extension of amebic liver abscess (10–20% of amebic liver abscesses penetrate through the diaphragm and into the lungs). Follow metronidazole with paromomycin 500 mg (PO) q8h × 7 days to eliminate intestinal focus.
**Prognosis:** Related to severity/extent of cysts.

### Pulmonary Paragonimiasis (Paragonimus westermani) Lung Fluke

**Clinical Presentation:** Mild infection; may be asymptomatic. Acute phase of infection is accompanied by abdominal pain, diarrhea and urticaria, followed by pleuritic chest pain/eosinophilic pleural effusion. Chronic symptoms occur within 6 months after exposure, with dyspnea/dry cough leading to productive cough ± hemoptysis. Complications include lung abscess, bronchiectasis, cough, and night sweats. Eosinophilia may be present acutely.
**Diagnostic Considerations:** Oriental lung fluke acquired by ingestion of freshwater crayfish/crabs. After penetration of the gut/peritoneal cavity, the fluke migrates through the diaphragm/pleural space and invades lung parenchyma. Incubation period is 2–20 days. Diagnosis by demonstrating operculated eggs in sputum, pleural fluid, or feces. Multiple sputum samples are needed to demonstrate P. westermani eggs. Charcot-Leyden crystals are seen in sputum, and characteristic chest x-ray findings of ring-shaped/crescent infiltrates with "thin-walled" cavities are evident in ~ 60%. Endemic in Asia, Africa, and Latin America. Chest x-ray findings take months to resolve.
**Pitfalls:** May have extrapulmonary (ectopic) organ involvement, e.g., cerebral, subcutaneous, abdominal. Up to 20% have normal chest x-rays. Commonest cause of eosinophilic pleural effusions in endemic areas. Diagnosis should be questioned if pleural effusion fluid does not have eosinophils.
**Prognosis:** Related to degree of lung damage, e.g., bronchiectasis and extrapulmonary organ involvement, especially CNS.

## Pulmonary Coin Lesions

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Dog heartworm | Dirofilaria immitis | No therapy necessary | |
| Aspergilloma | Aspergillus | No therapy if asymptomatic. Surgery for massive hemoptysis | Itraconazole 200 mg (PO) solution q24h × 3–6 months **or** Voriconazole (see "usual dose," p. 714) × 3–6 months |

### Dog Heartworm (Dirofilaria immitis)

**Clinical Presentation:** Asymptomatic "coin lesion" after bite of infected mosquito transmits parasite from dogs to humans. Differential diagnosis includes granulomas and malignancy.
**Diagnostic Considerations:** Diagnosis by specific serology or pathological demonstration of organism in granuloma, usually when a coin lesion is biopsied to rule out malignancy. Worldwide distribution. Acquired from pet dogs. Dirofilariasis causes dog heartworm in carrier, but presents as a solitary lung nodule in humans.
**Pitfalls:** Often confused with malignancy.
**Prognosis:** Excellent.

### Pulmonary Aspergilloma

**Clinical Presentation:** Coin lesion(s) ± productive cough, hemoptysis, wheezing. May be asymptomatic. Usually occurs in pre-existing cavitary lung lesions, especially TB with cavity > 2 cm.

**Diagnostic Considerations:** Diagnosis by chest x-ray appearance of fungus ball in cavity and Aspergillus precipitins/biopsy or by demonstrating Aspergillus hyphae and "fruiting bodies" (conidiophores) in respiratory specimens. May present with "crescent sign" on chest x-ray (white fungus ball silhouetted against black crescent of the cavity).

**Pitfalls:** Role of itraconazole or voriconazole as therapy is unclear.

**Prognosis:** Related to degree of hemoptysis.

## Pulmonary Infiltrates/Mass Lesions¶

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Pulmonary blastomycosis | Blastomyces dermatitidis | Mild illness: Itraconazole 200 mg (PO) TID × 3 days and then QD or BID for a total of 6–12 months (adequate serum levels should be confirmed). Moderately severe or severe illness: lipid amphotericin for 1–2 weeks followed by itraconazole as for mild illness. | Fluconazole has been disappointing; its use is limited to specialized settings such as CNS blastomycosis. Amphotericin B 0.7–1 mg/kg may be used as initial therapy instead of lipid amphotericin. |
| Pulmonary histoplasmosis | Histoplasma capsulatum | Mild illness: Therapy is not always needed, but symptoms lasting more than a month may be treated with Itraconazole 200 mg (PO) TID × 3 days and then QD or BID for a total of 6–12 weeks. Moderately severe or severe illness: lipid amphotericin for 1–2 weeks followed by Itraconazole as for mild illness. Chronic cavity histoplasmosis requires at least a year of therapy & confirmation of adequate blood levels. | Strategies are complex (See Wheat LJ et al. Clin Infect Dis 45:807–825, 2007). |
| Pulmonary paracoccidioidomycosis (South American blastomycosis) | Paracoccidioides brasiliensis | Itraconazole 200 mg (PO) q24h × 6 months **or** Ketoconazole 400 mg (PO) q24h × 18 months | Amphotericin B 0.5 mg/kg (IV) q24h until 1.5–2.5 grams given |

¶ **See Color Atlas** (center of book).

## Pulmonary Infiltrates/Mass Lesions (cont'd)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Pulmonary actinomycosis | Actinomyces israelii | Amoxicillin 1 gm (PO) q8h × 6 months<br>**or**<br>Doxycycline 100 mg (PO) q12h × 6 months | Clindamycin 300 mg (PO) q8h × 6 months<br>**or**<br>Chloramphenicol 500 mg (PO) q6h × 6 months |
| Pulmonary aspergillosis | Aspergillus | Systemic oral steroids | Itraconazole 200 mg (PO) q12h × 8 months |
| *BPA* | Aspergillus | See p. 323 | |
| *Acute invasive pneumonia/* aspergillus<br>*Chronic pneumonia* aspergillus | Aspergillus | Treat the same as on p. 165 | Treat the same as on p. 165 |
| Pulmonary sporotrichosis | Sporothrix schenckii | Lipid amphotericin (p. 525) (IV) q24h × 3 weeks<br>**or**<br>Amphotericin B 0.5 mg/kg (IV) q24h until 1–2 grams given | Itraconazole 200 mg (PO)* q12h until cured<br>**or**<br>Lipid amphotericin (p. 525) (IV) q24h until cured |
| Pulmonary coccidioidomycosis | Coccidioides immitis | Itraconazole 200 mg (PO)* q12h until cured<br>**or**<br>Fluconazole 800 mg (IV or PO) × 1 dose, then 400 mg (PO) q24h until cured | Amphotericin B 1 mg/kg (IV) q24h × 7 days†<br>**or**<br>Lipid amphotericin (p. 525) (IV) q24h × 7 days |
| Pulmonary nocardiosis | Nocardia asteroides | TMP–SMX 5–10 mg/kg/d (TMP) in 2–4 doses (IV) × 3–6 weeks, then 1 DS tablet (PO) q12h until cured | Minocycline 100 mg (PO) q12h until cured |

* Initiate therapy with Itraconazole 200 mg (IV) q12h × 7–14 days.

† Follow with Itraconazole 200 mg (PO) solution q12h until cured.

## Pulmonary Infiltrates/Mass Lesions (cont'd)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Pulmonary cryptococcosis | Cryptococcus neoformans | Fluconazole 800 mg (IV or PO) × 1 dose, then 400 mg (PO) q24h until cured | Amphotericin B 0.5 mg/kg (IV) q24h until 1–2 grams given<br>**or**<br>Lipid amphotericin (p. 525) (IV) q24h × 3 weeks |
| Pulmonary zygomycosis (mucormycosis) | Rhizopus/ Mucor/Absidia | Lipid amphotericin (p. 525) (IV) q24h × 1–2 weeks† *or* × 3 wks<br>**or**<br>Amphotericin B 1–1.5 mg/kg (IV) q24h × 1–2 wks† *or* until 2–3 grams given | Voriconazole (see "usual dose," p. 714) until cured<br>**or**<br>Isavuconazole 200 mg (IV) q8h × 48 hours, then 200 mg (IV/PO) q24h until cured<br>**or**<br>Itraconazole 200 mg (PO)* q12h until cured |
| Pulmonary pseudall-escheriasis | Pseudallescheria boydii/ Scedosporium apiospermum | Voriconazole (see "usual dose," p. 714) until cured | Itraconazole 200 mg (PO)* q12h until cured |

*BPA = bronchopulmonary aspergillosis.*

* Initiate therapy with itraconazole 200 mg (IV) q12h × 7–14 days.

† Follow with itraconazole 200 mg (PO) solution q12h until cured.

### Pulmonary Blastomycosis (Blastomyces dermatitidis)

**Clinical Presentation:** Highly variable. May present as a chronic/non-resolving pneumonia with fever/cough and characteristic "right-sided perihilar infiltrate" ± small pleural effusion.

**Diagnostic Considerations:** Usual sites of dissemination include skin, bones and prostate, not CNS or adrenals. Blastomyces serology may XR (false +) with Aspergillus, Coccidiodides, Histoplasma, or paracoccidiomycosis. β 1,3 D-glucan – , aspergillus galactomannan – .

**Pitfalls:** Dissemination to extra-pulmonary sites may occur years after pneumonia.

**Prognosis:** Related to severity/extent of infection. One-third of cases are self-limited and do not require treatment.

### Pulmonary Histoplasmosis (Histoplasma capsulatum)

**Clinical Presentation:** Acute primary infection presents as self-limiting flu-like illness with fever, headache, nonproductive cough, chills, and chest pain. Minority of patients become overtly ill with complicated respiratory or progressive pulmonary infection. Can cause arthralgias, E. nodosum, E. multiforme, or pericarditis. May occur in outbreaks. Chronic infection presents as chronic pneumonia resembling TB or chronic disseminated infection. Eosinophilia common.

**Diagnostic Considerations:** May be recovered from sputum or demonstrated in lung tissue specimens. Worldwide distribution, but most common in Central/South Central United States. Acute disseminated histoplasmosis suggests HIV. Intracellular (PMNs/monocytes) organisms may be seen in Wright/Giema stained peripheral blood smears/buffy coat smears in disseminated infection. Acute histoplasmosis with immunodiffusion (ID) assay M band precipitins; chronic histoplasmosis with ID assay M band precipitins or CF ≥ 1:32. Histoplasma urinary antigen useful in diagnosis of acute/disseminated histoplasmosis. Histoplasma serology may XR (false +) with coccidiomycosis, blastomycosis, TB or sarcoidosis. Histoplasma urinary antigen may XR with acute/chronic coccidiomycosis (false + histoplasma urinary antigen may provide a clue to the presence of coccidiomycosis). β 1,3 D-glucan +, aspergillus galactomannan +.

**Pitfalls:** Pleural effusion is uncommon. Do not treat old/inactive/minimal histoplasmosis, histoplasmosis pulmonary calcification, or histoplasmosis fibrosing mediastinitis. Differentiate from TB and kala-azar. Resembles kala-azar histologically, but rod-shaped kinetoplasts (kala-azar) are absent extracellularly.
**Prognosis:** Related to severity/extent of infection. No treatment is needed for self-limiting acutehistoplasmosis presenting as flu-like illness. HIV patients should receive life-long suppressive therapy with itraconazole 200 mg (PO) solution q24h.

## Pulmonary Paracoccidioidomycosis (South American Blastomycosis)

**Clinical Presentation:** Typically presents as a chronic pneumonia syndrome with productive cough, blood-tinged sputum, dyspnea, and chest pain. May also develop fever, malaise, weight loss, mucosal ulcerations in/around mouth and nose, dysphagia, changes in voice, cutaneous lesions on face/limbs, or cervical adenopathy. Can disseminate to prostate, epididymis, kidneys, or adrenals.
**Diagnostic Considerations:** Characteristic "pilot wheel" shaped yeast in sputum. Diagnosis by culture and stain (Gomori) of organism from clinical specimen. Found only in Latin American. One-third of cases have only pulmonary involvement. Skin test is non-specific/non-diagnostic.
**Pitfalls:** No distinguishing radiologic features. No clinical adrenal insufficiency, in contrast to TB or histoplasmosis. Hilar adenopathy/pleural effusions are uncommon.
**Prognosis:** Related to severity/extent of infection. HIV require life-long suppression with TMP–SMX 1 DS tablet (PO) q24h or itraconazole 200 mg (PO) solution q24h.

## Pulmonary Actinomycosis (Actinomyces israelii)

**Clinical Presentation:** Indolent, slowly progressive infiltrates involving the pulmonary parenchyma ± pleural space. Presents with fever, chest pain, weight loss. Cough/hemoptysis are less common. Chest wall sinuses frequently develop. Chest x-ray shows adjacent dense infiltrate. "Sulfur granules" are common in sinus drainage fluid.
**Diagnostic Considerations:** Diagnosis by stain/culture of drainage from sinuses or lung/bone biopsy specimens. Actinomyces are non-acid fast and anaerobic to microaerophilic.
**Pitfalls:** No CNS lesions, but bone erosion is common with chest lesions. Prior antibiotic therapy may interfere with isolation of organism.
**Prognosis:** Excellent when treated until lesions resolve. Use IV regimen in critically ill patients, then switch to oral regimen.

## Bronchopulmonary Aspergillosis (BPA/ABPA)

**Clinical Presentation:** Migratory pulmonary infiltrates in chronic asthmatics. Eosinophilia is common, and sputum shows Charcot-Leyden crystals/brown flecks containing Aspergillus.

**Diagnostic Considerations:** Diagnosis by Aspergillus in sputum and high-titers of Aspergillus precipitins in serum. BPA is an allergic reaction in chronic asthmatics, *not* an infectious disease. Pulmonary infiltrates with peripheral eosinophilia in chronic asthmatics suggests the diagnosis.
**Pitfalls:** Correct diagnosis is important since therapy is steroids, not antifungals.
**Prognosis:** Related to severity/duration of asthma and promptness of steroid therapy.

**Acute Invasive Aspergillus Pneumonia** (see p. 67)

**Chronic Aspergillus Pneumonia**
**Clinical Presentation:** Occurs in patients with AIDS, chronic granulomatous disease, alcoholism, diabetes, and those receiving steroids for chronic pulmonary disease. Usual features include chronic productive cough ± hemoptysis, low-grade fever, weight loss, and malaise. Chronic Aspergillus pneumonia resembles TB, histoplasmosis, melioidosis.
**Diagnostic Considerations:** Diagnosis by lung biopsy demonstrating septate hyphae invading lung parenchyma. Aspergillus may be in sputum, but is not diagnostic of aspergillus pneumonia. β 1,3 D-glucan + , aspergillus galactomannan + .

**Pitfalls:** May extend into chest wall, vertebral column, or brachial plexus.
**Prognosis:** Related to severity/extent of infection. Cavitation is a favorable prognostic sign.

**Pulmonary Sporotrichosis (Sporothrix schenckii)**
**Clinical Presentation:** Usually presents as productive cough, low-grade fever, and weight loss. Chest x-ray shows cavitary thin-walled lesions with associated infiltrate. Hemoptysis is unusual. Differential diagnosis includes other thin-walled cavitary lung lesions (e.g., coccidioidomycosis, atypical TB, paragonimiasis).
**Diagnostic Considerations:** Diagnosis by lung biopsy demonstrating invasive lung disease, not broncho-alveolar lavage. Usually a history of puncture/traumatic wound involving an extremity. May be associated with septic arthritis/osteomyelitis.
**Pitfalls:** Sporotrichosis in lungs implies disseminated disease. May need repeated attempts at culture.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

**Pulmonary Coccidioidomycosis (Coccidioides immitis)**
**Clinical Presentation:** Usually presents as a solitary, peripheral, thin-walled cavitary lesion in early or later stage of primary infection. May present as a solitary pulmonary nodule. E. nodosum and bilateral hilar adenopathy are common (in contrast to sporotrichosis). Hemoptysis is unusual.
**Diagnostic Considerations:** Diagnosis by demonstration of spherules with endospores in sputum/BAL or biopsy specimens/Coccidioides serology. Increased incidence of dissemination in Filipinos, Blacks, and American Indians. Eosinophils in CSF in disseminated infection with CNS involvement. May be associated with chronic meningitis/osteomyelitis. CF IgG titer ≥ 1:32 diagnostic of active disease. Coccidioides CF may XR (false +) with Blastomyces, Histoplasma, Cryptococci, Torulopsis, or TB (XR minimal with EIA). (False + histoplasma urinary antigen may provide a clue to the presence of coccidiomycosis.)
**Pitfalls:** Dissemination is preceded by ↓ Coccidioides titers/disappearance of Erythema nodosum.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

**Pulmonary Nocardiosis (Nocardia asteroides)**
**Clinical Presentation:** Usually presents as a dense lower lobe lung mass ± cavitation. May have associated mass lesions in CNS. Chest wall sinuses are more common with Actinomycosis.

**Diagnostic Considerations:** Diagnosis by demonstrating organisms by stain/culture of lung specimens. Nocardia are weakly acid-fast and aerobic.
**Pitfalls:** Use IV regimens in critically ill patients. HIV patients require life-long suppressive therapy with TMP–SMX or minocycline.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

## Pulmonary Cryptococcosis (Cryptococcus neoformans)

**Clinical Presentation:** Individual focus of infection is usually inapparent/minimal when patient presents with disseminated cryptococcal infection. Pneumonia is typically a minor part of disseminated disease; CNS manifestations usually predominate (e.g., headache, subtle cognitive changes, occasional meningeal signs, focal neurological deficits).
**Diagnostic Considerations:** Diagnosis by serum cryptococcal antigen, by demonstrating encapsulated yeasts in sputum/lung specimens, or by culture of pulmonary specimens. β 1,3 D-glucan – , aspergillus galactomannan – .
**Pitfalls:** Clinical presentation of isolated cryptococcal pneumonia is rare. In HIV, false + cryptococcal antigen may occur with BBL Port-A-Cul transport vials. Patients require life-long suppressive therapy with fluconazole.
**Prognosis:** Related to extent of dissemination/degree of immunosuppression.

## Pulmonary Zygomycosis (Mucormycosis) (Rhizopus/Mucor/Absidia/Cunninghamella)

**Clinical Presentation:** Progressive pneumonia with fever, dyspnea, hemoptysis and cough unresponsive to antibiotic therapy. Usually seen only in compromised hosts. Chest x-ray is not characteristic, but shows infiltrate with consolidation in > 50% of patients. Cavitation occurs in 40% as neutropenia resolves.
**Diagnostic Considerations:** Diagnosis by demonstrating branched non-septate "ribbon-like" hyphae with right angle branching in biopsy specimens in lung biopsy. Pleural effusion is not a feature of pulmonary mucormycosis. β 1,3 D-glucan – , aspergillus galactomannan – .
**Pitfalls:** Causes rhinocerebral mucormycosis in diabetics, pneumonia in leukopenic compromised hosts.
**Prognosis:** Related to degree of immunosuppression and underlying disease. Angioinvasive with a propensity for dissemination.

## Pulmonary Pseudallescheriasis (P. boydii/S. apiospermum)

**Clinical Presentation:** Progressive pulmonary infiltrates indistinguishable from Aspergillosis or Mucor. Usually seen only in compromised hosts (e.g., prolonged neutropenia, high-dose steroids, bone marrow or solid organ transplants, AIDS). Manifests as cough, fever, pleuritic pain, and often hemoptysis. No characteristic chest x-ray appearance.
**Diagnostic Considerations:** Diagnosis by culture of organisms in lung biopsy. Hemoptysis is common in patients with cavitary lesions. CNS involvement is rare.
**Pitfalls:** One of few invasive fungi unresponsive to amphotericin B deoxycholate. Cause of sinusitis in diabetics, and pneumonia in leukopenic compromised hosts.
**Prognosis:** Related to severity/extent of infection and degree of immunosuppression. Cavitary lesions causing hemoptysis often require surgical excision. Disseminated infection is often fatal.

# Parasites, Fungi, Unusual Organisms in Heart

## Chagas' Disease (Trypanosoma brucei cruzi) American Trypanosomiasis

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Chagas' disease (American trypanosomiasis) | Trypanosoma brucei cruzi | Benznidazole 2.5–3.5 mg/kg (PO) q12h × 60 days | Nifurtimox 2–3 mg/kg/day (PO) q6–8h × 90 days |

# Parasites, Fungi, Unusual Organisms in the Liver

## Liver Flukes

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Fascioliasis | Fasciola hepatica<br>Fasciola gigantica | Tridabendazole 10 mg/kg (PO) × 1 or 2 doses | Bithionol 30–50 mg/kg (PO) q48h × 20–30 days<br>**or**<br>Nitazoxanide 500 mg (PO) q12h × 7 days |
| Clonorchiasis/ Opisthorchiasis | Clonorchis sinensis<br>Opisthorchis viverrini | Praziquantel 25 mg/kg (PO) q8h × 2 days | C. sinensis/O. viverrini<br>Albendazole 10 mg/kg (PO) q24h × 7 days<br>O. viverrini: Tribendimidine 400 mg (PO) × 1 dose |

**Hepatic Fascioliasis (F. hepatica/F. gigantica)**

**Clinical Presentation:** Frequently asymptomatic, but may present acutely with fever, right upper quadrant pain, nausea, diarrhea, wheezing, urticaria, hepatomegaly, eosinophilia, anemia. ELISA, IHA, CF, CIE serology helpful with acute diagnosis. Aspiration of biliary fluid may show flukes/eggs. Chronic disease is associated with gallstones, cholecystitis, cholangitis, liver abscess, generalized adenopathy. Subacute nodules, hydrocele, lung/brain abscess can be seen in ectopic forms.

**Diagnostic Consideration:** Diagnosis by F. hepatica/F. gigantica eggs in stool. Endemic in sheep- raising areas (sheep liver flukes). Acquired from freshwater plants (watercress). Not associated with cholangiocarcinoma.

**Pitfalls:** May present as Katayama syndrome resembling schistosomiasis, with high fever, eosinophilia, and hepatosplenomegaly. Unlike other trematodes, praziquantel is ineffective. Chronic F. hepatica often asymptomatic, but may present with intermittent biliary colic. No eosinophilia. Abdominal ultrasound/CT shows crescentic/leaf shaped defects in gallbladder/hepatic ducts.

**Prognosis:** Related to extent/location of liver damage.

### Hepatic Clonorchiasis (C. sinensis)/Opisthorchiasis (O. viverrini)

**Clinical Presentation:** Frequently asymptomatic, but may present 2–4 weeks after ingestion of fluke with fever, tender hepatomegaly, rash, and eosinophilia. Chronically presents as recurrent cholangitis, chronic cholecystitis, or pancreatitis. Associated with cholangiocarcinoma (unlike fascioliasis).

**Diagnostic Considerations:** Diagnosis by visualizing C. sinensis/O. viverrini (operculated lemon-shaped) eggs in stool. Clonorchiasis is acquired from ingesting raw/inadequately cooked infected freshwater (Cyprinoid) fish in Southeast Asia. Opisthorchiasis is acquired from ingesting raw/inadequately cooked infected freshwater fish/crayfish from Laos, Cambodia, or Thailand.

**Pitfalls:** Cholecystitis with eosinophilia should suggest clonorchiasis or ascariasis.

**Prognosis:** Related to extent/location of hepatic damage. Associated with cholangiocarcinoma.

## Cystic Masses in Liver

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Hepatic amebiasis | Entamoeba histolytica | Metronidazole 750 mg (PO) q8h × 7–10 days | Tinidazole 2 gm/day (PO) in 3 divided doses × 3 days |
| Hepatic echinococcosis (hydatid cyst disease) | Echinococcus granulosus | Operable<br>Surgical resection **plus** Albendazole 400 mg* (PO) q12h × 1–6 months | Inoperable<br>Albendazole 400 mg* (PO) q12h × 1–6 months |

* If < 60 kg, give albendazole 7.5 mg/kg.

### Hepatic Amebiasis (Entamoeba histolytica)

**Clinical Presentation:** Presents insidiously with weight loss and night sweats or acutely ill with fever, nausea, vomiting, right upper quadrant pain. Typically, amebic liver abscesses are single, affect the right posterior lobe of liver, and do not show air/fluid levels. (In contrast, bacterial liver abscesses are usually multiple, and in all lobes of liver, and often show air/fluid levels.) Amebic liver abscesses do not calcify like hydatid cysts.

**Diagnostic Considerations:** Diagnosis by E. histolytica serology/E. histolytica in abscess wall. Worldwide distribution. Acquired by ingesting amebic cysts. Amebic liver abscess usually presents years after initial mild amebic dysenteric episode.

**Pitfalls:** Amebic abscess fluid ("anchovy paste") contains no PMNs or amebas; amebas are found only in abscess wall. Eosinophilia is not a feature of amebiasis.

**Prognosis:** Related to health of host/extrapulmonary spread.

### Hepatic Echinococcosis (Echinococcus granulosus) Hydatid Cyst Disease

**Clinical Presentation:** Right upper quadrant pain/mass when cysts enlarge enough to cause symptoms. Hepatic cysts are unilocular in 70%, multilocular in 30%.

**Diagnostic Considerations:** Diagnosis by demonstrating E. granulosus scolices/hooklets in cyst/hydatid sand. Serology is unreliable. Worldwide distribution in sheep/cattle raising areas. Acquired by ingestion of eggs from dogs.

**Pitfalls:** Eosinophilia not a feature of hydatid cyst disease. Hydatid cysts are multifaceted, loculated, and calcified.

**Prognosis:** Related to location/extent of extrahepatic cysts. Large cysts are best treated by surgical removal after injection with hypertonic saline, alcohol, or iodophor to kill germinal layer/daughter cysts. Percutaneous drainage under ultrasound guidance plus albendazole may be effective.

## Hepatomegaly

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Visceral leishmaniasis (Kala-azar) | Leishmania donovani | Antimony stibogluconate 20 mg/kg (IV/IM) q24h × 28 days **or** Lipid amphotericin (Immunocompetent adults: 3 mg/kg (IV) q24h on days 1–5,14, and 21; Immunocompromised adults: 4 mg/kg (IV) q24h on days 1–5, 10, 17, 24, 31, and 38)* | Miltefosine 2.5 mg/kg* (PO) q24h × 28 days **or** Paromomycin 15 mg/kg (IM) q24h × 21 days |
| Indian (Bihar state) visceral leishmaniasis (Kala-azar) | L. donovani | AmBisome (L-Amb)† 5 mg/kg (IV) × 1 dose, then Miltefosine 50 mg (PO with food) q12h × 7–14 days | |
| Schistosomiasis | Schistosoma mansoni | Praziquantel 20 mg/kg (PO) q12h × 2 doses | Oxamniquine 15 mg/kg (PO) × 1 dose¶ |
| | Schistosoma japonicum | Praziquantel 20 mg/kg (PO) q8h × 3 doses | None |

* Maximum 150 mg (PO)/day.

† Ultra short course therapy with AmBisome is 10 mg/kg (IV) × 2 days.

¶ In Africa, give 20 mg/kg (PO) q24h × 3 days.

### Visceral Leishmaniasis (Leishmania donovani) Kala-azar

**Clinical Presentation:** Subacute or chronic systemic cases manifest months to years after initial exposure to Leishmania, most often with fever, weight loss, anemia, hepatosplenomegaly ± generalized adenopathy. Long eyelashes in some. Laboratory abnormalities include leukopenia, anemia, and polyclonal gammopathy on SPEP. Incubation period is usually 3–8 months. May have atypical presentation in HIV (e.g., no splenomegaly). Acutely can mimic malaria with chills/temperature spikes. Post–kala-azar dermatitis may resemble leprosy, and is persistent/common on face.

**Diagnostic Considerations:** Double quotidian fever (double daily temperature spike) in persons from endemic areas with hepatosplenomegaly suggests the diagnosis. Kala-azar in children may have ↑ triglycerides/↓ HDL. Diagnosis by liver/bone marrow or buffy coat smear. Histologically, Kala-azar resembles histoplasmosis. Key diagnostic finding in tissue biopsy specimens is intracellular amastigotes with adjacent rod-shaped kinetoplasts. L. donovani serology is specific; immunochromatographic Anti-K39 strip test is also useful. Most common in Southern Europe, Middle East, Asia, Africa, South America. Facial lesion is a clue to the diagnosis.

**Pitfalls:** In acute cases, can mimic malaria with chills and temperature spikes, but no thrombocytopenia or atypical lymphocytes. Antimony resistance is common in India (Bihar state).

**Prognosis:** Related to degree of liver/spleen involvement.

**Hepatic Schistosomiasis (Schistosoma mansoni/japonicum)**

**Clinical Presentation:** May present acutely with Katayama fever (serum sickness-like illness with wheezing and eosinophilia) 4–8 weeks after exposure. May be accompanied or followed by fever/chills, headache, cough, abdominal pain, diarrhea, generalized lymphadenopathy, or hepatosplenomegaly. Laboratory abnormalities include leukocytosis, eosinophilia, and polyclonal gammopathy on SPEP. Resolves spontaneously after 2–4 weeks. After 10–15 years, may present chronically as hepatosplenic schistosomiasis, with pre-sinusoidal portal hypertension, hepatomegaly (L > R lobe enlargement), no jaundice, and intact liver function.

**Diagnostic Considerations:** Diagnosis by S. mansoni/S. japonicum eggs in stool/liver biopsy. Serology is good for acute (not chronic) schistosomiasis. CT/MRI of liver shows "turtle back" septal calcifications. Rare complications include cor pulmonale and protein-losing enteropathy. Increased incidence of hepatitis B/C and chronic Salmonella infections. Renal complications include glomerulonephritis and nephrotic syndrome.

**Pitfalls:** Chronic schistosomiasis is not associated with eosinophilia. S. hematobium does not infect the liver/spleen. Oxamniquine is contraindicated in pregnancy.

**Prognosis:** Related to egg burden.

# Parasites, Fungi, Unusual Organisms in Stool/Intestines

## Intestinal Protozoa

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Amebiasis | E. histolytica | See p. 88 | |
| Giardiasis | Giardia lamblia | Tinidazole 2 gm (PO) × 1 dose **or** Metronidazole 250 mg (PO) q8h × 5–7 days | |
| Isospora | Isospora belli | TMP–SMX 1 DS tablet (PO) q12h × 10 days **or** Nitazoxanide 500 mg (PO) × 3 days (for HIV, see p. 334) | Ciprofloxacin 500 mg (PO) q12h × 7 days **or** Pyrimethamine 75 mg (PO) q24h + folinic acid 10 mg (PO) q24h × 2 weeks then q12h × 3 weeks |
| Dientamoebiasis | Dientamoeba fragilis | Iodoquinol 650 mg (PO) q8h × 20 days | Doxycycline 100 mg (PO) q12h × 10 days **or** Metronidazole 500–750 mg (PO) q8h × 10 days |
| Blastocystis | Blastocystis hominis | Nitazoxanide 500 mg (PO) q12h × 3 days | Iodoquinol 650 mg (PO) q8h × 20 days **or** TMP–SMX 1 DS tablet (PO) q12h × 7 days |

## Intestinal Protozoa (cont'd)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Cyclospora | Cyclospora | TMP–SMX 1 DS (PO) q12h × 10 days **or** Nitazoxanide 500 mg (PO) q12h × 3 days (for HIV, see p. 335) | |
| Cryptosporidiosis | Cryptosporidia | Nitazoxanide 500 mg (PO) q12h × 3 days (for HIV, see p. 334) | |
| Balantidiasis | Balantidium coli | Doxycycline 100 mg (PO) q12h × 10 days | Iodoquinol 650 mg (PO) q8h × 20 days **or** Metronidazole 750 mg (PO) q8h × 5 days |

**Amebiasis (Entamoeba histolytica)** (see p. 91)

**Giardiasis (Giardia lamblia)** (see p. 90)

**Isosporiasis (Isospora belli)**
**Clinical Presentation:** Acute/subacute onset of diarrhea. Isospora belli is the only protozoa to cause diarrhea with eosinophils in stool.
**Diagnostic Considerations:** Diagnosis by demonstrating cysts in stool and organisms in intestinal biopsy specimen. Associated with HIV, immigration from Latin America, daycare centers, and mental institutions. If stool exam is negative, "string test"/duodenal aspirate and biopsy may be helpful.
**Pitfalls:** Difficult to eradicate; may last months. Multiple stool samples may be needed for diagnosis. Add folinic acid 10 mg (PO) q24 if pyrimethamine is used.
**Prognosis:** Related to adequacy of treatment/degree of immunosuppression.

**Dientamoebiasis (Dientamoeba fragilis)**
**Clinical Presentation:** Acute/subacute onset of diarrhea. No cyst stage. Lives only as trophozoite. Among intestinal protozoa, only D. fragilis and I. belli are associated with peripheral eosinophilia.
**Diagnostic Considerations:** Diagnosis by demonstrating trophozoites in stool/intestinal by trichrome stain. Mucus in diarrheal stools, not blood. May have abdominal pain. Diarrhea may last for months/years.
**Pitfalls:** Frequently associated with pinworm (Enterobius vermicularis) infection. Metronidazole failures common.
**Prognosis:** Related to adequacy of fluid replacement/underlying health of host.

**Blastocystis (Blastocystis hominis)**
**Clinical Presentation:** Acute/subacute onset of diarrhea.
**Diagnostic Considerations:** Diagnosis by demonstrating cysts and trophozoites in stool by trichrome stain. Trichrome stain reveals characteristic "halo" (slime capsule) in stool specimens.
**Pitfalls:** Uncommon GI pathogen. Consider as cause of diarrhea only after other pathogens excluded.
**Prognosis:** Related to adequacy of fluid replacement/underlying health of host.

**Cyclospora** (see p. 90; for HIV, see p. 335)

**Cryptosporidiosis** (see p. 90; for HIV, see p. 334)

**Balantidiasis (Balantidium coli)**

**Clinical Presentation:** Acute/subacute onset of diarrhea. Fecal WBCs only with mucosal invasion. Largest intestinal protozoa and only ciliated protozoa to infect humans.

**Diagnostic Considerations:** Diagnosis by demonstrating organism in stool/intestinal biopsy specimen. Identifying features include darkly staining "kidney shaped" nucleus and large size. Fulminant dysentery seen only in debilitated/compromised hosts.

**Pitfalls:** Stools not bloody. Diarrhea may be intermittent.

**Prognosis:** Related to adequacy of fluid replacement/underlying health of host.

## Intestinal Nematodes (Roundworms)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Capillariasis | Capillaria (Aonchotheca) philippinensis | Mebendazole 200 mg (PO) q12h × 20 days | Albendazole 400 mg (PO) q24h × 10 days |
| Angiostrongyliasis (rodent lung/ intestinal worm) | Angiostrongylus cantonensis | Albendazole 400 mg (PO) q12h × 2–3 weeks **plus** corticosteroids | Mebendazole 200–400 mg (PO) q8h × 10 days |
| Hookworm | Necator americanus/ Ancylostoma duodenale | Albendazole 400 mg (PO) × 1 dose **or** Mebendazole 100 mg (PO) q12h × 3 days or 500 mg (PO) × 1 dose | Pyrantel pamoate 11 mg/ kg (PO) q24h × 3 days (max. 1 gm/day) |
| Strongyloidiasis | Strongyloides stercoralis | Ivermectin 200 mcg/kg (PO) q24h × 2 days **or** Thiabendazole 25 mg/kg (PO) q12h × 2 days (max. 3 gm/day) | Albendazole 400 mg (PO) q24h × 3 days |
| Ascariasis | Ascaris lumbricoides | Albendazole 400 mg (PO) × 1 dose **plus** Pyrantel pamoate 11 mg/kg (PO) q24h × 3 days (max. 1gm/ day) **or** Mebendazole 100 mg (PO) q12h × 3 days or 500 mg (PO) × 1 dose | Ivermectin 200 mcg/kg (PO) × 1 dose* |
| Trichostrongyliasis | Trichostrongylus orientalis | Pyrantel pamoate 11 mg/kg (PO) × 1 dose (max. 1 gm) | Albendazole 400 mg (PO) × 1 dose **or** Mebendazole 100 mg (PO) q12h × 3 days |

* Avoid in young children and pregnant adults.

## Intestinal Nematodes (Roundworms) (cont'd)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Pinworm | Enterobius vermicularis | Pyrantel pamoate 11 mg/kg (PO) × 1 dose (max. 1 gm); repeat in 2 weeks **or** Albendazole 400 mg (PO) × 1 dose; repeat in 2 weeks | Ivermectin 200 mcg/kg (PO) × 1 dose **or** Mebendazole 100 mg (PO) × 1 dose; repeat in 2 weeks |
| Whipworm | Trichuris trichiura | Mebendazole 100 mg (PO) q12h × 3–7 days | Albendazole 400 mg (PO) q24h × 3 days **or** Ivermectin 200 mcg/kg (PO) q24h × 3 days |

### Capillariasis (Capillaria philippinensis)

**Clinical Presentation:** Intermittent voluminous watery diarrhea ± malabsorption. Fever is uncommon.
**Diagnostic Considerations:** Diagnosis by demonstrating ova or parasite in stools. Resembles Trichuris, but C. philippinensis ova are larger and have a "pitted shell" with prominent polar plugs. Peripheral eosinophilia is uncommon until after therapy.
**Pitfalls:** Serology is positive in 85%, but cross-reacts with other parasites.
**Prognosis:** Related to severity of malabsorption/extra-intestinal disease.

### Angiostrongyliasis (A. cantonensis) Rodent Lung/Intestinal Worm

**Clinical Presentation:** Presents as appendicitis (worm resides and deposits eggs in arteries/arterioles around ileocecum/appendix).
**Diagnostic Considerations:** Diagnosis by demonstrating organism in biopsied/excised tissue. May involve proximal small bowel, liver, CNS. When in CNS, a cause of eosinophilic meningitis.
**Pitfalls:** Can present as RLQ mass/fever resembling regional enteritis (Crohn's disease), but with eosinophilia and leukocytosis.
**Prognosis:** Related to severity of malabsorption and extra-intestinal disease.

### Hookworm (Necator americanus/Ancylostoma duodenale)

**Clinical Presentation:** Pruritic, vesicular eruptions at site of filariform larval entry ("ground itch"). Pulmonary symptoms and transient eosinophilia may occur during migratory phase to intestines. Later, abdominal pain, diarrhea, weight loss, hypoalbuminemia, and anemia develop.
**Diagnostic Considerations:** Diagnosis by demonstrating eggs in stools. Larvae rare in fresh stool specimens (eggs may hatch if stools allowed to stand too long prior to examination). N. americanus can ingest 0.3 ml of blood/worm/day, much greater than A. duodenale. Anemia may be severe with heavy infestation (up to 100 mL/day).
**Pitfalls:** Eggs in fresh stool, not rhabditiform larvae. Eggs in hyperinfection syndrome.
**Prognosis:** Related to severity of anemia/malabsorption.

### Strongyloidiasis (Strongyloides stercoralis)

**Clinical Presentation:** Pruritic, papular, erythematous rash. Pulmonary symptoms (cough, asthma) may occur during lung migration phase. May develop Loeffler's syndrome (pulmonary infiltrates with eosinophilia) or ARDS in heavy infections. Intestinal phase associated with colicky abdominal pain, diarrhea, and malabsorption.

**Diagnostic Considerations:** Diagnosis by demonstrating larvae in stool specimens/duodenal fluid. Usually asymptomatic in normal hosts, but causes "hyperinfection syndrome" in compromised hosts. CNS strongyloides (part of hyperinfection syndrome) should suggest diagnosis of HIV in non-immunosuppressed patients. Diarrhea/abdominal pain mimics regional enteritis (Crohn's disease) or ulcerative colitis. Malabsorption is common and mimics tropical sprue. Anemia is usually mild.
**Pitfalls:** Usually rhabditiform larvae (not eggs) in stools.
**Prognosis:** Related to severity of malabsorption.

## Ascariasis (Ascaris lumbricoides)

**Clinical Presentation:** Pulmonary symptoms (cough, asthma) may occur during larval lung migration phase. May develop Loeffler's syndrome (pulmonary infiltrates with eosinophilia), as with hookworm/Strongyloides. Intestinal symptoms develop late. Usually asymptomatic unless intestinal/biliary obstruction occurs. Can obstruct the appendix/pancreatic duct.
**Diagnostic Considerations:** Diagnosis by demonstrating eggs in stool specimens. Abdominal ultrasound can detect obstruction from adult worms. Most infections are asymptomatic; symptoms are related to "worm burden"/ectopic migration. Each female worm may produce up to 250,000 eggs/day.
**Pitfalls:** Lung involvement (bronchospasm, bronchopneumonia, lung abscess) is prominent in HIV.
**Prognosis:** Related to worm burden/extra-intestinal organ invasion.

## Trichostrongyliasis (Trichostrongylus orientalis)

**Clinical Presentation:** Mild intestinal symptoms with persistent eosinophilia.
**Diagnostic Considerations:** Diagnosis by demonstrating eggs in stool specimens. Most prevalent in the Middle East and Asia. Mild anemia. Eosinophilia is usually > 10%.
**Pitfalls:** Must differentiate eggs from hookworm, and rhabditiform larvae from Strongyloides. T. orientalis eggs have "pointed ends."
**Prognosis:** Related to extent of disease/underlying health of host.

## Pinworm (Enterobius vermicularis)

**Clinical Presentation:** Primarily affects children. Perianal pruritus (ectopic migration) is the main symptom. Worm lives in the cecum, but patients do not have intestinal symptoms.
**Diagnostic Considerations:** Scotch tape of anus at night can be used to detect eggs left by migrating female worms (Scotch tape test).
**Pitfalls:** Abdominal pain and diarrhea should prompt search for Dientamoeba fragilis, since co-infection is common.
**Prognosis:** Excellent.

## Whipworm (Trichuris trichiura)

**Clinical Presentation:** May present as "chronic appendicitis." Severe infestation may cause bloody diarrhea/abdominal pain ("Trichuris dysentery syndrome"), rectal prolapse.
**Diagnostic Considerations:** Diagnosis by demonstrating large eggs with bile-stained, triple-layered eggshell walls and doubly operculated transparent plugs. Most patients are asymptomatic or mildly anemic.
**Pitfalls:** Commonly co-exists with Ascaris, hookworm, or E. histolytica.
**Prognosis:** Related to severity/extent of dysentery. May need retreatment if heavy infection.

## Intestinal Cestodes (Tapeworms)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Beef tapeworm | Taenia saginata | Praziquantel 5–10 mg/kg (PO) × 1 dose | Niclosamide 2 gm (PO) × 1 dose **or** Nitazoxanide 500 mg (PO) q12h × 3 days |
| Pork tapeworm | Taenia solium | Praziquantel 5–10 mg/kg (PO) × 1 dose | Niclosamide 2 gm (PO) × 1 dose **or** Nitazoxanide 500 mg (PO) q12h × 3 days |
| Dwarf tapeworm | Hymenolepis nana | Praziquantel 25 mg/kg (PO) × 1 dose | Nitazoxanide 500 mg (PO) q12h × 3 days **or** Niclosamide 2 gm (PO) × 1 dose, then 1.5 gm q24h × 6 days |
| Fish tapeworm | Diphyllobothrium latum | Praziquantel 10 mg/kg (PO) × 1 dose | Niclosamide 2 gm (PO) × 1 dose **or** Nitazoxanide 500 mg (PO) q12h × 3 days |

### Beef Tapeworm (Taenia saginata)/Pork Tapeworm (Taenia solium)

**Clinical Presentation:** Usually mild symptoms (weight loss, anemia), since most infections are caused by a single tapeworm. Worm segments passed between BMs with T. saginata and with BMs with T. solium.
**Diagnostic Considerations:** Diagnosis by demonstrating proglottids in stool. Taenia eggs in stool cannot be speciated; all are brown and spherical with a radially-striated inner shell. T. saginata may survive for 10 years, T. solium for 25 years.
**Pitfalls:** Severe cases may cause appendicitis, intestinal obstruction/perforation.
**Prognosis:** Related to severity of malabsorption/intestinal obstruction.

### Dwarf Tapeworm (Hymenolepis nana)

**Clinical Presentation:** Usually asymptomatic.
**Diagnostic Considerations:** Diagnosis by demonstrating typical eggs in stool, with two shells enclosing inner oncosphere with hooklets. ELISA is positive in 85%, but cross-reacts with Taenia/Cysticercosis. GI symptoms develop with stool egg counts > 15,000/gm.
**Pitfalls:** Abdominal pain and diarrhea in heavy infestations.
**Prognosis:** Related to severity of malabsorption/underlying health of host.

### Fish Tapeworm (Diphyllobothrium latum)

**Clinical Presentation:** Symptoms secondary to macrocytic anemia from vitamin $B_{12}$ deficiency. Most infestations are asymptomatic.
**Diagnostic Considerations:** Diagnosis by demonstrating operculated eggs and proglottids in stool.

**Pitfalls:** Vitamin $B_{12}$ deficiency anemia requires prolonged infection (> 3 years).
**Prognosis:** Related to severity of $B_{12}$ deficiency anemia/underlying health of host.

## Intestinal Trematodes (Flukes/Flatworms)

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Fasciolopsiasis | Fasciolopsis buski | Praziquantel 25 mg/kg (PO) q8h × 3 doses |
| Heterophyiasis | Heterophyes heterophyes<br>Metagonimus yokogawai | Praziquantel 25 mg/kg (PO) q8h × 3 doses |

### Fasciolopsiasis (Fasciolopsis buski)

**Clinical Presentation:** Diarrhea with copious mucus in stool. Most cases are asymptomatic.
**Diagnostic Considerations:** Diagnosis by demonstrating eggs in stool. May have eosinophilia, low-grade fever ± malabsorption. Intestinal obstruction is the most serious complication.
**Pitfalls:** Mimics peptic ulcer disease with upper abdominal pain relieved by food.
**Prognosis:** Related to severity/extent of malabsorption/intestinal obstruction.

### Heterophyiasis (Heterophyes heterophyes/Metagonimus yokogawai)

**Clinical Presentation:** Usually asymptomatic or mild intestinal symptoms. Embolization of eggs may result in myocarditis, myocardial fibrosis, or cerebral hemorrhage. Eosinophilia may be present.
**Diagnostic Considerations:** Diagnosis by demonstrating large operculated eggs in stool. Small intestine fluke.
**Pitfalls:** Difficult to differentiate from clonorchis sinensis.
**Prognosis:** Related to extent/severity of extra-intestinal dissemination to heart, lungs, CNS.

## Other Intestinal Infections

| Subset | Pathogen | Preferred Therapy |
|---|---|---|
| Whipple's disease | Tropheryma whippelii | Ceftriaxone 2 gm (IV) q24h × 2 weeks*<br>**or**<br>Ceftriaxone 1 gm (IV) q24h × 2 weeks **plus**<br>Streptomycin 1 gm (IM) q24h × 2 weeks* |

* Follow with TMP–SMX 1 DS tablet (PO) q12h × 1 year or Doxycycline 100 mg (PO) q12h × 1 year.

### Whipple's Disease (Tropheryma whippelii)

**Clinical Presentation:** Diarrhea, fever, encephalopathy/dementia, weight loss, polyarthritis, myocarditis, pericarditis, general lymphadenopathy ± malabsorption.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by PAS staining macrophages in small bowel biopsy specimens.
**Pitfalls:** May present with dementia mimicking Alzheimer's disease, or FUO mimicking celiac disease or lymphoma. Optimum length of treatment is unknown. Relapses occur.
**Prognosis:** Related to severity/extent of extra-intestinal disease.

# Parasites, Fungi, Unusual Organisms in Skin/Muscle

## Infiltrative Skin/Subcutaneous Lesions

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Cutaneous leishmaniasis<br>*Old World* | Leishmania major<br>Leishmania tropica | Sodium stibogluconate 20 mg/kg (IV or IM) q24h × 20 days<br>**or**<br>Pentamidine 2–3 mg/kg (IM) q48h × 4–7 days<br>**or**<br>Lipid amphotericin 3 mg/kg (IV) q24h on days 1–5, 14, and 21<br>**or**<br>Miltefosine 2.5 mg/kg (PO) q24h × 28 days (max. 150 mg/day) |
| *New World* | Leishmania mexicana<br>Leishmania braziliensis | |
| Leprosy<br>*Lepromatous* | Mycobacterium leprae | Dapsone 100 mg (PO) q24h × 1–2 years **plus**<br>Clofazimine 50 mg (PO) q24h × 1–2 years **plus**<br>Rifampin 600 mg (PO) monthly × 1–2 years |
| *Non-lepromatous (tuberculoid)* | Mycobacterium leprae | Dapsone 100 mg (PO) q24h × 6 months **plus**<br>Rifampin 600 mg (PO) monthly × 6 months |
| Loa Loa (Loiasis) | L. loa | Diethylcarbamazine 2–3 mg/kg (PO) q8h × 2–3 weeks<br>**or**<br>Albendazole 200 mg (PO) q12h × 3 weeks |
| Erythrasma | Corynebacterium minutissimum | Erythromycin 250 mg (PO) q6h × 2 weeks |

### Cutaneous Leishmaniasis (Old World/New World)

**Clinical Presentation:** Variable presentation. Typically, a nodule develops then ulcerates, with a raised/erythematous outer border and a central area of granulation tissue. May be single or multiple. Usually non-pruritic/non-painful. Occurs weeks after travel to endemic areas (New World leishmaniasis: Latin America; Old World leishmaniasis: Central Asia).

**Diagnostic Considerations:** Diagnosis by demonstrating Leishmania amastigotes in biopsy specimen.

**Pitfalls:** Most skin lesions undergo spontaneous resolution. However, treatment is advisable for lesions caused by L. braziliensis or related species causing mucosal leishmaniasis.

**Prognosis:** Excellent.

### Lepromatous Leprosy (Mycobacterium leprae)

**Clinical Presentation:** Diffuse, symmetrical, red or brown skin lesions presenting as macules, papules, plaques, or nodules. May also present as diffuse thickening of skin, especially involving ear lobes, face, and extremities. Loss of eyebrows/body hair may occur.

**Diagnostic Considerations:** Diagnosis by demonstrating organism in acid fast stain of tissue specimens. Afebrile bacteremia is frequent, and buffy coat smears positive for M. leprae. Erythema nodosum and polyclonal gammopathy on SPEP are common, and lepromin skin test/PPD are negative (anergic). When present, peripheral neuropathy is often symmetrical and acral in distribution.
**Pitfalls:** Differential diagnosis is large. Consider leprosy in patients with unexplained skin diseases.
**Prognosis:** Good if treated early.

### Non-Lepromatous (Tuberculoid) Leprosy (Mycobacterium leprae)

**Clinical Presentation:** Small number of asymmetrical, hypopigmented skin lesions, which are often scaly with sharp borders and associated anesthesia. Asymmetric peripheral nerve trunk involvement is common.
**Diagnostic Considerations:** Diagnosis by demonstrating granulomas with few acid-fast bacilli. Differentiate from cutaneous leishmaniasis by skin biopsy. Lepromin skin test/PPD are positive and SPEP is normal (in contrast to lepromatous leprosy).
**Pitfalls:** Wide spectrum of presentations depending on immune status and duration of disease. Differential diagnosis is large. Consider leprosy in patients with unexplained skin diseases.
**Prognosis:** Good if treated early.

### Erythrasma (Corynebacterium minutissimum)

**Clinical Presentation:** Reddened/raised skin lesions on face/trunk. Not hot or pruritic.
**Diagnostic Considerations:** Differentiated from Tinea versicolor by culture. C. minutissimum skin lesions fluoresce red under UV light.
**Pitfalls:** Resembles Tinea versicolor, but lesions primarily involve the face, not trunk.
**Prognosis:** Excellent.

## Infiltrative Skin Lesions ± Ulcers/Sinus Tracts/Abscesses

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Cutaneous histoplasmosis | Histoplasma capsulatum | Treat as for disseminated histoplasmosis (p. 267) if part of systematic syndrome. If solely involves the skin, Itraconazole 200 mg (PO) q12h until resolution. |
| Cutaneous blastomycosis | Blastomyces dermatitidis | Treat the same as pulmonary infection (p. 267) |
| Cutaneous coccidioidomycosis | Coccidioides immitis | Treat the same as pulmonary infection (p. 268) |
| Cutaneous actinomycosis | Actinomyces israelii | Treat the same as pulmonary infection (p. 268) |
| Cutaneous nocardiosis | Nocardia sp. | Treat the same as pulmonary infection (p. 268) |
| Cutaneous amebiasis | Entamoeba histolytica | Treat the same as pulmonary infection (p. 265) |

## Infiltrative Skin Lesions ± Ulcers/Sinus Tracts/Abscesses (cont'd)

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Cutaneous mycobacteria<br>*Scrofula* | Mycobacterium tuberculosis | Treat same as pulmonary TB. See p. 53 |
| | M. scrofulaceum | Surgical excision is curative |
| *M. haemophilum* | M. haemophilum | Surgical excision/TMP–SMX 1 DS tablet (PO) q12h **or** Minocycline 100 mg (PO) q12h **or** quinolone (PO) until cured |
| *M. chelonae* | M. chelonae | Clarithromycin 500 mg (PO) q12h × 6 months |
| *M. fortuitum* | M. fortuitum | Minocycline 100 mg (PO) q12h × 6–12 months<br>**or**<br>Doxycycline 100 mg (PO) q12h × 6–12 months **plus** TMP–SMX 1 DS tablet (PO) q12h × 6–12 months |
| *Swimming pool granuloma* | M. marinum | Clarithromycin XL 1 gm (PO) q24h × 3 months **plus** Rifampin 600 mg (PO) q24h × 3 months<br>**or**<br>TMP–SMX 1 DS tablet (PO) q12h × 3 months **plus** Ethambutol 15 mg/kg (PO) q24h × 3 months<br>**or**<br>Doxycycline 100 mg (PO) q12h × 3 months |
| *Buruli ulcer* | M. ulcerans | TMP–SMX 1 DS tablet (PO) q12h **plus** Ethambutol 15 mg/kg (PO) q24h × 6 weeks |
| *Cutaneous MAI* | Mycobacterium avium-intracellulare | Ethambutol 15 mg/kg (PO) q24h **plus** Azithromycin 1200 mg (PO) weekly × 6 months |

### Cutaneous Histoplasmosis (Histoplasma capsulatum)

**Clinical Presentation:** Chronic, raised, verrucous lesions.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue staining.
**Pitfalls:** Skin nodules represent disseminated histoplasmosis, not isolated skin infection. Look for histoplasmosis elsewhere (e.g., lung, liver, bone marrow). Skin nodules (± chronic pneumonia) with osteolytic bone lesions suggests. African histoplasmosis due to H. capsulation var. duboisii.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Blastomyces (Blastomyces dermatitidis)

**Clinical Presentation:** Painless, erythematous, well-circumscribed, hyperkeratotic, crusted nodules or plaques that enlarge over time. Some may ulcerate and leave an undermined edge.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue staining. Blastomyces dermatitidis affects many organs.

**Pitfalls:** When found in skin, look for Blastomyces elsewhere (e.g., lungs, prostate).
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Coccidioidomycosis (Coccidioides immitis)

**Clinical Presentation:** Skin lesions take many forms, including raised verrucous lesions, cold subcutaneous abscesses, indolent ulcers, or small papules.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue staining.
**Pitfalls:** Skin nodules represent disseminated coccidioidomycosis, not isolated skin infection. Look for Coccidioides elsewhere (e.g., CNS, bone, lungs).
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Actinomycosis (Actinomyces israelii)

**Clinical Presentation:** Erythematous, uneven, indurated, woody, hard, cervicofacial tumor. Localized single/multiple sinus tracts in chest wall, abdominal wall, or inguinal/pelvic area may be present.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue staining.
**Pitfalls:** Look for underlying bone involvement.
**Prognosis:** Good with early/prolonged treatment.

### Cutaneous Nocardia (Nocardia brasiliensis)

**Clinical Presentation:** Subcutaneous abscesses may rupture to form chronically draining fistulas.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue staining. May present as "Madura foot."
**Pitfalls:** Look for underlying immunosuppressive disorder.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Amebiasis (Entamoeba histolytica)

**Clinical Presentation:** Ulcers with ragged edges, sinus tracts, amebomas, and strictures may develop around the anus/rectum or abdominal wall.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by tissue staining.
**Pitfalls:** If abdominal sinus tract is present, look for underlying ameboma and evidence of infection in other organs (e.g., CNS, lung, liver).
**Prognosis:** Related to extent of infection/degree of organ damage.

### Scrofula (Mycobacterium tuberculosis)

**Clinical Presentation:** Cold, chronic, anterior cervical adenopathy ± sinus tracts. Usually in children.
**Diagnostic Considerations:** Diagnosis by acid-fast stain and culture of node/drainage.
**Pitfalls:** Cured by antibiotic therapy alone. No need for surgical excision.
**Prognosis:** Excellent with treatment.

### Scrofula (Mycobacterium scrofulaceum)

**Clinical Presentation:** Cold, chronic, anterior cervical adenopathy ± sinus tracts. Usually in adults.
**Diagnostic Considerations:** Diagnosis by acid-fast stain and culture of node/drainage.
**Pitfalls:** Highly resistant to anti-TB therapy.
**Prognosis:** Excellent with surgical excision.

### Cutaneous Mycobacterium haemophilum

**Clinical presentation:** Particularly common in immunosuppressed/HIV patients, presents as multiple, painful cutaneous ulcers/abscesses ± draining fistulas.
**Diagnostic Considerations:** Diagnose by PCR, RT-PCR assay.
**Pitfalls:** Suspect M. haemophilum if drainage from ulcer/abscess is AFB smear + but fails to grow on AFB media. M. haemophilus grows only on AFB media supplemented with ferric containing compounds i.e., hemin, hemoglobin, or ferric ammonium citrate. Susceptible to minocycline, TMP–SMX, or quinolones, but most strains resistant to INH, EMB, RIF, PZA.
**Prognosis:** Good with surgical excision/prolonged treatment.

### Cutaneous Mycobacterium chelonae

**Clinical presentation:** Present as cold abscesses with draining fistulas.
**Diagnostic Considerations:** AF culture of wound drainage.
**Pitfalls:** Some strains clarithromycin resistant. May be susceptible to quinolones, doxycycline, or minocycline.
**Prognosis:** Good with effective therapy.

### Cutaneous Mycobacterium fortuitum

**Clinical Presentation:** Usually associated with chronic foreign body infection, especially infected breast implants. Associated with nail salon footbaths. Present as cold abscesses with draining fistulas.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by acid fast smear are culture of drainage/infected prosthetic material.
**Pitfalls:** Highly resistant to anti-TB therapy, may be susceptible to quinolones or linezolid.
**Prognosis:** Good with surgical excision/prolonged treatment.

### Swimming Pool Granuloma (Mycobacterium marinum)

**Clinical Presentation:** Begins as erythema with tenderness at inoculation site, followed by a papule or violaceous nodule that ulcerates and drains pus. May have sporotrichoid spread. Presents as a skin lesion unresponsive to antibiotics after abrasive water exposure (e.g., fish tank, swimming pool/lake).
**Diagnostic Considerations:** Diagnosis by demonstrating organism by acid-fast smear/culture.
**Pitfalls:** Resistant to INH/pyrazinamide. Surgical excision of isolated lesions may be needed.
**Prognosis:** Good with prolonged therapy.

### Buruli Ulcer (Mycobacterium ulcerans)

**Clinical Presentation:** Begin as a firm, painless, movable, subcutaneous nodule. In 1–2 months, nodule becomes fluctuant, ulcerates, and develops an undermined edge. May have edema around lesion and in extremity (if involved).
**Diagnostic Considerations:** Diagnosis by acid-fast stain and culture of punch biopsy of ulcer rim. Patient is usually from Africa, but M. ulcerans also exists in Asia, Australia, and Central/South America.
**Pitfalls:** Steroids/skin grafting sometimes needed.
**Prognosis:** Good with surgical excision.

### Cutaneous MAI (Mycobacterium avium-intracellulare)

**Clinical Presentation:** Nodules, abscesses, ulcers, plaques, ecthyma and draining sinuses can occur, but are uncommon in normal hosts and usually only seen in immunosuppressed patients.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by acid-fast staining and culture (for species identification) of tissue biopsy specimens.
**Pitfalls:** Usually represents disseminated infection. Look for non-cutaneous evidence of infection (e.g., lungs, bone marrow, liver/spleen).
**Prognosis:** Related to extent of organ damage/degree of immunosuppression.

## Skin Vesicles/Bullae

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Herpes simplex | Herpes simplex virus (HSV) | See p. 142 (for HIV, see p. 340) |
| Herpes zoster | Varicella zoster virus (VZV) | See p. 142 (for HIV, see p. 319, 343) |

## Subcutaneous Serpiginous Lesions

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Cutaneous larva migrans (creeping eruption) | Ancylostoma braziliense | Ivermectin 200 mcg/kg (PO) × 1 dose **or** Albendazole 400 mg (PO) q24h × 3–7 days. Children may be treated topically with albendazole ointment (10%) q8h × 10 days |
| Guinea worm | Dracunculus medinensis | Surgical removal of worm near skin surface. Metronidazole 250 mg (PO) q8h × 10 days facilitates worm removal |
| Cutaneous gnathostomiasis | Gnathostoma spinigerum | Surgical removal **or** Albendazole 400 mg (PO) q12h × 3 weeks **or** Ivermectin 200 mcg/kg (PO) q24h × 2 days |

### Cutaneous Larva Migrans (Ancylostoma braziliense) Creeping Eruption

**Clinical Presentation:** Intensely pruritic, migratory, subcutaneous, raised serpiginous lesions.
**Diagnostic Considerations:** Diagnosis by clinical appearance.
**Pitfalls:** Must be differentiated from "swimmer's itch" caused by schistosomal cercariae.
**Prognosis:** Excellent with treatment.

### Guinea Worm (Dracunculus medinensis)

**Clinical Presentation:** Serpiginous, raised, subcutaneous tract overlying worm.
**Diagnostic Considerations:** Diagnosis by demonstrating Dracunculus worm when surgically removed.
**Pitfalls:** Resembles cutaneous larva migrans, but worm is visible below the skin and lesions are serpiginous with Dracunculus. May be complicated by painful arthritis.
**Prognosis:** Excellent with treatment. Soaking extremity in warm water promotes emergence/removal of worm. Metronidazole can also be used to decrease inflammation and facilitate worm removal. Mebendazole 200–400 mg (PO) q12h × 6 days may kill worms directly.

**Cutaneous Gnathostomiasis (Gnathostoma spinigerum)**

**Clinical Presentation:** Painful, intermittent, subcutaneous swelling with local edema, intense pruritus, and leukocytosis with eosinophilia. Acquired by eating undercooked fish, frogs, and other intermediate larvae-containing hosts. May be complicated by eosinophilic meningitis.

**Diagnostic Considerations:** Diagnosis by demonstrating Gnathostoma in tissue specimens. Relatively common infection in Thailand and parts of Japan, South America, and Southeast Asia.

**Prognosis:** Good if limited to the skin and surgically removed. Poor with CNS involvement. Albendazole is preferred.

## Skin Papules/Nodules/Abscesses

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Bacillary angiomatosis | Bartonella henselae<br>Bartonella quintana | Doxycycline 100 mg (PO) q12h **or** azithromycin 250 mg (PO) q24h **or** any quinolone (PO) × 8 weeks |
| Cutaneous Alternaria | Alternaria alternata | Amphotericin B 0.7–1.0 mg/kg (IV) q24h × 2–3 grams‡<br>Alternate therapy: Voriconazole, itraconazole, posaconazole, caspofungin. (See Drug Summaries Chapter 11 for dosage.) Treat until cured. |
| Entomophthoromycosis | E. basidiobolus<br>E. conidiobolus | Amphotericin B 0.7–1.0 mg/kg (IV) q24h × 1–2 grams‡<br>**or**<br>TMP–SMX 1 DS tablet (PO) q24h until cured |
| Chromomycosis | Fonsecaea pedrosoi, compactum<br>Phialophora verrucosa, others | Few small lesions: Wide/deep surgical excision or cryosurgery with liquid nitrogen<br>Larger lesions: Itraconazole 200 mg (PO) solution q24h until lesions regress ± cryosurgery |
| Cutaneous Fusarium | Fusarium solani | Amphotericin B 0.7–1.0 mg/kg (IV) q24h × 2–3 grams‡<br>**or**<br>Voriconazole (see "usual dose," p. 714) |
| Cutaneous Penicillium | Penicillium marneffei | Amphotericin B 0.6 mg/kg (IV) q24h × 14 days,‡ then Itraconazole 200 mg (IV) q12 × 2 days followed by 200 mg (PO) q12h × 10 weeks. For HIV, continue with Itraconazole 200 mg (PO) q24h indefinitely |
| Cutaneous Prototheca | Prototheca wikermanii | Surgical excision. If excision is incomplete, add either Amphotericin B 0.7–1.0 mg/kg (IV) q24h × 2–3 grams‡ **or** Itraconazole 200 mg (PO)† q12h until cured |
| Trichosporon | Trichosporon beigelii | Amphotericin B 0.7–1.0 mg/kg (IV) q24h × 2–3 grams‡ |

‡ Liposomal amphotericin (p. 525) may be a suitable alternative.

† Initiate therapy with Itraconazole 200 mg (IV) q12h × 7–14 days.

## Skin Papules/Nodules/Abscesses (cont'd)

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Cutaneous aspergillosis* | Aspergillus sp. | Voriconazole (see "usual dose," p. 714)<br>**or**<br>Isavuconazole 200 mg (IV) q8h × 48 hours, then 200 mg (IV/PO) q24h until cured<br>**or**<br>Itraconazole 200 mg (IV) q12h × 7–14 days, then 200 mg (PO) solution q12h until cured |
| Cutaneous zygomycosis (mucormycosis) | Mucor/Rhizopus/ Absidia | Treat as for pulmonary zygomycosis (see p. 269) |
| Cutaneous coccidioido-mycosis | Coccidioides immitis | Fluconazole 800 mg (PO) × 1 dose, then 400 mg (PO) q24h until cured<br>**or**<br>Itraconazole 200 mg (PO)† q12h until cured<br>Alternate therapy<br>Amphotericin B 1 mg/kg (IV) q24h × 7 days, then 0.8 mg/kg (IV) q48h × 2–3 grams total dose‡ |
| Cutaneous histoplasmosis | Histoplasma capsulatum | See p. 284 |
| Cutaneous cryptococcosis | Cryptococcus neoformans | Amphotericin B 0.5 mg/kg (IV) q24h × 1–2 grams‡<br>**or**<br>Lipid amphotericin (p. 525) (IV) q24h × 3 weeks,<br>**then**<br>Fluconazole 800 mg (PO) × 1 dose, then 400 mg (PO) q24h × 8–10 weeks |
| Cutaneous sporotrichosis | Sporothrix schenckii | Itraconazole 200 mg (PO). If HIV, chronic suppressive therapy may be needed q24h until 2–4 weeks after all lesions have resolved (typically 3–6 months in total). |
| Nodular/pustular candidiasis | Candida sp. | If occurs in moist skin areas (under breasts, groin, etc.), therapy is for mucocutaneous candidiasis (see p. 147). Nodular candidiasis occuring in non-moist skin areas in compromised hosts is a manifestation of disseminated disease and should be treated as such (see p. 148–149) |
| Cutaneous onchocerciasis | Onchocerca volvulus | Ivermectin 150 mcg/kg (PO) × 1 dose, repeated q 4–6 months until asymptomatic **plus** Doxycycline 100 mg (PO) q12h × 6 weeks |

* Cutaneous aspergillus is a manifestation of disseminated aspergillosis.

† Initiate therapy with Itraconazole 200 mg (IV) q12h × 7–14 days.

‡ Lipid amphotericin (p. 525) may be a suitable alternative.

**Bacillary Angiomatosis (Bartonella henselae/B. quintana) Peliosis Hepatis**

**Clinical Presentation:** Skin lesions resemble Kaposi's sarcoma. Liver lesions resemble CMV hepatitis in HIV patients.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture of skin lesions or by blood culture after lysis-centrifugation.

**Pitfalls:** Requires life-long suppressive therapy.

**Prognosis:** Related to extent of infection/degree of immunosuppression.

**Cutaneous Alternaria (Alternaria alternata)**

**Clinical Presentation:** Bluish/purple papules that are often painful and non-pruritic. Usually seen only in leukopenic compromised hosts.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen.

**Pitfalls:** Skin lesions usually represent disseminated disease in compromised hosts, not local infection. Fluconazole and micafungin ineffective.

**Prognosis:** Poor and related to degree of immunosuppression.

**Cutaneous Entomophthoromycosis (E. basidiobolus/E. conidiobolus)**

**Clinical Presentation:** E. conidiobolus infection presents as swelling of nose, paranasal tissues and mouth, accompanied by nasal stuffiness, drainage, and sinus pain. Begins as swelling of inferior nasal turbinates and extends until generalized facial swelling occurs. Subcutaneous nodules can be palpated in tissue. E. basidiobolus infection presents as a non-painful, firm, slowly progressive, subcutaneous nodule of the trunk, arms, legs, or buttocks.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. Skin lesions usually represent disseminated disease in compromised hosts, not localized infection.

**Pitfalls:** Unlike Mucor, E. basidiobolus does not usually invade blood vessels, although tissue infarction/necrosis is occasionally seen in diabetics and immunocompromised patients.

**Prognosis:** May spontaneously resolve. Surgical removal of accessible nodules and reconstructive surgery may be helpful for disfigurement.

**Cutaneous Chromomycosis (F. pedrosoi/F. compactum, P. verrucosa, others)**

**Clinical Presentation:** Warty papule/nodule that enlarges slowly to form a scarred, verrucous plaque. May also begin as a pustule, plaque, or ulcer. Over time, typical papule/nodule ulcerates, and the center becomes dry/crusted with raised margins. Lesions can be pedunculated/cauliflower-like.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. Chromomycosis remains localized within cutaneous/subcutaneous tissues.

**Pitfalls:** May resemble other fungal diseases. Sclerotic bodies in tissue and exudate distinguish chromomycosis from other related fugal diseases.

**Prognosis:** Related to degree of organ damage.

**Cutaneous Fusarium (Fusarium solani)**

**Clinical Presentation:** Presents in compromised hosts as multiple papules or painful nodules, initially macular with central pallor, which then become raised, erythematous, and necrotic. Seen mostly in leukopenic compromised hosts (especially acute leukemia and bone marrow transplants). Also a cause of mycetoma/onychomycosis.

**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture from blood/tissue. β 1,3 D-glucan + , aspergillus galactomannan + .
**Pitfalls:** Skin lesions usually represent disseminated disease, not localized infection.
**Prognosis:** Poor/fair. Related to degree of immunosuppression. Amphotericin B lipid formulation (p. 525), colony-stimulating granulocyte factor, and granulocyte transfusions may be useful.

## Cutaneous Penicillium (Penicillium marneffei)

**Clinical Presentation:** Papules, pustules, nodules, ulcers, or abscesses. Mostly seen in HIV (requires life-long suppressive therapy with itraconazole).
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. Affects residents/visitors of Southeast Asia/Southern China.
**Pitfalls:** Lesions commonly become umbilicated and resemble molluscum contagiosum. May present as disseminated infection.
**Prognosis:** Poor and related to degree of immunosuppression.

## Cutaneous Prototheca (Prototheca wickermanii)

**Clinical Presentation:** Most common presentation is a single plaque or papulonodular lesion of the skin or subcutaneous tissue. Lesions are usually painless, slowly progressive (enlarge over weeks to months without healing), well-circumscribed, and may become eczematoid/ulcerated.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. Skin lesions in HIV are not different from normal hosts.
**Pitfalls:** Lesions are usually painless and may resemble eczema.
**Prognosis:** Poor/fair. Related to degree of immunosuppression. Surgical excision has been successful.

## Cutaneous Trichosporon (Trichosporon beigelii)

**Clinical Presentation:** Seen mostly in leukopenic compromised hosts (especially in acute leukemia, but also in HIV, burn wounds, and organ transplants). Usually presents as multiple red-bluish/purple papules, which are often painful and non-pruritic.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen.
**Pitfalls:** Skin lesions usually represent disseminated disease, not localized infection.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

## Cutaneous Aspergillosis (Aspergillus fumigatus)

**Clinical Presentation:** Seen at site of IV catheter insertion or adhesive dressing applied to skin in leukopenic, compromised hosts. Lesion is similar to pyoderma gangrenosum. May also invade burn wounds and cause rapidly progressive necrotic lesions.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. β 1,3 D-glucan + , aspergillus galactomannan + .
**Pitfalls:** Infiltrative/ulcerative skin lesions usually represent disseminated disease in compromised hosts, not localized infection. May cause invasive dermatitis/skin lesions in HIV.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

## Cutaneous Mucormycosis/Rhizopus/Absidia

**Clinical Presentation:** Necrotic skin lesion secondary to vascular invasion. Involves epidermis and dermis. Black eschars are evident.

**Diagnostic Considerations:** Diagnosis by demonstrating broad, non-septate hyphae with branches at right angles by stain/culture in tissue specimen.
**Pitfalls:** Skin lesions usually represent disseminated disease in compromised hosts, not localized infection. Contaminated elastic bandages have been associated with cutaneous Mucor.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Coccidioidomycosis (Coccidioides immitis)

**Clinical Presentation:** Skin lesions may take many forms, including verrucous granulomas, cold subcutaneous abscesses, indolent ulcers, or small papules.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen.
**Pitfalls:** Skin lesions usually represent disseminated disease in compromised hosts, not local infection.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Histoplasmosis (Histoplasma capsulatum)

**Clinical Presentation:** Common cutaneous findings include maculopapular eruption, petechiae, and ecchymosis. Histopathology reveals necrosis around superficial dermal vessels.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. $\beta$ 1,3 D-glucan + , aspergillus galactomannan + .
**Pitfalls:** Skin lesions usually represent disseminated disease in compromised hosts, not local infection.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Cryptococcosis (Cryptococcus neoformans)

**Clinical Presentation:** May present as single or multiple papules, pustules, erythematous indurated plaques, soft subcutaneous masses, draining sinus tracts, or ulcers with undermined edges.
**Diagnostic Considerations:** Diagnosis by demonstrating spherules with endospores by stain/culture in tissue specimen. $\beta$ 1,3 D-glucan – , aspergillus galactomannan – .
**Pitfalls:** Skin lesions usually represent disseminated disease in compromised hosts, not localized infection. In AIDS patients, umbilicated papules resemble molluscum contagiosum. In organ transplants, cellulitis with necrotizing vasculitis may occur.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

### Cutaneous Sporotrichosis (Sporothrix schenckii)

**Clinical Presentation:** Primary cutaneous lymphatic sporotrichosis starts as a small, firm, movable, subcutaneous nodule, which then becomes soft and breaks down to form a persistent, friable ulcer. Secondary lesions usually develop proximally along lymphatic channels, but do not involve lymph nodes. Plaque form does not spread locally.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by stain/culture in tissue specimen. Cutaneous disease arises at sites of minor trauma with inoculation of fungus into skin. Skin lesions usually represent disseminated disease in compromised hosts, not localized infection.
**Pitfalls:** HIV patients with $CD_4 < 200$ may have widespread lymphocutaneous disease that ulcerates and is associated with arthritis. Unusual in axilla due to increased temperature.
**Prognosis:** Related to extent of infection/degree of immunosuppression.

**Nodular/Pustular Candidiasis** (sepsis in chronic steroids, see p. 158)

**Cutaneous Onchocerciasis (Onchocerca volvulus)**

**Clinical Presentation:** Early manifestation is pruritic, papular rash with altered pigmentation. Later, papules, scaling, edema, and depigmentation may develop. Nodules develop in deep dermis/subcutaneous tissue (especially over bony prominences) or in deeper sites near joints, muscles, bones. Endemic in Middle East, Central Africa, Central America.

**Diagnostic Considerations:** Diagnosis by serology/demonstration of microfilaria in thin snips of involved skin or in anterior chamber (by slit lamp) if eye involvement. Intradermal edema produces "peau d'orange" effect with pitting around hair follicles/sebaceous glands.

**Pitfalls:** Ivermectin is effective against microfilaria, not adult worms. Adults live ~ 18 years.

**Prognosis:** Related to location/extent of organ damage.

## Rickettsia (Fever/Petechial Skin Rash)

| Subset | Pathogens | Preferred Therapy | Alternate Therapy |
|---|---|---|---|
| Rocky Mountain spotted fever (RMSF) | Rickettsia rickettsii (tick borne) | Doxycycline 200 mg (IV or PO) q12h × 3 days, then 100 mg (IV or PO) × 4 days | Any quinolone (IV or PO) × 7 days **or** Chloramphenicol 500 mg (IV or PO) q6h × 7 days |
| Epidemic (louse-borne) typhus, flying squirrel typhus | Rickettsia prowazekii | Same as RMSF | Same as RMSF |
| Murine (flea-borne) typhus | Rickettsia typhi | Same as RMSF | Same as RMSF |
| Scrub (chigger/mite-borne) typhus (Tsutsugamushi fever) | Rickettsia tsutsugamushi | Same as RMSF, **or** in mild cases Azithromycin 500 mg (PO) × 1 dose | Rifampin 600–900 mg (PO) q24h × 7 days |
| Rickettsialpox | Rickettsia akari | Same as RMSF | Same as RMSF |
| Tick typhus fevers (Mediterranean spotted fever, Boutonneuse fever, Israeli spotted fever) | Rickettsia conorii Rickettsia parkeri | Same as RMSF | Same as RMSF |
| African tick bite fever | Rickettsia africae | Same as RMSF | Same as RMSF |

## Rocky Mountain Spotted Fever (Rickettsia rickettsia) RMSF

**Clinical Presentation:** Fever with relative bradycardia, severe frontal headache, severe myalgias of abdomen/back/legs 3–12 days after tick bite. Rash begins as erythematous macules on wrists and ankles 3–5 days after tick bite, and progresses to petechiae/palpable purpura with confluent areas of ecchymosis. Periorbital edema, conjunctival suffusion, acute deafness, and edema of the dorsum of the hands/feet are important early signs. Abdominal pain can mimic acute abdomen, and meningismus and headache can mimic meningitis. Hepatosplenomegaly, cough, and coma may develop late. Laboratory findings include normal leukocyte count, thrombocytopenia, ↑ LFTs, and pre-renal azotemia. Hypotension/shock may occur secondary to myocarditis, which is the most common causes of death. Primary vector in United States is the Dermacentor tick; primary animal reservoir is small wild animals.

**Diagnosis:** Primarily a clinical diagnosis requiring a high index of suspicion and early empiric therapy. Early/rapid diagnosis can be made by DFA of biopsy specimen of rash (Weil-Felix reactions: OX-19: + + +, OX-2: +, OX-K: **–**). Specific R. rickettsii IFA, complement fixation, ELISA antibody titers are confirmatory. Include RMSF in differential diagnosis of any patient with fever and potential tick exposure, especially during the summer months.

**Pitfalls:** Most cases occur in eastern and southeastern United States, not Rocky Mountain area. Many cases go unrecognized due to nonspecific early findings. Early antibiotic therapy may blunt/eliminate serologic response. Patients with signs/symptoms of RMSF but without a rash should be considered as having ehrlichiosis ("spotless RMSF") until proven otherwise. Early therapy is essential; begin empiric therapy as soon as RMSF is suspected. Other adjunctive measures may be required.

**Prognosis:** Late (after day 5) initiation of treatment increases the risk of death by 5-fold. Adverse prognostic factors include myocarditis and severe encephalitis.

## Epidemic (Louse-Borne) Typhus (Rickettsia prowazekii)

**Clinical Presentation:** High fever with relative bradycardia, chills, headache, conjunctival suffusion, and myalgias. A macular, rubella-like, truncal rash develops in most on the fifth febrile day, which may become petechial and involve the extremities, but spares the palms/soles. Facial swelling/flushing occurs at end of first week, along with CNS symptoms (e.g., tinnitus, vertigo, delirium) and GI complaints (diarrhea, constipation, nausea, vomiting, abdominal pain). Hypotension, pneumonia, renal failure, gangrene, cerebral infarction may develop late. Laboratory findings include normal leukocyte count, thrombocytopenia, and ↑ serum creatinine/LFTs. Primary vector is the human body louse; primary reservoir is humans.

**Diagnosis:** Primarily a clinical diagnosis requiring a high index of suspicion and early empiric therapy (Weil-Felix reactions: OX-19: + + +, OX-2: +, OX-K: **–**). Specific R. prowazekii antibody titers are confirmatory. Consider epidemic (louse-borne) typhus in febrile impoverished persons infested with lice, especially in Africa and parts of Latin America. Rarely seen in the United States. Milder recrudescent form (Brill-Zinsser disease) is also rare.

**Pitfalls:** Many cases go unrecognized due to nonspecific early findings. Early therapy is essential.

**Prognosis:** Gangrene of nose, ear lobes, genitalia, toes, and fingers may develop in severe cases. Death occurs in 10–50% of untreated patients.

## Murine (Flea-Borne) Typhus (Rickettsia typhi)

**Clinical Presentation:** Similar to epidemic typhus but less severe, with fever in most, and headache, myalgias, and a macular rash in half. Laboratory findings include a normal leukocyte count, mild thrombocytopenia, and mildly ↑ LFTs. Primary vector is the Asian rat flea (Xenopsylla cheopis); primary reservoir is the commensal rat (Rattus genus). Uncommon in United States; most cases from Texas, California, Florida, Hawaii.

**Diagnosis:** Primarily a clinical diagnosis requiring a high index of suspicion. More common during summer and fall (Weil-Felix reactions: OX-19: + + +, OX-2: +, OX-K: –). Specific R. typhi antibody titers are confirmatory.

**Pitfalls:** Rash becomes maculopapular, compared to epidemic typhus, which remains macular. A similar illness is caused by R. felis.

**Prognosis:** Good if treated early. Death occurs in < 1%.

## Scrub Typhus (Rickettsia tsutsugamushi) Tsutsugamushi Fever

**Clinical Presentation:** Fever, chills, headache, myalgias, arthralgias, GI symptoms, other nonspecific complaints. Eschar at mite bite site (tache noire) ± regional adenopathy. A macular, truncal rash develops in most, usually in the first week, and may progress to involve the extremities and face, but spares the palms/soles. Vasculitis may lead to cardiopulmonary (ARDS) CNS (encephalitis) hematologic abnormalities during the second week. Hepatosplenomegaly is common. Laboratory abnormalities include normal/decreased WBC, relative lymphopenia, thrombocytopenia, ↑ serum transaminases. Primary vector/reservoir is the larval (chigger) trombiculid mite. Endemic areas include northern Australia, southeastern Asia, Indian subcontinent.

**Diagnosis:** Presumptive diagnosis is clinical (Weil-Felix reactions: OX-19: –, OX-2: –, OX-K: + + +). Specific R. tsutsugamushi serology is confirmatory.

**Pitfalls:** Incomplete therapy frequently results in relapse.

**Prognosis:** Excellent if treated early.

## Rickettsialpox (Rickettsia akari)

**Clinical Presentation:** Milder illness than other rickettsioses, with initial eschar at bite site, high fever, and generalized rash (usually erythematous papules which become vesicular and spares the palms/soles). Fever peak is usually < 104°F, occurs 1–3 weeks after mite bite, and lasts ~ 1 week without therapy. Headache, photophobia, marked diaphoresis, sore throat, GI complaints (nausea/vomiting following initial headache) may occur. Leukopenia may be present. Primary vector is the mouse mite; primary animal reservoir is the house mouse. Rare in the United States.

**Diagnosis:** Presumptive diagnosis by clinical presentation (Weil-Felix reactions: OX-19: –, OX-2: –, OX-K: ±). Specific R. akari serology is confirmatory.

**Pitfalls:** Do not confuse with African tick-bite fever, which may also have a vesicular rash.

**Prognosis:** Excellent even without therapy.

## Tick Typhus Fevers (Rickettsia conorii, Rickettsia parkeri) Mediterranean Spotted Fever, Boutonneuse Fever, Israeli Fever

**Clinical Presentation:** Similar to RMSF with fever, chills, myalgias, but less severe. Unlike RMSF, an eschar is usually present at the site of the tick bite ± regional adenopathy. Leukocyte count is normal and thrombocytopenia is common. Transmitted by the brown dog tick, Rhipicephalus sanguineus.

**Diagnosis:** Presumptive diagnosis by clinical presentation (Weil-Felix reactions: OX-19: +, OX-2: +, OX-K: +). Specific R. conorii serology is confirmatory.

**Pitfalls:** Suspect in travelers from endemic areas with a RMSF-like illness. Consider different diagnosis in absence of an eschar.

**Prognosis:** Good with early treatment. Prostration may be prolonged even with proper therapy.

### African Tick Bite Fever (Rickettsia africae)

**Clinical Presentation:** Similar to murine typhus with fever, chills, myalgias, but regional adenopathy and multiple eschars are common. Incubation period ~ 6 days. Amblyomma hebreum/variegatum tick vectors frequently bite humans multiple times.

**Diagnosis:** Presumptive diagnosis by clinical presentation (Weil-Felix reactions: OX-19: +, OX-2: +, OX-K: +). Specific R. africae serology is confirmatory.

**Pitfalls:** Rash is transient, and may be vesicular or absent.

**Prognosis:** Good even without therapy; excellent with therapy.

## Other Skin Lesions

| Subset | Pathogens | Topical Therapy | PO Therapy |
|---|---|---|---|
| Tinea versicolor (pityriasis) | Malassezia furfur (Pityrosporum orbiculare) | Clotrimazole cream (1%) or miconazole cream (2%) **or** Ketoconazole cream (2%) daily × 7 days | Ketoconazole 200 mg (PO) q24h × 7 days **or** Itraconazole 200 mg (PO) q24h × 7 days **or** Fluconazole 400 mg (PO) × 1 dose |
| Eosinophilic folliculitis | Malassezia furfur (Pityrosporum orbiculare) | Preferred Therapy<br>Ketoconazole cream (2%) topically × 2–3 weeks ± Ketoconazole 200 mg (PO) q24h × 2–3 weeks | |

### Tinea Versicolor/Pityriasis (Malassezia furfur)

**Clinical Presentation:** Hyper- or hypopigmented scaling papules (0.5–1 cm), which may coalesce into larger plaques. Most commonly affects the upper trunk and arms. May be asymptomatic or pruritic.

**Diagnostic Considerations:** M. furfur also causes eosinophilic folliculitis in HIV, and catheter-acquired sepsis mostly in neonates or immunosuppressed patients. Diagnosis is clinical.

**Pitfalls:** Skin pigmentation may take months to return to normal after adequate therapy.

**Prognosis:** Excellent.

### Eosinophilic Folliculitis (Malassezia furfur)

**Clinical Presentation:** Intensely pruritic folliculitis, usually on lower extremities.

**Diagnostic Considerations:** Tissue biopsy shows eosinophilic folliculitis. Diagnosis by demonstrating organism by culture on Sabouraud's agar overlaid with olive oil.

**Pitfalls:** Resembles folliculitis, but lesions are concentrated on lower extremities (not on trunk as with cutaneous candidiasis).

**Prognosis:** Related to degree of immunosuppression. Use oral therapy if topical therapy fails.

## Myositis

| Subset | Pathogens | Preferred Therapy |
|---|---|---|
| Chromomycosis | Cladosporium/Fonsecaea | Itraconazole 200 mg (PO) q24h until cured<br>**or**<br>Terbinafine 250 mg (PO) q24h until cured |
| Trichinosis | Trichinella spiralis | Albendazole 400 mg (PO) q12h × 8–14 days<br>**or**<br>Mebendazole 200–400 mg (PO) q8h × 3 days, then 400–500 mg q8h × 10 days |

### Chromomycosis (Cladosporium/Fonsecaea)

**Clinical Presentation:** Subcutaneous/soft tissue nodules or verrucous lesions.
**Diagnostic Considerations:** Diagnosis by demonstrating organism by culture/tissue biopsy specimen.
**Pitfalls:** May resemble Madura foot or cause ulcerative lesions in muscle.
**Prognosis:** Related to degree of immunosuppression.

### Trichinosis (Trichinella spiralis)

**Clinical Presentation:** Muscle tenderness, low-grade fevers, peripheral eosinophilia, conjunctival suffusion.
**Diagnostic Considerations:** Diagnosis by Trichinella serology or by demonstrating larvae in muscle biopsy.
**Pitfalls:** ESR is very low (near zero), unlike other causes of myositis, which have elevated ESRs.
**Prognosis:** Excellent with early treatment. Short-term steroids may be useful during acute phase. Therapy is ineffective against calcified larvae in muscle.

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Chapter 5

# HIV Infection

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## HIV INFECTION OVERVIEW

**Paul E. Sax, M.D.**

Infection with Human Immunodeficiency Virus (HIV-1) leads to a chronic and without treatment usually fatal infection characterized by progressive immunodeficiency, a long clinical latency period, and opportunistic infections. The hallmark of HIV disease is infection and viral replication within T-lymphocytes expressing the $CD_4$ antigen (helper-inducer lymphocytes), a critical component of normal cell-mediated immunity. Qualitative defects in $CD_4$ responsiveness and progressive depletion in $CD_4$ cell counts increase the risk for opportunistic infections such as Pneumocystis (carinii) jiroveci pneumonia, and neoplasms such as lymphoma and Kaposi's sarcoma. HIV infection can also disrupt blood monocyte, tissue macrophage, and B-lymphocyte (humoral immunity) function, predisposing to infection with encapsulated bacteria. Direct attack of $CD_4$-positive cells in the central and peripheral nervous system can cause HIV meningitis, peripheral neuropathy, and dementia. More than 1 million people in the United States and 30 million people worldwide are infected with HIV. Without treatment, the average time from acquisition of HIV to an AIDS-defining opportunistic infection is about 10 years; survival then averages 1–2 years. There is tremendous individual variability in these time intervals, with some patients progressing from acute HIV infection to death within 1–2 years, and others not manifesting HIV-related immunosuppression for > 20 years after HIV acquisition. Antiretroviral therapy and prophylaxis against opportunistic infections have markedly improved the overall prognosis of HIV disease. The approach to HIV infection is shown in Figure 5.1.

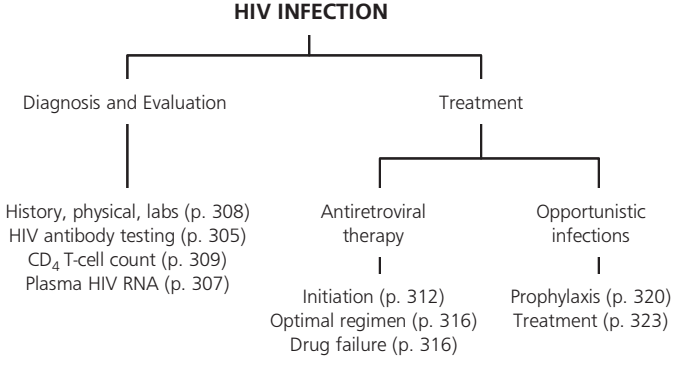


**Figure 5.1. Diagnosis, Evaluation, and Treatment of HIV Infection**

## STAGES OF HIV INFECTION

**A. Viral Transmission.** HIV infection is acquired primarily by sexual intercourse (anal, vaginal, infrequently oral), exposure to contaminated blood (primarily needle transmission), or maternal-fetus (perinatal) transmission. Sexual practices with the highest risk of transmission include unprotected receptive anal intercourse (especially with mucosal tearing), unprotected receptive vaginal intercourse (especially during menses), and unprotected rectal/vaginal intercourse in the presence of genital ulcers (e.g., primary syphilis, genital herpes, chancroid). Lower risk sexual practices include insertive anal/vaginal intercourse and oral-genital contact. The risk of transmission after a single encounter with an HIV source has been estimated to be 1 in 150 with needle sharing, 1 in 300 with occupational percutaneous exposure, 1 in 300–1000 with receptive anal intercourse, 1 in 500–1250 with receptive vaginal intercourse, 1 in 1000–3000 with insertive vaginal intercourse, and 1 in 3000 with insertive anal intercourse. Transmission risk increases with the number of encounters and with higher HIV RNA plasma levels. The mode of transmission does not affect the natural history of HIV disease.

**B. Acute (Primary) HIV Infection (p. 304).** Acute HIV occurs 1–4 weeks after transmission, and is accompanied by a burst of viral replication with a decline in $CD_4$ cell count. Most patients manifest a symptomatic mononucleosis-like syndrome, which is often overlooked. Acute HIV infection is confirmed by a high HIV RNA in the absence of HIV antibody.

**C. Seroconversion.** Development of a positive HIV antibody test usually occurs within 4 weeks of acute infection, and invariably (with few exceptions) by 6 months.

**D. Asymptomatic HIV Infection** lasts a variable amount of time (average 8–10 years), and is accompanied by a gradual decline in $CD_4$ cell counts and a relatively stable HIV RNA level (sometimes referred to as the viral "set point").

**E. Symptomatic HIV Infection.** Previously referred to as "AIDS Related Complex (ARC)," findings include thrush or vaginal candidiasis (persistent, frequent, or poorly responsive to treatment), cervical dysplasia/carcinoma in-situ, herpes zoster (recurrent episodes or involving multiple dermatomes), oral hairy leukoplakia, peripheral neuropathy, diarrhea, or constitutional symptoms (e.g., low-grade fevers, weight loss).

**F. AIDS** is defined by a $CD_4$ cell count < 200/mm$^3$, a $CD_4$ cell percentage of total lymphocytes <14%, or one of several AIDS-related opportunistic infections. Common opportunistic infections include Pneumocystis (carinii) jiroveci pneumonia, cryptococcal meningitis, recurrent bacterial pneumonia, Candida esophagitis, CNS toxoplasmosis, tuberculosis, and non-Hodgkin's lymphoma. Other AIDS indicators in HIV-infected patients include candidiasis of the bronchi, trachea, or lungs; disseminated/extrapulmonary coccidiomycosis, cryptococcosis, or histoplasmosis; chronic (>1 month) intestinal cryptosporidiosis or isosporiasis; Kaposi's sarcoma; lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia; disseminated/extrapulmonary Mycobacterium (avium-intracellulare, kansasii,

other species) infection; progressive multifocal leukoencephalopathy (PML); recurrent Salmonella septicemia; or HIV wasting syndrome.

**G. Advanced HIV Disease** is diagnosed when the $CD_4$ cell count is < 50/mm$^3$. Most AIDS-related deaths occur at this point. Common late stage opportunistic infections are caused by CMV disease (retinitis, colitis) or disseminated Mycobacterium avium-intracellulare (MAI).

## ACUTE (PRIMARY) HIV INFECTION

**A. Description.** Acute clinical illness associated with primary acquisition of HIV, occurring 1–4 weeks after viral transmission (range: 6 days to 6 weeks). Symptoms develop in 50–90%, but are often mistaken for the flu, mononucleosis, or other nonspecific viral syndrome. More severe symptoms may correlate with a higher viral set point and more rapid HIV disease progression. Even without therapy, most patients recover, reflecting development of a partially effective immune response and depletion of susceptible $CD_4$ cells.

**B. Differential Diagnosis** includes **EBV, CMV**, viral hepatitis, enteroviral infection, 2° syphilis, toxoplasmosis, HSV with erythema multiforme, drug reaction, Behcet's disease, acute lupus.

**C. Signs and Symptoms** usually reflect hematogenous dissemination of virus to lymphoreticular and neurologic sites:

- Fever (97%).
- Pharyngitis (73%). Typically non-exudative (unlike EBV, which is usually exudative).
- Rash (77%). Maculopapular viral exanthem of the face and trunk is most common, but can involve the extremities, palms and soles.
- Arthralgia/myalgia (58%).
- Neurologic symptoms (12%). Headache is most common. Neuropathy, Bell's palsy, and meningoencephalitis are rare, but may predict worse outcome.
- Oral/genital ulcerations, thrush, nausea, vomiting, diarrhea, weight loss.

**D. Laboratory Findings**

1. **CBC.** Lymphopenia followed by lymphocytosis (common). Atypical lymphocytosis is variable, but usually low level (unlike EBV, where atypical lymphocytosis may be 20–30% or higher). Thrombocytopenia occurs in some.
2. **Elevated transaminases** in some but not all patients.
3. **Depressed $CD_4$ cell count.** Can rarely be low enough to induce opportunistic infections.
4. **HIV antibody.** Usually negative, although persons with prolonged symptoms of acute HIV may have positive antibody tests if diagnosed late during the course of illness.

**E. Confirming the Diagnosis of Acute HIV Infection**

1. **Obtain HIV antibody** after informed consent (if required by state law) to exclude prior disease.
2. **Order viral load test (HIV RNA PCR),** preferably RT-PCR. HIV RNA confirms acute HIV infection prior to seroconversion. Most individuals will have very high HIV RNA (>100,000 copies/mL). Be suspicious of a false-positive test if the HIV RNA is low (< 20,000 copies/mL). For any positive test, it is important to repeat HIV RNA and HIV antibody testing. p24 antigen can also be used to establish the diagnosis, but is less sensitive than HIV RNA PCR.
3. **Order other tests/serologies if HIV RNA test is negative.** Order throat cultures for bacterial/viral respiratory pathogens, EBV VCA IgM/IgG, CMV IgM/IgG, HHV-6 IgM/IgG, and hepatitis serologies as appropriate to establish a diagnosis for patient's symptoms.

**F. Management of Acute HIV Infection**

1. **Initiate antiretroviral therapy.** The rationale behind this change is to treat a greater proportion of people with HIV, regardless of disease stage, is based on accumulating evidence of the benefits of earlier initiation of HIV treatment and, conversely, the potential for uncontrolled viral replication and $CD_4$ depletion.
2. **Obtain HIV resistance genotype** (see p. 317) because of a rising background prevalence of transmission of antiretroviral therapy-resistant virus. A genotype resistance test is preferred; therapy can be st arted pending results of the test.
3. **Possible benefits for treatment of acute HIV infection.** Possible (but unproven) benefits include hastening symptom resolution, reducing viral transmission, lowering virologic "set point," and preserving virus-specific $CD_4$ responses.

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## APPROACH TO HIV TESTING (Figure 5.2)

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**A. Standard HIV Antibody Tests.** Most patients produce antibody to HIV within 6–8 weeks of exposure; half will have a positive antibody test in 3–4 weeks, and nearly 100% will have detectable antibody by 6 months.

1. **ELISA.** Usual screening test. All positives must be confirmed with Western blot or other more specific tests.
2. **Western blot.** CDC criteria for interpretation: **positive:** at least two of the following bands: p24, gp41, gp160/120; **negative:** no bands; **indeterminate:** any HIV band, but does not meet criteria for positivity.
3. **Test performance.** Standard method is ELISA screen with Western blot confirmation.
   - **a. ELISA negative:** Western blot is not required (ELISA sensitivity 99.7%, specificity 98.5%). Obtain HIV RNA if acute HIV infection is suspected.
   - **b. ELISA positive:** Confirm with Western blot. Probability that ELISA and Western blot are both false-positives is extremely low (< 1 per 140,000). Absence of p31 band could be a clue to a false positive Western blot.
   - **c. Unexpected ELISA/Western blot:** Repeat test to exclude clerical/computer error.

4. **Indeterminate Western Blot.** Common clinical problem, affecting 4–20% of reactive ELISAs. Usually due to a single p24 band or weak other bands. Causes include seroconversion in progress, advanced HIV disease with loss of antibody response,

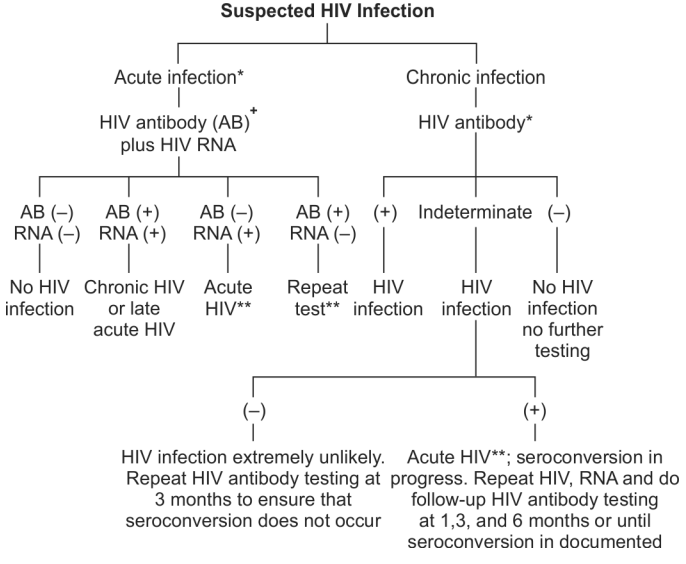


**Figure 5.2. Approach to HIV Testing**

(–) = negative test; (+) = positive test.

* Occurs 1–4 weeks after viral transmission. Most patients manifest a viral syndrome (fever, pharyngitis ± rash/arthralgias), which is often mistaken for the flu and therefore overlooked.

** HIV RNA in acute HIV infection should be very high (usually > 100,000 copies/mL).

\+ All positive ELISA tests must be confirmed by Western Blot; usually this is done automatically in clinical laboratories.

++ May be long-term non-progressor or laboratory error.

cross-reacting antibody from pregnancy, blood transfusions, organ transplantation, autoantibodies from collagen vascular disease, infection with HIV-2, influenza vaccination, or recipient of HIV vaccine. In low-risk patients, an indeterminate result almost never represents true HIV infection. Since seroconversion in progress is generally associated with high HIV RNA levels, the recommended approach is to order an HIV RNA test.

**B. Quantitative Plasma HIV RNA (HIV Viral Load Assays)**

1. **Description.** Measures amount of HIV RNA in plasma. High sensitivity of assays allows detection of virus in most patients not on antiviral therapy. Used to diagnose acute HIV infection and more commonly to monitor the response to antiretroviral therapy.
2. **Uses of HIV RNA Assay**
   a. **Confirms diagnosis of acute HIV infection.** A high HIV RNA with a negative HIV antibody test confirms acute HIV infection prior to seroconversion.
   b. **Helpful in initial evaluation of HIV infection.** Establishes baseline HIV RNA and helps (along with $CD_4$ cell count) determine whether to initiate or defer therapy, as HIV RNA correlates with rate of $CD_4$ decline.
   c. **Monitors response to antiviral therapy.** HIV RNA changes rapidly decline 2–4 weeks after starting or changing effective antiretroviral therapy, with slower decline thereafter. Patients with the greatest HIV RNA response have the best clinical outcome. No change in HIV RNA suggests therapy will be ineffective.
   d. **Estimates risk for opportunistic infection.** For patients with similar $CD_4$ cell counts, the risk of opportunistic infections is higher with higher HIV RNAs.
3. **Assays and Interpretation**
   a. **Tests, sensitivities, and dynamic range.** Three main assays, each with advantages and disadvantages, are widely used. Any assay can be used to diagnose acute HIV infection and guide/monitor therapy, but the same test should be used to follow patients longitudinally.
      1. **RT-PCR Amplicor** (Roche): Sensitivity = 400 copies/mL; dynamic range = 400–750,000 copies/mL.
      2. **RT-PCR Ultrasensitive 1.5** (Roche): Sensitivity = 50 copies/mL; dynamic range = 50–75,000 copies/mL.
      3. **bDNA Versant 3.0** (Bayer): Sensitivity = 75 copies/mL; dynamic range = 50–500,000 copies/mL.
   b. **Correlation between HIV RNA and $CD_4$.** HIV RNA assays correlate inversely with $CD_4$ cell counts, but do so imperfectly (e.g., some patients with high $CD_4$ counts have relatively high HIV RNA levels, and vice versa.) For any given $CD_4$, higher HIV RNA levels correlate with more rapid $CD_4$ decline. In response to antiretroviral therapy, changes in HIV RNA generally precede changes in $CD_4$ cell count.

c. **Significant change in HIV RNA assay** is defined by at least a 2-fold (0.3 log) change in viral RNA (accounts for normal variation in clinically stable patients), or a 3-fold (0.5 log) change in response to new antiretroviral therapy (accounts for intra-laboratory and patient variability). For example, if a HIV RNA result = 50,000 copies/mL, then the range of possible actual values = 25,000–100,000 copies/mL, and the value needed to demonstrate antiretroviral activity is ≤ 17,000 copies/mL.

4. **Indications for HIV RNA Testing.** Usually performed in conjunction with $CD_4$ cell counts. Indicated for the diagnosis of acute HIV infection, and for initial evaluation of newly diagnosed HIV. Also recommended 2–8 weeks after initiation of antiretroviral therapy and every 3–4 months in all HIV patients.

5. **When to Avoid HIV RNA Testing**

   a. **During acute illnesses and immunizations.** Patients with acute infections (opportunistic infection, bacterial pneumonia, even HSV recurrences) may experience significant (> 5-fold) rises in HIV RNA, which return to baseline 1–2 months after recovery. Although data are conflicting, many studies show at least a transient increase in HIV RNA levels following influenza and other immunizations, which return to baseline after 1–2 months.

   b. **When results of test would not influence therapy.** Frequent scenario in patients with advanced disease who have no antiretroviral options or cannot tolerate therapy.

   c. **As a screening test for HIV infection,** except if acute (primary) HIV disease is suspected during the HIV antibody window (i.e., first 3–6 weeks after viral transmission).

## INITIAL ASSESSMENT OF HIV INFECTION

A. **Clinical Evaluation.** History and physical exam should focus on diagnoses associated with HIV infection. Compared to patients without HIV, the severity, frequency, and duration of these conditions are usually increased in HIV disease.

   1. **Dermatologic:** Severe herpes simplex (oral/anogenital); herpes zoster (especially recurrent, cranial nerve, or disseminated); molluscum contagiosum; staphylococcal abscesses; tinea nail infections; Kaposi's sarcoma (from HHV-8 infection); petechiae (from ITP); seborrheic dermatitis; new or worsening psoriasis; eosinophilic pustular folliculitis; severe cutaneous drug eruptions (especially sulfonamides).

   2. **Oropharyngeal:** Oral candidiasis; oral hairy leukoplakia (from EBV); Kaposi's sarcoma (most commonly on palate or gums); gingivitis/periodontitis; warts; aphthous ulcers (especially esophageal/perianal).

3. **Constitutional symptoms:** Fatigue, fevers, chronic diarrhea, weight loss.
4. **Lymphatic:** Persistent, generalized lymphadenopathy.
5. **Others:** Active TB (especially extrapulmonary); non-Hodgkin's lymphoma (especially CNS); unexplained leukopenia, anemia, thrombocytopenia (especially ITP); myopathy; miscellaneous neurologic conditions (cranial/peripheral neuropathies, Guillain-Barre syndrome, mononeuritis multiplex, aseptic meningitis, cognitive impairment).

**B. Baseline Laboratory Testing (Table 5.1)**

**C. $CD_4$ Cell Count (lymphocyte subset analysis)**

1. **Overview.** Acute HIV infection is characterized by a decline in $CD_4$ cell count, followed by a gradual rise associated with clinical recovery. Chronic HIV infection shows progressive declines (~ 50–80 cells/year) in $CD_4$ cell count without treatment, followed by more rapid decline 1–2 years prior to opportunistic infection (AIDS-defining diagnosis). Cell counts remain stable over 5–10 years in 5% of patients, while others may show rapid declines (> 300 cells/year). Since variability exists within individual patients and between laboratories, it is useful to *repeat any value before making management decisions.*
2. **Uses of $CD_4$ Cell Count**
   a. **Gives context of degree of immunosuppression** for interpretation of symptoms/signs (Table 5.2).
   b. **Used to guide therapy.** Guidelines support $CD_4 < 500/mm^3$ as the threshold for initiating treatment, regardless of HIV RNA or symptoms. For prophylaxis against PCP, toxoplasmosis, and MAI/CMV infection, $CD_4$ cell counts of $200/mm^3$, $< 100/mm^3$, and $< 50/mm^3$ are used as threshold levels, respectively.
   c. **Provides estimate of risk of opportunistic infection or death.** $CD_4$ cell counts $< 50/mm^3$ are associated with a markedly increased risk of death (median survival 1 year), although some patients with low counts survive > 3 years even without antiretroviral therapy. Prognosis is heavily influenced by HIV RNA, presence/history of opportunistic infections or neoplasms, performance status, and the immune reconstitution response to antiretroviral therapy.

**D. HIV RNA Assay (HIV RNA PCR) (p. 307)**

**Table 5.1. Baseline Laboratory Testing for HIV-Infected Patients**

| Test | Rationale |
|---|---|
| Repeat HIV serology (ELISA/confirmatory Western blot) | Indicated for patients unable to document a prior positive test, and for "low risk" individuals with a positive test (to detect computer/clerical error). Repeat serology is now less important since HIV RNA testing provides an additional means of confirming HIV infection. |

**Table 5.1. Baseline Laboratory Testing for HIV-Infected Patients** (cont'd)

| Test | Rationale |
|---|---|
| CBC with differential, platelets | Detects cytopenias (e.g., ITP) seen in HIV. Needed to calculate $CD_4$ cell count. |
| Chemistry panel ("SMA 20") and fasting lipid panel | Detects renal dysfunction and electrolyte/LFT abnormalities, which may accompany HIV and associated infections (e.g., HIV nephropathy, HCV). Provides baseline lipid profile (many antiretroviral drugs can affect lipids). |
| $CD_4$ cell count | Determines the need for antiretroviral therapy and opportunistic infection (OI) prophylaxis. Best test for defining risk of OIs and prognosis. |
| HIV RNA assay ("viral load") | Provides a marker for the pace of HIV disease progression. Determines indication for and response to antiretroviral therapy. |
| Tuberculin skin test (standard 5 TU of PPD) | Detects latent TB infection and targets patients for preventive therapy. Anergy skin tests are no longer indicated due to poor predictive value. HIV is the most powerful co-factor for the development of active TB. |
| PAP smear | Risk of cervical cancer is nearly twice as high in HIV-positive women compared to uninfected controls. |
| HLA-B*5701 | Needed if abacavir therapy is planned, to assess risk for severe abacavir hypersensitivity reactions. |
| Toxoplasmosis serology (IgG) | Identifies patients at risk for subsequent cerebral/systemic toxoplasmosis and the need for prophylaxis. Those with negative tests should be counseled on how to avoid infection. |
| Syphilis serology (VDRL or RPR) | Identifies co-infection with syphilis, which is epidemiologically-linked to HIV. Disease may have accelerated course in HIV patients. |
| Hepatitis C serology (anti-HCV) | Identifies HCV infection and usually chronic carriage. If positive, follow with HCV genotype and HCV viral load assay. If the patient is antibody-negative and at high-risk for hepatitis, order HCV RNA to exclude a false-negative result. |
| Hepatitis B serologies (HBsAb, HBcAb, HBsAg) | Identifies patients who are immune to hepatitis B (HBsAb) or chronic carriers (HBsAg). If all three are negative, hepatitis B vaccine is indicated. |

**Table 5.1. Baseline Laboratory Testing for HIV-Infected Patients** (cont'd)

| Test | Rationale |
|---|---|
| G6PD screen | Identifies patients at risk for dapsone or primaquine-associated hemolysis. |
| CMV serology (IgG) | Identifies patients who should receive CMV-negative or leukocyte-depleted blood if transfused. |
| VZV serology (IgG) | Identifies patients at risk for varicella (chickenpox), and those who should avoid contact with active varicella or herpes zoster patients. Serology-negative patients exposed to chickenpox should receive varicella-zoster immune globulin (VZIG). |
| Chest x-ray | Sometimes ordered as a baseline test for future comparisons. May detect healed granulomatous diseases/other processes. Indicated in all tuberculin skin test positive patients. |

**Table 5.2. Use of $CD_4$ Cell Count for Interpretation of Patient Signs/Symptoms**

| $CD_4$ Cell Count (cells/mm$^3$) | Associated Conditions |
|---|---|
| > 500 | Most illnesses are similar to those in HIV-negative patients. Some increased risk of bacterial infections (pneumococcal pneumonia, sinusitis), herpes zoster, tuberculosis, skin conditions. |
| 200–500* | Bacterial infections (especially pneumococcal pneumonia, sinusitis), cutaneous Kaposi's sarcoma, vaginal candidiasis, ITP. |
| 50–200* | Thrush, oral hairy leukoplakia, classic HIV-associated opportunistic infections (e.g., P. [carinii] jiroveci pneumonia, cryptococcal meningitis, toxoplasmosis). For patients receiving prophylaxis, most opportunistic infection do not occur until $CD_4$ cell counts fall significantly below 100/mm$^3$. |
| < 50* | "Final common pathway" opportunistic infections (disseminated M. avium-intracellulare, CMV retinitis), HIV-associated wasting, neurologic disease (neuropathy, encephalopathy). |

* Patients remain at risk for all processes noted in earlier stages.

## INDICATIONS FOR TREATMENT OF HIV INFECTION

**Table 5.3. Initiation of Antiretroviral Therapy in HIV-1 Infected Patients**

| Clinical Condition and/or $CD_4$ count | Recommendation |
|---|---|
| Symptomatic HIV disease | ART strongly recommended regardless of $CD_4$ cell count |
| Pregnant women | |
| HIV-1 RNA > 100,000 copies/$mm^3$ | |
| Rapid decline in $CD_4$ cell count, >100 cells/$mm^3$ per year | |
| Acute hepatitis B coinfection | |
| Acute hepatitis C coinfection | |
| Active or high risk for cardiovascular disease | |
| HIV associated neuropathy | |
| Symptomatic primary HIV infection | |
| High risk for secondary HIV transmission (e.g., serodiscordant couples) | |
| Asymptomatic (any $CD_4$ cell count) | ART is recommended |

*ART = antiretroviral therapy.*

Adapted from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. http://aidsinfo.nih.gov/ConsentFiles/AdultandAdolescentGL.pdf, 2012.

**ANTIRETROVIRAL TREATMENT**

**Table 5.4. ART Therapy for Treatment-Naive Patients from DHHS Guidelines 2014**

| Regimen | Preferred Regimen | Alternate Regimen | Acceptable Regimen |
|---|---|---|---|
| NNRTI-based (1 NNRTI + 2 NRTIs) | Efavirenz (EFV) + Tenofovir (TDF) + Emtricitabine (FTC) (Atripla) | Efavirenz (EFV) (Sustiva) **plus** Abacavir (ABC) + Lamivudine (3TC) (Epzicom)<br>**or**<br>Rilpivirine (RPV) + Tenofovir (TDF) + Emtricitabine (FTC) (Complera)<br>*These regimens are recommended only when pre-ART plasma HIV RNA < 100,000 copies/ml* | None |
| PI-based (1 PI + 2 NRTIs) | Atazanavir (ATV) (Reyataz)/r **plus** Tenofovir (TDF) + Emtricitabine (FTC) (Truvada)<br>**or**<br>Darunavir (DRV) (Prezista)/ **plus** Tenofovir (TDF) + Emtricitabine (FTC) (Truvada) | Atazanavir (ATV) (Reyataz)/r **plus** Abacavir (ABC) + Lamivudine (3TC) (Epzicom)<br>*This regimen is recommended only when pre-ART plasma HIV RNA < 100,000 copies/ml* | Darunavir (DRV) (Prezista)/r **plus** Abacavir (ABC) + Lamivudine (3TC) (Epzicom)<br>**or**<br>Lopinavir (LPV)/r (Kaletra) (once[1] or twice daily) **plus** Abacavir (ABC) + Lamivudine (3TC) (Epzicom)<br>**or**<br>Lopinavir (LPV)/r (Kaletra) (once[1] or twice daily) **plus** Tenofovir (TDF) (Viread) **plus** Lamivudine (3TC) (Epivir)<br>Once daily LPV/r is not recommended for pregnant patients[1] |
| INSTI-based (1 INSTI + 2 NRTIs) | Raltegravir (RAL) (Isentress) plus Tenofovir (TDF) + Emtricitabine (FTC) (Truvada)<br>**or** | Raltegravir (RAL) (Isentress) **plus** Abacavir (ABC) + Lamivudine (3TC) (Epzicom) | None |

**Table 5.4. ART Therapy for Treatment-Naive Patients from DHHS Guidelines 2014** (cont'd)

| Regimen | Preferred Regimen | Alternate Regimen | Acceptable Regimen |
|---|---|---|---|
| | Elvitegravir (EVG) + Cobicistat (COBI) + Tenofovir (TDF + Emtricitabine (FTC) (Stribild)<br>**or**<br>Dolutegravir (DTG) + Abacavir (ABC) + Lamivudine (3TC) (Triumeq)<br>**or**<br>Dolutegravir (DTG) + (Tivicay) **plus** Tenofovir (TDF) + Emtricitabine (FTC) (Truvada) | | |

**Preferred Regimens for Pregnant Women**

Two-NRTI Backbone:

Abacavir (ABC) + Lamivudine (3TC) (Epzicom)

Tenofovir (TDF) + Emtricitabine (FTC) (Truvada) or Lamivudine (3TC) (Epivir)

Zidovudine (ZDV) + Lamivudine (3TC) (Kaletra)—most experience for use in pregnancy

PI-based Regimens:

Atazanavir (ATZ) (Reyataz)/r + a Preferred Two-NRTI Backbone (listed above)

Loplnavir (LPV)/r (Kaletra) (BID) + a Preferred Two-NRT Backbone (listed above)

NNRTI Regimen:

Efavirenz (EFV) (Sustiva) + a Preferred TWO-NRTI Backbone (listed above); may be initiated after the first 8 weeks of pregnancy

**Alternate Regimens**

PI-based:

Darunavir (DRV) (Prezista)/r + a Preferred Two-NRTI Backbone (listed above)

Saqulnavir (SQV) (Invirase)/r + a Preferred Two-NRTI Backbone (listed above)

NNRTI-based:

Nevirapine (NVP) (Viramune) + Preferred Two-NRTI Backbone (listed above)

INSTI-based:

Raltegravir (RAL) (isentress) + a Preferred Two-NRTI Backbone (listed above)

- Efavirenz should not be used during the first trimester of pregnancy or in women trying to conceive or in those not using effective and consistent contraception.
- Lamivudine may substitute for emtricitabine or vice versa.
- Abacavir should not be used in patients who test positive for HLA-B*5701 and should be used with caution in patients at high risk for cardiovascular disease or with pretreatment HIV-RNA > 100,000 copies/ml.
- Nevirapine should not be used in patients with moderate to severe hepatic impairment. It should not be used in women with pre-ARV $CD_4$ + > 250 cells/$mm^3$ or men with pre-ARV $CD_4$ + > 400 cells/$mm^3$.
- Atazanavir/r should not be used in patients who requires . 20 mg omeprazole per day.
- Atazanavir/r is generally preferred over atazanavir. Unboosted atazanavir may be used when ritonavir boosting is not possible.
- Lopinavir/r qd is not recommended for pregnant women.

Adapted from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/vguidelines/adultandadolescentgl.pdf, 2014.
Adapted from: Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. http://aidsinfo.nih.gov/contentfiles/vguidelines/perinatalgl.pdf, 2014.

**Table 5.5. Recommended initial Antiretroviral Therapy from IAS-USA Guidelines**

| | Recommended regimen | Alternate regimen | Comments |
|---|---|---|---|
| NNRTI-based | Efavirenz + Tenofovir + Emtricitabine<br><br>Efavirenz + Abacavir + Lamivudine | Nevirapine + Tenofovir + Emtricitabine<br><br>Nevirapine + Abacavir + Lamivudine<br><br>Rilpivirine + Tenofovir + Emtricitabine<br><br>Rilpivirine + Abacavir + Lamivudine | Abacavir only in HLA-B*5701-negative patients with HIV-1 RNA < 100000 copies/mL. Severe hepatotoxicity and rash with nevirapine are more common in initial therapy when CD4 cell count > 250/μL in women and > 400/μL in men |
| PI-based | Darunavir/r + Tenofovir + Emtricitabine<br><br>Atazanavir/r + Tenofovir + Emtricitabine<br><br>Atazanavir/r + Abacavir +Lamivudine | Darunavir/r + Abacavir + Lamivudine<br><br>Lopinavir/r + Tenofovir + Emtricitabine<br><br>Lopinavir/r + Abacavir + Lamivudine | Other alternative PIs include fosamprenavir/r and saquinavir/r but indications to use these options for initial treatment are rare |
| InSTI-based | Raltegravir + Tenofovir + Emtricitabine | Ralegravir + Abacavir + Lamivudine<br><br>Elvitegravir + Combicistat + Tenofovir + Emtricitabine | Raltegravir is given twice daily.<br>Experience with elvitegravir/combicistat/tenofovir/emtricitabine is limited to 48-week data |

Adapted from: Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA Panel. JAMA 308:387–402, 2012.

**Selection of Optimal Antiretroviral Therapy.** Selection of the optimal initial antiretroviral regimen must take into consideration antiviral potency, tolerability, and safety. In the DHHS and IAS-USA Guidelines (Tables 5.4 and 5.5).

## ANTIRETROVIRAL TREATMENT FAILURE (Table 5.6)

Antiretroviral treatment failure can be defined in various ways, as described below. Causes of treatment failure include inadequate adherence, preexisting drug resistance, regimen complexity, side effects, and suboptimal pharmacokinetics. All of these factors can lead to persistent viral replication and evolution of drug resistance. Poor medication adherence is the most common cause of treatment failure.

**A. Types of Treatment Failure**

1. **Virologic Failure** is most strictly defined as the inability to achieve or maintain virologic suppression. In a treatment-naïve patient, the HIV RNA level should be < 400 copies/mL after 24 weeks or < 50 copies/mL by 48 weeks after starting therapy. Virologic rebound is seen when there is repeated detection of HIV RNA after virologic suppression in either treatment-naïve or treatment-experienced patients.
2. **Immunologic Failure** can occur in the presence or absence of virologic failure and is defined as a failure to increase the $CD_4$ cell count by 25–50 cells/$mm^3$ above baseline during the first year of therapy, or as a decrease in $CD_4$ cell count to below baseline count while on therapy.
3. **Clinical Failure** is the occurrence or recurrence of HIV-related events after at least 3 months on potent antiretroviral therapy, excluding events related to an immune reconstitution syndrome.
4. **Usual Sequence of Treatment Failure.** Virologic failure usually occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months or years and may not occur in this order in all patients.

**B. Goals After Virologic Failure.** When patients have detectable HIV RNA on treatment, clinicians should attempt to identify the cause of their lack of response and set a treatment goal of achieving full virologic suppression (HIV RNA < 50 copies/mL). In addition to improving clinical and immunologic outcomes, this strategy will also prevent the selection of additional resistance mutations. Provided that medication adherence issues and regimen tolerability have been addressed, the regimen should be changed sooner than later. On the other hand, achieving an undetectable HIV RNA level in patients with an extensive prior treatment history may not be possible. The main goals in these patients should be partial suppression of HIV RNA below the pretreatment level to preserve immune function and prevent clinical progression.

**C. Resistance Testing and Selection of New Antiretroviral Therapy.** Genotypic assays characterize nucleotide sequences of the reverse transcriptase/protease portions of the virus, and identify resistance mutations associated with various drugs. Phenotypic assays

attempt to grow the virus in the presence of drugs, providing a more intuitively applicable measurement of resistance (similar to that done with bacteria). Compared to phenotypic assays, genotypic assays are faster (1–2 weeks vs. 2–4 weeks for results), less expensive ($400 vs. $1000), and have less inter-laboratory variability; however, mutations do not always correlate with resistance and results are difficult to interpret.

**Table 5.6. Management of Antiretroviral Treatment Failure**

| Type of Failure | Recommended Approach | Comments |
|---|---|---|
| Virologic failure<br>*Limited or intermediate prior treatment* | Assess for adherence and regimen tolerability. Obtain genotype resistance test. Select new regimen based on resistance test results and tolerability. | Usually associated with limited or no detectable resistance. If no resistance is found, consider re-testing for resistance 2–4 weeks after resuming antivirals. Stop NNRTI's if resistance is detected. Virologic suppression is likely if adherence is good. |
| *Extensive prior treatment* | Assess for adherence and regimen tolerability. Obtain resistance test – consider phenotype, "virtual phenotype," or phenotype-genotype combination if level of resistance is likely to be high. Obtain viral tropism assay to assess possible use of CCR5 antagonist. Select new regimen using at least 2 new active agents; if 2 new active agents not available, continue a "holding" regimen. | In patients with resistance to NRTI's, NNRTI's and PI's, the new regimen should generally contain at least: (1) at least one drug from a new drug class (integrase inhibitor, CCR5 antagonist, or fusion inhibitor); (2) a boosted PI with activity against resistant viruses (tipranavir or darunavir); and (3) one or two NRTI's, one of them 3TC or FTC. A holding regimen should always contain 3TC or FTC plus a boosted PI; NNRTI's should never be used. |
| *Low-level HIV RNA (50–1000 copies)* | Assess for adherence, drug-drug interactions, intercurrent illness, recent immunizations. Repeat test in 3–4 weeks. | For low-level viremia followed by undetectable HIV RNA ("blip"), no treatment change is necessary. If HIV RNA is persistently detectable at > 500 copies/mL, obtain resistance test as described above, and treat accordingly. If HIV RNA is persistently detectable at 50–500 copies/mL, consider regimen "intensification" with use of an additional agent. |

**Table 5.6. Management of Antiretroviral Treatment Failure** (cont'd)

| Type of Failure | Recommended Approach | Comments |
|---|---|---|
| Immunologic failure<br>*Detectable HIV RNA* | Assess for adherence and tolerability. If non-adherent, resume treatment after barriers to adherence are addressed. If adherent, obtain resistance testing and alter therapy as described above. | If HIV RNA is back to pre-treatment baseline, non-adherence is the most likely explanation. |
| *Suppressed HIV RNA* | Investigate for modifiable conditions that may be associated with impaired $CD_4$ response (chronic HCV, treatment with ZDV, TDF + ddI). If no modifiable conditions found, continue current regimen. | Prognosis for patients with suppressed HIV RNA and immunologic failure better than for those with comparable $CD_4$ cell counts and detectable viremia. |
| Clinical failure<br>*Detectable HIV RNA* | Treat OI with appropriate anti-infective therapy. Assess for antiretroviral adherence and tolerability. Send resistance test and choose new regimen based on results of test and other treatment options. | OI's (IRIS excluded) most commonly occur in those not on antiretroviral therapy due to poor compliance and/or regimen tolerability. |
| *Suppressed HIV RNA* | Continue current antiretrovirals. Treat OI with appropriate anti-infective therapy. If symptoms persist and IRIS is likely, use adjunctive corticosteroids. | IRIS most likely when baseline $CD_4$ cell count is low (< 200/$mm^3$); onset usually weeks-to-months after starting a potent regimen. IRIS been reported with virtually all OI's. True clinical progression with suppressed HIV RNA is unusual; IRIS should not be considered a sign of treatment failure. |

*IRIS = immune reconstitution inflammatory syndrome, OI = opportunistic infection.*

## PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS IN HIV (Tables 5.7 and 5.8)

Patients with HIV disease are at risk for infectious complications not otherwise seen in immunocompetent patients. Such opportunistic infections occur in proportion to the severity of immune system dysfunction (reflected by $CD_4$ cell count depletion). While community acquired infections (e.g., pneumococcal pneumonia) can occur at any $CD_4$ cell count, "classic" HIV-related opportunistic infections (PCP, toxoplasmosis, cryptococcus, disseminated M. avium-intracellulare, CMV) do not occur until $CD_4$ cell counts are dramatically reduced. Specifically, it is rare to encounter PCP in HIV patients with $CD_4 > 200/mm^3$, and CMV and disseminated MAI occur at median $CD_4$ cell counts $< 50/mm^3$.

**Table 5.7. Overview of Prophylaxis (See Table 5.8 for details)**

| Infection | Indication | Intervention |
|---|---|---|
| PCP | $CD_4 < 200/mm^3$ | TMP–SMX |
| TB (M. tuberculosis) | PPD > 5 mm (current or past) or contact with active case | INH |
| Toxoplasma | IgG Ab (+) and $CD_4 < 100/mm^3$ | TMP–SMX |
| MAI | $CD_4 < 50/mm^3$ | Azithromycin or Clarithromycin |
| S. pneumoniae | $CD_4 > 200/mm^3$ | Pneumococcal vaccine |
| Hepatitis B (HBV) | Susceptible patients | Hepatitis B vaccine |
| Hepatitis A (HAV) | HCV (+) and HA Ab (–); HCV (–) and HA Ab (–) gay men and travelers to endemic areas, chronic liver disease | Hepatitis A vaccine |
| Influenza | All patients | Annual flu vaccine Swine influenza ($H_1N_1$) vaccine |
| VZV | Exposure to chickenpox or shingles; no prior history | VZIG |

*Abbreviations: Ab = antibody; HAV = Hepatitis A virus; HCV = Hepatitis C virus; VZIG = varicella-zoster immune globulin; VZV = varicella- zoster virus; other abbreviations (p. xi).*

**Table 5.8. Prophylaxis of Opportunistic Infections in HIV**

| Infection | Indications and Prophylaxis | Comments |
|---|---|---|
| P. (carinii) jiroveci pneumonia (PCP) | Indications: $CD_4$ < 200/mm$^3$, oral thrush, constitutional symptoms, or previous history of PCP<br><br>Preferred prophylaxis: TMP–SMX 1 DS tablet (PO) q24h or 1 SS tablet (PO) q24h. 1 DS tablet (PO) 3×/week is also effective, but daily dosing may be slightly more effective<br><br>Alternate prophylaxis: Dapsone 100 mg (PO) q24h (preferred as second-line by most; more effective than aerosolized pentamidine when $CD_4$ cell count < 100)<br><br>**or**<br><br>Atovaquone 1500 mg (PO) q24h (comparably effective to dapsone and aerosolized pentamidine; more GI toxicity vs. dapsone, but less rash)<br><br>**or**<br><br>Aerosolized pentamidine 300 mg via Respirgard II nebulizer once monthly (exclude active pulmonary TB first to avoid nosocomial transmission) | Without prophylaxis, 80% of AIDS patients develop PCP, and 60–70% relapse within one year after the first episode. Prophylaxis with TMP–SMX also reduces the risk for toxoplasmosis and possibly bacterial infections. Among patients with prior non-life-threatening reactions to TMP–SMX, 55% can be successfully rechallenged with 1 SS tablet daily, and 80% can be rechallenged with gradual dose escalation using TMP–SMX elixir (8 mg TMP + 40 mg SMX/mL) given as 1 mL × 3 days, then 2 mL × 3 days, then 5 mL × 3 days, then 1 SS tablet (PO) q24h. Macrolide-regimens for MAI (azithromycin, clarithromycin) add to efficacy of PCP prophylaxis. Primary and secondary prophylaxis may be discontinued if $CD_4$ cell counts increase to > 200 cells/mm$^3$ for 3 months or longer in response to antiretroviral therapy (i.e., immune reconstitution). Prophylaxis should be resumed if the $CD_4$ cell count decreases to < 200/mm$^3$. |
| Toxoplasmosis | Indications: $CD_4$ < 100/mm$^3$ with positive toxoplasmosis serology (IgG)<br><br>Preferred prophylaxis: TMP–SMX 1 DS tablet (PO) q24h<br><br>Alternate prophylaxis: Dapsone 50 mg (PO) q24h + pyrimethamine 50 mg (PO) weekly + folinic acid 25 mg (PO) weekly<br><br>**or** | Incidence of toxoplasmosis in seronegative patients is too low to warrant chemoprophylaxis. Primary prophylaxis can be discontinued if $CD_4$ cell counts increase to > 200/mm$^3$ for at least 3 months in response to antiretroviral therapy. Secondary prophylaxis (chronic maintenance therapy) may be discontinued in patients who responded to initial therapy, remain asymptomatic, and whose $CD_4$ counts increase to > 200/mm$^3$ for 6 months or longer in response to |

**Table 5.8. Prophylaxis of Opportunistic Infections in HIV** (cont'd)

| Infection | Indications and Prophylaxis | Comments |
|---|---|---|
| | Dapsone 100 mg/pyrimethamine 50 mg twice weekly (no folinic acid)<br>**or**<br>Atovaquone 1500 mg (PO) q24h | antiretroviral therapy. Prophylaxis should be restarted if the $CD_4$ count decreases to < 200/mm$^3$. Some experts would obtain an MRI of the brain as part of the evaluation prior to stopping secondary prophylaxis. |
| M. tuberculosis (TB) | Indications: PPD induration ≥ 5 mm or history of positive PPD without prior treatment, or close contact with active case of TB. Must exclude active disease (chest x-ray mandatory). Indicated at any $CD_4$ cell count<br>Preferred prophylaxis: INH 300 mg (PO) q24h × 9 months + pyridoxine 50 mg (PO) q24h × 9 months<br>Alternate prophylaxis: Rifampin 600 mg (PO) q24h × 2 months + pyrazinamide 20 mg/kg (PO) q24h × 2 months. Rifampin should not be given to patients receiving PI's | Consider prophylaxis for skin test negative patients when the probability of prior TB exposure is > 10% (e.g., patients from developing countries, IV drug abusers in some cities, prisoners). However, a trial testing this strategy in the U.S. did not find a benefit for empiric prophylaxis. INH prophylaxis delayed progression to AIDS and prolonged life in Haitian cohort with positive PPD treated × 6 months. Rifampin plus pyrazinamide × 2 months was effective in a multinational clinical trial (but the combination may ↑ hepatotoxicity). Rifabutin may be substituted for rifampin in rifampin-containing regimens. |
| M. avium-intracellulare (MAI) | Indications: $CD_4$ < 50/mm$^3$<br>Preferred prophylaxis: Azithromycin 1200 mg (PO) once a week (fewest number of pills; fewest drug interactions; may add to efficacy of PCP prophylaxis)<br>**or**<br>Clarithromycin 500 mg (PO) q12h (more effective than rifabutin; associated with survival advantage; resistance detected in some breakthrough cases)<br>Alternate prophylaxis: Rifabutin (less effective). See TB (p. 326) for dosing | Macrolide options (azithromycin, clarithromycin) preferable to rifabutin. Azithromycin is preferred for patients on protease inhibitors (fewer drug interactions). Primary prophylaxis may be discontinued if $CD_4$ cell counts increase to > 100/mm$^3$ and HIV RNA suppresses for 3–6 months or longer in response to antiretroviral therapy. Secondary prophylaxis may be discontinued for $CD_4$ cell counts that increase to > 100/mm$^3$ × 6 months or longer in response to antiretroviral therapy if patients have completed 12 months of MAI therapy and have no evidence of disease. Resume MAI prophylaxis for $CD_4$ < 100/mm$^3$. |

**Table 5.8. Prophylaxis of Opportunistic Infections in HIV** (cont'd)

| Infection | Indications and Prophylaxis | Comments |
|---|---|---|
| Pneumococcus (S. pneumoniae) | Indications: $CD_4 > 200/mm^3$<br><br>Preferred prophylaxis: Pneumococcal polysaccharide (23 valent) vaccine.* Re-vaccinate × 1 at 5 years | Incidence of invasive pneumococcal disease is > 100-fold higher in HIV patients. Efficacy of vaccine is variable in clinical studies. |
| Influenza (human seasonal) | Indications: Generally recommended for all patients<br><br>Preferred prophylaxis: Influenza vaccine (inactivated whole virus and split virus vaccine)* | Give annually (optimally October–January). Some experts do not give vaccine if $CD_4$ is $< 100/mm^3$ (antibody response is poor). New intranasal live virus vaccine is contraindicated in immunosuppressed patients. |
| Hepatitis B (HBV) | Indications: All susceptible (anti-HBcAb negative and anti-HBsAg negative) patients<br><br>Preferred prophylaxis: Hepatitis B recombinant DNA vaccine* | Response rate is lower than in HIV-negative controls. Repeat series if no response, especially if $CD_4$ was low during initial series and is now increased. |
| Hepatitis A (HAV) | Indications: All susceptible patients who are also infected with hepatitis C; HAV-susceptible seronegative gay men or travelers to endemic areas; chronic liver disease; illegal drug users<br><br>Preferred prophylaxis: Hepatitis A vaccine* | Response rate is lower than in HIV-negative controls. |
| Measles, mumps, rubella | Indications: Patients born after 1957 and never vaccinated; patients vaccinated between 1963–1967<br><br>Preferred prophylaxis: MMR (measles, mumps, rubella) vaccine* | Single case of vaccine-strain measles pneumonia in severely immuno-compromised adult who received MMR; vaccine is therefore contraindicated in patients with severe immunodeficiency ($CD_4 < 200$). |

* Same dose as for normal hosts (see pp. 372–375). If possible, give vaccines early in course of HIV infection, while immune system may still respond. Alternatively, to increase the likelihood of response in patients with advanced HIV disease, vaccines may be administered after 6–12 months of effective antiretroviral therapy. Vaccines should be given when patients are clinically stable, not acutely ill (e.g., give during a routine office visit, rather than during hospitalization for an opportunistic infection). Live vaccines (e.g., oral polio, oral typhoid, Yellow fever) are generally contraindicated, but measles vaccine is well-tolerated in children, and MMR vaccine is recommended for adults as described above.

**Table 5.8. Prophylaxis of Opportunistic Infections in HIV** (cont'd)

| Infection | Indications and Prophylaxis | Comments |
|---|---|---|
| H. influenzae | Indications: Not generally recommended for adults<br>Preferred prophylaxis: H. influenzae type B polysaccharide vaccine* | Incidence of H. influenzae disease is increased in HIV patients, but 65% are caused by non-type B strains. Unclear whether vaccine offers protection. |
| Travel vaccines* | Indications: Travel to endemic areas | All considered safe except oral polio, yellow fever, and live oral typhoid—each a live virus vaccine. |

* Same dose as for normal hosts (see pp. 372–375). If possible, give vaccines early in course of HIV infection, while immune system may still respond. Alternatively, to increase the likelihood of response in patients with advanced HIV disease, vaccines may be administered after 6–12 months of effective antiretroviral therapy. Vaccines should be given when patients are clinically stable, not acutely ill (e.g., give during a routine office visit, rather than during hospitalization for an opportunistic infection). Live vaccines (e.g., oral polio, oral typhoid, Yellow fever) are generally contraindicated, but measles vaccine is well-tolerated in children, and MMR vaccine is recommended for adults as described above.

## TREATMENT OF OPPORTUNISTIC INFECTIONS IN HIV

Antiretroviral therapy (ART) and specific antimicrobial prophylaxis regimens have led to a dramatic decline in HIV-related opportunistic infections. Today, opportunistic infections occur predominantly in patients not receiving ART (due to undiagnosed HIV infection or nonacceptance of therapy), or in the period after starting ART (due to lack of immune reconstitution or from eliciting a previously absent inflammatory host response). Despite high rates of virologic failure in clinical practice, the rate of opportunistic infections in patients compliant with ART remains low, presumably due to continued immunologic response despite virologic failure, a phenomenon that may be linked to impaired "fitness" (virulence) of resistant HIV strains. For patients on or off ART, the absolute $CD_4$ cell count provides the best marker of risk for opportunistic infections.

# Respiratory Tract Opportunistic Infections

## Aspergillosis, Invasive Pulmonary

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Aspergillus fumigatus (rarely other species) | Voriconazole 400 mg (IV or PO) q12h × 2 days, then 200 mg (IV or PO) q12h until cured (typically 6–18 months) | Amphotericin B 1 mg/kg (IV) q24h until 2–3 gm total dose given (optimal duration of therapy poorly defined)<br>**or**<br>Lipid amphotericin (Abelcet or Ambisome) 5 mg/kg/day (IV) until cured |

**Clinical Presentation:** Pleuritic chest pain, hemoptysis, cough in a patient with advanced HIV disease. Additional risk factors include neutropenia and use of corticosteroids.

**Diagnostic Considerations:** Diagnosis by bronchoscopy with biopsy/culture. Open lung biopsy (usually video-assisted thorascopic surgery) is sometimes required. Radiographic appearance includes cavitation, nodules, sometimes focal consolidation. Dissemination to CNS may occur, and manifests as focal neurological deficits.

**Pitfalls:** Positive sputum culture for Aspergillus in advanced HIV disease should heighten awareness of possible infection.

**Therapeutic Considerations:** Decrease/discontinue corticosteroids, if possible. If present, treat neutropenia with granulocyte-colony stimulating factor (G-CSF) to achieve absolute neutrophil count > 1000/mm$^3$. There are insufficient data to recommend chronic suppressive or maintenance therapy.

**Prognosis:** Poor unless immune deficits can be corrected.

## Bacterial Pneumonia

| Usual Pathogens | Preferred Therapy | Comments |
|---|---|---|
| Streptococcus pneumoniae (most common)<br>Haemophilus influenzae<br>Pseudomonas aeruginosa | **Monotherapy with**<br>Levofloxacin 750 mg (PO/IV) q24h or Moxifloxacin 400 mg (PO/IV) q24h × 7–14 days, depending on severity<br>**or combination therapy with**<br>Ceftriaxone 1–2 gm (IV) q24h (or Cefotaxime 1 gm [IV] q8h)<br>**plus** Azithromycin 500 gm q24h × 7–14 days | For severe immunodeficiency ($CD_4$ < 100/mm$^3$), neutropenia, or a prior history of pseudomonas infection, broaden coverage to include *P. aeruginosa* and other gram-negative bacilli<br>by adding **either** Ceftazidime 1 gm (IV) q8h **or** Cefepime 1 gm (IV) q12h **or** Ciprofloxacin 750 mg (PO) q12h or 400 mg (IV) q8h. |

**Clinical Presentation:** HIV-infected patients with bacterial pneumonia present similar to those without HIV, with a relatively acute illness (over days) that is often associated with chills, rigors, pleuritic chest pain, and purulent sputum. Patients who have been ill over weeks to months are more likely have PCP, tuberculosis, or a fungal infection. Since bacterial pneumonia can occur at any $CD_4$ cell count, this infection is frequently the presenting symptom of HIV disease, prompting initial HIV testing and diagnosis.

**Diagnostic Considerations:** The most common pathogens are Streptococcus pneumoniae, followed by Haemophilus influenzae. The pathogens of atypical pneumonia (Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae) are rarely encountered, even with extensive laboratory investigation. A lobar infiltrate on chest radiography is a further predictor of bacterial pneumonia. Blood cultures should be obtained, as HIV patients have an increased rate of bacteremia compared to those without HIV.

**Pitfalls:** Sputum gram stain and culture are generally only helpful if collected prior to starting antibiotics, and only if a single organism predominates. HIV patients with bacterial pneumonia may rarely have a more subacute opportunistic infection concurrently, such as PCP or TB.

**Therapeutic Considerations:** Once improvement has occurred, a switch to oral therapy is generally safe. Patients with advanced HIV disease are at greater risk of bacteremic pneumonia due to gram-negative bacilli, and should be covered empirically for this condition.

**Prognosis:** Response to therapy is generally prompt and overall prognosis is good.

## Pneumocystis (carinii) jiroveci Pneumonia (PCP)

| Subset | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Severe disease ($pO_2$ < 70 mmHg, A-a gradient > 35) | TMP–SMX (5 mg/kg TMP) (IV) q6h × 21 days<br>**plus**<br>Prednisone 40 mg (PO) q12h on days 1–5, then 40 mg (PO) q24h on days 6–10, then 20 mg (PO) q24h on days 11–21. Methylprednisolone (IV) can be substituted at 75% of prednisone dose | Pentamidine 4 mg/kg (IV) q24h (infused over ≥ 60 minutes) × 21 days *plus* prednisone × 21 days. (Dose reduction of pentamidine to 3 mg/kg [IV] q24h may reduce toxicity)<br>**or**<br>Primaquine 30 mg (PO) q24h × 21 days plus clindamycin 600 mg (PO) q8h × 21 days |
| Mild or moderate disease ($pO_2$ > 70 mmHg, A-a gradient < 35) | TMP–SMX 2 DS tablets (PO) q6h × 21 days | Dapsone 100 mg (PO) q24h × 21 days plus TMP 5 mg/kg (PO) q8h × 21 days<br>**or**<br>Primaquine 30 mg (PO) q24h × 21 days *plus* clindamycin 600 mg (PO) q8h × 21 days<br>**or**<br>Atovaquone 750 mg (PO) q12h (with food) × 21 days |

**Clinical Presentation:** Fever, cough, dyspnea; often indolent presentation. Progressive SOB usually over a week. Physical exam is usually normal. Chest x-ray is variable, but commonly shows a diffuse interstitial pattern. High A-a gradient with exercise desaturation.

**Diagnostic Considerations:** Diagnosis by immunofluorescent stain of induced sputum or bronchoscopy specimen. Highly elevated LDH. β 1,3 D-glucan + , aspergillus galactomannan – .

**Pitfalls:** Slight worsening of symptoms is common after starting therapy, especially if not treated with steroids. Do not overlook superimposed bacterial pneumonia or other secondary infections, especially while on pentamidine. Patients receiving second-line agents for PCP prophylaxis—in particular aerosolized pentamidine–may present with atypical radiographic findings, including apical infiltrates, multiple small-walled cysts, pleural effusions, pneumothorax, or single/multiple nodules.

**Therapeutic Considerations:** Outpatient therapy is possible for mild disease, but only when close follow-up is assured. Adverse reactions to TMP–SMX (rash, fever, GI symptoms, hepatitis, hyperkalemia, leukopenia, hemolytic anemia) occur in 25–50% of patients, many of whom will need a second-line regimen to complete therapy (e.g., trimethoprim-dapsone or atovaquone). Unless an adverse reaction to TMP–SMX is particularly severe (e.g., Stevens-Johnson syndrome or other life-threatening problem), TMP–SMX may be considered for PCP prophylaxis, since prophylaxis requires a much lower dose (only 10–15% of treatment dose). Patients being treated for severe PCP with TMP–SMX who do not improve after one week may be switched to pentamidine, although there are no prospective data to confirm this approach. In general, patients receiving antiretroviral therapy when PCP develops should have their treatment continued, since intermittent antiretroviral therapy can lead to drug resistance. For newly-diagnosed or antiretroviral-naive HIV patients, treatment of PCP may be completed before starting antiretroviral therapy. Steroids should be tapered, not discontinued

abruptly. Adjunctive steroids increase the risk of thrush/herpes simplex infection, but probably not CMV, TB, or disseminated fungal infection.

**Prognosis:** Usually responds to treatment. Adverse prognostic factors include ↑ A-a gradient, hypoxemia, ↑ LDH.

## Pulmonary Tuberculosis (for isolates sensitive to INH and rifampin)

| Pathogen | Patients NOT Receiving PI's or NNRTI's | Patients Receiving PI's or NNRTI's* |
|---|---|---|
| Mycobacterium tuberculosis (TB) | Initial phase (8 weeks)<br>INH 300 mg (PO) q24h<br>**plus**<br>Rifampin† 600 mg (PO) q24h<br>**plus**<br>Pyrazinamide (PZA) 25 mg/kg (PO) q24h<br>**plus**<br>Ethambutol (EMB)<br>15–20 mg/kg (PO) q24h<br><br>Continuation phase (18 weeks)<br>INH 300 mg (PO) q24h<br>**plus**<br>Rifampin† 600 mg (PO) q24h | Initial phase (8 weeks)<br>INH 300 mg (PO) q24h<br>**plus**<br>Rifabutin*<br>**plus**<br>PZA 25 mg/kg (PO) q24h<br>**plus**<br>EMB 15 mg/kg (PO) q24h × 8 weeks.<br><br>Continuation phase (18 weeks)<br>INH 300 mg (PO) q24h<br>**plus**<br>Rifabutin* |

* Rifabutin dose: If PI is nelfinavir, indinavir, amprenavir or fosamprenavir, then rifabutin dose is 150 mg (PO) q24h. If PI is ritonavir, lopinavir/ritonavir or atazanavir, then rifabutin dose is 150 mg (PO) 2–3 times weekly. If NNRTI is efavirenz, then rifabutin dose is 450 mg (PO) q24h or 600 mg (PO) 2–3 times weekly. If NNRTI is nevirapine, then rifabutin dose is 300 mg (PO) q24h. Rifabutin is **contraindicated** in patients receiving delavirdine rilpivirine, etravirine + ritonavir boosted PI or hard-gel saquinavir. Patients receiving PI's AND NNRTI's: as above, except adjust rifabutin to 300 mg (PO) q24h.

† For patients receiving triple NRTI regimens, substitute rifabutin 300 mg (PO) q24h for rifampin.

**Clinical Presentation:** May present atypically. HIV patients with high (> 500/mm$^3$) $CD_4$ cell counts are more likely to have a typical pulmonary presentation, but patients with advanced HIV disease may have a diffuse interstitial pattern, hilar adenopathy, or a normal chest x-ray. Tuberculin skin testing (TST) is helpful if positive, but unreliable if negative due to anergy.

**Diagnostic Considerations:** In many urban areas, TB is one of the most common HIV-related respiratory illnesses. In other areas, HIV-related TB occurs infrequently except in immigrants or patients arriving from highly TB endemic areas. Maintain a high Index of suspicion for TB in HIV patients with unexplained fevers/pulmonary infiltrates.

**Pitfalls:** Extrapulmonary and pulmonary TB often coexist, especially in advanced HIV disease.

**Therapeutic Considerations:** Treatment by directly observed therapy (DOT) is strongly recommended for all HIV patients. If patients have cavitary disease or either positive sputum cultures or lack of clinical response at 2 months, total duration of therapy should be increased up to 9 months. If hepatic transaminases are elevated (AST > 3 times normal) before treatment initiation, treatment options include: (1) standard therapy with frequent monitoring; (2) rifamycin (rifampin or rifabutin) + EMB + PZA for 6 months; or

(3) INH + rifamycin + EMB for 2 months, then INH + rifamycin for 7 months. Once-weekly rifapentine is not recommended for HIV patients. Non-severe immune reconstitution inflammatory syndrome (IRIS) may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs); severe cases should be treated with corticosteroids. In all cases of IRIS, antiretroviral therapy should be continued if possible. Monitor carefully for signs of rifabutin drug toxicity (arthralgias, uveitis, leukopenia).

**Prognosis:** Usually responds to treatment. Relapse rates are related to the degree of immunosuppression and local risk of re-exposure to TB.

# CNS Opportunistic Infections

## CMV Retinitis

| Preferred Therapy, Duration of Therapy, Chronic Maintenance | Alternate Therapy | Other Options/Issues |
|---|---|---|
| Preferred therapy for CMV retinitis<br>*For immediate sight-threatening lesions*<br>Ganciclovir intraocular implant + valganciclovir 900 mg (PO) q12h for 14–21 days, then q24h daily)<br>One dose of intravitreal ganciclovir may be administered immediately after diagnosis until ganciclovir implant can be placed<br><br>*For small peripheral lesions*<br>Valganciclovir 900 mg (PO) q12h × 14–21 days, then 900 mg (PO) q24h | Alternative therapy for CMV retinitis<br>Ganciclovir 5 mg/kg (IV) q12h × 14–21 days, then 5 mg/kg (IV) q24h;<br>**or**<br>Ganciclovir 5 mg/kg (IV) q12h × 14–21 days, then valganciclovir 900 mg (PO) q24h<br>**or**<br>Foscarnet 60 mg/kg (IV) q8h or 90 mg/kg (IV) q12h × 14–21 days, then 90–120 mg/kg (IV) q24h;<br>**or**<br>Cidofovir 5 mg/kg (IV) q week × 2 weeks, then 5 mg/kg (IV) every other week with saline hydration before and after therapy plus probenecid 2 g (PO) 3 hours before the dose followed by 1 g (PO) 2 hours after the dose, and 1 g (PO) 8 hours after the dose (total of 4 g)<br>**Note:** This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid | The choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), level of immunosuppression, and other factors such as concomitant medications and ability to adhere to treatment<br><br>Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART<br><br>In patients with CMV neurological disease, localized morbidity might occur because of IRIS, a brief delay in initiation of ART until clinical improvement might be prudent<br><br>Maintenance therapy for CMV retinitis can be safely discontinued in patients with inactive disease and sustained $CD_4$+ count |

## CMV Retinitis (cont'd)

| Preferred Therapy, Duration of Therapy, Chronic Maintenance | Alternate Therapy | Other Options/Issues |
|---|---|---|
| Preferred chronic maintenance therapy (secondary prophylaxis) for CMV retinitis<br>Valganciclovir 900 mg (PO) daily<br>**or**<br>Ganciclovir implant (may be replaced every 6–8 months if $CD_4$+ count remains < 100 cells/$\mu$L) + Valganciclovir 900 mg (PO) q24h until immune recovery | Alternative chronic maintenance (secondary prophylaxis) for CMV retinitis<br>Ganciclovir 5 mg/kg IV 5–7 times weekly<br>**or**<br>Foscarnet 90–120 mg/kg (IV) q24h<br>**or**<br>Cidofovir 5 mg/kg (IV) of other week with saline hydration and probenecid (as above) | (> 100 cells/mm$^3$ for ≥ 3–6 months); consultation with ophthalmologist is advised<br><br>Patients with CMV retinitis who discontinued maintenance therapy should undergo regular eye examination, optimally every 3 months, for early detection of relapse or immune recovery uveitis (IRU)<br><br>IRU might develop in the setting of immune reconstitution.<br><br>Treatment of IRU: periocular corticosteroid or short courses of systemic steroid |

## CMV Encephalitis

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Cytomegalovirus (CMV) | Acute therapy<br>Ganciclovir (GCV) 5 mg/kg (IV) q12h until symptomatic improvement (typically > 3 weeks). *For severe cases*, consider acute therapy with Ganciclovir 5 mg/kg (IV) q12h plus Foscarnet 90 mg/kg (IV) q24h until improvement<br><br>Follow with lifelong suppressive therapy<br>Valganciclovir 900 mg (PO) q24h | Acute therapy<br>Foscarnet 60 mg/kg (IV) q8h or 90 mg/kg (IV) q12h × 3 weeks<br><br>Follow with lifelong suppressive therapy<br>Valganciclovir 900 mg (PO) q24h |

### CMV Retinitis

**Clinical Presentation:** Blurred vision, scotomata, field cuts common. Often bilateral, even when initial symptoms are unilateral.

**Diagnostic Considerations:** Diagnosis by characteristic hemorrhagic ("tomato soup and milk") retinitis on funduscopic exam. Consult ophthalmology in suspected cases.
**Pitfalls:** May develop immune reconstitution vitreitis after starting antiretroviral therapy.
**Therapeutic Considerations:** Oral valganciclovir is the preferred option for initial and maintenance therapy. Lifelong maintenance therapy for CMV retinitis is required for $CD_4$ counts < 100/mm$^3$, but may be discontinued if $CD_4$ counts increase to > 100–150/mm$^3$ for 6 or more months in response to antiretroviral therapy (in consultation with ophthalmologist). Patients with CMV retinitis who discontinue therapy should undergo regular eye exams to monitor for relapse. Ganciclovir intraocular implants might need to be replaced every 6–8 months for patients who remain immunosuppressed with $CD_4$ < 100–150/mm$^3$. Immune recovery uveitis (IRU) may develop in the setting of immune reconstitution due to ART and be treated by ophthalmologist with periocular corticosteroid, sometimes systemic corticosteroid.
**Prognosis:** Good initial response to therapy. High relapse rate unless $CD_4$ improves with antiretroviral therapy.

### CMV Encephalitis

**Clinical Presentation:** Encephalitis presents as fever, mental status changes, and headache evolving over 1–2 weeks. True meningismus is rare. CMV encephalitis occurs in advanced HIV disease ($CD_4$ < 50/mm$^3$), often in patients with prior CMV retinitis. Polyradiculitis presents as rapidly evolving weakness/sensory disturbances in the lower extremities, often with bladder/bowel incontinence. Anesthesia in "saddle distribution" with ↓ sphincter tone possible.
**Diagnostic Considerations:** CSF may show lymphocytic or neutrophilic pleocytosis; glucose is often decreased. For CMV encephalitis, characteristic findings on brain MRI include confluent periventricular abnormalities with variable degrees of enhancement. Diagnosis is confirmed by CSF CMV PCR (preferred), CMV culture, or brain biopsy.
**Pitfalls:** For CMV encephalitis, a wide spectrum of radiographic findings are possible, including mass lesions (rare). Obtain ophthalmologic evaluation to exclude active retinitis. For polyradiculitis, obtain sagittal MRI of the spinal cord to exclude mass lesions, and CSF cytology to exclude lymphomatous involvement (can cause similar symptoms).
**Therapeutic Considerations:** For any established CMV disease, optimization of antiretroviral therapy is important along with initiating anti-CMV therapy. Ganciclovir plus foscarnet may be beneficial as initial therapy for severe cases. Consider discontinuation of valganciclovir maintenance therapy if $CD_4$ increases to > 100–150/mm$^3$ × 6 months or longer in response to antiretroviral therapy.
**Prognosis:** Unless $CD_4$ cell count increases in response to antiretroviral therapy, response to anti-CMV treatment is usually transient, followed by progression of symptoms.

## Cryptococcal Meningitis

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Cryptococcus neoformans | Acute infection (induction therapy)<br>Amphotericin B 0.7 mg/kg (IV) q24h × 2 weeks ± flucytosine (5-FC) 25 mg/kg (PO) q6h × 2 weeks<br>**or** | Acute infection (induction therapy)<br>Amphotericin B 0.7 mg/kg/day (IV) × 2 weeks<br>**or**<br>Fluconazole 400–800 mg (IV or PO) q24h × 6 weeks (less severe disease)<br>**or** |

## Cryptococcal Meningitis (cont'd)

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| | Lipid amphotericin 4 mg/kg (IV) q24h × 2 weeks ± flucytosine (5-FC) 25 mg/kg (PO) q6h × 2 weeks<br><br>Consolidation therapy<br>Fluconazole 400 mg (PO) q24h × 8 weeks or until CSF cultures are sterile<br><br>Chronic maintenance therapy (secondary prophylaxis)<br>Fluconazole 200 mg (PO) q24h | Fluconazole 400–800 mg (IV or PO) q24h *plus* flucytosine (5-FC) 25 mg/kg (PO) q6h × 4–6 weeks<br><br>Consolidation therapy<br>Itraconazole 200 mg (PO) q12h × 8 weeks or until CSF cultures are sterile<br><br>Chronic maintenance therapy<br>Itraconazole 200 mg (PO) q24h for intolerance to fluconazole or failed fluconazole therapy |

**Clinical Presentation:** Often indolent onset of fever, headache, subtle cognitive deficits. Occasional meningeal signs and focal neurologic findings, though non-specific presentation is most common.
**Diagnostic Considerations:** Diagnosis usually by cryptococcal antigen; India ink stain of CSF is less sensitive. Diagnosis is essentially excluded with a negative serum cryptococcal antigen (sensitivity of test in AIDS patients approaches 100%). If serum cryptococcal antigen is positive, CSF antigen may be negative in disseminated disease without spread to CNS/meninges. Brain imaging is often normal, but CSF analysis is usually abnormal with a markedly elevated opening pressure.
**Pitfalls:** Be sure to obtain a CSF opening pressure, since reduction of increased intracranial pressure is critical for successful treatment. Remove sufficient CSF during the initial lumbar puncture (LP) to reduce closing pressure to < 200 mm $H_2O$ or 50% of opening pressure. Increased intracranial pressure requires repeat daily lumbar punctures until CSF pressure stabilizes; persistently elevated pressure should prompt placement of a lumbar drain or ventriculo-peritoneal shunting. Adjunctive corticosteroids are not recommended.
**Therapeutic Considerations:** Optimal total dose/duration of amphotericin B prior to fluconazole switch is unknown (2–3 weeks is reasonable if patient is doing well). Treatment with 5-FC is optional; however, since 5-FC is associated with more rapid sterilization of CSF, it is reasonable to start 5-FC and then discontinue it for toxicity (neutropenia, nausea). Fluconazole is preferred over itraconazole for lifelong maintenance therapy. Consider discontinuation of chronic maintenance therapy in patients who remain asymptomatic with $CD_4$ >100–200/$mm^3$ for > 6 months due to ART.
**Prognosis:** Variable. Mortality up to 40%. Adverse prognostic factors include increased intracranial pressure, abnormal mental status.

## Progressive Multifocal Encephalopathy (PML)

| Pathogen | Therapy |
|---|---|
| Reactivation of latent papovavirus (JC strain most common) | Effective antiretroviral therapy with immune reconstitution |

**Clinical Presentation:** Hemiparesis, ataxia, aphasia, other focal neurologic defects, which may progress over weeks to months. Usually alert without headache or seizures on presentation.
**Diagnostic Considerations:** Demyelinating disease caused by reactivation of latent papovavirus (JC strain most common). Diagnosis by clinical presentation and MRI showing patchy demyelination of white matter ± cerebellum/brainstem. JC virus PCR of CSF is useful for noninvasive diagnosis. In confusing or atypical presentation, biopsy may be needed to distinguish PML from other opportunistic infections, CNS lymphoma, or HIV encephalitis/encephalopathy.
**Pitfalls:** Primary HIV-related encephalopathy has a similar appearance on MRI.
**Therapeutic Considerations:** Most effective therapy is antiretroviral therapy with immune reconstitution. Some patients experience worsening neurologic symptoms once ART is initiated due to immune reconstitution induced inflammation. ART should be continued, with consideration of adjunctive steroids. Randomized controlled trials have evaluated cidofovir and vidarabine—neither is effective nor recommended.
**Prognosis:** Rapid progression of neurologic deficits over weeks to months is common. Best chance for survival is immune reconstitution in response to antiretroviral therapy, although some patients will have progressive disease despite immune recovery.

## Toxoplasma Encephalitis

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Toxoplasma gondii | Acute therapy (× 6–8 weeks until good clinical response)<br>Pyrimethamine 200 mg (PO) × 1 dose, then 50 mg (< 60 kg body weight) or 75 mg (> 60 kg) (PO) q24h<br>**plus**<br>Sulfadiazine 1000 mg (< 60 kg) or 1500 mg (> 60 kg) (PO) q6h<br>**plus**<br>Leucovorin 10–25 mg (PO) q24h<br>*For severely ill patients who cannot take oral medications*, treat with TMP–SMX (5 mg/kg TMP and 25 mg/kg SMX) (IV) q12h | Acute therapy (× 6–8 weeks until good clinical response)<br>Pyrimethamine 200 mg (PO) × 1 dose, then 50 mg (< 60 kg body weight) or 75 mg (> 60 kg) (PO) q24h *plus* clindamycin 600 mg (IV or PO) q6h plus leucovorin 10 mg (PO) q24h<br>**or**<br>TMP–SMX (5 mg/kg TMP (IV or PO) q12h<br>**or**<br>Atovaquone 1500 mg (PO) q12h (with meals or nutritional supplement) plus pyrimethamine (as above)<br>**or**<br>Atovaquone 1500 mg (PO) q12h (with meals or nutritional supplement) *plus* sulfadiazine 1000–1500 mg (PO) q6h<br>**or**<br>Atovaquone 1500 mg (PO) q12h (with meals)<br>**or**<br>Pyrimethamine (see above) *plus* leucovorin 10 mg (PO) q24h *plus* azithromycin 900–1200 mg (PO) q24h |

## Toxoplasma Encephalitis (cont'd)

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| | Follow with lifelong suppressive therapy<br>Sulfadiazine 500–1000 mg (PO) q6h<br>**plus**<br>Pyrimethamine 50 mg (PO) q24h<br>**plus**<br>Leucovorin 10–25 mg (PO) q24h | Lifelong suppressive therapy<br>Clindamycin 600 mg (PO) q8h plus pyrimethamine 50 mg (PO) q24h *plus* leucovorin 10–25 mg (PO) q24h (2nd choice regimen)<br>**or**<br>Atovaquone 750 mg (PO) q12h ± pyrimethamine 25 mg (PO) q24h *plus* leucovorin 10 mg (PO) q24h (3rd choice regimen) |

**Clinical Presentation:** Wide spectrum of neurologic symptoms, including sensorimotor deficits, seizures, confusion, ataxia. Fever/headache are common.
**Diagnostic Considerations:** Diagnosis by characteristic radiographic appearance and response to empiric therapy in a for T. gondii seropositive patient.
**Pitfalls:** Use leucovorin (folinic acid) 10 mg (PO) daily with pyrimethamine-containing regimens, not folate/folic acid. Radiographic improvement may lag behind clinical response.
**Therapeutic Considerations:** Alternate agents include atovaquone, azithromycin, clarithromycin, minocycline (all with pyrimethamine if possible). Decadron 4 mg (PO or IV) q6h is useful for edema/mass effect. Chronic suppressive therapy can be discontinued if patients are free from signs and symptoms of disease and have a $CD_4$ cell count > 200/mm$^3$ for > 6 months due to ART.
**Prognosis:** Usually responds to treatment if able to tolerate drugs. Clinical response is evident by 1 week in 70%, by 2 weeks in 90%. Radiographic improvement is usually apparent by 2 weeks. Neurologic recovery is variable.

# Gastrointestinal Tract Opportunistic Infections

## Campylobacter (C. jejuni) Enteritis

| Subset | Preferred Therapy |
|---|---|
| Mild disease | Might withhold therapy unless symptoms persist for several days |
| Moderate disease | Ciprofloxacin 500 mg (PO) q12h × 1 week<br>**or**<br>Azithromycin 500 mg (PO) q24h × 1 week |
| Bacteremia | Ciprofloxacin 500 mg (PO) q12h × 2 weeks*<br>**or**<br>Azithromycin 500 mg (PO) q24h × 2 weeks* |

* Consider addition of aminoglycoside in bacteremic patients.

**Clinical Presentation:** Acute onset of diarrhea, sometimes bloody; constitutional symptoms may be prominent.

**Diagnostic Considerations:** Diagnosis by stool culture; bacteremia may rarely occur, so blood cultures also indicated. Suspect campylobacter in AIDS patient with diarrhea and curved gram-negative rods in blood culture. Non-jejuni species may be more strongly correlated with bacteremia.
**Therapeutic Considerations:** Optimal therapy not well defined. Treat with quinolone or azithromycin; modify therapy based on susceptibility testing. Quinolone resistance can occur and correlates with treatment failure. Role of aminoglycoside is unclear.
**Prognosis:** Depends on underlying immune status; prognosis is generally good.

## Clostridium difficile Diarrhea/Colitis

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| C. difficile | Metronidazole 500 mg (PO) q8h × 10–14 days. Avoid use of other C. difficile associated antibiotics if possible. | Vancomycin 125 mg (PO) q6h × 10–14 days. Avoid use of C. difficile associated antibiotics if possible. |

**Clinical Presentation:** Diarrhea and abdominal pain following antibiotic therapy. Diarrhea may be watery or bloody. Proton pump inhibitors increase the risk. Among antibiotics, clindamycin and beta-lactams are most frequent. Rarely due to aminoglycosides, linezolid, doxycycline, TMP–SMX, carbapenems, daptomycin, vancomycin.
**Diagnostic Considerations:** Most common cause of bacterial diarrhea in U.S. among HIV patients. Watery diarrhea with positive C. difficile toxin in stool specimen. C. difficile stool toxin test is sufficiently sensitive/specific. If positive, no need to retest until negative (endpoint is end of diarrhea); if negative, no need to retest (repeat tests will be negative). C. difficile colitis may be distinguished clinically from C. difficile diarrhea by temperature > 102°F, ↑ WBC, ↑ ESR, and/or abdominal pain. C. difficile virulent epidemic strain is type B1 (toxinotype III), which produces 20-times the amount of toxin A/B compared to less virulent strains.
**Pitfalls:** In a patient with C. difficile diarrhea, C. difficile colitis is suggested by the presence of ↑ WBC, ↑ ESR, abdominal pain and temperature > 102°F; confirm diagnosis with CT of abdomen, which will show colonic wall thickening. New virulent strain of C. difficile may present with colitis with temperature ≤ 102°F, little/no ↑ WBC, and little/no abdominal pain; confirm diagnosis with CT/MRI of abdomen. C. difficile toxin may remain positive in stools for weeks following treatment; do not treat positive stool toxin unless patient has symptoms.
**Therapeutic Considerations:** Initiate therapy for mild disease with metronidazole; symptoms usually begin to improve within 2–3 days. For moderate or severe disease, or with evidence of colitis clinically (leukocytosis, fever, colonic thickening on CT scan), vancomycin has become the preferred agent in many centers due to concern for the more virulent strain, and based on the results of some observational studies suggesting vancomycin is more effective. The duration of therapy should be extended beyond 14 days if other systemic antibiotics must be continued. Relapse occurs in 10–25% of patients, and rates may be higher in patients with HIV due to the frequent need for other antimicrobial therapy. First relapses can be treated with a repeat of the initial regimen of metronidazole or vancomycin. For multiple relapses, a long-term taper is appropriate: week 1–125 mg 4x/day; week 2–125 mg 2x/day; week 3–125 mg once daily; week 4–125 mg every other day; weeks 5 and 6–125 mg every three days. Every effort should be made to resume a normal diet and to avoid other antibacterial therapies. Probiotic treatments (such as lactobacillus or Saccharomyces boulardii) have not yet been shown to reduce the risk of relapse in controlled clinical trials.
**Prognosis:** Prognosis with C. difficile colitis is related to severity of the colitis.

## CMV Esophagitis/Colitis

| Infection | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Initial infection | Ganciclovir 5 mg/kg (IV) q12h × 3–4 weeks or until signs and symptoms have resolved.<br>**or**<br>Valganciclovir 900 mg (PO) q12h can be used if able to tolerate oral intake. Maintenance therapy is generally not necessary but should be considered after relapses | Foscarnet 90 mg/kg (IV) q12h × 3–4 weeks or until signs and symptoms have resolved<br>**or**<br>Cidofovir 5 mg/kg (IV) q every other week with saline hydration and probenecid (see CMV retinitis) |
| Relapses | Valganciclovir 900 mg (PO) q24h indefinitely; consider discontinuation if $CD_4 > 200/mm^3$ for ≥ 6 months on ART | |

**Clinical Presentation:** Localizing symptoms, including odynophagia, abdominal pain, diarrhea, sometimes bloody stools.
**Diagnostic Considerations:** Diagnosis by finding CMV inclusions on biopsy. CMV can affect the entire GI tract, resulting in oral/esophageal ulcers, gastritis, and colitis (most common). CMV colitis varies greatly in severity, but typically causes fever, abdominal cramping, and sometimes bloody stools.
**Pitfalls:** CMV colitis may cause colonic perforation and should be considered in any AIDS patient presenting with an acute abdomen, especially if radiography demonstrates free intraperitoneal air.
**Therapeutic Considerations:** Duration of therapy is dependent on clinical response, typically 3–4 weeks. Consider chronic suppressive therapy for recurrent disease. Screen for CMV retinitis.
**Prognosis:** Relapse rate is greatly reduced with immune reconstitution due to antiretroviral therapy.

## Cryptosporidia Enteritis

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Cryptosporidium sp. | Effective ART with immune reconstitution to $CD_4 > 100/mm^3$ can result in complete resolution of symptoms and clearance of infection | Nitazoxanide 500 mg (PO) q12h × 4–6 weeks<br>**or**<br>Paromomycin 1 gm (PO) q12h × 2–4 weeks |

**Clinical Presentation:** High-volume watery diarrhea with weight loss and electrolyte disturbances, especially in advanced HIV disease.
**Diagnostic Considerations:** Spore-forming protozoa. Diagnosis by AFB smear of stool demonstrating characteristic oocyte. Malabsorption may occur.
**Pitfalls:** No fecal leukocytes; organisms are not visualized on standard ova and parasite exams (need to request special stains).
**Therapeutic Considerations:** Anecdotal reports of antimicrobial success. Newest agent nitazoxanide may be effective in some settings, but no increase in cure rate for nitazoxanide if $CD_4 < 50/mm^3$. Immune reconstitution in response to antiretroviral therapy is the most effective therapy, and may induce prolonged remissions and cure. Anti-diarrheal agents (Lomotil, Pepto-Bismol) are useful to control symptoms. Hyperalimentation may be required for severe cases.
**Prognosis:** Related to degree of immunosuppression/response to antiretroviral therapy.

## Isospora (Isospora belli) Enteritis

| Subset | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Acute infection | TMP 160 mg and SMX 800 mg (IV or PO) q6h × 10 days<br>**or**<br>TMP 320 mg and SMX 1600 mg (IV or PO) q12h × 10–14 days | Pyrimethamine 50–75 mg (PO) q24h *plus* leucovorin 5–10 mg (PO) q24h<br>**or**<br>Ciprofloxacin 500 mg (PO) q12h or other fluoroquinolones |
| Chronic maintenance therapy for $CD_4 < 200$ (secondary prophylaxis) | TMP 320 mg *plus* SMX 1600 mg (PO) q24h* | Pyrimethamine 25 mg (PO) q24h *plus* leucovorin 5–10 mg (PO) q24h* |

* Discontinuation of secondary prophylaxis may be considered if $CD_4 > 200/mm^3$ for > 3 months.

**Clinical Presentation:** Severe chronic diarrhea without fever/fecal leukocytes.
**Diagnostic Considerations:** Spore-forming protozoa (Isospora belli). Oocyst on AFB smear of stool larger that cryptosporidium (20–30 microns vs. 4–6 microns). More common in HIV patients from the tropics (e.g., Haiti). Less common than cryptosporidium or microsporidia. Malabsorption may occur.
**Pitfalls:** Multiple relapses are possible.
**Therapeutic Considerations:** Chronic suppressive therapy may be required if $CD_4$ does not increase.
**Prognosis:** Related to degree of immunosuppression/response to antiretroviral therapy.
**Comments:** Immune reconstitution with ART results in fewer relapses.

## Microsporidia Enteritis

| Pathogen | Therapy* |
|---|---|
| Microsporidia other than Enterocytozoon bienuesi | Albendazole 400 mg (PO) q12h (continue until $CD_4 > 200/mm^3$) |
| Enterocytozoon bienuesi | Nitazoxanide 1 gm (PO) q12h × 60 days<br>**or**<br>Fumagillin 60 mg (PO) q24h (not available in the U.S.) |
| Trachipleistophora or Brachiola | Itraconazole 400 mg (PO) q24h plus albendazole 400 mg (PO) q12h |

* Regardless of species, ART with immune reconstitution is a critical component of treatment.

**Clinical Presentation:** Intermittent chronic diarrhea without fever/fecal leukocytes.
**Diagnostic Considerations:** Spore-forming protozoa (S. intestinalis, E. bieneusi). Diagnosis by modified trichrome or fluorescent antibody stain of stool. Microsporidia can rarely disseminate to sinuses/cornea. Severe malabsorption may occur.
**Pitfalls:** Microsporidia is too small for detection by routine microscopic examination of stool.
**Therapeutic Considerations:** Albendazole is less effective for E. bieneusi than S. intestinalis, but speciation is usually not possible. May consider treatment discontinuation for $CD_4 < 200/mm^3$ if patient remains asymptomatic (no signs or symptoms of microsporidiosis). If ocular infection is present, continue treatment indefinitely.
**Prognosis:** Related to degree of immunosuppression/response to antiretroviral therapy.

## Oropharyngeal/Esophageal Candidiasis

| Infection | Therapy | Fluconazole-Resistance |
|---|---|---|
| Oropharyngeal candidiasis (thrush) | Preferred therapy<br>Fluconazole 100 mg (PO) q24h × 1–2 weeks<br><br>Alternate therapy<br>Itraconazole oral solution 200 mg (PO) q24h × 1–2 weeks **or** Clotrimazole troches 10 mg (PO) 5x/day × 1–2 weeks **or** nystatin suspension 4–6 mL q6h or 1–2 flavored pastilles 4–5x/day × 1–2 weeks | Fluconazole at doses up to 800 mg (PO) q24h × 1–2 weeks<br>**or**<br>Caspofungin 70 mg (IV) on day 1, then 50 mg (IV) q24h × 1–2 weeks<br>**or**<br>Micafugin 150 mg (IV) q24h × 1–2 weeks |
| Esophageal candidiasis | Preferred therapy<br>Fluconazole 100 mg (up to 400 mg) (IV or PO) q24h × 1–2 weeks<br><br>Alternate therapy<br>Itraconazole oral solution 200 mg (PO) q24h × 2–3 weeks **or** Voriconazole 200 mg (PO) q24h × 2–3 weeks **or** Caspofungin 50 mg (IV) q24h × 2–3 weeks | Amphotericin B 0.3 mg/kg (IV) q24h × 1–2 weeks<br>**or**<br>Lipid amphotericin 3–5 mg/kg (IV) q24h × 1–2 weeks |

### Oral Thrush (Candida)

**Clinical Presentation:** Dysphagia/odynophagia. More common/severe in advanced HIV disease.
**Diagnostic Considerations:** Pseudomembranous (most common), erythematous, and hyperplastic (leukoplakia) forms. Pseudomembranes (white plaques on inflamed base) on buccal muscosa/tongue/gingiva/palate scrape off easily, hyperplastic lesions do not. Diagnosis by clinical appearance ± KOH/gram stain of scraping showing yeast/pseudomycelia. Other oral lesions in AIDS patients include herpes simplex, aphthous ulcers, Kaposi's sarcoma, oral hairy leukoplakia.
**Pitfalls:** Patients may be asymptomatic.
**Therapeutic Considerations:** Fluconazole is superior to topical therapy in preventing relapses of thrush and treating Candida esophagitis. Continuous treatment with fluconazole may lead to fluconazole-resistance, which is best treated initially with itraconazole suspension and, if no response, with IV caspofungin or amphotericin. Chronic suppressive therapy is usually only considered for severely immunosuppressed patients.
**Prognosis:** Improvement in symptoms are often seen within 24–48 hours.

### Candida Esophagitis

**Clinical Presentation:** Dysphagia/odynophagia, almost always in the setting of oropharyngeal thrush. Fever is uncommon.
**Diagnostic Considerations:** Most common cause of esophagitis in HIV disease. For persistent symptoms despite therapy, endoscopy with biopsy/culture is recommended to confirm diagnosis and assess azole-resistance.

**Pitfalls:** May extend into stomach. Other common causes of esophagitis include CMV, herpes simplex, and aphthous ulcers. Rarely, Kaposi's sarcoma, non-Hodgkin's lymphoma, zidovudine, dideoxycytidine, and other infections may cause esophageal symptoms.
**Therapeutic Considerations:** Systemic therapy is preferred over topical therapy. Failure to improve on empiric therapy mandates endoscopy to look for other causes, especially herpes viruses/aphthous ulcers. Consider maintenance therapy with fluconazole for frequent relapses, although the risk of fluconazole resistance is increased. Fluconazole-resistance is best treated initially with itraconazole suspension and, if no response, with IV caspofungin, micafungin, or amphotericin.
**Prognosis:** Relapse rate related to degree of immunosuppression.

## Salmonella Gastroenteritis (non-S. typhi)

| Subset | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Mild disease | Ciprofloxacin 750 mg (PO) q12h × 1–2 weeks | TMP–SMX 1 DS (PO) q12h × 2 weeks **or** Ceftriaxone 2 gm (IV) q24h × 2 weeks **or** Cefotaxime 1 gm (IV) q8h × 2 weeks |
| $CD_4 < 200$ | Ciprofloxacin 750 mg (PO) q12h × 4–6 weeks | |
| Bacteremia | Ciprofloxacin 750 mg (PO) q12h × 4–6 weeks, then 500 mg (PO) q12h indefinitely | |

**Clinical Presentation:** Patients with HIV are at markedly increased risk of developing salmonellosis. Three different presentations may be seen: (1) self-limited gastroenteritis, as typically seen in immunocompetent hosts; (2) a more severe and prolonged diarrheal disease, associated with fever, bloody diarrhea, and weight loss; or (3) Salmonella septicemia, which may present with or without gastrointestinal symptoms.
**Diagnostic Considerations:** The diagnosis is established through cultures of stool and blood. Given the high rate of bacteremia associated with Salmonella gastroenteritis—especially in advanced HIV disease—blood cultures should be obtained in any HIV patient presenting with diarrhea and fever.
**Pitfalls:** A distinctive feature of salmonella bacteremia in patients with AIDS is its propensity for relapse (rate > 20%).
**Therapeutic Considerations:** The mainstay of treatment is a fluoroquinolone; greatest experience is with ciprofloxacin, but newer quinolones (moxifloxacin, levofloxacin) may also be effective. For uncomplicated salmonellosis in an HIV patient with $CD_4 > 200/mm^3$, 1–2 weeks of treatment is reasonable to reduce the risk of extraintestinal spread. For patients with advanced HIV disease ($CD_4 < 200/mm^3$) or who have salmonella bacteremia, at least 4–6 weeks of treatment is required. Chronic suppressive therapy, given for several months or until antiretroviral therapy-induced immune reconstitution ensues, is indicated for patients who relapse after cessation of therapy. Consider using ZDV as part of the antiretroviral regimen (ZDV is active against Salmonella).
**Prognosis:** Usually responds well to treatment. Relapse rate in AIDS patients with bacteremia is > 20%.

## Shigella (Shigella sp.) Enteritis

| Subset | Preferred Therapy | Alternate Therapy |
|---|---|---|
| No bacteremia | Fluoroquinolone (IV or PO) × 3–7 days | TMP–SMX 1 DS tablet (PO) q12h × 3–7 days<br>**or**<br>Azithromycin 500 mg (PO) on day 1, then 250 mg (PO) q24h × 4 days |
| Bacteremia | Extend treatment duration to 14 days | Extend treatment duration to 14 days |

**Clinical Presentation:** Acute onset of bloody diarrhea/mucus.
**Diagnostic Considerations:** Diagnosis by demonstrating organism in stool specimens**.** Shigella ulcers in colon are linear, serpiginous, and rarely lead to perforation. More common in gay men.
**Therapeutic Considerations:** Shigella dysentery is more acute/fulminating than amebic dysentery. Shigella has no carrier state, unlike Entamoeba. Shigella infections acquired outside of United States have high rates of TMP–SMX resistance. Therapy is indicated to shorten the duration of illness and to prevent spread of infection. Shigella has no carrier state.
**Prognosis:** Good if treated early. Severity of illness related to Shigella species: S. dysenteriae (most severe) > S. flexneri > S. boydii/S. sonnei (mildest).

### TREATMENT OF OTHER OPPORTUNISTIC INFECTIONS IN HIV

## Candida Vaginitis

| Pathogen | Therapy |
|---|---|
| Candida albicans | Intravaginal miconazole suppository 200 mg q24h × 3 days or miconazole 3% × 7 days **or** Nystatin vaginal tablet 100,000U q24h × 14 days **or** Itraconazole 200 mg (PO) q12h × 1 day (or 200 mg q24h × 3 days) **or** Fluconazole 150 mg (PO) × 1 dose |

**Clinical Presentation:** White, cheesy, vaginal discharge or vulvar rash ± itching/pain. Local infection not a sign of disseminated disease.
**Diagnostic Considerations:** Local infection. Not a manifestation of disseminated disease.
**Pitfalls:** Women with advanced AIDS receiving fluconazole may develop fluconazole-resistant Candida.
**Therapeutic Considerations:** For recurrence, consider maintenance with fluconazole 100–200 mg (PO) weekly.
**Prognosis:** Good response to therapy. Relapses are common.

## Coccidioidomycosis (C. immitis) Infection

| Infection | Therapy* |
|---|---|
| Non-meningeal infection | Acute therapy (diffuse pulmonary or disseminated disease)<br>Amphotericin B 0.5–1.0 mg/kg (IV) q24h until clinical improvement (usually 500–1000 mg total dose). Some specialists add an azole to amphotericin B therapy<br><br>Acute therapy (milder disease)<br>Fluconazole 400–800 mg (PO) q24h or Itraconazole 200 mg (PO) q12h<br>Chronic maintenance therapy (secondary prophylaxis)<br>Preferred: Fluconazole 400 mg (PO) q24h indefinitely; alternative: or Itraconazole 200 mg capsule (PO) q12h indefinitely |
| Meningeal infection* | Acute therapy<br>Fluconazole 400–800 mg (IV) or (PO) q24h. Intrathecal amphotericin B if no response to azole therapy<br><br>Chronic maintenance therapy (secondary prophylaxis)<br>Fluconazole 400 mg (PO) q24h or itraconazole 200 mg capsule (PO) q12h indefinitely |

* Therapy for meningeal infection should be lifelong with fluconazole 400–800 mg q24h. There are insufficient data to recommend discontinuation of chronic maintenance therapy in other settings.

**Clinical Presentation:** Typically a complication of advanced HIV infection ($CD_4$ cell count < 200/mm$^3$). Most patients present with disseminated disease, which can manifest as fever, diffuse pulmonary infiltrates, adenopathy, skin lesions (multiple forms – verrucous, cold abscesses, ulcers, nodules), and/or bone lesions. Approximately 10% will have spread to the CNS in the form of meningitis (fever, headache, altered mental status).

**Diagnostic Considerations:** Consider the diagnosis in any patient with advanced HIV-related immunosuppression who has been in a C. immitis endemic area (Southwestern US, northern Mexico) and presents with a systemic febrile syndrome. Diagnosis can be made by culture of the organism, visualization of characteristic spherules on histopathology, or a positive complement-fixation antibody (≥ 1:16). In meningeal cases, CSF profile shows low glucose, high protein, and lymphocytic pleocytosis.

**Pitfalls:** Antibody titers often negative on presentation. CSF profile of meningitis can be similar to TB.

**Prognosis:** Related to extent of infection and degree of immunosuppression. Clinical response tends to be slow, especially with a high disease burden and advanced HIV disease. Meningeal disease is treated life-long regardless of $CD_4$ recovery.

## Extrapulmonary Tuberculosis

| Pathogen | Therapy |
|---|---|
| Mycobacterium tuberculosis | Treat the same as pulmonary TB (see p. 326). May require longer duration of therapy based on clinical response |

**Clinical Presentation:** Multiple presentations possible (e.g., lymphadenitis, osteomyelitis, meningitis, hepatitis). Dissemination is more common in patients with low $CD_4$ cell counts (< 100/mm$^3$).

**Diagnostic Considerations:** Diagnosis by isolator blood cultures or tissue biopsy.
**Pitfalls:** Patients with disseminated disease frequently have pulmonary disease, which has implications for infection control.
**Therapeutic Considerations:** Response to therapy may be slower than in normal hosts.
**Prognosis:** Usually responsive to therapy.

## Herpes Simplex Virus (HSV) Disease

| Infection | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Orolabial lesions or initial/recurrent genital HSV | Famciclovir 500 mg (PO) q12h × 1–2 weeks **or** valacyclovir 1 gm (PO) q12h × 1–2 weeks **or** acyclovir 400 mg (PO) q8h × 1–2 weeks | Acyclovir-resistant HSV<br>Foscarnet 60–100 mg/kg (IV) q12h until clinical response<br>**or**<br>Cidofovir 5 mg/kg (IV) weekly until clinical response |
| Moderate-to-severe mucocutaneous HSV | Initial therapy: Acyclovir 5 mg/kg (IV) q8h × 2–7 days. If improvement, switch to famciclovir 500 mg (PO) q12h **or** valacyclovir 1 gm (PO) q12h **or** acyclovir 400 mg (PO) q8h to complete 7–10 days | Acyclovir-resistant HSV<br>Foscarnet 60–100 mg/kg (IV) q12h until clinical response<br>**or**<br>Cidofovir 5 mg/kg (IV) weekly until clinical response |
| HSV keratitis | Trifluridine 1% ophthalmic solution, one drop onto cornea q2h, not to exceed 9 drops per day and no longer than 21 days. Treatment in conjunction with ophthalmology consultation | Acyclovir-resistant HSV<br>Foscarnet 60–100 mg/kg (IV) q12h until clinical response<br>**or**<br>Cidofovir 5 mg/kg (IV) weekly until clinical response |
| HSV encephalitis | Acyclovir 10 mg/kg (IV) q8h × 2–3 weeks<br>**or**<br>Valacyclovir 1 gm (PO) q6h × 2–3 weeks | Acyclovir-resistant HSV<br>Foscarnet 60–100 mg/kg (IV) q12h until clinical response **or** Cidofovir 5 mg/kg (IV) weekly until response |
| Multiple mucocutaneous (oral or anogenital) relapses (chronic suppressive therapy) | Acyclovir 400 mg (PO) q12h<br>**or**<br>Famciclovir 250 mg (PO) q12h<br>**or**<br>Valacyclovir 500 mg (PO) q12h | Patients may be able to titrate dose downward to maintain response |

### Herpes Simplex (genital/oral)

**Clinical Presentation:** Painful, grouped vesicles on an erythematous base that rupture, crust, and heal within 2 weeks. Lesions may be chronic, severe, ulcerative with advanced immunosuppression.
**Diagnostic Considerations:** Diagnosis by viral culture of swab from lesion base/roof of blister; alternative diagnostic techniques include Tzanck prep or immunofluorescence staining.

**Pitfalls:** Acyclovir prophylaxis is not required in patients receiving ganciclovir or foscarnet.
**Therapeutic Considerations:** In refractory cases, consider acyclovir resistance and treat with foscarnet. Topical trifluridine ophthalmic solution (Viroptic 1%) may be considered for direct application to small, localized areas of refractory disease; clean with hydrogen peroxide, then debride lightly with gauze, apply trifluridine, and cover with bacitracin/polymyxin ointment and nonadsorbent gauze; topical cidofovir (requires compounding) also may be tried. Chronic suppressive therapy with oral acyclovir, famciclovir, or valacyclovir may be indicated for patients with frequent recurrences, dosing similar to HIV-negative patients.
**Prognosis:** Responds well to treatment except in severely immunocompromised patients, in whom acyclovir resistance may develop. Prognosis for HSV meningitis is excellent.

### Herpes Encephalitis (HSV-1)

**Clinical Presentation:** Acute onset of fever and change in mental status.
**Diagnostic Considerations:** EEG is abnormal early (< 72 hours), showing unilateral temporal lobe abnormalities. Brain MRI is abnormal before CT scan, which may require several days before a temporal lobe focus is seen. Definitive diagnosis is by CSF PCR for HSV-1 DNA. Profound decrease in sensorium is characteristic of HSV meningoencephalitis. CSF may have PMN predominance and low glucose levels, unlike other viral causes of meningitis. A different clinical entity is HSV meningitis, which is usually associated with HSV-2 and can recur with lymphocytic meningitis.
**Pitfalls:** Rule out noninfectious causes of encephalopathy. Surprisingly, HIV encephalitis is a relatively rare cause of encephalitis in patients with HIV.
**Therapeutic Considerations:** Treat as soon as possible since neurological deficits may be mild and reversible early on, but severe and irreversible later.
**Prognosis:** Related to extent of brain injury and early antiviral therapy. Prognosis for HSV meningitis is excellent.

## Histoplasmosis (H. capsulatum), Disseminated

| Subset | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Acute phase (3–10 days or until clinically improved) | Liposomal amphotericin B 3 mg/kg × 1–2 weeks or other lipid associated formulations at 5 mg/kg | Amphotericin B doxycholate 0.7–1 mg/kg **or** Intravenous itraconazole (200 mg q12 × 4 doses then 200 mg q24) |
| Continuation phase | Itraconazole 200 (PO) TID × 3 days and then QD or BID for atleast 12 months (adequate serum levels should be confirmed). Immunosuppressed patients may require lifelong suppressive therapy. | Itraconazole oral solution 200 mg (PO) q12h × 12 weeks **or** Fluconazole 800 mg (PO) q24h × 12 weeks |
| Meningitis | Amphotericin B deoxycholate 0.7 mg/kg (IV) q24h × 12–16 weeks **or** Liposomal amphotericin B 4 mg/kg (IV) q24h × 12–16 weeks | Fluconazole 800 mg (PO) q24h × 12 weeks |

* Duration of therapy dependent on response to therapy.

**Clinical Presentation:** Two general forms: Mild disease with fever/lymph node enlargement (e.g., cervical adenitis), or severe disease with fever, wasting ± diarrhea/meningitis/GI ulcerations.
**Diagnostic Considerations:** Diagnosis by urine/serum histoplasmosis antigen, sometimes by culture of bone marrow/liver or isolator blood cultures. May occur in patients months to years after having lived/moved from an endemic area.
**Pitfalls:** Relapse is common after discontinuation of therapy. Cultures may take 7–21 days to turn positive.
**Therapeutic Considerations:** Initial therapy depends on severity of illness on presentation. Extremely sick patients should be started on amphotericin B deoxycholate, with duration of IV therapy dependent on response to treatment. Mildly ill patients can be started on itraconazole. All patients require chronic suppressive therapy, with possible discontinuation for immune reconstitution with $CD_4$ counts > 100/$mm^3$ for at least 6 months. HIV patients with $CD_4$ > 500/$mm^3$ and acute pulmonary histoplasmosis might not require therapy, but a short course of itraconazole (4–8 weeks) is reasonable to prevent systemic spread.
**Prognosis:** Usually responds to treatment, except in fulminant cases.

## Mycobacterium avium-intracellulare (MAI)

| Pathogen | Preferred Therapy | Alternate Therapy |
|---|---|---|
| Mycobacterium avium-intracellulare (MAI) | At least 2 drugs as initial therapy<br>Clarithromycin 500 mg (PO) q12h plus ethambutol 15 mg/kg (PO) q24h (usually 800 mg or 1200 mg daily). Consider adding third drug, rifabutin 300 mg (PO) q24h, for patients with $CD_4$ < 50/$mm^3$, high mycobacterial loads and severely symptomatic disease. Duration of therapy is **lifelong**, although consider discontinuation in asymptomatic patients with > 12 months therapy and $CD_4$ > 100/$mm^3$ for > 6 months in response to ART | Alternative to clarithromycin<br>Azithromycin 500–600 mg (PO) q24h<br><br>Alternative 3rd or 4th drug for severe symptoms or disseminated disease<br>Ciprofloxacin 500–750 mg (PO) q12h<br>**or**<br>Levofloxacin 500 mg (PO) q24h<br>**or**<br>Amikacin 10–15 mg/kg (IV) q24h |

**Clinical Presentation:** Typically presents as a febrile wasting illness in advanced HIV disease ($CD_4$ < 50/$mm^3$). Focal invasive disease is possible, especially in patients with advanced immunosuppression after starting antiretroviral therapy. Focal disease likely reflects restoration of pathogen-specific immune response to subclinical infection ("immune reconstitution inflammatory syndrome" [IRIS]), and typically manifests as lymphadenitis (mesenteric, cervical, thoracic) or rarely disease in the spine mimicking Pott's disease. Immune reconstitution syndrome usually occurs within weeks to months after starting antiretroviral therapy for the first time, but may occur a year or more later.
**Diagnostic Considerations:** Diagnosis by isolation of organism from a normally sterile body site (blood, lymph node, bone marrow, liver biopsy). Lysis centrifugation (DuPont Isolator) is the preferred blood culture method. Anemia/↑ alkaline phosphatase are occasionally seen.

**Pitfalls:** Isolator blood cultures may be negative, especially in immune reconstitution inflammatory syndrome initially.
**Therapeutic Considerations:** Some studies suggest benefit for addition of rifabutin 300 mg (PO) q24h, others do not. Rifabutin may require dosage adjustment with NNRTI's and PI's. For concurrent use with nelfinavir, indinavir, or amprenavir, decrease rifabutin to 150 mg (PO) q24h. For concurrent use with ritonavir, decrease rifabutin to 150 mg (PO) 2–3x/week. For concurrent use with efavirenz, increase rifabutin to 450–600 mg (PO) q24h. The dose of PI's or NNRTI's may need to be increased by 20–25%. Monitor carefully for rifabutin drug toxicity (arthralgias, uveitis, leukopenia). Treat IRIS initially with NSAIDs; if symptoms persist, systemic corticosteroids (prednisone 20–40 mg daily) for 4–8 weeks can be used. Some patients will require a more prolonged course of corticosteroids with a slow taper over months. Azithromycin is often better tolerated than clarithromycin and has fewer drug-drug interactions. Optimal long-term management is unknown, though most studies suggest that treatment can be discontinued in asymptomatic patients with > 12 months of therapy and $CD_4$ > 100/$mm^3$ for > 6 months.
**Prognosis:** Depends on immune reconstitution in response to antiretroviral therapy. Adverse prognostic factors include high-grade bacteremia or severe wasting.

## Varicella Zoster Virus (VZV)

| Infection | Preferred Therapy |
|---|---|
| Primary VZV infection (chickenpox) | Acyclovir 10 mg/kg (IV) q8h × 7–10 days. Can start with or change to oral therapy with Valacyclovir 1 gm (PO) q8h or Famciclovir 500 mg (PO) q8h after defervescence if no evidence of visceral involvement exists |
| Local dermatomal herpes zoster | Famciclovir 500 mg (PO) q8h × 7–10 days **or** Valacyclovir 1 gm (PO) q8h × 7–10 days |
| Extensive cutaneous or visceral involvement | Acyclovir 10 mg/kg (IV) q8h until cutaneous and visceral disease has clearly resolved and the patient is clinically improved |
| Acute retinal necrosis | Acyclovir 10 mg/kg (IV) q8h until progression stops, then Valacyclovir 1 gm (PO) q8h × 6 weeks. Treat in conjunction with close ophthalmologic consultation |

**Clinical Presentation:** Primary varicella (chickenpox) presents as clear vesicles on an erythematous base that heal with crusting and sometimes scarring. Zoster usually presents as painful tense vesicles on an erythematous base in a dermatomal distribution. In patients with HIV, primary varicella is more severe/prolonged, and zoster is more likely to involve multiple dermatomes/disseminate. VZV can rarely cause acute retinal necrosis, which requires close consultation with ophthalmology.
**Diagnostic Considerations:** Diagnosis is usually clinical. In atypical cases, immunofluorescence can be used to distinguish herpes zoster from herpes simplex.
**Pitfalls:** Extend treatment beyond 7–10 days if new vesicles are still forming after initial treatment period. Corticosteroids for dermatomal zoster are not recommended in HIV-positive patients.
**Therapeutic Considerations:** IV therapy is generally indicated for severe disease/cranial nerve zoster.
**Prognosis:** Usually responds slowly to treatment.

## Hepatitis B Virus (HBV)

| Preferred Therapy, Duration of Therapy, Chronic Maintenance | Alternate Therapy | Other Options/Issues |
|---|---|---|
| Therapy for patients who require ART<br>Patients should be treated with agents active against both HIV and HBV or with agents with independent activity against each virus | Treatment for patients who do not require ART<br>Use agents with sole activity against HBV and with the least potential of selecting HIV resistance mutations | Emtricitabine, entecavir, lamivudine, or tenofovir should not be used for the treatment of HBV infection in patients who are not receiving combination ART |
| Consider tenofovir + emtricitabine as part of HIV and HBV regimen | Consider early initiation of ART, especially for patients with high HBV DNA *For patients with $CD_4$+ count > 350 cells/μL, HBeAg (-), HBV DNA > 2,000 IU/mL (> 20,000 copies/mL)* Adefovir 10 mg PO daily | Among patients coinfected with HIV, HBV, and HCV, consideration of starting ART should be the first priority. If ART is not required, an interferon-based regimen, which suppresses both HCV & HBV, should be considered |
| *Lamivudine or emtricitabine-naïve patients*<br>[Lamivudine 150 mg PO BID (or 300 mg PO daily) or emtricitabine 200 mg PO daily] + tenofovir (TDF) 300 mg PO daily (+ additional agent[s] active against HIV) | | If IFN-based treatment for HCV has failed, treatment of chronic HBV with nucleoside or nucleotide analogs is recommended |
| *Lamivudine or emtricitabine-experienced patients with detectable HBV DNA (assume lamivudine-resistance)*<br>*If not on TDF*: Add TDF 300 mg PO daily as part of an ART regimen + lamivudine or emtricitabine;<br>**or**<br>Adefovir 10 mg PO daily + lamivudine or emtricitabine + other combination ART;<br>**or** | *For patients with $CD_4$+ count > 350 cells/μL, HBeAg (+), HBV DNA > 20,000 IU/mL (> 200,000 copies/mL), and elevated ALT* | Cross-resistance to emtricitabine or telbivudine should be assumed in patients with suspected or proven 3TC resistance<br>When changing ART regimens, continue agents with anti-HBV activity because of the risk of IRIS |

## Hepatitis B Virus (HBV) (cont'd)

| Preferred Therapy, Duration of Therapy, Chronic Maintenance | Alternate Therapy | Other Options/Issues |
|---|---|---|
| Entecavir 1 mg PO daily can be considered in patients with complete HIV suppression (while on ART) who do not demonstrate YMDD (M204V/I) motif mutations in HBV DNA<br><br>Duration of therapy: Because of the high rates of relapse, certain specialists recommend continuing therapy indefinitely | Peginterferon alfa-2a 180 $\mu$g SQ weekly x 48 weeks—with careful follow-up of HBeAg conversion | If anti-HBV therapy is discontinued and a flare occurs, therapy should be reinstituted, as it can be potentially life saving |

Adapted from: Sax PE, Cohen CJ, Kuritzkes DR. HIV Essentials, 7th edition. Jones & Bartlett, Sudbury, MA, 2014.

**Epidemiology:** Hepatitis B virus (HBV) infection is relatively common in patients with HIV, with approximately 60% showing some evidence of prior exposure. Chronic hepatitis B infection interacts with HIV infection in several important ways:

- HBV increases the risk of liver-related death and hepatotoxicity from antiretroviral therapy
- 3TC, FTC, and tenofovir each have anti-HBV activity. Thus selection of antiretroviral therapy for patients with HBV can have clinical and resistance implications for HBV as well as HIV. This is most notable with 3TC and FTC, as a high proportion of coinfected patients will develop HBV-associated resistance to these drugs after several years of therapy. This resistance reduces response to subsequent non-3TC or FTC anti-HBV therapy.
- Cessation of anti-HBV therapy may lead to exacerbations of underlying liver disease; in some cases, these flares have been fatal.
- Immune reconstitution may lead to worsening of liver status, presumably because HBV disease is immune mediated. This is sometimes associated with loss of HBEAg.
- Entecavir can no longer be recommended for HIV/HBV coinfected patients, as it has anti-HIV activity and may select for HIV resistance mutation M184V. If needed, it should be used only with a fully suppressive HIV regimen.

**Diagnostic Consideration:** Obtain HBSAb, HBSAg, and HBCAb at baseline in all patients. If negative, hepatitis B vaccination is indicated. If chronic HBV infection (positive HBSAg) is identified, obtain HBEAg, HBEAb, and HBV DNA levels. As with HCV infection, vaccination with hepatitis A vaccine and counseling to avoid alcohol are important components of preventive care. Isolated Hepatitis B Core Antibody: Many patients with HIV have antibody to hepatitis B core (anti-HBc) but are negative for both HBSAg and HBSAb. This phenomenon appears to be more common in those with HCV coinfection (Clin Infec Dis 2003 36:1602–6). In this scenario, diagnostic considerations include: (1) recently acquired HBV, before development of HBSAb; (2) chronic HBV, with HBSAg below the levels of detection; (3) immunity to HBV, with HBSAb below the levels of detection; (4) false-positive anti-HBV core. As the incidence of HBV is relatively low in most populations and anti-HBc alone is usually a stable phenomenon over years, recent acquisition of HBV is rarely the explanation. We recommend checking HBV DNA in this situation:

If positive, this indicates chronic HBV; if negative, then low-level immunity or false-positive anti-HBV core remain as possible explanations; since distinguishing between these possibilities cannot be done, we recommend immunization with the hepatitis B vaccine series. It is useful to measure HBV serologic markers periodically in this population, as improvement in immune status due to ART may lead to increasing titers of HBSAb and subsequently confirm immunity.

**Therapeutic Considerations:** The optimal treatment for HBV infection is in evolution. Current guidelines suggest treatment of HBV in all patients with active HBV replication, defined as a detectable HBEAg or HBV DNA. Pending long-term studies defining optimal management, the recommendations set forth in the grid above are reasonable. Patients being treated with regimens for HBV should be monitored for ALT every 3–4 months. HBV DNA levels provide a good marker for efficacy of therapy and should be added to regular laboratory monitoring. The goal of therapy is to reduce HBV DNA to as low a level as possible, preferably below the limits of detection. The duration of HBV therapy is not well established; with development of HBEAb, while some individuals without HIV can stop therapy after reversion of HBEAg to negative, there are no clear stopping rules for HIV-coinfected patients.

## Hepatitis C Virus (HCV)

| Subset | Pathogens | Therapy |
|---|---|---|
| | HIV | **Genotype 1 (includes 1a & 1b)**<br>Preferred therapies:<br>Ledipasvir[6] 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg (PO) q24h + dasabuvir[7] 250 mg (Viekira Pak) (PO) q12h + ribavirin[1,2] x weeks[3]<br>Sofosbuvir 400 mg (Savaidi) (PO) q24h + Simeprevir[4,8] 150 mg (Olysio) (PO) q24h ± ribavirin[1] x weeks[3] |
| | | **Genotype 2**<br>Preferred therapy:<br>Sofosbuvir 400 mg (Savaidi) (PO) q24h + ribavirin[1] x 12 weeks (16 weeks in cirrhosis) |
| | | **Genotype 3**<br>Preferred therapies:<br>Sofosbuvir 400 mg (Savaidi) (PO) q24h + ribavirin[1] x 24 weeks<br>Alternate therapy:<br>Sofosbuvir 400 mg (Savaidi) (PO) q24h + pegylated IFN alfa-2a/2b[5] ribavirin[1] x 12 weeks |
| | | **Genotype 4**<br>Preferred therapies:<br>Ledipasvir[6] 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg (Viekira Pak minus dasabuvir) (PO) q24h + ribavirin[1] x 12 weeks<br>Sofosbuvir 400 mg (Sovaidi) (PO) q24h + ribavirin[1] x 24 weeks<br>Alternative therapies:<br>Sofosbuvir 400 mg (Sovaidi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirin[1] x 12 weeks<br>Sofosbuvir 400 mg (Sovaidi) (PO) q24h + simeprevir[8] 150 mg (Olysio) (PO) q24h ± ribavirin[1] x 12 weeks |

## Hepatitis C Virus (HCV) (cont'd)

| Subset | Pathogens | Therapy |
|---|---|---|
| | | **Genotype 5**<br>Preferred therapy:<br>Sofosbuvir 400 mg (Sovaidi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirin[1] x 12 weeks<br>Alternate therapy:<br>Pegylated IFN alfa-2a/2b[5] + ribavirini x 48 weeks |
| | | **Genotype 6**<br>Preferred therapy:<br>Ledipasvir[6] 90 mg/sofosbuvir 400 mg (Harvoni) (PO) q24h x 12 weeks<br>Alternate therapy:<br>Sofosbuvir 400 mg (Sovaidi) (PO) q24h + pegylated IFN alfa-2a/2b[5] + ribavirini x 12 weeks |

[1]Ribavirin should be dosed as following:

Weight < 75 kg: RibavirIn 1000 mg (PO) daily in 2 divided doses (400 mg in AM, 600 mg in PM)

Weight > 75 kg: Ribavirin 1200 mg (PO) daily in 2 divided doses (600 mg q12h)

[2]In Genotype 1b, ribavirin is only indicated in cirrhosis

[3]12 week therapy without cirrhosis; 24 week therapy with cirrhosis

[4]Simperevir may be ineffective in patients with HCV genotype 1a Q80K polymorphism

[5]Pegylated IFN alfa-2a should be dosed 180 µg (SC) weekly. Pegylated IFN alfa-2b should be dosed 1.5 µg/kg (SC) weekly. Both types of pegylated IFN alfa are approved to treat genotype 1

[6]Ledlpasvir increases tenofovir levels, increasing risk of nephrotoxicity; avoid combination when CrCl < 60 ml/min. Avoid combination with ritonavir-boosted regimens due to potentiation of this effect, unless regimen cannot be changed. Monitor for tenofovir nephrotoxicity.

[7]Due to concerns for significant interactions, parftaprevir/ritonavir/ombitasvir/dasabuvir, should only be co-administered with the following: raitegravir, dolutegravir, enfuviritide, tenofovir, emtricitabine, lamivudine, and atazanavir. The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir/dasabuvir & then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination.

[8]Due to concerns for significant interactions, simeprevir should only be co-administered with the following: raitegravir, dolutegravir, rilpivire, maraviroc, enfuviritide, tenofovir, emtricitbine, lamivudine and abacavir.

Due to concerns for significant drug interactions, the following combinations are NOT recommended:

Ledipasvir/sofosbuvir and cobicistat & elvitegravir; sofosbuvir or ledipasvir/sofosbubvir with tipranavir; paritaprevir/ritonavir/ombitasvir/dasabuvir and efavirenz, rilpivirine, darunavir or ritonavir-boosted lopinavir; simeprevir and efavirenz, etravirine, nevirapine, cobicistat or any HIV protease inhibitors; ribavirin and didanosine, stavudine or zidovudine.

For patients with CD4 count < 200 cells/µl, Initiation of ART may be considered before HCV treatment.

Adapted from: American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. 2014.

**Epidemiology:** Hepatitis C virus (HCV) infection is transmitted primarily through blood exposure; sexual and perinatal transmission are also possible but less efficient. A notable exception is sexually transmitted HCV among gay men. Since modes of transmission of HIV and HCV are similar, there are high rates of HCV coinfection in HIV—an estimated 16% of HIV patients overall, including 80% or more of IDUs and 5–10% of gay men. Genotype 1 accounts for 75% of HCV in the United States. HIV accelerates the progression of chronic HCV infection to cirrhosis, liver failure, and hepatocellular carcinoma. Data are conflicting regarding the independent effect of HCV on HIV disease progression, but several studies have shown a markedly higher rate of antiretroviral therapy-induced hepatotoxicity in those with chronic HCV. In some series, liver failure from HCV is one of the leading causes of death in HIV/HCV coinfected individuals.

**Clinical Presentation:** Persistently elevated liver transaminases; usually asymptomatic.

Diagnostic Considerations: All HIV-positive patients should be tested for HCV antibody. If the antibody test is negative but the likelihood of HCV infection is high (IDU, unexplained increase in LFTs), obtain an HCV RNA since false-negative antibody tests may occur, especially in advanced HIV disease. Since LFT elevation does not correlate well with underlying HCV activity, a liver biopsy is the best way to assess the degree of fibrosis and inflammation.

**Therapeutic Considerations:**

*Once Diagnosis is Established*. Advise patients to abstain from alcohol and administer vaccinations for hepatitis A and B (if non-immune). Also obtain HCV RNA levels with genotype assessment. HCV RNA levels do not have prognostic significance for underlying degree of liver disease, but higher levels make treatment for cure less likely. Genotype results also correlate with cure rates (reported cure rates: 60–75% for genotypes 2 and 3; 15–25% for genotype 1). Some clinicians elect to treat HCV without a liver biopsy due to: the risks, costs, and discomfort of the test; the potential to underestimate the degree of HCV activity due to sampling error; and the high rate of treatment success for genotypes 2 and 3.

*Optimal Patient Characteristics for HCV Treatment in HIV* include no active psychiatric disease or substance abuse; stable HIV disease with undetectable HIV RNA and higher $CD_4$ cell count; receiving an antiretroviral regimen that does not contain ddI (in particular), d4T, or ZDV; and adherent to medications, follow-up visits, and blood test monitoring. Only a small proportion of patients will meet all these criteria; therefore, to maximize treatment effect, it is important to optimize clinical status prior to starting HCV therapy. Patients should be fully educated regarding the goals and risks of treatment, with provision of written information about side effects, local support groups, and whom to contact with questions. It is useful to administer the first dose of treatment in the office in order to provide instructions on injection techniques.

*Choice of Drug Therapy*. The treatment of choice for HCV infection is pegylated interferon plus ribavirin. All patients should also receive hepatitis A vaccine and counseling to avoid alcohol use.

- Pegylated Interferon. Two different formulations of pegylated interferon are available for treatment of HCV infection: (1) peginterferon alfa-2a (Pegasys), supplied as a pre-mixed solution and administered subcutaneously as a fixed dose of 180 mcg once a week; and (2) peginterferon alfa-2b (Peg-Intron), supplied as a powder that is reconstituted in saline and administered subcutaneously as a weight-based dose once a week. Efficacy and toxicity of these two peginterferon preparations appear to be similar. Three clinical trials have shown that pegylated interferon plus ribavirin is more effective than standard interferon plus ribavirin (N Engl J Med 2004;351:451–9; N Engl J Med 2004;351:438–50; JAMA 2004;292:2839–48). Interferon has numerous side effects, the most important of which are listed in Table 5.9.
- Ribavirin. Ribavirin is available in 200-mg capsules. Although the dose used in clinical trials was 800 mg daily (400 mg BID), it appears that a higher initial dose is associated with greater efficacy. Standard dose is now 400 mg qAM and 600 mg qPM for weight < 75 kg, and 600 mg qAM and

600 mg qPM for weight > 75 kg. Ribavirin causes hemolytic anemia that predictably leads to a measurable decline in hemoglobin; this stabilizes by week 4–8 of treatment. Hemolytic anemia may be exacerbated in patients receiving ZDV; if possible an alternative NRTI should be chosen, with preference for tenofovir or abacavir. For symptomatic anemia or patients with coexisting conditions exacerbated by anemia, erythropoietin is used to maintain hemoglobin levels > 10 gm/dL or higher as needed. The typical starting dose of erythropoietin is 40,000 units SQ once a week. ddI is contraindicated during ribavirin administration due to an increased risk of mitochondrial toxicity and hepatic decompensation (Clin Infect Dis 2004;38:e79–e80). d4T should also be avoided because of its potential for inducing mitochondrial toxicity itself. Finally, some data suggest that ABC may interact with ribavirin, reducing efficacy of HCV therapy. Another common side effect of ribavirin is GI distress, which can overlap with a similar effect of interferon. Ribavirin is pregnancy category × (potent teratogen), and can only be used in sexually active women of childbearing potential if they are using 2 forms of birth control. Pregnancy should be avoided until at least 6 months after stopping ribavirin.

*Monitoring*. The monitoring plan for HIV/HCV coinfected patients consists of both safety and efficacy evaluations (Table 5.10). Results of HCV RNA testing are used to decide between completing 48 weeks of HCV therapy vs. discontinuing treatment at 12 or 24 weeks due to low probability of cure (Figure 5.3).

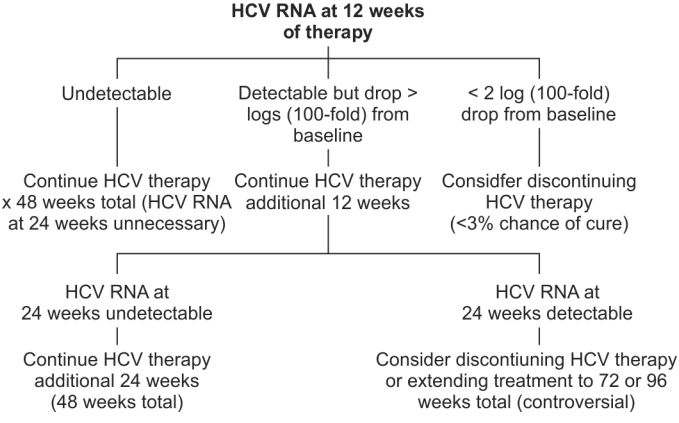


**Figure 5.3. Management of HCV Infection Based on HCV RNA Testing**

HCV RNA should be assessed at week 12. If the HCV viral load has not dropped by more than 2 logs (100–fold), then the likelihood of achieving a cure is extremely low. Many patients and providers will elect to discontinue therapy at this point, although theoretically low-dose peg-interferon may help improve liver fibrosis independent of its antiviral effect. (This strategy is being tested in clinical trials.) HCV RNA should be measured at weeks 24 and 48. If undetectable at week 48, additional measurements should be obtained at weeks 4, 12, and 24 after stopping treatment. An undetectable HCV RNA at week 24 post-treatment is the current standard for assessing a "sustained virologic response" (SVR), which can be equated with cure. Importantly, patients cured of HCV are susceptible to re-acquisition and should be cautioned about resuming high-risk behavior.

**Table 5.9. Adverse Effects Associated with Interferon**

| Side Effect | Comments |
|---|---|
| Fatigue and flu-like symptoms (fever, chills, muscle aches, headache) | Dose at night so that some initial symptoms can be slept through. Symptoms may not peak until 48–78 hours after weekly dose and can be managed with acetaminophen (maximum 1300 mg/day) or ibuprofen plus good hydration. Fatigue is sometimes a manifestation of thyroid dysregulation or anemia; monitor thyroid function tests and CBC |
| Depression | Interferon can aggravate life-threatening psychiatric conditions. Low threshold for initiating anti-depressant therapy. Patients with a pre-existing history of depression or other psychiatric disease should be followed closely by mental health professionals during HCV treatment |
| Leukopenia, thrombocytopenia, anemia | Cytopenias are more common in HIV/HCV co-infection. Can treat with G-CSF 300 mcg 3x/week if absolute neutrophil count is < 500/mm$^3$. If neutropenia persists, decrease dose of interferon. If platelet count falls to < 80,000/mm$^3$, also consider decreasing interferon dose (some clinicians tolerate counts down to 50,000/mm$^3$). Low threshold for use of erythropoietin (EPO) 40,000 U/week for anemia (see section on ribavirin) |
| Mouth ulcers | Topical viscous lidocaine or sucralfate is helpful in some |
| Gastrointestinal symptoms | Nausea and anorexia are the most common, often leading to weight loss. Advise patients to eat several small meals daily rather than a few large meals |
| Hair loss | Reversible after completion of therapy |

**Table 5.10. Monitoring Plan During Treatment for HCV Infection**

| | Weeks of Treatment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **24–28** |
| CBC | X | X | X | X | X | X | X | X | q4 weeks |
| LFTs + metabolic panel | X | | X | X | X | X | X | X | q4 weeks |
| HCV RNA | X | | X¶ | | X* | | | X** | q12 weeks |
| HIV RNA + $CD_4$ profile | X | | | | X† | | | X | q12 weeks |
| TSH | X | | | | X | | | X | q12 weeks |
| Depression | X | X | X | X | X | X | X | X | ongoing |

* Patients who have not dropped ≥ 2 logs from baseline HCV RNA at 12 weeks (early virologic response) have < 3% chance of obtaining a sustained viral response (undetectable HCV RNA 6 months post-treatment). Optimally, the HCV RNA will be undetectable by week 12 ('complete' early virologic response). One proposed strategy for patients with low-level detectable HCV RNA at week 12 ('partial' early virologic response) is to lengthen the course of therapy to 72 weeks or longer to reduce the risk of relapse; this is currently under investigation.

** If undetectable HCV RNA at 24 weeks, continue therapy for an additional 24 weeks (if known genotype 2 or 3 discuss option to stop, but some experts agree co-infected patients should continue treatment for 48 weeks to decrease risk of relapse). If HCV RNA is positive at 24 weeks, consider discontinuing HCV therapy. Even in patients without viral response, treatment may improve liver histology. Also see Figure 5.1.

† *Anticipate decrease in absolute cell count but stable $CD_4$%.*

¶ Check HCV RNA at week 4; if no decline in HIV RNA is seen, response is extremely unlikely. In contrast, ≥ 1 log decline can be very motivating and treatment should be continued. Best chance at cure is with an undetectable HIV RNA at 4 weeks, sometimes called a 'rapid virologic response.'

**Table 5.10. Monitoring Plan During Treatment for HCV Infection** (cont'd)

| | Weeks of Treatment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **24–28** |
| Ophthalmologic exam | X‡ | | | | X | | | X | q12 weeks |
| PT | X | | | | | X | | | q12 weeks |
| Pregnancy test | Perform at regular intervals if appropriate | | | | | | | | |

‡ Necessary for patients with a history of retinopathy; IFN package insert recommends screening for all patients prior to treatment. Many clinicians choose to defer the initial exam and monitor for disturbances in vision and loss of color perception.

Adapted from: Sax PE, Cohen CJ, Kuritzkes DR. HIV Essentials (6th Ed), Jones & Bartlett, Sudbury, MA, 2013.

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# Chapter 6

# Prophylaxis and Immunizations

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* For additional information on the prophylaxis of opportunistic infections in HIV see Chapter 5, p. 320.

## SURGICAL PROPHYLAXIS

Antibiotic prophylaxis is designed to prevent infection for a defined period of time. **Prophylaxis is most likely to be effective when given for a short duration against a single pathogen with a known sensitivity pattern,** and least likely to be effective when given for a long duration against multiple organisms with varying/unpredictable sensitivity patterns (Table 6.1). It is a common misconception that antibiotics used for prophylaxis should not be used for therapy and vice versa. **The only difference between prophylaxis and therapy is the inoculum size and the duration of antibiotic administration:** In prophylaxis, there is no infection, so the inoculum is minimal/none and antibiotics are administered only for the duration of exposure/surgical procedure. With therapy, the inoculum is large (infection already exists), and antibiotics are continued until the infection is eradicated.

**Table 6.1. Factors Affecting the Efficacy of Surgical Antibiotic Prophylaxis**

| Number of Organisms | Susceptibility Pattern | Duration of Protection | Efficacy of Prophylaxis |
|---|---|---|---|
| Single organism | Predictable | Short | Excellent |
| Multiple organisms | Predictable | Short | Excellent |
| Single organism | Unpredictable | Short | Good |
| Single organism | Predictable | Long | Good |
| Multiple organisms | Unpredictable | Long | Poor/none |

**Antibiotic prophylaxis is designed to achieve effective antibiotic serum/tissue concentrations at the time of initial surgical incision, and is maintained throughout the "vulnerable period" of the procedure (i.e., time between skin incision and skin closure)** (Table 6.2). If prophylaxis is given too early, antibiotic levels will be suboptimal/nonexistent when protection is needed. Properly timed pre-operative antibiotic prophylaxis is desirable for optimal effectiveness since **antibiotics given after skin closure are unlikely to be effective.** When no infection exists prior to surgery (clean/clean contaminated surgery), single-dose prophylaxis is preferred. When infection is present/likely prior to surgery ("dirty" surgery, e.g., perforated colon, TURP in the presence of positive urine cultures, repair of open fracture), antibiotics are given for > 1 day and represent early therapy, not true prophylaxis. Parenteral cephalosporins are commonly used for surgical prophylaxis, and ordinarily given as a bolus injection/rapid IV infusion 15–60 minutes prior to the procedure. Prophylaxis with vancomycin or gentamicin is given by slow IV infusion over 1–2 hours, starting ~1–2 hours prior to the procedure.

**Table 6.2. Surgical Prophylaxis**

| Procedure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| CNS shunt (VP/VA) placement, craniotomy, open CNS trauma | S. epidermidis (CoNS)<br>S. aureus (MSSA) | MRSA/MRSE unlikely Ceftriaxone 1 gm (IV) × 1 dose<br><br>MRSA/MRSE likely Linezolid 600 mg (IV) × 1 dose | MRSA/MRSE unlikely Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose<br><br>MRSA/MRSE likely Linezolid 600 mg (PO) × 1 dose<br>**or**<br>Vancomycin 1 gm (IV) × 1 dose<br>**or**<br>Minocycline 200 mg (IV) × 1 dose | Administer immediately prior to procedure. Vancomycin protects against wound infections, but may not prevent CNS infections. Give vancomycin slowly IV over 1 hour prior to procedure. |
| Thoracic (non-cardiac) surgery | S. aureus (MSSA) | Cefazolin 1 gm (IV) × 1 dose<br>**or**<br>Ceftriaxone 1 gm (IV) × 1 dose | Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose | Administer immediately prior to procedure. |
| Cardiac valve replacement surgery | S. epidermidis (MSSE/MRSE)<br>S. aureus (MSSA/MRSA)<br>Enterobacter | Vancomycin 1 gm (IV) × 1 dose<br>**plus**<br>Gentamicin 120 mg (IV) × 1 dose | Linezolid 600 mg (IV) × 1 dose<br>**plus**<br>Gentamicin 120 mg (IV) × 1 dose | Administer vancomycin and gentamicin slowly IV over 1 hour prior to procedure. |
| Coronary artery bypass graft (CABG) surgery | S. aureus (MSSA) | Cefazolin 2 gm (IV) × 1 dose<br>**or**<br>Ceftriaxone 1 gm (IV) × 1 dose | Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose | Administer immediately prior to procedure. Except for ceftriaxone, repeat dose intraoperatively for procedures lasting > 3 hours. |
| Biliary tract surgery | E. coli<br>Klebsiella<br>E. faecalis (VSE) | Meropenem 1 gm (IV) × 1 dose<br>**or**<br>Piperacillin 4 gm (IV) × 1 dose | Ampicillin/sulbactam 3 gm (IV) × 1 dose | Administer immediately prior to procedure (anaerobic coverage unnecessary). |

**Table 6.2. Surgical Prophylaxis** (cont'd)

| Procedure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Hepatic surgery | E. coli<br>Klebsiella<br>E. faecalis (VSE)<br>B. fragilis | Ampicillin/ sulbactam 3 gm (IV) × 1 dose<br>**or**<br>Piperacillin 4 gm (IV) × 1 dose | Meropenem 1 gm (IV) × 1 dose<br>**or**<br>Moxifloxacin 400 mg (IV) × 1 dose | Administer immediately prior to procedure. |
| Stomach, upper small bowel surgery | S. aureus (MSSA)Group A streptococci | Ceftriaxone 1 gm (IV) × 1 dose<br>**or**<br>Cefazolin 1 gm (IV) × 1 dose | Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose | Administer immediately prior to procedure (anaerobic coverage unnecessary). |
| Distal small bowel, colon surgery | E. coli<br>Klebsiella<br>B. fragilis | Oral<br>Neomycin*<br>**plus either**<br>Erythromycin base*<br>**or**<br>Metronidazole*<br>Parenteral<br>Ertapenem 1 gm (IV) × 1 dose | Piperacillin 3 gm (IV) × 1 dose<br>**or**<br>Cefoxitin 2 gm (IV) × 1 dose<br>**or combination therapy with**<br>Metronidazole 1 gm (IV) × 1 dose<br>**plus either**<br>Ceftriaxone 1 gm (IV) × 1 dose<br>**or**<br>Levofloxacin 500 mg (IV) × 1 dose<br>**or**<br>Gentamicin 240 mg (IV) × 1 dose | Administer immediately prior to procedure. Give gentamicin slowly IV over 1 hour. |
| Pelvic (OB/GYN) surgery | Aerobic GNBs<br>Anaerobic streptococci<br>B. fragilis | Ceftriaxone 1 gm (IV) × 1 dose **plus** Metronidazole 1 gm (IV) × 1 dose | Cefotetan 2 gm (IV) × 1 dose **or** Cefoxitin 2 gm (IV) × 1 dose **or** Ceftizoxime 2 gm (IV) × 1 dose | Administer immediately prior to procedure. |

* After appropriate diet and catharsis give either neomycin 1 gm (PO) plus erythromycin base 1 gm (PO) at 1 pm, 2 pm, and 11 pm, or give neomycin 2 gm (PO) plus metronidazole 2 gm (PO) at 7 pm and 11 pm the day before an 8 am operation.

**Table 6.2. Surgical Prophylaxis** (cont'd)

| Procedure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Orthopedic prosthetic implant surgery (total hip/knee replacement) | S. epidermidis (CoNS)<br>S. aureus (MSSA) | MRSA/MRSE unlikely<br>Cefazolin 2 gm (IV) × 1 dose<br>MRSA/MRSE likely<br>Vancomycin 1 gm (IV) × 1 dose | MRSA/MRSE unlikely<br>Ceftriaxone 1 gm (IV) × 1 dose<br>MRSA/MRSE likely<br>Linezolid 600 mg (IV) × 1 dose | Administer immediately prior to procedure. Post-operative doses are ineffective and unnecessary. |
| Arthroscopy | S. aureus (MSSA) | Cefazolin 1 gm (IV) × 1 dose<br>**or**<br>Ceftriaxone 1 gm (IV) × 1 dose | Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose | Pre-procedure prophylaxis is usually unnecessary in clean surgical procedures. |
| Orthopedic surgery (open fracture) | S. aureus (MSSA)<br>Aerobic GNBs | Ceftriaxone 1 gm (IV) × 1 week | Clindamycin 600 mg (IV) q8h × 1 week<br>**plus**<br>Gentamicin 240 mg (IV) q24h × 1 week | Represents early therapy, not true prophylaxis. Duration of post-op antibiotics depends on severity of infection. |
| Urological implant surgery | S. aureus (MSSA)<br>Aerobic GNBs<br>bacilli | Ceftriaxone 1 gm (IV) × 1 dose | Cefotaxime 2 gm (IV) × 1 dose<br>**or**<br>Ceftizoxime 2 gm (IV) × 1 dose | Administer immediately prior to procedure. |
| TURP, cystoscopy | P. aeruginosa<br>P. cepacia<br>P. maltophilia<br>E. faecalis (VRE)<br>Aerobic GNBs | Ciprofloxacin 400 mg (IV) × 1 dose<br>**or**<br>Piperacillin 4 gm (IV) × 1 dose | Levofloxacin 500 mg (IV) × 1 dose<br>**or**<br>Gatifloxacin 400 mg (IV) × 1 dose | Prophylaxis given to TURP patients with positive pre-op urine cultures. Represents early therapy, not true prophylaxis. No prophylaxis required for TURP if pre-op urine culture is negative. |
| | E. faecium (VRE) | Linezolid 600 mg (IV) × 1 dose | Quinupristin/dalfopristin 7.5 mg/kg (IV) × 1 dose | |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus; MSSE/MRSE = methicillin-sensitive/resistant S. epidermidis.*

## POST-EXPOSURE PROPHYLAXIS

Some infectious diseases can be prevented by post-exposure prophylaxis (PEP). To be maximally effective, PEP should be administered within 24 hours of the exposure, since the effectiveness of prophylaxis > 24 hours after exposure decreases. PEP is usually reserved for persons with close/intimate contact with an infected individual. Casual contact does not warrant PEP.

**Table 6.3. Post-Exposure Prophylaxis**

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Meningitis | N. meningitidis | Any quinolone (PO) × 1 dose | Minocycline 100 mg (PO) q12h × 2 days **or** Rifampin 600 mg (PO) q12h × 2 days | Must be administered within 24 hours of close face-to-face exposure to be effective. Otherwise, observe and treat if infection develops. |
| | H. influenzae | Rifampin 600 mg (PO) q24h × 3 days | Any quinolone (PO) × 3 days | Must be administered within 24 hours of close face-to-face exposure to be effective. H. influenzae requires 3 days of prophylaxis. |
| Influenza | Influenza A or B | Oseltamivir (Tamiflu) 75 mg (PO) q24h for duration of outbreak (or at least 7 days after close contact to an infected person).§ | Rimantadine 100 mg (PO) q12h* for duration of outbreak (or at least 7–10 days after close contact to infected person) **or** Amantidine 200 mg (PO) q24h† for 7–10 days or outbreak | Give to non-immunized contacts and high-risk contacts even if immunized. Begin at onset of outbreak or within 3 days of close contact to an infected person. Oseltamivir is active against both influenza A and B; rimantadine and amantadine are only active against influenza A. Oseltamivir may be ineffective due to resistance. |

§ Dose for CrCl > 30–60 mL/min = 30 mg (PO) q24h; for CrCl >10–30 mL/min = 30 mg (PO) q48h.

**Table 6.3. Post-Exposure Prophylaxis** (cont'd)

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Avian influenza | Influenza A ($H_5N_1$) | Oseltamivir (as for viral influenza, above) | Rimantadine **or** Amantadine† (as for viral influenza, above) | Oseltamivir may be ineffective due to resistance. |
| Swine influenza | Influenza A ($H_1N_1$) | Oseltamavir above (as for viral influenza, above) | None | Amantadine/rimantadine ineffective<br>Continue PEP for swine influenza ($H_1N_1$) × 10 days post-close exposure.‡ |
| Pertussis | B. pertussis | Erythromycin 500 mg (PO) q6h × 2 weeks | TMP–SMX 1 SS tablet (PO) q12h × 2 weeks **or** Levofloxacin 500 mg (PO) q24h × 2 weeks | Administer as soon as possible after exposure. Effectiveness is greatly reduced after 24 hours. |
| Diphtheria | C. diphtheriae | Erythromycin 500 mg (PO) q6h × 1 week **or** Benzathine penicillin 1.2 mu (IM) × 1 dose | Azithromycin 500 mg (PO) q24h × 3 days | Administer as soon as possible after exposure. Effectiveness is greatly reduced after 24 hours. |
| TB | M. tuberculosis | Rifampin 600 mg (PO) q24h × 4 months§ **or** INH 300 mg (PO) q24h × 9 months | Rifapentine 900 mg (PO) q week **plus** INH 900 mg (PO) q week × 3 months (D.O.T.) | For INH, monitor SGOT/SGPT weekly × 4, then monthly. Mild elevations are common and resolve spontaneously. D/C INH if SGOT/SGPT levels ≥ 5 × normal. |

* For elderly, severe liver dysfunction, or CrCl < 10 cc/min, give 100 mg (PO) q24h.

† For age ≥ 65 years, give 100 mg (PO) q24h. For renal dysfunction, give 200 mg (PO) load followed by 100 mg q24h (CrCl 30–50 ml/min), 100 mg q48h (CrCl 15–29 ml/min), or 200 mg weekly (CrCl < 15 ml/min).

‡ *Pediatric prophylaxis:* < 15 kg: 30 mg PO qd for 10 days, > 15-24 kg: 45 mg PO qd for 10 days, 24-40 kg: 60 mg PO qd for 10 days, > 40 kg: same as adults.

§ INH preferred if patient uses contact lens, has HIV, or is taking medications that may interact with rifampin.

**Table 6.3. Post-Exposure Prophylaxis** (cont'd)

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Gonorrhea (GC) | N. gonorrhoeae | Ceftriaxone 125 mg (IM) × 1 dose | Spectinomycin 2 gm (IM) × 1 dose **or** Any oral quinolone × 1 dose | Administer as soon as possible after sexual exposure (≤ 72 hours). Ceftriaxone also treats incubating syphilis. |
| Syphilis | T. pallidum | Benzathine penicillin 2.4 mu (IM) × 1 dose | Doxycycline 100 mg (PO) q12h × 1 week | Administer as soon as possible after sexual exposure. Obtain HIV serology. |
| Chancroid | H. ducreyi | Ceftriaxone 250 mg (IM) × 1 dose | Azithromycin 1 gm (PO) × 1 dose **or** Any oral quinolone × 3 days | Administer as soon as possible after sexual exposure. Obtain HIV and syphilis serologies. |
| Non-gonococcal urethritis (NGU) | C. trachomatis U. urealyticum M. genitalium | Azithromycin 1 gm (PO) × 1 dose **or** Doxycycline 100 mg (PO) q12h × 1 week | Any oral quinolone × 1 week | Administer as soon as possible after sexual exposure. Also test for gonorrhea/Ureaplasma. |
| Varicella (chicken-pox) | VZV | Preferred: For exposure < 72 hours, give varicella-zoster immune globulin (VZIG) 625 mcg (IM) × 1 dose to immuno-compromised hosts and pregnant women (esp. with respiratory conditions). For others or exposure > 72 hours, consider acyclovir 800 mg (PO) 5x/day × 5–10 days<br>Alternate: Varicella vaccine 0.5 mL (SC) × 1 dose. Repeat in 4 weeks | | Administer as soon as possible after exposure (≤ 72 hours). Varicella vaccine is a live attenuated vaccine and should not be given to immunocompromised or pregnant patients. If varicella develops, start acyclovir treatment immediately. |

**Table 6.3. Post-Exposure Prophylaxis** (cont'd)

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Hepatitis A (HAV) | Hepatitis A virus | HAV vaccine 1 mL (IM) × 1 dose | Immune serum globulin (IG) 0.02 mL/kg (IM) × 1 dose | Give HAV vaccine alone if within 14 days after exposure. |
| Hepatitis B (HBV) | Hepatitis B virus | Unvaccinated<br>Hepatitis B immune globulin (HBIG) 0.06 mL/kg (IM) × 1 dose<br>**plus**<br>HBV vaccine (40 mcg HBsAg/mL) deep deltoid (IM) at 0, 1, 6 months (can use 10-mcg dose in healthy adults < 40 years) | Previously vaccinated<br>*Known responder* (anti-HBsAg antibody levels ≥ 10 IU/mL): No treatment.<br>*Known non-responder* (anti-HBsAg antibody levels < 10 IU/mL): Treat as if unvaccinated.<br>*Antibody status unknown:* Obtain HBsAg antibody levels to determine immunity status. If testing is not possible or results are not available within 24 hours of exposure, give HBIG plus 1 dose of HBV vaccine (booster). | |
| Hepatitis C (HCV) | Hepatitis C virus | None | | |
| Rocky Mountain spotted fever | R. rickettsia | Doxycycline 100 mg (PO) q12h × 1 week | Any oral quinolone × 1 week | Administer prophylaxis after removal of Dermacentor tick. |
| Lyme disease | B. burgdorferi | Doxycycline 200 mg (PO) × 1 dose | Amoxicillin* 1 gm (PO) q8h × 3 days **or**<br>Any oral 1st gen. cephalosporin* × 3 days<br>**or**<br>Azithromycin* 500 mg (PO) q24h × 3 days | If tick is in place ≥ 72 hours or is grossly engorged, prophylaxis may be given after tick is removed. Otherwise, prophylaxis is usually not recommended. |

*HDCV = human diploid cell vaccine, HRIG = human rabies immune globulin, PCEC = purified chick embryo cells, RVA = rabies vaccine absorbed.*

* All or as much of the full dose of HRIG should be injected into the wound, and the remaining vaccine should be injected IM into the deltoid. Do not give HRIG at the same site or through the same syringe with PCEC, RVA, or HDCV.

**Table 6.3. Post-Exposure Prophylaxis** (cont'd)

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| | | * Although experience is limited, single-dose prophylaxis with these agents is probably also effective. | | |
| Zoonotic diseases (plague, anthrax) | B. anthracis<br>Y. pestis | Doxycycline 100 mg (PO) q12h for duration of exposure | Any oral quinolone for duration of exposure | Continued for the duration of a naturally-acquired exposure/outbreak. See p. 363 for bioterrorist plague/anthrax recommendations. |
| Rabies | Rabies virus | <u>No Previous Immunization</u><br>HRIG 20 IU/kg*<br>**plus either**<br>PCEC 1 mL (IM) in deltoid<br>**or**<br>RVA 1 mL (IM) in deltoid<br>**or**<br>HDCV 1 mL (IM) in deltoid<br>PCEC, RVA, HDCV given on days 0, 3, 7, 14, and 28 post-exposure | <u>Previous Immunization</u><br>PCEC 1 mL (IM) in deltoid on days 0 and 3<br>**or**<br>RVA 1 mL (IM) in deltoid on days 0 and 3<br>**or**<br>HDCV 1 mL (IM) in deltoid on days 0 and 3 | Following unprovoked or suspicious dog or cat bite, immediately begin prophylaxis if animal develops rabies during a 10-day observation period. If dog or cat is suspected of being rabid, begin vaccination sequence immediately. Raccoon, skunk, bat, fox, and most wild carnivore bites should be regarded as rabid, and bite victims should be vaccinated against rabies immediately (contact local health department regarding rabies potential of animals in your area). All potential rabies wounds should immediately be thoroughly cleaned with soap and water. Do not inject rabies vaccine IV (may cause hypotension/shock). Serum sickness may occur with HDCV. |

*HDCV = human diploid cell vaccine, HRIG = human rabies immune globulin, PCEC = purified chick embryo cells, RVA = rabies vaccine absorbed.*

* All or as much of the full dose of HRIG should be injected into the wound, and the remaining vaccine should be injected IM into the deltoid. Do not give HRIG at the same site or through the same syringe with PCEC, RVA, or HDCV.

**Table 6.3. Post-Exposure Prophylaxis** (cont'd)

| Exposure | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| **BIOTERRORIST AGENTS** | | | | |
| Anthrax *Inhalation/ cutaneous* | B. anthracis | Doxycycline 100 mg (PO) q12h × 60 days **or** Ciprofloxacin 500 mg (PO) q12h × 60 days **or** Levofloxacin 500 mg (PO) q24h × 60 days | Amoxicillin 1 gm (PO) q8h × 60 days | Duration of anthrax PEP based on longest incubation period of inhaled spores in nares. |
| Tularemia pneumonia | F. tularensis | Doxycycline 100 mg (PO) q12h × 2 weeks | Ciprofloxacin 500 mg (PO) q12h × 2 weeks **or** Levofloxacin 500 mg (PO) q24h × 2 weeks | Duration of PEP for tularemia is 2 weeks, not 1 week as for plague. |
| Pneumonic plague | Y. pestis | Doxycycline 100 mg (PO) q12h × 7 days **or** Ciprofloxacin 500 mg (PO) q12h × 7 days **or** Levofloxacin 500 mg (PO) q24h × 7 days | Chloramphenicol 500 mg (PO) q6h × 7 days | Pneumonic plague should be considered bioterrorism since most natural cases of plague are bubonic plague. |
| Smallpox | Variola virus | Smallpox vaccine ≤ 4 days after exposure | None | Smallpox vaccine is protective when diluted 1:5. |
| Viral hemorrhagic fever | Lassa fever | Ribavarin loading dose: 35mg/kg (PO) (not to exceed 2.5 g), then 15 mg/kg (PO) (not to exceed 1g) q8h × 10 days | None | Decrease maintenance dose to 7.5 mg/kg (PO) q8h if CrCl < 50/ml/min. |

## CHRONIC MEDICAL PROPHYLAXIS

Some infectious diseases are prone to recurrence/relapse and may benefit from intermittent or chronic suppressive therapy. The goal of suppressive therapy is to minimize the frequency/severity of recurrent infectious episodes.

**Table 6.4. Chronic Medical Prophylaxis**

| Disorder | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Asplenia/ impaired splenic function | S. pneumoniae<br>H. influenzae<br>N. meningitidis | Amoxicillin 1 gm (PO) q24h indefinitely | Respiratory quinolone* (PO) q24h indefinitely | Long-term prophylaxis effective. Vaccines may be given but are not always protective. Use amoxicillin in children. |
| UTIs (recurrent) | Gram-negative bacilli Enterococci | Nitrofurantoin 100 mg (PO) q24h × 6 months | Amoxicillin 500 mg (PO) q24h × 6 mos **or** TMP–SMX 1 SS tablet (PO) q24h × 6 months | Prophylaxis for reinfection UTIs (≥ 3 per year). Relapse UTIs should be investigated for stones, abscesses, or structural problems. |
| Asymptomatic bacteriuria in pregnancy | Gram-negative bacilli | Nitrofurantoin 100 mg (PO) q24h × 1 week | Amoxicillin 1 gm (PO) q24h × 1 week | Prophylaxis prevents symptomatic infections. |
| Prophylaxis of fungal infections in neutropenic patients† | Candida albicans<br>Non-albicans Candida<br>Aspergillus | Posaconazole 200 mg (PO) q8h **or** Itraconazole 200 mg (PO) q12h | | Prophylaxis given until neutropenia resolves (absolute neutrophil count ≥ 500 cells/mm$^3$). |
| Recurrent genital herpes (< 6 episodes/ year) | H. simplex (HSV-2) | Famciclovir 125 mg (PO) q12h × 5 days **or** Valacyclovir 500 mg (PO) q24h × 5 days | Acyclovir 200 mg (PO) 5x/day × 5 days | Begin therapy as soon as lesions appear. (For HIV disease, see Ch. 5.) Famciclovir 1 gm (PO) q12h × 1 day ↓ lesion progression by 2 days. |
| Recurrent genital herpes (> 6 episodes/ year) | H. simplex (HSV-2) | Famciclovir 250 mg (PO) q12h × 1 year **or** Valacyclovir 1 gm (PO) q24h × 1 year | Acyclovir 400 mg (PO) q12h × 1 year | Suppressive therapy is indicated for frequent recurrences. (For HIV disease, see Ch. 5.) |

**Table 6.4. Chronic Medical Prophylaxis** (cont'd)

| Disorder | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Acute exacerbation of chronic bronchitis (AECB) | S. pneumoniae H. influenzae M. catarrhalis | Moxifloxacin 400 mg or levofloxacin 500 mg or gatifloxacin 400 mg or gemifloxacin 320 mg (PO) q24h × 5 days **or** Amoxicillin/clavulanic acid XR 2 tablets (PO) q12h × 5 days **or** Clarithromycin XL 1 gm (PO) q24h × 5 days **or** Doxycycline 100 mg (PO) q12h × 5 days **or** Azithromycin 500 mg (PO) × 3 days | | Treat each episode individually. |
| Acute rheumatic fever (ARF) | Group A streptococci | Benzathine penicillin 1.2 mu (IM) monthly until age 30 | Amoxicillin 500 mg (PO) q24h **or** Azithromycin 500 mg (PO) q72h until age 30 | Group A streptococcal pharyngitis and acute rheumatic fever are uncommon after age 30. |
| Neonatal Group B streptococcal (GBS) infection (primary prevention) | Group B streptococci | Ampicillin 2 gm (IV) q4h at onset of labor until delivery | Clindamycin 600 mg (IV) q8h at onset of labor until delivery **or** Vancomycin 1 gm (IV) q12h at onset of labor until delivery | Indications: previous infant with GBS infection, maternal GBS colonization/infection during pregnancy, vaginal/rectal culture of GBS after week 35 of gestation, delivery ≤ week 37 of gestation without labor/ruptured membranes, ruptured membranes ≥ 12 hrs, or intrapartum temp ≥ 100.4°F. |

* Levofloxacin 500 mg (PO) or gatifloxacin 400 mg (PO) q24h or moxifloxacin 400 mg (PO).
† During induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS).

**Table 6.5. HIV Pre-Exposure Prophylaxis (PrEP)**

| Disorder | Usual Organisms | Preferred Prophylaxis | Alternate Prophylaxis | Comments |
|---|---|---|---|---|
| Repeated potential HIV exposures | HIV | Truvada 1 tablet (PO) q24h × 90 days (recheck HIV status) | | Avoid if CrCl < 60 ml/min. Avoid if breast feeding. |

**Table 6.6. HIV Post-Exposure Prophylaxis (PEP)**

| Exposure | Preferred regimen | Recommended regimen | Alternate recommended regimen | Comments |
|---|---|---|---|---|
| HIV | **Truvada 1** tablet (PO) q24h [tenofovir (TDF) 300 mg (PO) q24h + emtricitabine (FTC) 200 mg (PO) q24h] × 4 weeks **plus either** Raltegravir (RAL) 400 mg (PO) q12h × 4 weeks **or** Dolutegravir (DTG) 50 mg (PO) q24h × 4 weeks | **Truvada 1** tablet (PO) q24h [tenofovir (TDF) 300 mg (PO) q24h + emtricitabine (FTC) 200 mg (PO) q24h] × 4 weeks **plus** (*one of the following*) Darunavir (DRV) 800 mg (PO) q24h × 4 weeks **or** Atazanavir (ATZ) 300 mg (PO) q24h × 4 weeks **or** Fosamprenavir (FPV)1400 mg (PO) q24h × 4 weeks **plus** Ritonavir (RTV) 100 mg (PO) q24h × 4 weeks | **Truvada 1** tablet (PO) q24h [tenofovir (TDF) 300 mg (PO) q24h + emtricitabine (FTC) 200 mg (PO) q24h] × 4 weeks **plus** Zidovudine (ZDV) 300 mg (PO) q12h × 4 weeks **or** **Truvada 1** tablet (PO) q24h [tenofovir (TDF) 300 mg (PO) q24h + emtricitabine (FTC) 200 mg (PO) q24h] × 4 weeks **plus** **Kaletra** 2 tablets (PO) q12h [lopinavir (LPV) 200 mg (PO) q12h + ritonavir (RTV) 50 mg (PO) q12h] × 4 weeks | … |

**Table 6.7. HIV: Prophylaxis of Opportunistic Infections**

| Disorder | Usual organism | Indication for Prophylaxis | Intervention |
|---|---|---|---|
| HIV | PCP | $CD_4 < 200/mm^3$ | TMP-SMX: 1 SS tablet or 1 DS tablet (PO) q24h **or** Atovaquone 1500 mg (PO) q24h |
| | TB | PPD > 5 mm (current or past) or contact with active case | INH: 300 mg (PO) q24h × 9 months Rifabutin: Dose based on concomitant ART × 4 months |
| | Toxoplasmosis | IgG (+) and $CD_4 < 100/mm^3$ | TMP-SMX: 1 DS tablet (PO) q24h |
| | MAI | $CD_4 < 50/mm^3$ | Azithromycin: 1200 mg (PO) q week |
| | S.pneumoniae | $CD_4 > 200/mm^3$ | Pneumococcal vaccine |
| | Hepatitis B (HBV) | Susceptible patients | Hepatitis B vaccine |
| | Hepatitis A (HAV) | Susceptible patients | Hepatitis A vaccine |
| | Influenza | All patients | Annual influenza vaccine |
| | VZV | $CD_4 > 200/mm^3$, VZV antibody negative | VZV vaccine |

**Table 6.8. Transplant Prophylaxis (BMT/SOT)**

| Exposure | Usual organism | Preferred prophylaxis | Alternate prophylaxis | Comments |
|---|---|---|---|---|
| Herpes simplex (HSV) | Herpes simplex | HSV → < 6 recurrences/year<br>Valacyclovir 500 mg (PO) q24h × 30 days<br>***or***<br>Famciclovir 1 g (PO) q12 × 30 days<br><br>HSV → > 6 recurrences/year<br>Valacyclovir 1 gm (PO) q24h × 90 days<br>***or***<br>Famciclovir 250 mg (PO) q12 × 30 days | Acyclovir 400 mg (PO) q8h × 30 days post-BMT<br><br>Acyclovir 400 mg (PO) q8h × 90 days post-BMT | Acute prophylaxis<br>Nearly all post-tranplant HSV infections occur < 1 month. Transplants receiving CMV prophylaxis with ganciclovir, or valganciclovir are protected against HSV (see CMV prophylaxis).<br><br>Chronic prophylaxis<br>Valacyclovir 500 mg (PO) q12h<br>***or***<br>Famciclovir 500 mg (PO) q12h<br>***or***<br>Acyclovir 400 mg (PO) q8h |
| Varicella zoster virus (VZV) | Varicella zoster virus | VZV seropositive recipient<br>Valacyclovir 500 mg (PO) q12h post-transplant x 4–24 months | Acyclovir 400 mg (PO) q8h post-transplant x 4–24 months | Post-transplant VZV infections occur later than HSV.<br>> 95% of adults are VZV seropositive. In transplants, most VZV infections are due to reactivation rather than primary infection. Patients may develop shingles after prophylaxis is discontinued. |
| | | VZV seronegative recipient (VZV seropositive graft)<br>Valacyclovir 1 g (PO) q8h post-transplant x 4–24 months | Acyclovir 800mg (PO) 5x/day post-transplant x 4–24 months | Transplant recipients on CMV prophylaxis with gangciclovir or valganciclovir do not require VZV prophylaxis. |

**Table 6.8. Transplant Prophylaxis (BMT/SOT)** (cont'd)

| Exposure | Usual organism | Preferred prophylaxis | Alternate prophylaxis | Comments |
|---|---|---|---|---|
| Cytomegalovirus (CMV) | Transplants (SOT) D+/R-, D+/R+, D-/R+ | Valganciclovir 900 mg (PO) q24h × 3–6 months | Ganciclovir 5 mg/kg (IV) q24h × 3–6 months | Alternately, preemptive therapy may be used. When quantitative CMV PCR/pp 65 antigenemia levels become +/↑.<br>D-/R- patients should receive CMV negative blood and leukocyte depleted RBCs but do not require antiviral prophylaxis. |
| PCP | SOT/BMT (with GVHD) | TMP-SMX 1 DS tablet (PO) q week × 12 months | TMP-SMX 1 SS tablet (PO) q24h × 12 months<br>***or***<br>Atovaquone 1500 mg (PO) q24h × 12 months (with a meal) | See Drug Summaries for drug-drug interactions. |
| Toxoplasmosis | Heart transplants | TMP-SMX 1 DS tablet (PO) q24h | Atovaquone 1500 mg (PO) q24h (take with a meal) | See Drug Summaries for drug-drug interactions. |
| *Candida sp.* | Liver/pancreas transplants | Fluconazole 400 mg (IV/PO) q24h × 4 weeks | Posaconazole 200 mg (PO) q8h × 4 weeks | See Drug Summaries for drug-drug interactions. |
| *Aspergillus sp.* | Allogeneic BMT/lung transplants | Voriconazole 200 mg (PO) q12h | Posaconazole 200 mg (PO) q8h | Until engrafted (BMT); duration in lung transplants unclear.<br>See Drug Summaries for drug-drug interactions. |

GVHD = graft vs. host disease.

## ENDOCARDITIS PROPHYLAXIS

***Endocarditis prophylaxis is now recommended only for previous endocarditis, prosthetic cardiac valve or prosthetic cardiac valve material, congenital heart disease (CHD), unrepaired cyanotic CHD, including palliative shunts and conduits, completely repaired congenital heart defects with prosthetic material/devices (placed by surgery or by catheter intervention during the first 6 months post-procedure), repaired CHD with residual defects adjacent to the site of prosthetic patch/device, and cardiac transplantation with cardiac valvupathy.***

**Table 6.9. Previous Indications for Infective Endocarditis (IE) Prophylaxis***

| Subset | Prophylaxis Recommended (Column A) | Prophylaxis Not Recommended (Column B) |
|---|---|---|
| Cardiac conditions | • Ostium primum ASD<br>• Prosthetic heart valves, including bioprosthetic and homograft valves<br>• Previous infective endocarditis<br>• Most congenital cardiac malformations<br>• Rheumatic valve disease<br>• Hypertrophic cardiomyopathy<br>• MVP with significant valvular regurgitation<br>• Calcific aortic stenosis | • Isolated ostium secundum ASD<br>• Surgical repair without residue beyond 6 months of ostium secundum ASD or PDA<br>• Previous coronary artery bypass surgery<br>• MVP without valvular regurgitation<br>• Physiologic, functional, or innocent murmurs<br>• Previous Kawasaki's cardiac disease or rheumatic fever without valve disease |
| Procedures | • Dental procedures known to induce gingival/mucosal bleeding, including dental cleaning<br>• Tonsillectomy or adenoidectomy<br>• Surgical operations involving intestinal or respiratory mucosa<br>• Cystoscopy or urethral dilation<br>• Urethral catheterization or urinary tract surgery if UTI is present<br>• Prostate surgery<br>• I & D of infected tissue | • Dental procedures not likely to induce gingival bleeding<br>• Tympanostomy tube insertion<br>• Flexible bronchoscopy ± biopsy<br>• Endotracheal intubation<br>• Endoscopy ± gastrointestinal biopsy<br>• Cesarean section<br>• D & C, IUD insertion/removal, or therapeutic abortion in the absence of infection<br>• Cardiac pacemaker/defibrillator insertion |

* Wilson W, et al. Prevention of Infective Endocarditis. Circulation 116:1736–1754, 2007.

**Table 6.9. Previous Indications for Infective Endocarditis (IE) Prophylaxis*** (cont'd)

| Subset | Prophylaxis Recommended (Column A) | Prophylaxis Not Recommended (Column B) |
|---|---|---|
| | • Biopsies of infected respiratory mucosa or infected skin/soft tissues<br>• Any surgical procedure involving an infected field | • Coronary stent implantation<br>• Percutaneous transluminal coronary angioplasty (PTCA)<br>• Cardiac catheterization |

*ASD = atrial septal defect, D & C = dilatation and curettage, I & D = incision and drain, IUD = intrauterine device, MVP = mitral valve prolapse, PDA = patent ductus arteriosus, UTI = urinary tract infection.*

* Prophylaxis is indicated for patients with cardiac conditions in Column A undergoing procedures in Column A. Prophylaxis is not recommended for patients or procedures in Column B. See Tables 6.9 and 6.10 for prophylaxis regimens for above-the-waist and below-the-waist procedures, respectively.

**Table 6.10. Endocarditis Prophylaxis for Above-the-Waist (Dental, Oral, Esophageal, Respiratory Tract) Procedures***

| Prophylaxis | Reaction to Penicillin | Antibiotic Regimen |
|---|---|---|
| Oral prophylaxis | None | Amoxicillin 2 gm (PO) 1 hour pre-procedure† |
| | Non-anaphylactoid | Cephalexin 1 gm (PO) 1 hour pre-procedure |
| | Anaphylactoid | Clindamycin 300 mg (PO) 1 hour pre-procedure†† |
| IV prophylaxis | None | Ampicillin 2 gm (IV) 30 minutes pre-procedure |
| | Non-anaphylactoid | Cefazolin 1 gm (IV) 15 minutes pre-procedure |
| | Anaphylactoid | Clindamycin 600 mg (IV) 30 minutes pre-procedure |

* Endocarditis prophylaxis is directed against viridans streptococci, the usual SBE pathogen above the waist. Macrolide regimens are less effective than other regimens; clarithromycin/azithromycin regimens (500 mg PO 1 hour pre-procedure) are of unproven efficacy.

† Some recommend a 3 gm dose of amoxicillin, which is excessive given the sensitivity of viridans streptococci to amoxicillin.

†† Some recommend a 600 mg dose of clindamycin, but a 300 mg dose gives adequate blood levels and is better tolerated (less diarrhea).

**Table 6.11. Endocarditis Prophylaxis for Below-the-Waist (Genitourinary, Gastrointestinal) Procedures Involving an Infected Field*†**

| Prophylaxis | Reaction to Penicillin | Antibiotic Regimen |
|---|---|---|
| Oral prophylaxis | None | Amoxicillin 2 gm (PO) 1 hour pre-procedure |
| | Non-anaphylactoid, anaphylactoid | Linezolid 600 mg (PO) 1 hour pre-procedure |

**Table 6.11. Endocarditis Prophylaxis for Below-the-Waist (Genitourinary, Gastrointestinal) Procedures Involving an Infected Field*†** (cont'd)

| Prophylaxis | Reaction to Penicillin | Antibiotic Regimen |
|---|---|---|
| IV prophylaxis | None | Ampicillin 2 gm (IV) 30 minutes pre-procedure<br>**plus**<br>Gentamicin 80 mg (IM) or (IV) over 1 hour 60 minutes pre-procedure |
| | Non-anaphylactoid, anaphylactoid | Vancomycin 1 gm (IV) over 1 hour 60 minutes pre-procedure<br>**plus**<br>Gentamicin 80 mg (IM) or (IV) over 1 hour 60 minutes pre-procedure |

* Endocarditis prophylaxis is directed against E. faecalis, the usual SBE pathogen below the waist.

† Seto TB. The case for infectious endocarditis prophylaxis. Arch Intern Med 167:327–330, 2007. Harrison JL, Hoen B, Prendergast BD. Antibiotic Prophylaxis for Infective Endocarditis. Lancet 371: 1317–1319, 2008.

**Table 6.12. Q Fever Endocarditis Prophylaxis**

| Prophylaxis | Antibiotic Regimen |
|---|---|
| PO prophylaxis (for significant valvulopathy* in acute Q fever | Doxycycline 100 mg (PO) of q12 h × 12 months<br>**Plus**<br>Hydroxychloroquine 200 mg (PO) q8h × 12 months |

* Significant valvulopathy: history of rheumatic fever, aortic bicuspid valve, ≥ 2 valve stenosis/regurgitation, MVP, remodeled/thickened valve.

## TRAVEL PROPHYLAXIS

**Travelers may acquire infectious diseases from ingestion of fecally-contaminated water/food, exchange of infected body secretions, inhalation of aerosolized droplets, direct inoculation via insect bites, or from close contact with infected birds/animals.**

Recommendations to prevent infection in travelers consist of general travel precautions (Table 6.12), and specific travel prophylaxis regimens (Table 6.13).

**Table 6.13. General Infectious Disease Travel Precautions**

| Exposure | Risk | Precautions |
|---|---|---|
| Unsafe water (fecally-contaminated) | Diarrhea/dysentery, viral hepatitis (HAV) | • Avoid ingestion of unbottled/unpotable water. Be sure bottled water has an unbroken seal and has not been opened/refilled with tap water.<br>• Avoid ice cubes made from water of uncertain of origin/handling, and drinking from unclean glasses.<br>• Drink only pasteurized bottled drinks. Be sure bottles/cans are opened by you or in your presence. |

**Table 6.13. General Infectious Disease Travel Precautions** (cont'd)

| Exposure | Risk | Precautions |
|---|---|---|
| | | • Avoid drinking unpasteurized/warm milk; beer, wine, and pure alcoholic beverages are safe.<br>• Eat only canned fruit or fresh fruit peeled by you or in your presence with clean utensils.<br>• Avoid eating soft cheeses.<br>• Avoid eating raw tomatoes/uncooked vegetables that may have been exposed to contaminated water.<br>• Avoid using hotel water for tooth brushing/rinsing unless certain of purity. Many hotels use common lines for bath/sink water that is unsuitable for drinking.<br>• Avoid wading/swimming/bathing in lakes or rivers. |
| Food-borne (fecally-contaminated) | Diarrhea/dysentery | • Eat only seafood/poultry/meats that are freshly cooked and served hot. Avoid eating at roadside stands or small local restaurants with questionable sanitary practices.<br>• "Boil it, peel it, or forget it." |
| Body fluid secretions | Viral hepatitis (HBV, HCV, etc.), STDs, HIV/other retroviruses | • Do not share utensils/glasses/straws or engage in "risky behaviors" involving body secretion exchange.<br>• Avoid blood transfusion (use blood expanders instead).<br>• Treat dental problems before travel. |
| Animal bite | Animal bite-associated infections | • Do not pet/play with stray dogs/cats. Rabies and other infections are common in wild (and some urban) animals. |
| Flying insects | Malaria, arthropod-borne infections | • Avoid flying/biting insects by wearing dark protective clothing (long sleeves/pants) and using insect repellent on clothes/exposed skin, especially during evening hours.<br>• Minimize dawn-to-dusk outdoor exposure.<br>• Use screens/mosquito nets when possible.<br>• Do not use perfume, after shave, or scented deodorants/toiletries that will attract flying insects. |

**Table 6.14. Travel Prophylaxis Regimens**

| Exposure | Usual Pathogens | Prophylaxis Regimens | Comments |
|---|---|---|---|
| | E. coli Salmonella<br>Shigella<br>Non-cholera vibrios<br>V. cholerae<br>Aeromonas<br>Plesiomonas<br>Rotavirus<br>Norwalk virus<br>Giardia lamblia<br>Campylobacter | Doxycycline 100 mg (PO) q24h for duration of exposure<br>**or**<br>Any quinolone (PO) for duration of exposure<br>**or**<br>TMP–SMX 1 SS tablet (PO) q24h for duration of exposure | Observe without prophylaxis and treat mild diarrhea symptomatically with loperamide (2 mg). Persons with medical conditions adversely affected by dehydration caused by diarrhea may begin prophylaxis after arrival in country and continue for 1 day after returning home. Should severe diarrhea/dysentery occur, continue/switch to a quinolone, maximize oral hydration, and see a physician if possible. |

**Table 6.14. Travel Prophylaxis Regimens** (cont'd)

| Exposure | Usual Pathogens | Prophylaxis Regimens | Comments |
|---|---|---|---|
| Traveler's diarrhea | Yersinia<br>Cryptosporidium<br>Cyclospora<br>Enteroviruses<br>Amebiasis | | Anti-spasmodics may be used for symptomatic relief of mild, watery diarrhea but are contraindicated in severe diarrhea/dysentery. Bismuth subsalicylate is less effective than antibiotic prophylaxis. Most cases are due to enterotoxigenic E. coli. TMP–SMX is active against some bacterial pathogens and Cyclospora, but not against E. histolytica or enteroviral pathogens (e.g., Rotavirus, Norwalk agent). Doxycycline is active against most bacterial pathogens and E. histolytica, but misses Campylobacter, Cryptosporidium, Cyclospora, Giardia, and enteroviral pathogens. Rifaxamin only active against E.coli. Antibiotics are inactive against viral/parasitic pathogens causing diarrhea. |
| Meningococcal meningitis | N. meningitidis | Pre-travel prophylaxis<br>Meningococcal conjugate vaccine 0.5 mL (IM) ≥ 1 month prior to travel to endemic/epidemic areas<br><br>Post-exposure prophylaxis<br>See p. 358 | Acquired via close face-to-face contact (airborne aerosol/droplet exposure). Vaccine is highly protective against N. meningitidis serotypes A, C, Y, and W-135, but misses serotype B. For areas with serogroup B may use meningococcal group B vaccine. Alternately, consider chemoprophylaxis. |
| Hepatitis A (HAV) | Hepatitis A virus | HAV vaccine 1 mL (IM) prior to travel, then follow with a one-time booster 3, 6 months later | HAV vaccine is better than immune globulin for prophylaxis. Take care to avoid direct/indirect ingestion of fecally contaminated water. HAV vaccine is recommended for travel to all developing countries. Protective antibody titers develop after 2 weeks. |
| Typhoid fever | S. typhi | ViCPS vaccine 0.5 mL (IM). Booster every 2 years for repeat travelers | For the oral vaccine, do not co-administer with antibiotics. Contraindicated in compromised hosts and children < 6 years old. |

**Table 6.14. Travel Prophylaxis Regimens** (cont'd)

| Exposure | Usual Pathogens | Prophylaxis Regimens | Comments |
|---|---|---|---|
| | | **or**<br>Oral Ty21a vaccine 1 capsule (PO) q48h × 4 doses. Booster every 5 years for repeat travelers | Take oral capsules with cold water. Degree of protective immunity is limited with vaccine. Some prefer chemoprophylaxis the same as for Traveler's diarrhea (p. 373). |
| Yellow fever | Yellow fever virus | Yellow fever vaccine 0.5 mL (SC). Booster every 10 years for repeat travelers | Vaccine is often required for travel to or from Tropical South America or Tropical Central Africa. Administer 1 month apart from other live vaccines. Contraindicated in children < 4 months old; caution in children < 1 year old. Reactions may occur in persons with egg allergies. Immunity is probably life long, but a booster every 10 years is needed for vaccination certification by some countries. |
| Japanese encephalitis (JE) | Japanese encephalitis virus | JE vaccine 1 mL (SC) on days 0, 7, and 14 or 30. Booster schedule not established | Recommended for travelers planning prolonged (> 3 week) visits during the rainy season to rural, endemic areas of Asia (e.g., Eastern Russia, Indian subcontinent, China, Southeast Asia, Thailand, Korea, Laos, Cambodia, Vietnam, Malaysia, Philippines). Administer 3, 2 weeks before exposure. Children < 3 years may be given 0.5 mL (SC) on same schedule as adults. |
| Rabies | Rabies virus | HDCV, PCEC, or RVA 1 mL (IM) on days 0, 7, and 21 or 28 prior to travel | Avoid contact with wild dogs/animals during travel. Dose of rabies vaccine for adults and children are the same. A booster dose prior to travel is recommended if antibody levels are measured and are low. |

**Table 6.14. Travel Prophylaxis Regimens** (cont'd)

| Exposure | Usual Pathogens | Prophylaxis Regimens | Comments |
|---|---|---|---|
| | | **or**<br>HDCV 0.1 mL (ID) on days 0, 7, and 21 or 28 prior to travel | |
| Tetanus<br>Diphtheria<br>Pertussis | C. tetani<br>C. diphtheriae<br>B. pertussis | Tdap 0.5 ml (IM) | Tdap preferred to Td since Tdap also boosts pertussis immunity. |

**Table 6.15. Malaria Prophylaxis**

| Drug | Area of Exposure | Adult Dose | Comments |
|---|---|---|---|
| Atovaquone/ proguanil (Malarone) | Prophylaxis in all areas | Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride. 1 adult tablet orally, daily | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance < 30 mL/min). Atovaquone/ proguanil should be taken with food or a milk drink. Not recommended prophylaxis for pregnant women, and women breastfeeding. |
| Chloroquine phosphate (Aralen and generic) | Prophylaxis only in areas with chloroquine-sensitive malaria | 300 mg base (500 mg salt) orally, once/week | Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. |
| Doxycycline | Prophylaxis in all areas | 100 mg orally, (with food) daily | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children < 8 years and in pregnancy. |

**Table 6.15. Malaria Prophylaxis** (cont'd)

| Drug | Area of Exposure | Adult Dose | Comments |
|---|---|---|---|
| Hydroxy-chloroquine sulfate (Plaquenil) | An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive malaria | 310 mg base (400 mg salt) orally, once/week | Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. |
| Mefloquine (Larium) | Prophylaxis in areas with mefloquine-sensitive malaria (mefloquine resistance in SE Asia) | 228 mg base (250 mg salt) orally, once/week | Begin at least 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in persons allergic to mefloquine or related compounds (e.g., quinine, quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities. |
| Primaquine† | Prophylaxis for short-duration travel to areas with principally P. vivax | 30 mg base (52.6 mg salt) orally, daily | Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas.<br><br>Contraindicated in persons with G6PD deficiency, pregnancy and breastfeeding unless the infant being breastfed has a documented normal G6PD level. |

**Table 6.15. Malaria Prophylaxis** (cont'd)

| Drug | Area of Exposure | Adult Dose | Comments |
|---|---|---|---|
| Primaquine | Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease the risk for relapses of P. vivax and P. ovale | 30 mg base (52.6 mg salt) orally, once/day for 14 days after departure from the malarious area. | Indicated for persons who have had prolonged exposure to P. vivax and P. ovale or both. Contraindicated in persons with G6PD† deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level. |

*HDCV = human diploid cell vaccine, PCEC = purified chick embryo cell vaccine, RVA = rabies vaccine absorbed, RIG = rabies immune globulin.*

† Glucose-6-phosphate dehydrogenase. Those who take primaquine should have a normal G6PD level before starting the medication.

## TETANUS PROPHYLAXIS

**Current information suggests that immunity lasts for decades/life-time after tetanus immunization.** A tetanus booster should not be routinely given for minor wounds, but is recommended for wounds with high tetanus potential (e.g., massive crush wounds, soil-contaminated wounds, or deep puncture wounds).

**Table 6.16. Tetanus Prophylaxis in Routine Wound Management**

| History of Adsorbed Tetanus Toxoid | Wound Type | Recommendations |
|---|---|---|
| Unknown or < 3 doses | Clean, minor wounds | Td‡ or Tdap‡ |
| | Tetanus-prone wounds† | (Td‡ or Tdap‡) plus TIG |
| ≥ 3 doses | Clean, minor wounds | No prophylaxis needed |
| | Tetanus-prone wounds† | Td‡ if > 10 years since last dose* |

*DT = diphtheria and tetanus toxoids adsorbed (pediatrics), DTP = diphtheria and tetanus toxoids and pertussis vaccine adsorbed, Td = tetanus and diphtheria toxoids adsorbed (adult), TIG = tetanus immune globulin, Tdap = tetanus and diphtheria toxoids and pertussis vaccine absorbed.*

† For example, massive crush wounds; wounds contaminated with dirt, soil, feces, or saliva; deep puncture wounds; or significant burn wounds or frostbite.

‡ For children < 7 years, DTP (DT if pertussis is contraindicated) is preferred to tetanus toxoid alone. For children ≥ 7 years old and adults, Tdap is preferred to Td or tetanus toxoid alone.

* More frequent booster doses are unnecessary and can increase side effects. Protection lasts > 20 yrs
Adapted from: Centers for Disease Control and Prevention. MMWR Rep 40 (RR-10):1–28. 1991.

## IMMUNIZATIONS

**Immunizations are designed to reduce infections in large populations, and may prevent/decrease the severity of infection in non-immunized individuals.** Compromised hosts with altered immune systems may not develop protective antibody titers to antigenic components of various vaccines. **Immunizations are not fully protective, but are recommended** (depending on the vaccine) for most normal hosts, since some protection is better than none.

**Table 6.17. Adult Immunizations**

| Vaccine | Indications | Dosage | Comments |
|---|---|---|---|
| Bacille Calmette Guérin (BCG) | Possibly beneficial for adults at high-risk of multiple-drug resistant tuberculosis. | Primary: 1 dose (intradermal). Booster not recommended. | Live attenuated vaccine induces a positive PPD which may remain positive for years/life. Contraindicated in immunocompromised hosts. Injection site infection or disseminated infection are rare. |
| Hemophilus influenzae (type B) | For those at increased risk for invasive disease, e.g., functional or anatomic asplenia, HIV, immunoglobulin deficiency, complement deficiency ($C_{1-3}$), stem cell transplants, chemotherapy or radiation therapy. | Primary: 0.5 mL dose (IM). Booster not recommended. | Capsular polysaccharide conjugated to diphtheria toxoid. Benefit uncertain. Safety in pregnancy unknown. Mild local reaction in 10%. |
| Hepatitis A (HAV) | All children beginning age 12 to 23 months and adults at increased risk of HAV. | Primary: 1 mL dose (IM). One-time booster ≥ 6 months later. Booster not routinely recommended. | Inactivated whole virus. Pregnancy risk not fully evaluated. Mild soreness at injection site. Occasional headache/malaise. |
| Hepatitis B (HBV) | Household/sexual contact with carrier, IV drug use, multiple sex partners (heterosexual), homosexual male activity, blood product recipients, hemodialysis, occupational exposure to blood, | Primary (3 dose series): Recombivax 10 mcg (1 mL) or Engerix-B 20 mcg (1 mL) IM in deltoid at 0, 1, and 6 months. Alternate schedule for Engerix-B: 4 dose series at 0, 1, 2, and 12 months. Booster | Recombinant vaccine comprised of hepatitis B surface antigen. For compromised hosts (including dialysis patients), use specially packaged Recombivax 40-mcg doses (1 mL vial containing 40 mcg/mL). HBsAb titers should be obtained 6 months after 3-dose primary series. Those with non-protective titers (≤ 10 mIU/mL) should receive 1 dose monthly |

**Table 6.17. Adult Immunizations** (cont'd)

| Vaccine | Indications | Dosage | Comments |
|---|---|---|---|
| | residents/staff of institutions for developmentally disabled, prison inmates, residence ≥ 6 months in areas of high endemicity, others at high risk. | not routinely recommended. | up to a maximum of 3 doses and retest for HbsAb titers. Pregnancy not a contraindication in high-risk females. Mild local reaction in 10–20%. Occasional fever, headache, fatigue, nausea. Twinrix 1 mL (IM) (combination of Hepatitis A inactivated vaccine and Hepatitis B recombinant vaccine) is available for adults on a 0, 1, and 6-month schedule or 0, 7 days, 21–30 days, and 12 month schedules. |
| Herpes zoster (VZV) | Adults ≥ 60 years to reduce the frequency of shingles/ prevent post-herpetic neuralgia. Use in those with previous H. zoster is not yet defined. Protection best in 60–69 year group; efficacy decreases with increasing age. | Primary: 0.65 mL (SC). Need for revaccination not yet defined. Vaccine must be stored frozen and used within 30 minutes after thawing. | Duration of protection is at least 4 years. Injection site reactions in 48%. Contraindicated in immunocompromised hosts (with immunosuppressive disorder or receiving immunosuppressive drug) or untreated TB. Not indicated for therapy of H. zoster or post-herpetic neuralgia. |
| Influenza | All adults. | Annual vaccine. Single 0.5 mL dose (IM) before flu season is optimal, but can be given anytime during flu season. (2 A strains + 1 B strain) | High dose (HD) vaccine has 4× the antigen content as the standard dose (SD) vaccine. Quadrivalent (2 A strains + 2 B strain) and trivalent inactivated whole and split virus vaccines available. Contraindications include anaphylaxis to eggs or sensitivity to thimerosal. Mild local reaction common. Malaise/ myalgias in some. For pregnancy, administer in 2nd or 3rd trimester during flu season. High titer (HD) inactivated vaccine indicated for adults ≥ 65 years, but enhanced protective efficacy (vs. SD) not yet demonstrated. |

**Table 6.17. Adult Immunizations** (cont'd)

| Vaccine | Indications | Dosage | Comments |
|---|---|---|---|
| Measles | Adults born after 1956 without live-virus immunization or measles diagnosed by a physician or immunologic test. Also indicated for revaccination of persons given killed measles vaccine between 1963–67. | Primary: 0.5 mL dose (SC). A second dose (≥ 1 month later) is recommended for certain adults at increased risk of exposure (e.g., healthcare workers, travelers to developing countries). No routine booster. | Live virus vaccine (usually given in MMR). Contraindicated in compromised hosts, pregnancy, history of anaphylaxis to eggs or neomycin. Ineffective if given 3–11 months after blood products. Side effects include low-grade fever 5–21 days after vaccination, rash, and local reactions in if previously immunized with killed vaccine (1963–67). |
| Meningo-coccus (invasive disease) | Patients with splenic dysfunction or with complement defects ($C_{7-9}$) laboratory workers. May be given to 1st year college students living in dormitories. | Meningococcal conjugate vaccine 0.5 mL (IM). Primary: 0.5 mL (IM) then again at months 2 and 6 (3 dose series) | Also used in epidemic control of N. meningitides serogroups A, C, Y, and W-135. For sero-group B use meningococcal group B vaccine. |
| Mumps | Non-immune adults. | Primary: 0.5 mL dose (SC). No routine booster. | Live attenuated vaccine (usually given in MMR). Contraindicated in immunocompromised hosts, pregnancy, history of anaphylaxis to eggs or neomycin. |
| Papilloma (human) Virus (HPV) | Females up to 26 years of age. Contraindicated in pregnancy. Suggested for males up to 26 years of age. | Primary: 0.5 mL (IM). Second dose: 2 months after 1st dose. Third dose: 6 months after 1st dose. | Quadrivalent HPV vaccine to prevent cervical, vulvar, vaginal and cancers caused by HPV types 6, 11, 16, 18. 9 valent HPV vaccine includes HPV types 52, 58, 31, 33, 45, 6, 11, 16, 18. |
| Pertussis | Use Tdap instead of Td in booster dose. | A Single Tdap booster dose 0.5 mL (IM). | Recommended since adults may get pertussis or transmit it to susceptible infants. |

**Table 6.17. Adult Immunizations** (cont'd)

| Vaccine | Indications | Dosage | Comments |
|---|---|---|---|
| Pneumococcus (S. Pneumoniae) | Immunocompetent hosts ≥ 65 years old, or > 19 years old with diabetes, CSF leaks, or chronic cardiac, pulmonary or liver disease. Also for immunocompromised hosts > 19 years old with functional/anatomic asplenia,* leukemia, lymphoma, multiple myeloma, widespread malignancy, chronic renal failure, bone marrow/organ transplant, or on immunosuppressive/steroid therapy. | PPSV-23<br>PCV-13<br>Primary: 0.5 mL dose (IM). No booster.<br>Primary: 0.5 mL dose (SC or IM). A one-time booster at 5 years is recommended for immuno – compromised hosts > 2 years old and for those who received the vaccine before age 65 for high-risk conditions. | *Pneumococcal vaccine naïve persons aged ≥ 65*. Give PCV-13, then give PPSV-23 6-12 months later (minimal interval 8 weeks).<br>*Persons who previously received PPSV-23 at age ≥ 65*. Give PCV-13 >1 year later after PPSV-23 given.<br>*Persons who previously received PPSV-23 before age 65 years who are now age ≥ 65*. Give PCV-13 when ≥ 65 years give > 1 year later (minimum interval between sequential administration of PCV-13 and PPSV-23 is 8 weeks). If this window is missed, PPSV-23 can be given 6-12 months after PCV-13. |
| Rubella | Non-immune adults, particularly women of childbearing age. | Primary: 0.5 mL dose (SC). No routine booster. | Live virus (RA 27/3 strain) vaccine (usually given in MMR). Contraindicated in immunocompromised hosts, pregnancy, history of anaphylactic reaction to neomycin. Joint pains and transient arthralgias in up to 40%, beginning 3–25 days after vaccination and lasting 1–11 days; arthritis in < 2%. |
| Tetanus-diphtheria | Adults | Primary: Td two 0.5 mL doses (IM), 1–2 months apart; third dose 6–12 months after second dose. Booster: a single Tdap 0.5 mL (IM) is recommended. Tdap should be substituted for one of the three Td doses. | Adsorbed toxoid vaccine. Contraindicated if hypersensitivity/neurological reaction or severe local reaction to previous doses. Side effects include local reactions, occasional fever, systemic symptoms, Arthus-like reaction in persons with multiple previous boosters, and systemic allergy (rare). |

PCV-13 = 13 valent pneumococcal conjugate vaccine (contains strains: 1, 3, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
PPSV-23 = 23 valent pneumococcal polysaccharide vaccine (contains strains: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F).
*Pneumococcal polysaccharide vaccine may be given before splenectomy, but is in effective post-splenectomy, the conjugate vaccine is more effective.

**Table 6.17. Adult Immunizations** (cont'd)

| Vaccine | Indications | Dosage | Comments |
|---|---|---|---|
| Varicella (VZV) chickenpox | Non-immune adolescents and adults, especially healthcare workers and others likely to be exposed. | Primary: Two 0.5 mL doses (SC), 4–8 weeks apart. Vaccine must be stored frozen and used within 30 minutes after thawing and reconstitution. No routine booster. | Live attenuated vaccine. Contraindications include pregnancy, active untreated TB, immunocompromised host, malignancy of bone marrow or lymphatic system, anaphylactic reaction to gelatin/neomycin, or blood product recipient within previous 6 months (may prevent development of protective antibody). Mild febrile illness in 10%. Injection site symptoms in 25–30% (local rash in 3%). Mild diffuse rash in 5%. |

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Chapter 7

# Pediatric Infectious Diseases and Pediatric Drug Summaries

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This chapter pertains to infectious diseases and antimicrobial agents in the pediatric population. It is organized by clinical syndrome, patient subset, and in some cases, specific organism. Clinical summaries immediately follow each treatment grid. Therapeutic recommendations are based on antimicrobial effectiveness, reliability, cost, safety, and resistance potential. Antimicrobial agents and duration of therapy are listed in the treatment grids; corresponding drug dosages are provided on pages 414–422 and represent the usual dosages for normal renal and hepatic function. Drug dosages in infants/children are generally based on weight, up to adult dosage as maximum. ***For any treatment category, i.e., preferred IV therapy, alternate IV therapy, PO therapy recommended drugs are equally effective and not ranked by priority.*** Please refer to other pediatric drug references and the manufacturer's package inserts for dosage adjustments, side effects, drug interactions, and other important prescribing information.

"IV-to-PO Switch" in the last column of the shaded title bar in each treatment grid indicates the clinical syndrome can be treated either by IV therapy alone or IV followed by PO therapy, but

*not* by PO therapy alone. "PO Therapy or IV-to-PO Switch" indicates the clinical syndrome can be treated by IV therapy alone, PO therapy alone, or IV followed by PO therapy (unless otherwise indicated in the footnotes under each treatment grid). Most patients on IV therapy able to take oral medications should be switched to PO equivalent therapy after clinical improvement.

# Empiric Therapy of CNS Infections

## Acute Bacterial Meningitis

| Subset (age) | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† |
|---|---|---|---|
| Neonate (0–30 days) | Group B streptococci<br>E. coli<br>Listeria monocytogenes<br>Other gram-negatives (e.g., Citrobacter, Serratia) and gram-positives (e.g., Enterococci) | Ampicillin **plus** Gentamicin* | Ampicillin **plus** Cefotaxime* |
| 1–3 months | Overlap neonate and > 3 months | Vancomycin **plus** **either** Cefotaxime **or** Ceftriaxone* | Ampicillin **plus** **either** Cefotaxime **or** Ceftriaxone* |
| > 3 months | S. pneumoniae<br>N. meningitidis<br>H. influenzae B (very rare)<br>Non-typable H. influenzae (rare) | Before culture results: Vancomycin **plus** **either** Ceftriaxone **or** Cefotaxime*<br><br>After culture results Discontinue vancomycin if penicillin-susceptible S. pneumoniae, N. meningitidis, or H. influenzae is isolated | Meropenem*<br><br>Severe penicillin allergy Vancomycin **plus** **either** Rifampin **or** Chloramphenicol* |

## Acute Bacterial Meningitis (cont'd)

| Subset (age) | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† |
|---|---|---|---|
| CNS shunt infection<br><br>(Treat initially for S. epidermidis; if later identified as MSSA, treat accordingly) | S. epidermidis<br>S. aureus (MRSA) | Vancomycin **with or without** Rifampin 10 mg/kg (IV or PO) q12h × 7–10 days after shunt removal | Linezolid × 7–10 days after shunt removal<br><br>If MSSA isolated<br>Nafcillin **with or without** Rifampin 10 mg/kg (PO) q12h × 7–10 days after shunt removal |
| | S. aureus (MSSA) | Nafcillin × 7–10 days after shunt removal | Vancomycin × 7–10 days after shunt removal |
| | Enterobacteriaceae | Cefotaxime **or** Ceftriaxone × 7–10 days after shunt removal | Meropenem × 7–10 days after shunt removal |

*MRSA/MSSA = methicillin-resistant/sensitive S. aureus.* Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† **See pp. 414–422 for drug dosages.**

* Duration of therapy: Group B strep ≥ 14 days (with ventricilitis 4 weeks); E. coli, Citrobacter, Serratia ≥ 21 days; Listeria 10–14 days; Enterococcus ≥ 14 days; S. pneumoniae 10–14 days; H. influenzae ≥ 10 days; N. meningitidis 4–7 days.

### Acute Bacterial Meningitis (Normal Hosts)

**Clinical Presentation:** Fever, headache, stiff neck (or bulging anterior fontanelle in infants), irritability, vomiting, lethargy, evolving over hours to 1–2 days. The younger the child, the more nonspecific the presentation (e.g., irritability, lethargy, fever, poor feeding).

**Diagnostic Considerations:** Diagnosis by CSF chemistries, gram stain, culture. CSF findings are similar to those in adults: pleocytosis (100–5000 WBCs/mm$^3$; predominately PMNs), ↑ protein, ↓↓ glucose. Normal CSF values differ by age:

| | WBC/mm$^3$ (range); %PMNs | Protein, mg/dL (range) | Glucose, mg/dL (range) |
|---|---|---|---|
| Preterm | 9 (0–25); 57% PMNs | 115 (65–150) | 50 (24–63) |
| Term newborn | 8 (0–22); 61% PMNs | 90 (20–170) | 52 (34–119) |
| Child | 0 (0–7); 0% PMNs | (5–40) | (40–80) |

Modified from *The Harriet Lane Handbook*, 20th edition.

**Pitfalls:** The younger the child, the more nonspecific the presentation. With prior antibiotic use (e.g., oral therapy for otitis media), partially-treated meningitis (CSF lactic acid levels 4-6 nm/L) is a concern. Especially in the summer season, rapid viral diagnosis (especially enteroviral PCR) can exclude ABM and prevent unnecessary hospitalization and antibiotic use. HSV PCR can also be helpful in excluding ABM.
**Therapeutic Considerations:** Meningitic doses of antibiotics are required for the *entire* course of treatment. Repeat lumbar puncture (LP) is indicated at 24–48 hours if not responding clinically or in situations where a resistant organism is a concern (e.g., penicillin-resistant S. pneumonia, or neonate with gram-negative bacillary meningitis). Dexamethasone (0.3 mg/kg IV q12h × 2 days) may reduce neurologic sequelae (e.g., hearing loss) in children ≥ 6 weeks of age when given before/with the first dose of antibiotics.
**Prognosis:** Varies with causative agent and age at presentation. Overall mortality < 5% in US (higher in developing countries). Morbidity 30–35% with hearing loss the most common neurologic sequella. Incidence of neurologic sequelae: S. pneumoniae > H. influenzae > N. meningitidis. Use of H. influenzae (type B) and pneumococcal conjugate vaccines in routine childhood immunizations have greatly reduced the incidence of meningitis caused by these pathogens. Neonates are at increased risk of mortality and major neurologic sequelae, and there is a significant incidence of brain abscesses in neonates with gram-negative meningitis (especially Citrobacter and Serratia infections).

### Acute Bacterial Meningitis (CNS Shunt Infections)

**Clinical Presentation:** Indolent (lethargy, irritability, vomiting) or acute (high fever, depressed mental status).
**Diagnostic Considerations:** Diagnosis by CSF gram stain/culture, often obtained by shunt tap.
**Pitfalls:** Blood cultures are usually negative for shunt pathogens and CSF WBCs may be low.
**Therapeutic Considerations:** High risk of nafcillin resistance with coagulase-negative staphylococcal infection. The addition of rifampin to vancomycin may improve clearance of bacteria. Removal of prosthetic material is usually necessary to achieve a cure.
**Prognosis:** Good with removal of prosthetic material.

## Encephalitis

| Subset | Usual Pathogens | IV Therapy† | IV-to-PO Switch† |
|---|---|---|---|
| Herpes | HSV-1 | Acyclovir × 14–21 days | Treat IV only |
| Arbovirus | WNV, SLE, Powassan encephalitis, EEE, WEE, VEE, JE, CE | No specific therapy | |
| Mycoplasma | M. pneumoniae | Doxycycline **or** Minocycline × 2–4 weeks | Doxycycline **or** minocycline × 2–4 weeks |

## Encephalitis (cont'd)

| Subset | Usual Pathogens | IV Therapy† | IV-to-PO Switch† |
|---|---|---|---|
| Respiratory viruses | Influenza, Enteroviruses, Measles | No specific therapy | |

*WNV = West Nile Virus, SLE = St. Louis encephalitis, EEE = Eastern equine encephalitis, WEE = Western equine encephalitis, VEE = Venezuelan equine encephalitis, JE = Japanese encephalitis, CE = California encephalitis.*

† **See pp. 414–422 for drug dosages.**

### Herpes Encephalitis (HSV-1)

**Clinical Presentation:** Acute onset of fever and mental status/behavioral changes. High fever with intractable seizures and profoundly depressed sensorium may dominate the clinical picture.

**Diagnostic Considerations:** Diagnosis by CSF PCR for HSV-1. CSF findings include ↑ RBC/WBC, ↓ glucose, and ↑↑ protein. Classic EEG changes with temporal lobe spikes may be present early. Brain biopsy is rarely, if ever, indicated.

**Pitfalls:** MRI/CT scan can be normal initially. Delays in diagnosis and therapy adversely affect outcome.

**Therapeutic Considerations:** HSV is the only treatable viral encephalitis in normal hosts.

**Prognosis:** Antiviral therapy improves survival based on level of consciousness at presentation. Mortality is 10–20%, and major neurologic sequellae are frequent in survivors.

### Arboviral Encephalitis

**Clinical Presentation:** Acute onset of fever, headache, altered mental status. Usually seasonal (more common in summer/fall), based on vector/travel history. Can be very severe with high mortality. Symptomatic West Nile encephalitis is rare in children.

**Diagnostic Considerations:** Serological studies are the primary means of diagnosis. PCR "encephalitis panels" are being developed for clinical use.

**Therapeutic Considerations:** No specific antiviral therapy. Supportive therapy is crucial.

**Pitfalls:** Be sure to elicit potential exposures/travel history in children with fever/altered mental status.

**Prognosis:** Varies with agent. Severe residual deficits and high mortality rates can occur, especially with Eastern Equine encephalitis.

### Mycoplasma Encephalitis

**Clinical Presentation:** Acute onset of fever and mental status changes. Prodromal cough, sore throat, respiratory symptoms may occur.

**Diagnostic Considerations:** CSF shows mild pleocytosis with a predominance of mononuclear cells, normal or mildly ↓ glucose, and mildly ↑ protein. Mycoplasma IgG/IgM titers are elevated.

**Pitfalls:** CSF findings can be confused with viral encephalitis.

**Therapeutic Considerations:** Often self-limited illness even without antibiotic therapy. Doxycycline or minocycline penetrate CNS and can be used in children > 8 years of age. Macrolides may treat pulmonary infection but do not penetrate CNS.

**Prognosis:** Good. Neurologic sequelae are rare.

**Respiratory Virus Encephalitis**

**Clinical Presentation:** Encephalitis may occur during or immediately after an acute respiratory illness. Influenza encephalitis, although rare, may be especially severe with a number of deaths reported every year in previously healthy children and adolescents.

**Diagnostic Considerations:** Rarely, adenoviruses have been recovered from CSF or brain in cases of encephalitis. Encephalitis has also been described very rarely in association with RSV and parainfluenza infections as well.

**Pitfalls:** Most cases of encephalitis remain undiagnosed, in part due to failure to consider and test for respiratory viruses.

**Therapeutic Considerations:** No evidence to date suggests a benefit of anti-influenza therapy in influenza encephalitis.

**Prognosis:** Generally self-limited with recovery, but death has been reported with influenza encephalitis. Adenovirus, measles, and mumps encephalitis in immunocompromised hosts may also be severe.

# Empiric Therapy of HEENT Infections

## Periorbital (Preseptal) Cellulitis/Orbital Cellulitis

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† | IV-to-PO Switch† |
|---|---|---|---|---|
| Periorbital cellulitis | S. pneumoniae<br>H. influenzae<br>M. catarrhalis<br>S. aureus | **Combination therapy with** Nafcillin* **plus either** Ceftriaxone **or** Cefotaxime × 10–14 days | Ampicillin-sulbactam × 10–14 days | Amoxicillin/clavulanate **or** Cefuroxime **or** Cefpodoxime **or** Cefdinir × 10–14 days |
| Orbital cellulitis | S. pneumoniae<br>H. influenzae<br>M. catarrhalis<br>S. aureus<br>Anaerobes<br>Group A streptococci | **Combination therapy with** Nafcillin **plus** Ceftriaxone × 10–14 days | Piperacillin/tazobactam **or** Ampicillin-sulbactam **or** Ticarcillin/clavulanate × 10–14 days | Amoxicillin/clavulanate **or** Cefuroxime **or** Cefpodoxime **or** Cefdinir × 10–14 days |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

* Clindamycin or vancomycin if CA-MRSA likely.

† See pp. 414–422 for drug dosages.

**Clinical Presentation:** Periorbital and orbital cellulitis are bacterial infections. Fever, lid swelling, and erythema around the eye often in conjunction with acute sinusitis. In periorbital cellulitis the infection is

anterior to the orbital septum. Orbital cellulitis involves the orbit proper, extraocular muscles/nerves, and possibly the orbital nerve. Proptosis and limitation of ocular mobility define orbital cellulitis.

**Diagnostic Considerations:** CT scan is used to differentiate preseptal from periorbital cellulitis and identify the extent of orbital involvement when present.

**Pitfalls:** Failure to recognize orbital involvement leading to optic nerve damage or CNS extension/cavernous sinus thrombosis. CT scan cannot differentiate phlegmon from abscess.

**Therapeutic Considerations:** Orbital cellulitis is more emergent than periorbital cellulitis and should be treated with IV antibiotics initially. Surgical drainage may be indicated if a well defined abscess is present or in more severe disease.

**Prognosis:** Good with prompt antimicrobial therapy and ophthalmologic surgery if needed.

## Sinusitis

| Subset | Usual Pathogens | IV Therapy† (Hospitalized) | PO Therapy or IV-to-PO Switch† (Ambulatory) |
|---|---|---|---|
| Acute | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Ceftriaxone **or** cefuroxime × 1–2 weeks | Amoxicillin **or** Amoxicillin/clavulanic acid **or** 2nd or 3rd generation cephalosporin **or** Clarithromycin* × 10–14 days **or** Azithromycin* × 5 days |
| Chronic | Same as acute + oral anaerobes | Requires prolonged antimicrobial therapy (2–4 weeks) | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement (usually < 72 hrs).

* Macrolides may be less effective and should be reserved for penicillin- and cephalosporin-allergic patients.

† **See pp. 414–422 for drug dosages.**

**Clinical Presentation:** Nasal discharge and cough frequently with headache, facial pain, and low-grade fever lasting > 10–14 days. Can also present acutely with high fever (≥ 104°F) and purulent nasal discharge ± intense headache for ≥ 3 days.

**Diagnostic Considerations:** Acute sinusitis is a clinical diagnosis. Imaging studies are not routinely indicated. Overlap with acute viral infection and allergic symptoms may make diagnosis difficult.

**Pitfalls:** Transillumination, sinus tenderness to percussion, and color of nasal mucus are not reliable indicators of sinusitis.

**Therapeutic Considerations:** Microbiology/antibiotics are similar to acute otitis media, but duration of therapy is 10–14 days. Failure to respond to initial antibiotic therapy suggests a resistant pathogen or an alternative diagnosis. There are insufficient data to support long-course antibiotic treatment. Rarely, quinolones may be considered as 3rd line alternative.

**Prognosis:** Good. For frequent recurrences, consider radiologic studies and ENT/allergy consultation.

## Otitis Externa

| Subset | Usual Pathogens | Topical Therapy |
|---|---|---|
| "Swimmer's ear" | Pseudomonas sp.<br>Enterobacteriaceae<br>S. aureus | Polymyxin B plus neomycin **plus** hydrocortisone (eardrops) q6h × 7–10 days<br>**or**<br>Ciprofloxacin (otic solution) q12h × 7–10 days<br>**plus**<br>Dexamethasone or hydrocortisone ear drops<br>**or**<br>Ofloxacin (otic solution) q12h × 7–10 days |

**Clinical Presentation:** Ear pain, itching, and sensation of fullness. Pain is exacerbated by tugging on the pinna or tragus of the outer ear. Purulent discharge may be visible in the external ear canal. Fever is generally absent.

**Diagnostic Considerations:** Otitis externa is a clinical diagnosis. A recent history of swimming or cleaning with cotton swabs is often elicited. Malignant otitis externa, as seen in elderly adults with diabetes mellitus, is extremely rare in children but may be seen in immunocompromised hosts.

**Pitfalls:** Failure to recognize a ruptured tympanic membrane may lead to a misdiagnosis of otitis externa based on purulence in the canal.

**Therapeutic Considerations:** Local cleansing (e.g., 2% acetic acid) and topical therapy with corticosporin-polymixin B-neomycin suspension is usually sufficient. Oral antibiotics should be considered for fever/cervical adenitis.

**Prognosis:** Excellent. Cleansing with 2% acetic acid drops after swimming prevents recurrences.

## Acute Otitis Media

| Subset | Usual Pathogens | IV/IM Therapy† | PO Therapy† |
|---|---|---|---|
| Initial uncomplicated bacterial infection | S. pneumoniae<br>H. influenzae<br>M. catarrhalis | Ceftriaxone × 1 dose | Amoxicillin × 10 days **or** Azithromycin§ (1-, 3-, or 5-day regimen) **or** Erythromycin-sulfisoxazole × 10 days** **or** TMP–SMX × 10 days** |
| Treatment failure or resistant organism* | MRSP Beta-lactamase positive H. influenzae | Ceftriaxone q24h × 3 doses | Amoxicillin/clavulanic acid **or** cephalosporin × 10 days‡* |

*DRSP = drug-resistant S. pneumoniae.* Pediatric doses are provided; acute otitis media is uncommon in adults. For chronic otitis media, prolonged antimicrobial therapy is required.

† **See pp. 414–422 for drug dosages.**

* Treatment failure = persistent symptoms and otoscopy abnormalities 48–72 hours after starting initial antimicrobial therapy. For risk factors for DRSP, see Therapeutic Considerations, below. If still fails after recommended therapy, consider clindamycin for resistant S. pneumoniae or tympanocentesis for gram stain and culture.

** In children > 6 years of age with mild-moderate acute otitis media, a 5–7 day course of antimicrobial theory may be adequate.

†† ES-600 = 600 mg amoxicillin/5 mL.

‡ 10-day course with either cefuroxime axetil 15 mg/kg (PO) q12h or cefdinir 7 mg/kg (PO) q12h or 14 mg/kg (PO) q24h or cefpodoxime 5 mg/kg (PO) q12h may be used.

§ Macrolides and TMP-SMX may be less effective and should be reserved for penicillin or cephalosporin allergic patients.

**Clinical Presentation:** Fever, otalgia, hearing loss. Nonspecific presentation is more common in younger children (irritability, fever). Key to diagnosis is examination of the tympanic membrane. Acute otitis media requires evidence of inflammation *and* effusion. Uncommon in adults.
**Diagnostic Considerations:** Diagnosis is made by finding an opaque, hyperemic, bulging tympanic membrane with loss of landmarks and decreased mobility on pneumatic otoscopy.
**Pitfalls:** Otitis media with effusion (i.e., tympanic membrane retracted or in normal position with decreased mobility or mobility with negative pressure; fluid present behind the drum but normal in color) usually resolves spontaneously and should not be treated with antibiotics.
**Therapeutic Considerations:** American Academy of Pediatrics guidelines suggest initial observation without antibiotics for non-severe otitis media or in children > 6 month of age. Risk factors for infection with drug-resistant S. pneumoniae (DRSP) include antibiotic therapy in past 30 days, failure to respond within 48–72 hours of therapy, day care attendance, and antimicrobial prophylaxis. Quinolones not approved for therapy.
**Prognosis:** Excellent, but tends to recur. Chronic otitis, cholesteatomas, mastoiditis are rare complications. Tympanostomy tubes/adenoidectomy for frequent recurrences of otitis media are the leading surgical procedures in children.

## Mastoiditis

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|---|
| Acute | S. pneumoniae<br>S. aureus<br>Group A streptococci<br>H. influenzae | Nafcillin **or** Clindamycin **or** Vancomycin (if CA-MRSA suspected) **plus either** Ceftriaxone **or** Cefotaxime × 10–14 days | Ampicillin-sulbactam × 10–14 days | Amoxicillin/clavulanate **or** Cefpodoxime **or** Cefdinir **or** Cefuroxime axetil × 10–14 days |
| Chronic | Polymicrobial, including P. aeruginosa, S. aureus, anaerobes, Enterobacteriaceae | Piperacillin/Tazobactam **or** Ticarcillin/clavulanate × 10–14 days | Meropenem **or** Imipenem × 10–14 days | None |

Duration of therapy represents total time IV, IV + PO, or PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.
† **See pp. 414–422 for drug dosages.**

**Clinical Presentation:** Fever and otalgia with postauricular swelling/erythema pushing the ear superiorly and laterally. The presentation may be more subtle (e.g., less toxic, less swelling, Bell's palsy alone) in older children partially treated with antibiotics. Concomitant otitis media is rare.
**Diagnostic Considerations:** Acute mastoiditis is diagnosed clinically, but CT scan is definitive. Tympanocentesis through intact ear drum for aspirate and insertion of tympanostomy tube are helpful for microbiology and drainage, respectively. Chronic mastoiditis is often polymicrobial, including anaerobes and P. aeruginosa. Tuberculosis rarely presents as chronic mastoiditis.

**Pitfalls:** Do not overlook mastoiditis in older child with unresponsive otitis. Orbital involvement may lead to optic nerve damage or CNS extension/cavernous sinus thrombosis.
**Therapeutic Considerations:** Treatment is based on microbiology and requires at least 3 weeks of antibiotics.
**Prognosis:** Good with early treatment.

## Pharyngitis

| Subset | Usual Pathogens | IV or IM Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|
| Exudative (culture) | Group A streptococci | Benzathine penicillin IM × 1 dose | Penicillin V **or** Amoxicillin × 10 days. *Alternate*: Azithromycin 12 mg/kg/day × 5 days **or** Cephalexin **or** Cefadroxil **or** Erythromycin **or** Clarithromycin **or** Clindamycin × 10 days |
| Asymptomatic carrier | Group A streptococci | No treatment indicated | No treatment indicated |
| Persistent/recurrent disease | Group A streptococci | Clindamycin | Amoxicillin/clavulanate × 10 days **or combination therapy with either** Penicillin V **or** Amoxicillin × 10 days plus Rifampin added on days 7–10 |
| Exudative, sexually active | N. gonorrhoeae | Ceftriaxone (IM) × 1 dose | |
| Lemierre's Syndrome (jugular vein septic thrombophlebitis)‡ | Fusobacterium necrophorum | Clindamycin (IV) **or** Penicillin G (IV) × 4–6 weeks | Clindamycin **or** Penicillin VK × 4–6 weeks |
| Vesicular, ulcerative | Enteroviruses HSV 1 or 2 | Primary HSV: Acyclovir × 5–7 days | Primary HSV: Acyclovir **or** Valacyclovir × 5–7 days |

Duration of therapy represents total time IV, IM, IV + PO, or PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.
† **See pp. 414–422 for drug dosages.**
‡ Treat only IV or IV-to-PO switch.

**Clinical Presentation:** Acute sore throat and fever with tender cervical lymphadenitis. Primary clinical consideration is differentiating Group A streptococci (GAS) from viral/other causes (e.g., adenovirus, enterovirus, respiratory viruses, other strep groups [C, G], Arcanobacterium hemolyticum, M. pneumoniae, C. pneumoniae, EBV). GAS is less likely with concomitant coryza, conjunctivitis, hoarseness, cough, acute stomatitis, discrete oral ulcerations, or diarrhea—children with these manifestations should not be cultured routinely.

**Diagnostic Considerations:** Laboratory testing for GAS is recommended, since clinical differentiation of viral pharyngitis from GAS is not possible. Rapid tests for GAS antigens are reliable with excellent specificities, but due to variable sensitivities of the assays, a negative rapid test should be confirmed by a throat culture. The accuracy of antigen and culture tests is dependent on obtaining a good throat swab containing pharyngeal/tonsillar secretions.

**Pitfalls:** Be sure to obtain a good throat swab. Post-treatment testing is generally not recommended unless the patient is at high risk for rheumatic fever (e.g., family history, ongoing outbreak) or is still symptomatic after 10 days of therapy. Asymptomatic GAS carriers do not require antibiotic therapy, but identifying a "true carrier" may be difficult. Eradication of GAS carriage should be considered in the following situations: an outbreak of acute rheumatic fever or post-streptococcal glomerulonephritis; an outbreak of GAS in a closed community; a family history of rheumatic fever; multiple episodes of GAS infection within the family for many weeks despite therapy; family anxiety about the presence of GAS; or tonsillectomy is being considered based on persistent carriage. Eradication is achieved using the same antimicrobial regimen as for "persistent/recurrent disease" (see treatment grid p. 395).

**Therapeutic Considerations:** Penicillin V (or amoxicillin) is the drug of choice for GAS pharyngitis. Erythromycin is still considered the drug of choice for penicillin-allergic individuals, although macrolide-resistant GAS strains are being reported. First-generation cephalosporins are also useful alternatives. Broader spectrum agents, although likely effective, should not be used routinely. Macrolides or sulfonamides may not eradicate GAS pharyngitis. When eradication of carriage is indicated amoxicillin, amoxicillin/clavulanate or clindamycin alone or penicillin plus rifampin may be useful.

**Prognosis:** Excellent. Rheumatic fever is rare in the US.

# Empiric Therapy of Lower Respiratory Tract Infections

## Community-Acquired Pneumonia

| Subset (age) | Usual Pathogens | IV Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|
| Community-acquired pneumonia *Birth to 20 days* | Group B streptococci, Gram-negative enteric bacteria | Ampicillin **Plus either** Gentamicin **or** Cefotaxime × 10–21 days | Not applicable |

Duration of therapy represents total time IV or IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† **See pp. 414–422 for drug dosages.**

## **Community-Acquired Pneumonia** (cont'd)

| Subset (age) | Usual Pathogens | IV Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|
| *3 weeks to 3 months* | RSV<br>Parainfluenza<br>Human metapneumovirus (hmpv) | None (supportive care) | None |
| | C. trachomatis<br>S. pneumoniae<br>B. pertussis<br>S. aureus | Cefotaxime **or** Ceftriaxone × 10–14 days*.<br>Alternative: Ampicillin **or** Clindamycin* | Afebrile: Erythromycin × 14 days **or** Azithromycin × 5–7 days.<br>Lobar, febrile: Amoxicillin **or** amoxicillin/clavulanic acid **or** Cefdinir **or** Cefuroxime **or** Cefpodoxime × 10–14 days |
| *> 3 months to < 5 years* | Viruses (RSV, parainfluenza, influenza, adenovirus, rhinoviruses) | RSV: consider ribavirin.§ For infants at highest risk for severe RSV infection, consider palivizumab 15 mg/kg/month × 1–2 seasons for prevention. Influenza: Oseltamivir (influenza A, B).¶ Routine immunization for all children > 6 months | |
| | S. pneumoniae<br>H. influenzae<br>M. pneumoniae | Ampicillin** **or** Ceftriaxone **or** Cefotaxime × 10–14 days* | Amoxicillin **or** Amoxicillin/clavulanate **or** Clarithromycin **or** Azithromycin × 10–14 days |
| *5–15 years* | M. pneumoniae<br>C. pneumoniae<br>S. pneumoniae | Ceftriaxone **plus** a macrolide × 10–14 days* | Amoxicillin **plus** a macrolide **or** Doxycycline (age > 8 years) × 10–14 days |
| Pertussis | Bordetella spp.‡<br>certain Adenoviruses<br>M. pneumoniae<br>C. trachomatis<br>C. pneumoniae | Azithromycin × 5 days **or** Erythromycin × 14 days | Erythromycin estolate × 14 days **or** Clarithromycin × 7 days **or** Azithromycin × 5 days. If macrolide-intolerant: TMP–SMX × 14 days |
| Tuberculosis | M. tuberculosis | See pp. 400–401 | See pp. 400–401 |

Duration of therapy represents total time IV or IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† **See pp. 414–422 for drug dosages.**

* If chronic cough of more insidious onset, consider adding IV or PO macrolide (azithromycin, clarithromycin, erythromycin) to cover Pertussis/C. trachomatis (3 weeks–3 months of age), Mycoplasma (> 5 years of age), or Mycoplasma/C. pneumoniae (5–15 years of age).

** If fully immunized against H. influenzae and S. pneumoniae.

‡ B. pertussis, B. parapertussis, B. bronchiseptica.

§ Use should be limited to the most severely ill with RSV, i.e., transplant patients.

¶ Influenza A strains now circulating are amantadine resistant.

## Community-Acquired Pneumonia

**Clinical Presentation:** Fever ± dyspnea, cough, tachypnea with infiltrates on chest x-ray.

**Diagnostic Considerations:** Usual pathogens differ by age. In neonates, pneumonia is typically diffuse and part of early-onset sepsis. In young infants, there is significant overlap between signs and symptoms of bronchiolitis (primarily due to RSVU) and pneumonia. Severe pneumonia is usually due to bacterial infection, although the organism is frequently not isolated (e.g., blood cultures are positive in only 10–20% of children < 2 years of age with bacterial pneumonia). In young infants, Chlamydia trachomatis can be detected by or culture of nasopharyngeal (NP) secretions. Mycoplasma pneumonia, suggested by high titer cold agglutinins > 1:64. Diagnosis by nucleic acid amplification testing or ↑ IgM titers. Although cases in children < 5 years have been reported. Respiratory viruses (RSV, influenza, adenoviruses, parainfluenza viruses, hMPV) can also be detected by PCR of throat/nasal secretions. If child lives in area with high prevalence of tuberculosis, consider tuberculosis in the differential diagnosis of primary pneumonia.

**Pitfalls:** Reliance on upper airway specimen for gram stain/culture leads to misdiagnosis and mistreatment, as true deep sputum specimen is rarely obtainable in children.

**Therapeutic Considerations:** Therapy is primarily empiric based on child's age, clinical/epidemiologic features and chest x-ray findings. Mycoplasma requires 2–3 weeks of treatment; C. pneumoniae may require up to 4 weeks of treatment. Routine use of pneumococcal vaccines has decreased the incidence of pneumococcal pneumonia.

**Prognosis:** Varies with pathogen, clinical condition at presentation, and underlying health status. Prognosis is worse in children with chronic lung disease, congenital heart disease, immunodeficiency, neuromuscular disease, hemoglobinopathy.

## Lower Respiratory Tract Infections due to Respiratory Viruses

**Clinical Presentation:** Viruses cause the majority of lower respiratory tract infections (LRTIs) in children. Respiratory syncytial virus (RSV) is the leading cause of LRTI in young infants, manifesting as bronchiolitis/viral pneumonia and causing annual mid-winter epidemics. The risk of secondary bacterial infection (other than possibly otitis media) is very low. Fever is typically low grade and usually improves over 3–5 days, even if hospitalized. Influenza viruses are another major cause of winter epidemic LRTIs in children of all ages. Hospitalization rates in infants under one year of age rival those in the > 65 year old population. Characteristic findings include high fever and diffuse inflammation of the airways. Young infants may have prominent GI symptoms as well. Secondary bacterial infection (otitis media, pneumonia, sepsis) are frequent complications of influenza. Primary influenza pneumonia, encephalopathy, and myocarditis are rare, severe complications. Other respiratory viruses associated with LRTIs in children include parainfluenza type 3 (viral pneumonia), parainfluenza types 1 and 2 (croup), adenoviruses, and human metapneumovirus (hMPV). Influenza in children resembles that in adults, but in children, lymphocytosis is usual. Atypical lymphocytes are common in children, but not in adults. Thrombocytopenia is common in both children and adults.

**Diagnostic Considerations:** Viral syndromes are often diagnosed based on clinical assessment alone. For confirmation or in more severe cases, rapid diagnosis by PCR.

**Pitfalls:** Routine use of corticosteroids or bronchodilators in RSV bronchiolitis are not supported by clinical evidence. Overuse of the diagnosis of "flu" (e.g., stomach flu, summer flu) has led to diluted appreciation for true influenza and its severity. Influenza vaccine (RIDT) has been traditionally underutilized in children. As in adults, a negative rapid influenza diagnostic test does not rule out influenza. ILI with negative RIDTs should be retested by PCR for respiratory viruses.

**Therapeutic Considerations:** For most viral LRTIs treatment is primarily supportive (e.g., adequate hydration, fever control, supplemental oxygen for severe illness). Ribavirin is approved for RSV infection but is very rarely used due to uncertain clinical benefit, high cost, and cumbersome method of administration (prolonged aerosol). For infants at greatest risk of severe RSV disease (e.g., premature infants, infants with underlying chronic lung disease or congenital heart disease), monthly prophylaxis with palivizumab (synagis) 15 mg/kg/month (IM) decreases RSV hospitalization rates. Per American Academy of Pediatrics guidelines, palivizumab is indicated for infants with chronic lung disease and ≤ 32 weeks gestational age (GA) or congenital heart disease who are 12 months of age at start of RSV season. For premature infants, palivizumab is considered for premature infants < 29 weeks GA for a maximum of 5 doses through the winter season are recommended.

Annual influenza vaccination is indicated for all individuals > 6 months of age. All circulating influenza A strains are resistant to amantadine. The neuraminidase inhibitors oseltamivir and zanamivir have pediatric indications for treatment and prophylaxis of influenza (Table 7.1).

**Table 7.1. Influenza Antiviral Medication Dosing Recommendations**

| Antiviral | | Treatment | Chemoprophylaxis |
|---|---|---|---|
| **Oseltamivir*** | | | |
| **Adults** | | 75-mg capsule twice per day 3 5 days | 75-mg capsule once per day 3 10 days |
| **Children** (age, 12 months or older), weight: | 15 kg or less | 60 mg per day divided into 2 doses | 30 mg once per day |
| | 15–23 kg | 90 mg per day divided into 2 doses | 45 mg once per day |
| | 24–40 kg | 120 mg per day divided into 2 doses | 60 mg once per day |
| | > 40 kg | 150 mg per day divided into 2 doses | 75 mg once per day |
| **Zanamivir** | | | |
| **Adults** | | Two 5-mg inhalations (10 mg total) twice per day | Two 5-mg inhalations (10 mg total) once per day |
| **Children** | | Two 5-mg inhalations (10 mg total) twice per day (age, 7 years or older) | Two 5-mg inhalations (10 mg total) once per day (age, 5 years or older) |

* CDC recommends oseltamivir 3 mg/kg (PO) q12h × 5 days for full term infants <12 months of age. Lower doses recommended for pre-term infants.

**Prognosis:** Most children with viral LRTIs do well and recover without sequelae. Infants hospitalized with RSV infection have higher rates of wheezing episodes over the next 10 years. The highest rates of hospitalization from influenza occur in children < 2 years of age and in the elderly.

## Pertussis

**Clinical Presentation:** Upper respiratory tract symptoms (congestion, rhinorrhea) over 1–2 weeks (catarrhal stage) progressing to paroxysms of cough (paroxysmal stage) lasting 2–4 weeks, often with a characteristic inspiratory whoop, followed by a convalescent stage lasting 1–2 weeks during which

cough paroxysms decrease in frequency and severity. Fever is low grade or absent. In children < 6 months, whoop is frequently absent and apnea may occur. Duration of classic pertussis is 6–10 weeks. Older children and adults may present with persistent cough (without whoop) lasting 2–6 weeks. Complications include seizures, secondary bacterial pneumonia, encephalopathy, death; risk of complications is greatest in children < 1 year.

**Diagnostic Considerations:** Diagnosis is usually based on nature of cough and duration of symptoms. Laboratory diagnosis may be difficult. A positive culture for Bordetella pertussis from a nasopharyngeal swab inoculated on fresh selective media is diagnostic, but the organism is difficult to recover after 3–4 weeks of illness. PCR of nasal secretions is the best rapid diagnostic test for pertussis.

**Pitfalls:** Be sure to consider pertussis in older children and adults with prolonged coughing illness. Family contacts of index case should receive post-exposure antimicrobial prophylaxis. Virtually all children should be vaccinated against pertussis. A single booster dose of acellular pertussis is recommended at 11–12 years of age (additional guidelines for catch-up for older adolescents and adults up to 64 years of age). Pregnant women should be vaccinated during the 2nd – 3rd trimester of each pregnancy to protect themselves and provide passive immunity to their infants. Relative precautions to further pertussis immunization include: seizure within 3 days of a dose; persistent, severe, inconsolable crying for ≥ 3 hours within 48 hours of a dose; collapse or shock-like state within 48 hours of a dose; or temperature of ≥ 40.5° C without other cause within 48 hours of a dose.

**Therapeutic Considerations:** Infants < 6 months frequently require hospitalization. By the paroxysmal stage, antibiotics have minimal effect on the course of the illness but are still indicated to decrease transmission. An association has been made between oral erythromycin and infantile hypertrophic pyloric stenosis in infants < 6 weeks of age; consider an alternative macrolide (azithromycin or clarithromycin) in these cases.

**Prognosis:** Good. Despite the prolonged course, long-term pulmonary sequelae have not been described after pertussis. Children < 1 year are at greatest risk of morbidity and mortality, although mortality rates remain very low.

### Tuberculosis

| Subset | Pathogen | PO or IM Therapy (see footnote for drug dosages) |
|---|---|---|
| Latent infection (positive PPD, clinically well, negative chest x-ray) | M. tuberculosis | INH × 9 months **or** Rifampin × 6 months (if INH-resistant) **or** INH unavailable and child at risk |
| Pulmonary and extrapulmonary TB (except meningitis) | M. tuberculosis | INH **plus** Rifampin **plus** PZA × 2 months followed by INH **plus** Rifampin × 4 months† |

Duration of therapy represents total time IV or IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

† If drug resistance is a concern, EMB or streptomycin (IM) is added (4-drug regimen in areas where MDR TB is prevalent) to the initial regimen until drug susceptibilities are determined.

**Tuberculosis** (cont'd)

| Subset | Pathogen | PO or IM Therapy (see footnote for drug dosages) |
|---|---|---|
| Meningitis | M. tuberculosis | INH **plus** Rifampin **plus** PZA **plus either** Streptomycin (IM) **or** Ethionamide × 2 months, followed by INH **plus** Rifampin × 7–10 months (i.e., 9–12 months total therapy)‡ |
| Congenital | M. tuberculosis | INH **plus** rifampin **plus** PZA **plus** streptomycin (IM) |

Duration of therapy represents total time IV or IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

‡ Plus steroids.

| TB Drug | Daily dosage (mg/kg) | Twice weekly dosage (mg/kg) |
|---|---|---|
| Isoniazid (INH) | 10–15 | 20–30 |
| Rifampin (RIF) | 10–20 | 10–20 |
| Ethambutol (EMB) | 15–25 | 50 |
| Pyrazinamide (PZA) | 20–40 | 50 |
| Streptomycin | 20–40 (IM) | – |
| Ethionamide | 15–20 (in 2–3 divided doses/day) | – |

Alternative drugs (capreomycin, ciprofloxacin, levofloxacin, cycloserine, kanamycin, para-aminosalicylic acid) are used less commonly and should be administered in consultation with an expert in the treatment of tuberculosis.

## Tuberculosis

**Clinical Presentation:** Most children diagnosed with tuberculosis have asymptomatic infection detected by tuberculin skin testing. Symptomatic disease typically presents 1–6 months after infection with fever, growth delay, weight loss, night sweats, and cough. Extrapulmonary involvement may present with meningitis, lymphadenopathy, bone, joint, or skin involvement.

**Diagnostic Considerations:** A positive tuberculin skin test indicates likely infection with M. tuberculosis. Tuberculin reactivity develops 2–12 weeks after infection. Children < 8 years old cannot produce sputum for AFB smear and culture. Interferon gamma release assays (IGRAs) may be used to diagnose TB in children > 5 years. Testing recommended only for children or increased risk, e.g., HIV, immigrants from TB endemic areas clinical and those with clinical findings suggestive of TB.

**Pitfalls:** Tuberculosis may be missed if not considering the diagnosis in children at increased epidemiological risk for exposure. Tuberculous meningitis often presents insidiously with nonspecific irritability and lethargy weeks prior to the development of frank neurological defects.

**Therapeutic Considerations:** Choice of initial therapy depends on stage of disease and likelihood of resistant organisms (based on index case, geographical region of acquisition). For HIV-infected patients, duration of therapy is prolonged to ≥ 12 months. For tuberculosis meningitis and miliary disease, the addition of corticosteroids to anti-TB therapy is beneficial.

**Prognosis:** Varies with extent of disease, drug resistance and underlying immune status, but is generally good for pulmonary disease in children. Bone infection may result in orthopedic sequelae (e.g., Pott's disease of the spine with vertebral collapse). The prognosis for meningitis is guarded once focal neurological deficits and persistent depression of mental status occur.

# Empiric Therapy of Vascular Infections

## Central Venous Catheter (CVC) Infections (Broviac, Hickman, Mediport)

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† |
|---|---|---|---|
| Empiric; immunocompromised host | S. aureus¶<br>Enterobacteriaceae<br>Pseudomonas<br>Viridans<br>Streptococci<br>Enterococcus | Meropenem **or** Piperacillin/tazobactam **or** cefepime × 7–14 days | Piperacillin/tazobactam **plus** an aminoglycoside × 7–14 days |
| Isolate-based | S. aureus<br>*MSSA* | Nafcillin **or** Oxacillin for ≥ 2 weeks | Cefazolin **or** Vancomycin (preferred if severe beta-lactam allergy) for ≥ 2 weeks |
| | *MRSA* | Vancomycin **with or without** Gentamicin for ≥ 2 weeks | Linezolid **or** Quinupristin/dalfopristin for ≥ 2 weeks (addition of Rifampin may be of benefit, for MRSA) |
| | Enterobacteriaceae<br>Pseudomonas | Piperacillin/tazobactam **or** Ticarcillin/clavulanate **with or without** an aminoglycoside* for ≥ 2 weeks | Meropenem **or** Imipenem **with or without** an aminoglycoside* for ≥ 2 weeks |
| | ESBL-producing gram-negative bacilli | Meropenem **or** Ertapenem **with or without** an aminoglycoside* for ≥ 2 weeks | — |

## Central Venous Catheter Infections (Broviac, Hickman, Mediport) (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† |
|---|---|---|---|
| | Candida | Amphotericin B × 2–6 weeks‡ | Fluconazole **or** Caspofungin **or** liposomal amphotericin B (if renal dysfunction) × 2–6 weeks‡ |

*MSSA/MRSA = methicillin-sensitive/resistant S. aureus.* Duration of therapy represents total time IV.

† **See pp. 414–422 for drug dosages.**

* Gentamicin, tobramycin, or amikacin.

‡ Based on promptness of line removal, clearance of blood cultures, evidence of metastatic foci.

¶ If severely ill or suspicion of MRSA based on local epidemiology, include vancomycin in initial regimen pending culture results.

**Clinical Presentation:** Fever ± site tenderness, erythema.

**Diagnostic considerations:** Quantitative blood cultures from the peripheral blood/vascular catheter are best used to make the diagnosis. However in clinical practice these are not often obtained, and the diagnosis is based on culture results in conjunction with one or more of the following features: local phlebitis or inflammation at the catheter insertion site; embolic disease distal to the catheter; sepsis refractory to appropriate therapy; resolution of fever after device removal; or clustered infections caused by infusion-associated organisms.

**Pitfalls:** It may be difficult to differentiate infection from contamination in blood cultures, especially with coagulase-negative staphylococci. Multiple positive cultures with the same organism and/or clinical features noted above suggest infection, not colonization. Semiquantitative culture of the catheter tip yielding ≥ 15 colonies may also be useful in confirming the diagnosis but requires removal of the device.

**Therapeutic Considerations:** Indications for catheter removal include septic shock, tunnel infection, failure to respond to treatment within 48–72 hours, or infection with Candida, atypical mycobacteria, or possibly S. aureus. Otherwise attempt to retain the catheter while treating with antibiotics. Localized exit site infections (erythema, induration, tenderness, purulence) within 2 cm of the exit site should be treated topically (e.g., Neosporin, Bacitracin, Bactroban) in conjunction with systemic therapy.

**Prognosis:** Major complications (septic emboli, endocarditis, vasculitis) are rare with aggressive therapy. Recrudescent infection can occur after therapy/apparent clearance and can often be successfully treated with additional courses of antibiotics; persistence ultimately requires line removal.

# Empiric Therapy of Gastrointestinal Infections

## Acute Diarrheal Syndromes (Gastroenteritis)

| Subset | Usual Pathogens | Preferred Therapy† | Alternate Therapy† |
|---|---|---|---|
| Community-acquired | Viruses (Rotavirus, Norwalk agent, enteric adenovirus, enteroviruses) | No specific therapy indicated | No specific therapy indicated |

## Acute Diarrheal Syndromes (Gastroenteritis) (cont'd)

| Subset | Usual Pathogens | Preferred Therapy† | Alternate Therapy† |
|---|---|---|---|
| | Salmonella non-typhi | Ceftriaxone (IV) **or** Cefotaxime (IV) × 10–14 days* | TMP–SMX (IV or PO) **or** Amoxicillin (PO) **or** cefixime (PO) × 10–14 days |
| | Shigella | Ceftriaxone (IV) **or** Azithromycin (PO) × 5 days | TMP–SMX (PO) **or** Cefixime (PO) **or** Ampicillin (PO) × 5 days |
| | Campylobacter | Erythromycin (PO) × 7 days **or** Azithromycin (PO) × 5 days | Doxycycline (PO) (> 8 year old) × 7 days |
| | Yersinia enterocolitica | TMP–SMX (PO) × 5–7 days | Cefotaxime (IV) **or** Doxycycline (PO) × 5–7 days |
| Traveler's diarrhea | E. coli | TMP–SMX (PO) × 3 days | Azithromycin (PO) × 3 days |
| Typhoid (enteric) fever | Salmonella typhi | Ceftriaxone (IV) **or** Cefotaxime (IV) × 10–14 days | TMP–SMX (IV or PO) **or** Amoxicillin (PO) **or** Cefixime (PO) × 10–14 days |
| Antibiotic-associated colitis | Clostridium difficile | Metronidazole (PO) × 7–10 days **or** Nitazoxanide (PO) × 3 days | Vancomycin (PO) × 7–10 days |
| Chronic watery diarrhea | Giardia lamblia‡ | Metronidazole (PO) × 5–7 days **or** Nitazoxanide (PO) × 3 days | Tinidazole (PO) × 1 dose **or** Furazolidone (PO) × 7–10 days **or** Albendazole × 5–7 days |
| | Cryptosporidia‡ | Nitazoxanide (PO) × 3 days | Human immunoglobulin (PO) **or** bovine colostrum (PO) for immunocompromised hosts |
| Acute dysentery | E. histolytica | Metronidazole (PO) × 10 days **followed by either** Iodoquinol (PO) × 20 days **or** Paromomycin (PO) × 7 days | Tinidazole (PO) × 3–5 days **followed by either** Iodoquinol (PO) × 20 days **or** Paromomycin (PO) × 7 days |

## Acute Diarrheal Syndromes (Gastroenteritis) (cont'd)

| Subset | Usual Pathogens | Preferred Therapy† | Alternate Therapy† |
|---|---|---|---|
| | Shigella** | Ceftriaxone (IV) **or** Azithromycin (PO) × 5 days | TMP–SMX (PO) **or** Cefixime (PO) **or** Ampicillin (PO) × 5 days |

† **See pp. 414–422 for drug dosages.**

* Therapy only indicated in child < 3 to 6 months of age, immunocompromised host, or toxic appearing child.

** Mild cases acquire no antibiotic therapy. However, antibiotic therapy shortens durations of symptoms and by decreasing the duration of diarrhea limits potential syneral.

‡ May also present as acute watery diarrhea.

### Acute Gastroenteritis (Community-Acquired)

**Clinical Presentation:** Typically presents with the acute onset of diarrhea with fever. This is not an indication for antibiotic therapy unless illness is severe (≥ 6 unformed stools/day, fever ≥ 102° F, bloody stools). Travel history regarding risk for potential E. coli and parasitic exposures is important.

**Diagnostic Considerations:** In the absence of blood in the stools viruses are the most common cause of acute community-acquired gastroenteritis. Rotaviruses are the most common cause of acute gastroenteritis in 4–24 month old children. Enteric adenoviruses, Norwalk-like virus, enteroviruses and astroviruses are common causes of gastroenteritis in older children. Commercially available antigen tests using ELISA or latex agglutination techniques are readily available to detect rotavirus. Testing for the other viral agents may not be as readily available. Inflammatory changes (presence of white blood cells and/or blood) in the stool are more consistent with bacterial infection. When requesting stool cultures, it may be necessary to order special conditions/media for the detection of yersinia or E. coli O157.

**Pitfalls:** Antimotility drugs may worsen the course of illness in children with colitis. Empiric therapy with antibiotics may prolong the carriage of Salmonella or increase the risk for developing hemolytic uremic syndrome (HUS) with E. coli O157 infection. The benefit of antibiotics in treating diarrhea caused by yersinia is also unproven. Thus, antibiotic therapy is not routinely indicated prior to culture results in most instances of mild diarrheal disease, especially as most such infections are self-limited.

**Therapeutic Considerations:** As above, pending cultures in the absence of severe symptoms or dysentery antibiotics may not be indicated. Overall, the fluoroquinolones have the most complete spectrum for pathogens causing bacterial diarrhea but are not presently approved for use in children < 18 years of age.

**Prognosis:** Good. Up to 5–10% of children with E. coli O157 are at risk for hemolytic-uremic syndrome.

### Giardiasis (Giardia lamblia)

**Clinical Presentation:** Giardia lamblia is the most common parasite causing diarrheal illness in children. Giardiasis may present as acute watery diarrhea with abdominal pain and bloating or as a chronic, intermittent illness with foul smelling stools, abdominal distension, and anorexia.

**Diagnostic Considerations:** Trophozoites or cysts of Giardia lamblia can be identified in direct examination of infected stools with 75%–95% sensitivity on a single specimen. Testing 3 or more stools further

increases sensitivity of detection. If giardiasis is suspected with negative stool tests, examination of duodenal contents (Entero- or string test) may be helpful.
**Pitfalls:** Asymptomatic infection is commonly seen in children in day care; therefore, indications to treat must take into account stool testing results *and* clinical findings.
**Therapeutic Considerations:** Treatment failures occur commonly, and retreatment with the same initial drug is recommended. Furazolidone is the only pediatric liquid available for treating giardiasis < 3 years of age.
**Prognosis:** Good.

## Cryptosporidiosis

**Clinical Presentation:** Usually presents as fever, vomiting, and non-bloody, watery diarrhea. Infection may also be asymptomatic. More severe and chronic infection is seen in immunocompromised patients (e.g., HIV infection). Cryptosporidia parasite is resistant to chlorine and maybe transmitted in swimming pools. Transmission can also occur from livestock, and a major outbreak through contamination of a public water supply has been reported.
**Diagnostic Considerations:** Cryptosporidium cysts are detected by microscopic examination of Kinyoun-stained stool specimens using a sucrose floatation method or formalin-ethyl acetate method to concentrate oocysts. This test is not part of routine stool ova and parasite examination and must be specifically requested. Shedding is intermittent; therefore, 3 stool samples should be submitted for optimal detection.
**Pitfalls:** The oocysts of cryptosporidium are small and may be missed by an inexperienced exam-iner. A commercially available ELISA test is available but may have false-positive and false-negative results.
**Therapeutic Considerations:** Treatment failures are frequent. In immunocompromised hosts oral human immune globulin and bovine colostrum are beneficial. Improvement in $CD_4$ counts with antiretroviral therapy in HIV-infected patients shortens the clinical illness.
**Prognosis:** Good. Recovery may take months.

## Amebiasis (Entamoeba histolytica)

**Clinical Presentation:** E. histolytica can lead to a spectrum of clinical illnesses from asymptomatic infection to acute dysentery to fulminant colitis. Disseminated disease, primarily manifest as hepatic abscesses, can also occur. E. histolytica is most prevalent in developing countries and is transmitted by the fecal-oral route.
**Diagnostic Considerations:** Trophozoites or cysts of E. histolytica can be identified in stool specimens. In more severe disease (amebic colitis, hepatic abscesses), serum antibodies can be detected.
**Pitfalls:** Treatment with steroids or antimotility drugs can worsen symptoms and should not be used.
**Therapeutic Considerations:** Treatment is two-staged to eliminate tissue-invading trophozoites and organisms in the intestinal lumen. Surgical drainage of large hepatic abscesses may be beneficial.
**Prognosis:** Good.

## Clostridirim difficile Colitis

**Clinical Presentation:** Classically occurs in a child receiving antibiotic therapy and presents as diarrhea, cramping, bloody/mucousy stools, abdominal tenderness, fever, and toxicity. It may also present weeks after a course of antibiotics.

**Diagnostic Considerations:** C. difficile toxin can be detected with commercially available immunoassays. Endoscopic finding of pseudomembranous colitis is the definitive method of diagnosis although rarely indicated.
**Pitfalls:** C. difficile may be normal flora in infants < 1 year of age and probably does not cause illness in this age group. The finding of C. difficile toxin in an infant should not be equated with cause and additional evaluations should be perused. Antimotility drugs may worsen symptoms and should be avoided.
**Therapeutic Considerations:** Cessation of antibiotics is recommended if possible in the presence of significant C. difficile colitis. Patients with severe symptoms or persistent diarrhea × 2–3 days after discontinuing antibiotics should then be treated with oral metronidazole or oral vancomycin. Up to ~25% relapse after a single course; re-treatment using the same initial antibiotic is recommended. For persistent infection alternate therapies such as nitazoxanide, rifaximin, tinidazole, oral immune globulin therapy, toxin binders or repopulating intestinal flora may be considered.
**Prognosis:** Good.

# Empiric Therapy of Bone and Joint Infections

## Septic Arthritis

| Subset | Usual Pathogens | Preferred IV Therapy†* | Alternate IV Therapy†* | IV-to-PO Switch† |
|---|---|---|---|---|
| Newborns (≤ 3 months) | S. aureus‡<br>Group B streptococci<br>Enterobacteriaceae<br>N. gonorrhoeae | **Combination therapy with** Nafcillin **or** Vancomycin **plus either** Ceftriaxone **or** Cefotaxime* | **Combination therapy with** Vancomycin **or** Clindamycin **plus either** ceftriaxone **or** cefotaxime **or** gentamicin **or** tobramycin* | Not applicable |
| Child (> 3 months to 14 years) | S. aureus‡<br>Group A streptococci<br>S. pneumoniae<br>Gram-negative bacilli<br>N. meningitidis<br>(H. influenzae type b if unvaccinated)<br>Kingella | **Combination therapy with** Nafcillin **or** Vancomycin **plus either** Ceftriaxone **or** Cefotaxime* | **Combination therapy with** Vancomycin **or** Clindamycin **plus either** Ceftriaxone **or** Cefotaxime* | Dicloxacillin **or** Cephalexin **or** Clindamycin (PO) after 1 week of IV therapy* |

† **See pp. 414–422 for drug dosages.**
* Total duration of therapy for non-gonococcal septic arthritis ≥ 3 weeks based on clinical response.
‡ If CA-MRSA is suspected based on clinical presentation/local epidemiology, consider empiric coverage for CA-MRSA with clindamycin, TMP–SMX, doxycycline, or vancomycin pending culture results.

## Septic Arthritis (cont'd)

| Subset | Usual Pathogens | Preferred IV Therapy†* | Alternate IV Therapy†* | IV-to-PO Switch† |
|---|---|---|---|---|
| Adolescents (sexually active) | As above plus N. gonorrhoeae (typically 2 or 3 joints involved) | **Combination therapy with** Nafcillin **or** Vancomycin **plus either** Ceftriaxone **or** Cefotaxime* | If GC isolated and penicillin allergy: Azithromycin | GC arthritis with prompt response to IV therapy may switch to Cefixime to complete 7 days of total therapy |

Duration of therapy represents total time IV or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement. Taper to individual drug therapy once organism isolated and sensitivities are available.

† **See pp. 414–422 for drug dosages**.

* Total duration of therapy for non-gonococcal septic arthritis ≥ 3 weeks based on clinical response.

‡ If CA-MRSA is suspected based on clinical presentation/local epidemiology, consider empiric coverage for CA-MRSA with clindamycin, TMP–SMX, doxycycline, or vancomycin pending culture results.

**Clinical Presentation:** Varies with age of the child. Presentation is often nonspecific in infants (i.e., fever, poor feeding, tachycardia). Physical exam findings can be subtle: asymmetrical tissue folds, unilateral swelling of an extremity, subtle changes in limb/joint position. In older children, signs and symptoms are more localized to the involved joint. Commonly affected joints: hips, elbows, knees.

**Diagnostic Considerations:** Joint aspiration (large-bore needle) shows 50,000–250,000 WBCs/$mm^3$ with a marked predominance of PMNs. Gram stain/culture of joint fluid confirm the diagnosis. Toxic synovitis, Lyme arthritis, rheumatoid arthritis, traumatic arthritis, and sympathetic effusion from adjacent osteomyelitis can mimic septic arthritis on presentation, but joint fluid has fewer WBCs and cultures are negative. Multiple joint involvement is more typical of rheumatic/Lyme disease. In young infants, persistence of the nutrient artery can lead to osteomyelitis and septic arthritis.

**Pitfalls:** Septic arthritis of the hip is an emergency concomitant condition requiring prompt joint aspiration and irrigation to minimize the risk of femoral head necrosis, which may occur within 24 hours. Toxic synovitis of the hip, which is treated with anti-inflammatory agents and observation, typically causes less fever, pain, and leukocytosis than septic arthritis; however, at times the two can not be differentiated and aspiration of the joint is indicated. In sexually active adolescents, consider N. gonorrhoeae and culture aspirate appropriately.

**Therapeutic Considerations:** Therapy is recommended for at least 3–4 weeks (IV followed by oral therapy), for a total antibiotic course of 4–6 weeks based on clinical response and laboratory parameters (WBC, ESR, CRP). Intra-articular therapy is not helpful. Empiric coverage is broader than for osteomyelitis in children.

**Prognosis:** Good with prompt joint aspiration and at least 3 weeks of antibiotics.

## Acute Osteomyelitis, Osteochondritis, Diskitis

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† | IV-to-PO Switch or PO Therapy† |
|---|---|---|---|---|
| Acute osteomyelitis<br>Newborn (0–3 months) | S. aureus§<br>Gram-negative bacilli<br>Group B streptococci | **Combination therapy with** Nafcillin **or** Oxacillin **plus either** Cefotaxime **or** Ceftriaxone × 4–6 weeks | Vancomycin **plus either** Cefotaxime **or** Ceftriaxone × 4–6 weeks | Not applicable |
| > 3 months* | S. aureus§<br>Group A streptococci<br>Gram-negative bacteria (rare)<br>Salmonella (sickle cell disease) | Nafcillin **or** Oxacillin **or** Cefazolin × 4–6 weeks | Clindamycin **or** Ampicillin-sulbactam **or** Vancomycin × 4–6 weeks | Cephalexin **or** Clindamycin **or** Cefadroxil × 4–6 weeks |
| Osteochondritis | P. aeruginosa<br>S. aureus§ | Ticarcillin clavulanate × 7–10 days after surgery **or combination therapy with** Nafcillin plus Ceftazidime × 7–10 days after surgery | Piperacillin/tazobactam **or** Ciprofloxacin × 7–10 days after surgery | Ciprofloxacin** × 7–10 days after surgery |
| Diskitis | S. aureus, K. kingae<br>Enterobacteriaceae<br>S. pneumoniae<br>S. epidermidis | PO Therapy: Cephalexin **or** Cefadroxil **or** Clindamycin × 3–4 weeks or ESR returns to normal†† | | |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

† **See pp. 414–422 for drug dosages.**

** Not approved for children but might consider in adolescent.

* Treat only IV or IV-to-PO switch.

†† Add gram-negative coverage only if culture proven.

§ If CA-MRSA is suspected based on clinical presentation/local epidemiology, consider empiric coverage for CA-MRSA with clindamycin, TMP–SMX, doxycycline, or vancomycin pending culture results.

### Acute Osteomyelitis

**Clinical Presentation:** Acute onset of fever and pain/decreased movement around the infected area. Can be difficult to localize, especially in younger children. Occurs primarily via hematogenous spread (vs. direct inoculation) to metaphysis of long bones.

**Diagnostic Considerations:** Acute phase reactants are elevated (ESR, CRP, WBC). X-rays may not reveal osteolytic lesions for > 7 days, but soft tissue swelling and periosteal reaction may be seen as early as

3 days. Bone scan/MRI reveal changes in the first 24 hours, but bone scans are insensitive in neonates. Blood cultures may be positive, especially in younger children. Definitive diagnosis by bone aspirate for gram stain and culture, but empiric therapy is often initiated based on clinical history and the presence of an acute lytic lesion on MRI, bone scan, or x-ray.

**Pitfalls:** Bony changes on x-ray may not be present initially. It may be difficult to differentiate cellulitis from osteomyelitis, even on bone scan.

**Therapeutic Considerations:** Initiate empiric therapy by IV route. Treatment is required ≥ 4 weeks, but children with a prompt clinical response can complete therapy with high-dose oral antibiotics. With adequate treatment, CPR and ESR normalize over 2 weeks and 4 weeks, respectively.

**Prognosis:** Good with 4–6 weeks of total therapy. Long-term growth of affected bone may be impaired.

## Osteochondritis of the Foot ("Puncture Wound Osteomyelitis")

**Clinical Presentation:** Tenderness, erythema, and swelling several days to weeks after a nail puncture wound through a sneaker/tennis shoe (Pseudomonas found in foam layer between sole and lining of shoe). Fever and other systemic complaints are rare. Develops in 1–2% of puncture wounds of foot.

**Diagnostic Considerations:** P. aeruginosa is the primary pathogen, although infection with S. aureus is also a concern.

**Pitfalls:** Antibiotics with surgical debridement of necrotic cartilage.

**Therapeutic Considerations:** With prompt debridement, 7–10 days of antibiotic therapy is usually sufficient.

**Prognosis:** Good with debridement and antibiotics.

## Diskitis

**Clinical Presentation:** Typically involves the lumbar region and occurs in children < 6 years old. Presents with gradual onset (over weeks) of irritability and refusal to walk. Fever is low-grade or absent. Older children may be able to localize pain to back, hip, or abdomen. Pain is exacerbated by motion of the spine and can be localized by percussion of the vertebral bodies.

**Diagnostic Considerations:** ESR is elevated, but WBC count is normal. X-rays are usually normal initially, but later reveal disk space narrowing and sclerosis of the vertebrae. Increased disk space uptake can be seen on bone scan. MRI is very sensitive for assessing disk space involvement.

**Therapeutic Considerations:** Diskitis is probably a low-grade bacterial infection, but the role of antibiotic therapy is unclear. Bed rest and anti-inflammatory medications are the mainstays of treatment. Immobilization may be required for severe cases. Oral antibiotics are given for 3–4 weeks or until the ESR returns to normal.

**Pitfalls:** Difficult to isolate an organism, even with needle aspiration of disk space. S. aureus is the most common pathogen, but diskitis can also be caused by coagulase-negative staphylococcus, K. kingae, coliforms, S. pneumoniae.

**Prognosis:** Fusion of involved vertebrae may occur as the infection resolves. Otherwise, outcome is generally good.

# Empiric Therapy of Skin and Soft Tissue Infections

## Skin and Soft Tissue Infections

| Subset | Usual Pathogens | Preferred IV Therapy† | Alternate IV Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|---|
| Cellulitis, impetigo | S. aureus<br>Group A streptococci | Cefazolin **or** nafcillin **or** oxacillin × 7–10 days | Clindamycin‡ × 7–10 days | Cephalexin **or** Cefadroxil **or** Dicloxacillin **or** Clindamycin **or** amoxicillin/clavulanate **or** Erythromycin **or** Azithromycin × 7–10 days |
| Severe pyodermas, abscesses | CA-MRSA | Vancomycin **plus** Clindamycin × 7–14 days | Vancomycin or Linezolid × 7–14 days | TMP–SMX or Doxycycline × 7–14 days** |
| Animal bite wounds (dog/cat) | Group A streptococci<br>P. multocida<br>Capnocytophaga S. aureus | Ampicillin-sulbactam × 7–10 days | Piperacillin **or** Ticarcillin × 7–10 days<br><br>Penicillin allergy:<br>Clindamycin **plus** TMP–SMX × 7–10 days (dog bites); Doxycycline **or** Cefuroxime × 7–10 days (cat bites) | Amoxicillin/clavulanate **or** Doxycycline × 7–10 days |
| Human bite wounds | Oral anaerobes<br>E. corrodens<br>Group A streptococci<br>S. aureus | Ampicillin-sulbactam × 5–7 days | Piperacillin **or** Ticarcillin × 5–7 days<br><br>Penicillin allergic patient:<br>Clindamycin **plus** TMP–SMX × 5–7 days | Amoxicillin/clavulanate **or** Doxycycline × 5–7 days |
| Cat scratch disease (CSD)* | Bartonella henselae | Gentamicin × 10–14 days | — | Azithromycin × 5 days **or** TMP–SMX **or** Ciprofloxacin **or** Rifampin × 10–14 days |

† **See pp. 414–422 for drug dosages.**

** In children > 8 years of age.

* No well-controlled trials of antibiotic treatment for CSD to demonstrate benefit.

‡ Preferred therapy for patients in geographic regions with a high prevalence of MRSA or for those with penicillin/cephalosporin allergy.

## Skin and Soft Tissue Infections (cont'd)

| Subset | Pathogens | IV Therapy† | PO Therapy or IV-to-PO Switch† |
|---|---|---|---|
| Chicken pox *Immuno-compromised host* | VZV | Acyclovir × 7–10 days | Acyclovir **or** Valacyclovir × 7–10 days |
| *Immuno-competent host* | VZV | Acyclovir × 5 days | Acyclovir **or** Valacyclovir × 5 days |
| H. zoster (Shingles) | VZV | Same as for chicken pox | Acyclovir **or** Valacyclovir × 10 days (for individuals ≥ 12 years of age) |

Duration of therapy represents total time IV, PO, or IV + PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy soon after clinical improvement.

† **See pp. 414–422 for drug dosages.**

### Cellulitis

**Clinical Presentation:** Erythema, warmth, and tenderness of skin. Impetigo is characterized by a vesiculopapular rash with honey-colored discharge.

**Diagnostic Considerations:** Primarily a clinical diagnosis. Group A streptococci is the primary pathogens in healthy children. Cellulitis, alone without a pustular component, is caused by streptococci (not staphylococci).

**Pitfalls:** Differential diagnosis of cellulitis may include hypersensitivity to insect bites. Herpetic whitlow (HSV) may be mistaken for a bacterial skin or paronychial infection.

**Therapeutic Considerations:** First generation cephalosporin or semi-synthetic penicillin with anti-staphylococcal activity (i.e., dicloxacillin, nafcillin, oxacillin) are drugs of choice. Increasing incidence of community-acquired MRSA may affect treatment decisions.

**Prognosis:** Excellent. Impetigo may only require topical treatment (Mupirocin).

### Bite Wounds

**Clinical Presentation:** 80% of animal bite wounds in children are from dogs, and 15%–50% of dog bites become infected. More than 50% of cat bites become infected, and due to their long teeth, there is an increased risk of inoculation into bone/joints with development of osteomyelitis/septic arthritis. Human bite wounds are most prone to infection, and 75%–90% of all human bites become infected.

**Diagnostic Considerations:** Clinical diagnosis. Culture of wound exudate may yield organism.

**Pitfalls:** Failure to assess depth of infection, especially with cat bites, may result in late identification of bone/joint infection. Macrolides are ineffective against P. multocida.

**Therapeutic Considerations:** It is important to cover oral anaerobes, S. aureus, and Group A streptococci in human bite wounds. P. multocida is an important pathogen in cat and dog bite wounds. Facial/hand lesions require plastic surgery evaluation. Recurrent debridement may be necessary, especially with human bite wound infections of hand. Assess tetanus immunization status for all bite wounds

(p. 377). For human bites consider the risk of HIV and hepatitis B. For dog bites consider the risk of rabies. Antimicrobial therapy initiated within 8 hours of a bite wound and administered for 2–3 days may decrease the rate of infection.
**Prognosis:** Good with early debridement and antibiotics.

## Cat Scratch Disease (CSD)

**Clinical Presentation:** Classic presentation is a papular lesion at site of cat scratch with lymphadenitis in the draining region (axillary, epitrochlear, inguinal, cervical most commonly). Frequently associated with fever/malaise 1–2 weeks after scratch. Infection can present with conjunctivitis and ipsilateral preauricular lymph node (Parinaud oculoglandular syndrome). Unusual presentations in normal hosts include encephalitis, hepatitis, microabscesses in liver/spleen, fever of unknown origin, osteolytic lesions.
**Diagnostic Considerations:** Most often secondary to kitten scratch with Bartonella henselae. Diagnosed using specific serology for antibodies to B. henselae.
**Pitfalls:** Failure to obtain history of kitten exposure. Surgical excision of lymph node is generally not necessary.
**Therapeutic Considerations:** Most lesions are self-limited and resolve over 2–4 months. If lymph nodes are fluctuant, I&D may be indicated. Antibiotic therapy may be helpful in severe cases with hepatosplenomegaly. Doxycycline, erythromycin, or azithromycin are helpful in immunocompromised hosts.
**Prognosis:** Very good with spontaneous resolution over 2–4 months.

## Chicken Pox/Shingles (VZV)

**Clinical Presentation:** Primary illness is chicken pox, a generalized pruritic, vesicular rash with fever that erupts in crops of lesions over 3–5 days followed by crusting and recovery. Complications include bacterial superinfection of skin lesions, sepsis, cerebellar ataxia, thrombocytopenia, hepatitis, pneumonia and encephalitis. The disease tends to be more severe in adolescents and adults, particularly if immunocompromised. Primary infection early in pregnancy can rarely result in varicella embryopathy with imb atrophy and CNS malformations in the neonate. Reactivation disease (shingles) may occur in children and in normal hosts and remains localized to a single dermatome. Post-herpetic neuralgia occurs less often in children than adults. Reactivation disease in immunocompromised hosts can spread and re-disseminate.
**Diagnostic Considerations:** The characteristic eruption of chicken pox occurs in waves—multiple stages appear at the same time, from new papules and vesicles to more advanced larger crusted lesions—and is unique to varicella. Direct fluorescent antibody staining of a scraped lesion or PCR can confirm the diagnosis.
**Pitfalls:** Initially lesions may be primarily papular, and if the diagnosis is not considered, exposure of others can occur.
**Therapeutic Considerations:** Antiviral therapy with acyclovir, if started within 24 hours of rash, should be considered for children > 12 years of age, those on steroid or salicylate therapy, and those with underlying chronic pulmonary, skin, or immunosuppressive states. Oral administration is acceptable, although IV therapy may be preferred for immunocompromised hosts at risk of disseminated disease. More severe varicella has been observed in individuals acquiring the infection from a household contact, presumably due to a higher inoculum with closer contact; non-immune household contacts may be considered for acyclovir therapy at onset of rash in child. Additionally,

individuals ≥ 13 years may develop more extensive varicella than younger children. Immunocompromised children or pregnant women without a history of varicella or immunization may benefit from prophylaxis with varicella zoster immune globulin (VZIG) within 96 hours of varicella exposure. Newborns whose mothers develop chicken pox within 5 days before or 48 hours after delivery and exposed premature infants are also candidates for VZIG. A like-attenuated varicella vaccine has been licensed since 1995 for use in individuals ≥ 12 months of age who have not had chicken pox. A two-dose vaccine schedule is recommended for children ≥ 12 months of age.

**Prognosis:** Overall prognosis is good with complete recovery and minimal risk of scarring unless immunosuppressed host with disseminated disease. Although rare, Group A streptococcal toxic shock syndrome (manifest as cellulitis or in conjunction with necrotizing fasciitis complicating varicella skin lesions) and Group A streptococcal septicemia, which can occur in the absence of apparent secondarily infected skin lesions, may be fatal complications of varicella in normal children.

## Common Pediatric Antimicrobial Drugs

| Drug | Dosage in Neonates | Dosage in Infants/Children* |
|---|---|---|
| Acyclovir | 20 mg/kg (IV) q8h × 14–21 days. Dosing interval may need to be increased for infants < 34 weeks post-maturational age (GA + CA) or if significant renal impairment or liver failure followed by<br>Chronic suppression: 75 mg/kg (PO) q12h × 6 months | HSV encephalitis: 10 mg/kg (IV) q8h × 14–21 days<br>Primary HSV infection: 10–20 mg/kg (PO) q6h × 5–10 days **or** 5 mg/kg/dose (IV) q8h × 5 days<br>Varicella in immunocompromised hosts: 10 mg/kg (IV) q8h × 7–10 days<br>Varicella in immunocompetent hosts: 20 mg/kg (PO) q6h × 5 days (maximum 800 mg/dose) |
| Albendazole | Not applicable | 400 mg (PO) q24h |
| Amikacin** | *During first week of life* dosing is based on gestational age (administer IV dose over 30 min)<br>• ≤ 27 weeks (or asphyxia, PDA, or indomethacin): 18 mg/kg (IV) q48h<br>• 28–30 weeks: 18 mg/kg (IV) q36h<br>• 31–33 weeks: 16 mg/kg (IV) q36h<br>• ≥ 34 weeks: 15 mg/kg (IV) q24h | 5–7.5 mg/kg (IV or IM) q8h |

| Drug | Dosage in Neonates | | | Dosage in Infants/Children* |
|---|---|---|---|---|
| | *After first week of life*: Initial dose of 15 mg/kg, then draw serum concentrations 30 min after end of infusion (peak) and 12–24 hours later (trough) to determine dosing interval. Aim for peak of 20–30 mcg/mL and trough of 2–5 mcg/mL | | | |
| Amoxicillin | Not indicated | | | 22.5–45 mg/kg (PO) q12h |
| Amoxicillin-clavulanate | Not indicated | | | 22.5–45 mg/kg (of amoxicillin component) (PO) q12h |
| Amphotericin B (conventional) | 0.5–1 mg/kg (IV over 2–6 hours) q24-48h (Some authorities recommend an initial test dose of 0.1–0.5 mg/kg IV over 2–6 hours) | | | |
| Ampicillin | 25–50 mg/kg/dose (IV or IM).<br>Severe Group B streptococcal sepsis: 100 mg/kg/dose. Dosing interval is based on gestational age (GA) and chronological age (CA): | | | 25–50 mg/kg (IV or IM) q6h |
| | **GA + CA (weeks)** | **CA (days)** | **Interval (hours)** | |
| | ≤ 29 | 0–28<br>> 28 | 12<br>8 | |
| | 30–36 | 0–14<br>> 14 | 12<br>8 | |
| | ≥ 37 | 0–7<br>> 7 | 12<br>8 | |
| Ampicillin-sulbactam | Not indicated | | | 25–50 mg/kg (of ampicillin component) (IV) q6h |
| Azithromycin | Not indicated | | | Otitis media/sinusitis: 30 mg/kg (PO) × 1 dose **or** 10 mg/kg (PO) q24h × 3 days **or** 10 mg/kg (PO) on day 1 followed by 5 mg/kg (PO) q24h on days 2–5<br>Pharyngitis/tonsillitis: 12 mg/kg (PO) q24h × 5 days |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.
** Drug can be given IM but absorption may be variable.

| Drug | Dosage in Neonates | Dosage in Infants/Children* |
|---|---|---|
| | | Community-acquired pneumonia (not indicated for moderate or severe disease): 10 mg/kg (PO) × 5 days **or** 10 mg/kg (IV or PO) on day 1 followed by 5 mg/kg (IV or PO) q24h on days 2–5<br>Skin/soft tissue infections (including Cat Scratch Disease): 10 mg/kg (PO) on day 1 followed by 5 mg/kg (PO) q24h on days 2–5 |
| Aztreonam | 30 mg/kg (IV or IM). See *ampicillin* for dosing interval (p. 415) | 30 mg/kg (IV or IM) q6-8h |
| Caspofungin | 70 mg/m$^2$ loading dose, then 25 mg/m$^2$ (IV) q24h | 70 mg/m$^2$ loading dose, then 50 mg/m$^2$ (IV) q24h (> 3 months) |
| Cefadroxil | Not indicated | 15 mg/kg (PO) q12h |
| Cefazolin | 25 mg/kg (IV or IM). See *ampicillin* for dosing interval (p. 415) | 25–100 mg/kg/day (IV or IM) divided q6–q8h |
| Cefdinir | Not indicated | 7 mg/kg (PO) q12h or 14 mg/kg (PO) q24h |
| Cefepime | 50 mg/kg (IV) q12h | 33.3–50 mg/kg (IV or IM) q8h |
| Cefotaxime | 50 mg/kg (IV or IM).<br>(25 mg/kg/dose is adequate for gonococcal infection). See *ampicillin* for dosing interval (p. 415) | 25–50 mg/kg (IV or IM) q6–8h |
| Cefotetan | Not indicated | 20–40 mg/kg (IV or IM) q12h |
| Cefoxitin | 25–33 mg/kg/dose (IV or IM). See *ampicillin* for dosing interval (p. 415) | 80–160 mg/kg/day (IV or IM) divided q4–8h |
| Cefpodoxime | Not indicated | 5 mg/kg (PO) q12h |
| Cefprozil | Not indicated | 15 mg/kg (PO) q12h |
| Ceftazidime | 30 mg/kg/dose (IV or IM). See *ampicillin* for dosing interval (p. 415) | 25–50 mg/kg (IV or IM) q8h |
| Ceftibuten | Not indicated | 9 mg/kg (PO) q24h |
| Ceftizoxime | Not indicated | 50 mg/kg (IV or IM) q6–8h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

| Drug | Dosage in Neonates | | | Dosage in Infants/Children* |
|---|---|---|---|---|
| Ceftriaxone‡ | Sepsis and disseminated gonococcal infection: 50 mg/kg (IV or IM) q24h<br>Meningitis: 100 mg/kg loading dose followed by 80 mg/kg (IV or IM) q24h<br>Uncomplicated gonococcal ophthalmia:<br>50 mg/kg (maximum 125 mg) as a single dose (IV or IM) | | | 50 mg/kg (IV or IM) q24h. Meningitis: 50 mg/kg (IV or IM) q12h or 100 mg/kg (IV or IM) q24h<br>Acute otitis media: 50 mg/kg (IM) × 1 dose (or 3 doses IM q24h in high-risk patients) |
| Cefuroxime | Not indicated | | | 10–15 mg/kg (PO) q12h<br>25–50 mg/kg (IV or IM) q8h |
| Cephalexin | Not indicated | | | 6.25–25 mg/kg (PO) q6h |
| Cephalothin | Not indicated | | | 25 mg/kg (IV or IM) q4-6h |
| Clarithromycin | Not indicated | | | 7.5 mg/kg (PO) q12h |
| Clindamycin | 5.0–7.5 mg (IV or PO). Dosing interval is based on gestational age (GA) and chronological age (CA) | | | 5–10 mg/kg (IV or IM) q6-8h or 10–30 mg/kg/day (PO) divided q6-8h |
| | **GA + CA (weeks)** | **CA (days)** | **Interval (hours)** | |
| | < 29 | 0–28<br>> 28 | 12<br>8 | |
| | 30–36 | 0–14<br>> 14 | 12<br>8 | |
| | 37–44 | 0–7<br>> 7 | 8<br>6 | |
| Dicloxacillin | Not indicated | | | 6.25–12.5 mg/kg (PO) q6h |
| Doxycycline | Contraindicated | | | > 45 kg: 100 mg (PO) q12h<br>≤ 45 kg: 1.1–2.5 mg/kg (PO) q12h<br>Use only in children > 8 years (unless RMSF)<br><br>1–2 mg/kg (IV) q12–24h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

‡ Do not use in presence of hyperbilirubinemia.

| Drug | Dosage in Neonates | | | Dosage in Infants/Children* |
|---|---|---|---|---|
| Erythromycin | Chlamydia pneumonitis/conjunctivitis or pertussis: 12.5 mg/kg (PO) q6h (E. estolate preferred)<br>Other infections: E. estolate 10 mg/kg (PO) q8h **or** E. ethylsuccinate 10 mg/kg (PO) q6h<br>Severe infections and PO not possible: 5–10 mg/kg (IV over ≥ 60 min) q6h | | | 10–12.5 mg/kg (PO) q6–8h<br>5–12.5 mg/kg (IV) q6h |
| Ertapenem | Not indicated | | | 15 mg/kg (IV) q12h (not to exceed 1 gm/day) |
| Ethambutol | See p. 401 | | | See p. 401 |
| Ethionamide | See p. 401 | | | See p. 401 |
| Fluconazole | Systemic infection or meningitis: 12 mg/kg (IV over 30 min or PO) × 1 dose, then 6 mg/kg/dose (IV or PO) with dosing interval based on gestational age (GA) and chronological age (CA) (below)<br>Prophylaxis (e.g., extremely low birth weight infants in NICU with high rates of fungal disease): 3 mg/kg/dose (IV or PO) according to dosing interval grid (below)<br>Thrush: 6 mg/kg (PO) × 1 dose, then 3 mg/kg (PO) q24h | | | 10 mg/kg (IV or PO) loading dose followed by 12 mg/kg (IV or PO) q24h |
| | **GA + CA (weeks)** | **CA (days)** | **Interval (weeks)** | |
| | ≤ 29 | 0–14<br>> 14 | 72<br>48 | |
| | 30–36 | 0–14<br>> 14 | 48<br>24 | |
| | 37–44 | 0–7<br>> 7 | 48<br>24 | |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

| Drug | Dosage in Neonates | Dosage in Infants/Children* |
|---|---|---|
| Gentamicin** | *During first week of life* dosing is based on gestational age (administer IV dose over 30 min):<br>• ≤ 29 weeks (or asphyxia, PDA, or indomethacin): 5 mg/kg (IV) q48h<br>• 30–33 weeks: 4.5 mg/kg (IV) q48h<br>• 34–37 weeks: 4 mg/kg (IV) q36h<br>• ≥ 38 weeks: 4 mg/kg (IV) q24h<br>*After first week of life:* Initial dose of 4 mg/kg, then draw serum concentrations 30 min after end of infusion (peak) and 12–24 hours later (trough) to determine dosing interval. Aim for peak of 5–12 mcg/mL and trough of 0.5–1 mcg/mL | 2–2.5 mg/kg (IV or IM) q8h<br>**or**<br>4.5–7.5 mg/kg (IV) q24h |
| Imipenem | 20–25 mg/kg (IV) q12h | 15–25 mg/kg (IV or IM) q6h |
| Iodoquinol | No information | 10–13.3 mg/kg (PO) q8h |
| Isoniazid | See p. 401 | See p. 401 |
| Linezolid | 10 mg/kg (IV) q12h | 10 mg/kg (IV) q8h |
| Liposomal/ lipid complex Amphotericin preparations | 1–5 mg/kg (IV over 2 hours) q24h | 3–6 mg/kg (IV) q24h |
| Meropenem | 20 mg/kg (IV) q12h | 10 mg/kg (IV) q8h (skin); 20 mg/kg (IV) q8h (intraabdominal); 40 mg/kg (IV) q8h (meningitis) |
| Methenamine mandelate | Not indicated | 15–25 mg (PO) q6–8h |
| Metronidazole | 15 mg/kg (IV or PO) × 1 dose, then 7.5 mg/kg/dose (IV or PO) with dosing interval based on gestational age (GA) and chronological age (CA): | 5–12.5 mg/kg (PO) q8h<br>15 mg/kg (IV) × 1 dose followed by 7.5 mg/kg (IV) q6h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.
** Drug can be given IM but absorption may be variable.

| Drug | Dosage in Neonates | | | Dosage in Infants/Children* |
|---|---|---|---|---|
| | GA + CA (weeks) | CA (days) | Interval (hours) | |
| | ≤ 29 | 0–28<br>> 28 | 24<br>48 | |
| | 30–36 | 0–14<br>> 14 | 24<br>12 | |
| | 37–44 | 0–7<br>> 7 | 24<br>12 | |
| Micafungin | 10 mg/kg (IV) of q24h | | | 4–12 mg/kg (IV) q24 (higher dose for patients < 8 year of age |
| Mupirocin | Not indicated | | | Nasal cream: ½ of single use tube into nostril q12h × 5 days;<br>Cream: apply q8h × 5–10 days |
| Nafcillin | 25–50 mg/kg/dose (IV). See *ampicillin* for dosing interval (p. 415) | | | 12.5–50 mg/kg (IV or IM) q6h |
| Nitazoxanide | Not applicable | | | Children 1–3 years old: 100 mg (PO) q12h; children 4–11 years old: 200 mg (PO) q12h |
| Nitrofurantoin | Not indicated | | | UTI: 1.25–1.75 mg/kg (PO) q6h<br>UTI prophylaxis: 1–2 mg/kg (PO) q24h |
| Nystatin | Oral: 1 mL (preterm) to 2 mL (term) of 100,000 U/mL suspension applied with swab to each side of mouth q6h until 3 days after resolution of lesions<br>Topical: Apply ointment or cream to affected area q6h until 3 days after resolution of lesions. | | | Suspension: 4–6 mL swish and swallow 4×/day<br>Troche: 1–2 troches 4–5×/ day |
| Oxacillin | 25–50 mg/kg/dose (IV). See *ampicillin* for dosing interval (p. 415) | | | 25–50 mg/kg (IV or IM) q6h |
| Paromomycin | Not applicable | | | 10 mg/kg (PO) q8h |
| Penicillin G | 25,000–50,000 IU/kg/dose (IV). See *ampicillin* for dosing interval (p. 415)<br>Meningitis: 75,000–100,000 IU/kg | | | 12,500–75,000 U/kg (IV or IM) q4–6h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

| Drug | Dosage in Neonates | Dosage in Infants/Children* |
|---|---|---|
| | (IV) in meningitis (IV).† Q8–12h based on GA + CA, See *ampicillin* for dosing interval (p. 415). Crystalline penicillin G: IM: procaine penicillin G q24 hours. Congenital syphilis: Aqueous penicillin G 50,000 IU/kg (slow IV push) q12h × 7 days, then q8h to complete 10–14 days **or** procaine penicillin G 50,000 IU/kg (IM) q24h × 10–14 days | |
| Penicillin V | Not indicated | 6.25–12.5 mg/kg (PO) q6-8h |
| Piperacillin | 50–100 mg/kg/dose (IV or IM). See *ampicillin* for dosing interval (p. 415) | 25–75 mg/kg (IV or IM) q6h; may increase to q4h in severe infection, especially with pseudomonas |
| Piperacillin-tazobactam | Not indicated | 100–300 mg/kg/day (IV) (of piperacillin component) divided q6-8h |
| Pyrazinamide | See p. 401 | See p. 401 |
| Quinupristin/dalfopristin | No information | 7.5 mg/kg (IV) q12h |
| Rifampin | 10–20 mg/kg (PO) q24h **or** 5–10 mg/kg (IV) q24h | 20 mg/kg (PO) q24h **or** 10 mg/kg (PO) q12h<br><br>10–20 mg/kg/day (IV) divided q12–24h |
| Streptomycin | See p. 401 | See p. 401 |
| Sulfisoxazole | Contraindicated | 30–35 mg/kg (PO) q6h<br>Otitis media prophylaxis: 37.5 mg/kg (PO) q12h |
| Tetracycline | Contraindicated | 5–12.5 mg/kg (PO) q6h. Use only in children > 8 years |
| Ticarcillin | 75–100 mg/kg/dose (IV). See *ampicillin* for dosing interval (p. 415) | 25–75 mg/kg (IV or IM) q6h |
| Ticarcillin-clavulanate | 75–100 mg/kg/dose (of ticarcillin component) (IV). See *ampicillin* for dosing interval (p. 415) | 25–75 mg/kg (of ticarcillin component) (IV or IM) q6h |
| Tinidazole | Not applicable | 50–60 mg/kg (PO) q24h |
| Tobramycin | Same as gentamicin (p. 419) | 2–2.5 mg/kg (IV or IM) q8h or 4.5–7.5 mg/kg (IV) of q24h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

| Drug | Dosage in Neonates | | | Dosage in Infants/Children* |
|---|---|---|---|---|
| Trimethoprim-sulfamethoxazole (TMP–SMX) | Contraindicated | | | UTI: 4–5 mg/kg (of trimethoprim component) (PO) q12h<br>Pneumocystis carinii pneumonia (PCP) 5 mg/kg (PO) q6h (typically after initial IV therapy)<br>UTI prophylaxis: 2–4 mg/kg (PO) q24h<br>*IV dosing*<br>PCP or severe infection: 5 mg/kg (of trimethoprim component) (IV) q6h<br>Minor infections: 4–6 mg/kg (of trimethoprim component) (IV) q12h |
| Vancomycin | Bacteremia: 10 mg/kg/dose (IV)<br>Meningitis: 15 mg/kg/dose (IV).<br>Administer IV dose over 60 min.<br>Dosing interval is based on gestational age (GA) and chronological age (CA): | | | 10–20 mg/kg (IV) q6h |
| | **GA + CA (weeks)** | **CA (days)** | **Interval (weeks)** | |
| | ≤ 29 | 0–14<br>> 14 | 18<br>12 | |
| | 30–36 | 0–14<br>> 14 | 12<br>8 | |
| | 37–44 | 0–7<br>> 7 | 12<br>8 | |
| Voriconazole | Not applicable | | | 7 mg/kg (IV) q12h<br>8 mg/kg (PO) q12h × 1 day, then 7 mg/kg (PO) q12h |

* Dosages are generally based on weight (mg/kg), up to adult dose as maximum.

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Chapter 8

# CHEST X-RAY ATLAS

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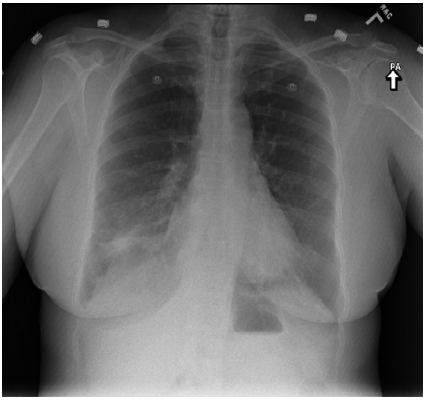
**Chest X-Ray Patterns**



This atlas has been developed to assist in the management of patients who present with respiratory symptoms and chest x-ray abnormalities. Eight common chest x-ray patterns are provided. Common infections and noninfectious etiologies are followed by usual clinical features, which can be used to identify the disorder and help guide empiric/specific therapy.

## UNILATERAL FOCAL SEGMENTAL/LOBAR INFILTRATE WITHOUT EFFUSION




### Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| S. pneumoniae | Elderly, smokers, COPD, ↓ humoral immunity (multiple myeloma, SLE, CLL, hyposplenism). | Fever, chills, no relative bradycardia. Chest signs related to extent of consolidation. | ↑ WBC, ↓ platelets (overwhelming infection/ hyposplenism), normal LFTs. Sputum with abundant PMNs and gram-positive diplococci. Blood cultures usually positive. | Consolidation usually limited to one lobe (RLL most common) ± air bronchogram. Pleural effusion very uncommon. Empyema not uncommon. No cavitation. |
| H. influenzae | Recent contact with H. influenzae URI. | Fever, chills. | ↑ WBC. Sputum/ pleural effusion with gram-negative pleomorphic bacilli. Blood cultures often positive. | Usually RLL with small/moderate effusion. No empyema. No cavitation. |

## **Infectious Causes** (cont'd)

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| M. catarrhalis | Chronic/heavy smoker, COPD. | Nonspecific. | Sputum with gram-negative/variable diplococci. Blood cultures negative. | Usually lower lobe ± consolidation. No pleural effusion or cavitation. |
| K. pneumoniae | Nosocomial pneumonia or history of alcoholism in patient with community-acquired pneumonia. | Fever, chills, signs of alcoholic cirrhosis, signs of consolidation over involved lobe. | ↑ WBC, ↓ platelets, ↑ SGOT/SGPT (2° to alcoholism). "Red currant jelly" sputum with PMNs and plump gram-negative encapsulated bacilli. | "Bulging fissure" sign secondary to expanded lobar volume. Empyema rather than pleural effusion. Cavitation in 5–7 days (thick walled). |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↓ $PO_4^{=}$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute and convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Psittacosis | Recent bird contact with psittacine birds. Severe headache. | Fever/chills, ± relative bradycardia, Horder's spots on face, epistaxis, ± splenomegaly. Signs of consolidation common. | ↑/normal WBC, ↑ LFTs. Sputum with few PMNs. ↑ C. psittaci titers. | Dense infiltrate. Consolidation common. Pleural effusion/ cavitation rare. |
| Q fever | Recent contact with sheep or parturient cats. | Fever/chills, ± relative bradycardia, splenomegaly, ± hepatomegaly. | ↑/normal WBC, ↑ LFTs. Sputum with no bacteria/ few PMNs (caution–biohazard). Acute Q fever with ↑ in phase II ELISA antigens. | Dense consolidation. Cavitation/ pleural effusion rare. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Atelectasis | Ineffectual moist recurrent cough characteristic of post-operative atelectasis. | Fevers ≤ 102°F. If large, signs of volume loss (↓ respiratory excursion, ↑ diaphragm, mediastinum shift toward affected side). If small, ↓ breath sounds over affected segment/lobe. | ↑ WBC (left shift), normal platelets. Other lab results related to underlying cause of atelectasis. | Segmental infiltrate. RUL/RML atelectasis obscures right heart border. In LUL atelectasis, may be triangular infiltrate extending to upper anterior mediastinum mimicking malignancy. LLL atelectasis causes ↑ density of heart shadow. No cavitation or pleural effusion. |

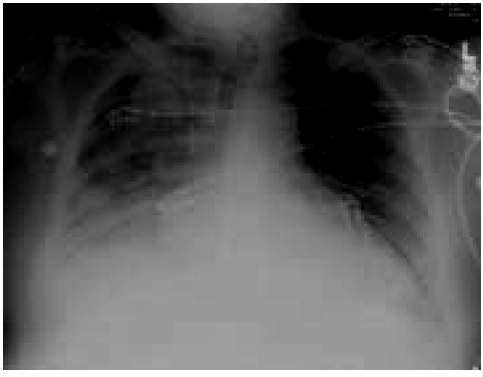
## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Pulmonary embolus/ infarct | Acute onset dyspnea/ pleuritic chest pain. History of lower extremity trauma, stasis or hypercoagulable disorder. | ↑ pulse/ respiratory rate. | ↑ fibrin split products and D-dimers ± ↑ total bilirubin. Bloody pleural effusion. ECG with RV strain/P-pulmonale (large embolus). Positive V/Q scan and CT pulmonary angiogram. | Normal or show non-specific pleural-based infiltrates resembling atelectasis. Focal segmental/lobar hyperlucency (Westermark's sign) in some. "Hampton's hump" with infarct. Resolving infarcts ↓ in size but maintain shape/density ("melting ice cube"). |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, ↑$\alpha_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |
| Alveolar cell carcinoma | Fever, ↑ appetite with weight loss, night sweats. | ± dullness over lobe with large lower lobe lesions. | Positive cytology by BAL/lung biopsy. | Well/ill-defined circumscribed peripheral infiltrates ± air bronchograms. May be multifocal/ multilobar. Hilar adenopathy present. Stranding to the hilum ("pleural tail" sign). ± pleural effusion if lower lobe infiltrate. No cavitation. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Aspiration pneumonia | Swallowing disorder 2° to CNS/GI disorder; impaired consciousness; recent aspiration 2° to dental, upper GI, or pulmonary procedure. | Unremarkable. | ↑ WBC, ↑ ESR. | Infiltrate usually involves superior segments of lower lobes (or posterior segments of upper lobes if aspiration occurred supine). Focal infiltrate initially, which may be followed in 7 days by cavitation/lung abscess. |

## UNILATERAL FOCAL SEGMENTAL/LOBAR INFILTRATE WITH EFFUSION



### Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Klebsiella pneumoniae | Nosocomial pneumonia or history of alcoholism in patient with community-acquired pneumonia. | Fever, chills, signs of alcoholic cirrhosis, signs of consolidation over involved lobe. | ↑ WBC, ↓ platelets, SGOT/SGPT (2° to alcoholism). "Red currant jelly" sputum with PMNs and plump gram-negative encapsulated bacilli. | "Bulging fissure" sign secondary to expanded lobar volume. Empyema rather than pleural effusion. Usually cavitation in 5–7 days (thick walled). |
| H. influenzae | Recent contact with H. influenzae URI. | Fever, chills. | ↑ WBC. Sputum/ pleural effusion with gram-negative pleomorphic bacilli. Blood cultures often positive. | Usually RLL with small/ moderate effusion. No empyema. No cavitation. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| TB (primary) | Recent TB contact. | Unilateral lower lobe dullness related to size of pleural effusion. | PPD (–)/anergic. Exudative pleural effusion (pleural fluid with ↑ lymphocytes, ↑ glucose, ± RBCs). | Lower lobe infiltrate with small/moderate pleural effusion. No cavitation or apical infiltrates. Hilar adenopathy asymmetrical when present. |
| Coccidio-mycosis (chronic) | Previous exposure in endemic coccidiomycosis areas. Asymptomatic. | ± E. nodosum. | Normal WBC, no eosinophilia in chronic phase. Complement fixation IgG titer ≥ 1:32 indicates active disease. | Thick/thin-walled cavities < 3 cm ± calcifications. Air fluid level rare unless secondarily infected. Cavities usually in anterior segments of upper lobes (vs. posterior segments with TB). No surrounding tissue reaction. Pleural effusion common. |
| Tularemia | History of recent deer fly, rabbit, or tick exposure. Tularemia pneumonia may complicate any of the clinical presentations of tularemia. | Fever, chills, no relative bradycardia. Chest findings related to extent of infiltrate/ consolidation and pleural effusion. | Normal/↑ WBC, normal LFTs. Sputum/pleural effusion with gram-negative coccobacilli (caution–biohazard). Bloody pleural effusion. Tularemia serology with ↑ microagglutination titer ≥ 1:160 acutely and ≥ 4-fold rise between acute and convalescent titers. | Pleural effusion ± hilar adenopathy. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Adenovirus | Recent URI. | Fever, chills, myalgias. Sore throat and conjunctivitis not always present with adenoviral pneumonia. Chest exam ± signs of consolidation. | ↑ adenoviral titers and positive adenoviral cultures of respiratory secretions. Respiratory viral FA panel + for adenovirus. | Ill-defined infiltrate(s) without cavitation ± pleural effusion. |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/ splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↓ $PO_4^{=}$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute/ convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |
| Group A streptococci | Recent exposure or recent blunt chest trauma ± chest pain. | Fever/chills. Physical signs related to size of pleural effusion. | ↑ WBC. Pleural fluid is serosanguineous. Sputum/pleural fluid with gram-positive cocci in pairs/chains. Positive pleural fluid/ blood cultures. | Unilateral infiltrate may be obscured by large pleural effusion. No empyema. No cavitation. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Rhodococcus equi | Insidious onset of fever, dyspnea, chest pain, ± hemoptysis. Immuno-suppressed patients with ↓ cell-mediated immunity or exposure to cattle, horses, pigs. | Unremarkable. | Normal/↑ WBC. Sputum/pleural fluid with gram-positive pleomorphic weakly acid-fast bacilli. Sputum, pleural fluid, blood cultures positive for R. equi. | Segmental infiltrate with upper lobe predominance ± cavitation. Air-fluid levels and pleural effusion common. |

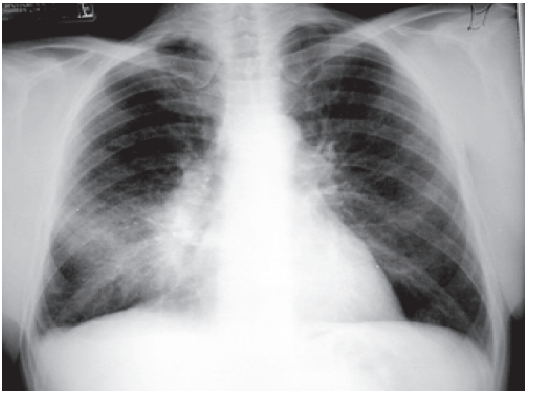
## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Pulmonary embolus/ infarct | Acute onset dyspnea/ pleuritic chest pain. History of lower extremity trauma, stasis or hypercoagulable disorder. | ↑ pulse/ respiratory rate. | ↑ fibrin split products and D-dimers ± ↑ total bilirubin. Bloody pleural effusion. ECG with RV strain/P-pulmonale (large embolus). Positive V/Q scan and CT pulmonary angiogram. | Normal or show non-specific pleural-based infiltrates resembling atelectasis. Focal segmental/ lobar hyperlucency (Westermark's sign) in some. "Hampton's hump" with infarct. Resolving infarcts ↓ in size but maintain shape/ density ("melting ice cube"). |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, ↑$\propto_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |
| Alveolar cell carcinoma | Fever, ↑ appetite with weight loss, night sweats. | ± dullness over lobe with large lower lobe lesions. | Positive cytology by BAL/lung biopsy. | Well/ill-defined circumscribed peripheral infiltrates ± air bronchograms. May be multifocal/ multilobar. Hilar adenopathy present. Stranding to the hilum ("pleural tail" sign). ± pleural effusion if lower lobe infiltrate. No cavitation. |
| Radiation pneumonitis | History of mantle radiation for lymphoma, lung cancer, or breast cancer. | Nonspecific. | Nonspecific. | Symmetrical infiltrates in the distribution of radiation therapy after 1 month. Infiltrates have "straight edges"± air bronchograms. Fibrosis common over radiation field after 9–12 months. Usually no pleural effusions (small, if present). |

## UNILATERAL ILL-DEFINED INFILTRATES WITHOUT EFFUSION



### Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Mycoplasma pneumoniae | Prolonged dry/ nonproductive cough. No laryngitis. Mild sore throat/ear. Watery diarrhea. | Usually fevers ≤102°F without relative bradycardia. Myalgias, bullous myringitis or otitis, non-exudative pharyngitis, E. multiforme. Chest exam with rales and no signs of consolidation or effusion. | Normal/↑ WBC; normal platelets, LFTs, $PO_4^{=}$, CPK. ↑ cold agglutinins (early). ↑ IgM (not IgG) Mycoplasma pneumoniae titers. Respiratory secretions culture positive for Mycoplasma pneumoniae. | Ill-defined usually lower lobe indistinct infiltrates. No consolidation or air bronchograms. Small/no pleural effusion. |

## **Infectious Causes** (cont'd)

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Chlamydophilia (Chlamydia) pneumoniae | Prolonged "mycoplasma-like" illness with laryngitis. | Low-grade fevers, myalgias, non-exudate pharyngitis, laryngitis. No relative bradycardia, ear findings, or rash. Chest exam without signs of consolidation or pleural effusion. | ↑ WBC, normal platelets, normal LFTs. No cold agglutinins. ↑ IgM (not IgG) C. pneumoniae titers. Respiratory secretions culture positive for C. pneumoniae. | Ill-defined, usually lower lobe indistinct infiltrate(s). May be "funnel shaped." No consolidation, cavitation, or pleural effusion. |
| Adenovirus | Recent URI. | Fever, chills, myalgias. Sore throat and conjunctivitis not always present with adenoviral pneumonia. Chest exam ± signs of consolidation. | ↑ adenoviral titers and positive adenoviral cultures of respiratory secretions. Respiratory viral FA panel + for adenovirus. | Ill-defined infiltrate(s) without cavitation ± pleural effusion. Only viral cause of focal lobar pneumonia. |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↓ $PO_4^{=}$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute/convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Psittacosis | Recent bird contact with psittacine birds. Severe headache. | Fever/chills, ± relative bradycardia, ± Horder's spots on face, epistaxis, ± splenomegaly. Signs of consolidation common. | ↑/normal WBC, ↑ LFTs. Sputum with few PMNs. ↑ C. psittaci titers. | Dense infiltrate. Consolidation common. Pleural effusion/ cavitation rare. |
| Q fever | Recent contact with sheep or parturient cats. | Fever/chills, ± relative bradycardia, splenomegaly, ± hepatomegaly. | ↑/normal WBC, ↑ LFTs. Sputum with no bacteria/few PMNs (caution–biohazard). Acute Q fever with ↑ in phase II ELISA antigens. | Dense consolidation. Cavitation/ pleural effusion rare. |
| Nocardia | Fevers, night sweats, fatigue, ↓ cell-mediated immunity (e.g., HIV, organ transplants, PAP, immunosup-pressive therapy). | Unremarkable. | Normal/↑ WBC, ↑ ESR. Sputum with gram-positive AFB. | Dense large infiltrates. May cavitate and mimic TB, lymphoma, or squamous cell carcinoma. No calcification ± pleural effusion. |
| Actinomycosis | Recent dental work. | ± chest wall sinus tracts. | Normal/↑ WBC, ↑ ESR. Sputum with gram-positive filamentous anaerobic bacilli. | Dense infiltrates extending to chest wall. No hilar adenopathy. Cavitation rare. ± pleural effusion rare. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Cryptococcus neoformans | Exposure to air conditioner or pigeons. | Unremarkable. | Normal WBC. Cryptococcal serology with ↑ C. neoformans antigen levels. | Dense lower nodular mass lesions. No calcification or cavitation. ± pleural effusion. |
| Aspiration pneumonia | Swallowing disorder 2° to CNS/GI disorder; impaired consciousness; recent aspiration 2° to dental, upper GI, or pulmonary procedure. | Unremarkable. | ↑ WBC, ↑ ESR. | Infiltrate usually involves superior segments of lower lobes (or posterior segments of upper lobes if aspiration occurred supine). Focal infiltrate initially, which may be followed in 7 days by cavitation/lung abscess. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Bronchogenic carcinoma | Fever, ↓ appetite with weight loss, cough ± hemoptysis. Cough with copious clear/mucoid sputum in large cell anaplastic carcinoma. Increased risk in smokers, aluminum/uranium miners, cavitary lung disease (adenocarcinoma), previous radiation therapy from lymphoma/breast cancer. | Paraneoplastic syndromes especially with small (oat) cell/squamous cell carcinoma ± hypertrophic pulmonary osteoarthropathy. | Normal/↑ WBC, ↑ platelets, ↑ ESR, findings related to underlying malignancy, ± clubbing. | Small/squamous cell carcinomas present as central lesions/hilar masses. Adenocarcinoma/large cell anaplastic carcinomas are usually peripheral initially. "Tumor tendrils" extending into surrounding lung tissue is characteristic. No calcifications (may be present on chest CT). Cavitation with squamous cell carcinoma. ± pleural effusions. |
| Lymphangitic metastases | History of breast, thyroid, pancreas, cervical, prostate, or lung carcinoma. | Findings related to underlying malignancy. | Normal/↑ WBC, ↑ ESR. | Interstitial indistinct pulmonary infiltrates (may be reticulonodular) with lower lobe predominance Usually unilateral but may be bilateral. No consolidation or cavitation ± pleural effusions. |
| Lung contusion | Recent closed chest trauma, chest pain. | Chest wall contusion over infiltrate. | ↑ WBC (left shift). | Patchy ill-defined infiltrate(s) ± rib fractures/pneumothorax in area of infiltrate. Infiltrate clears within 1 week. |

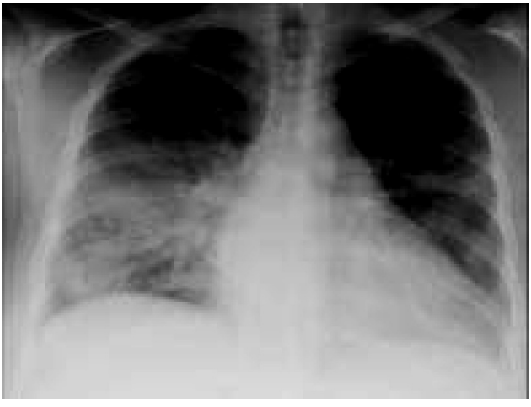
## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Congestive heart failure | Coronary heart disease, valvular heart disease, cardiomyopathy. | No/low-grade fevers ↑ pulse and respiratory rate, positive jugular venous distension and hepatojugular reflex, cardiomegaly, $S_3$, ascites, hepatomegaly, pedal edema. | ↑ WBC (left shift), normal platelets, mildly ↑ SGOT/SGPT. | Cardiomegaly, pleural effusion (R > [R + L] > L). Kerley B lines with vascular redistribution to upper lobes. Typically bilateral rather than unilateral. |
| Alveolar cell carcinoma | Fever, ↑ appetite with weight loss, night sweats. | ± dullness over lobe with large lower lobe lesions. | Positive cytology by BAL/lung biopsy. | Well/ill-defined circumscribed peripheral infiltrates ± air bronchograms. May be multifocal/multilobar. Hilar adenopathy present. Stranding to the hilum ("pleural tail" sign). ± pleural effusion if lower lobe infiltrate. No cavitation. |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, ↑$\alpha_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Pulmonary hemorrhage | History of closed chest trauma or hemorrhagic disorder. | ↑ WBC (left shift), ↑ pulse rate, respiratory rate. Signs of closed chest trauma. | Anemia plus findings secondary to underlying hemorrhagic disorder. | Localized or diffuse fluffy alveolar infiltrate(s). No cavitation, consolidation, or effusion. |
| Systemic lupus erythematosus (SLE) | Fatigue, chest pain. History of SLE. | Fever/myalgias, alopecia, malar rash, "cytoid bodies" in retina, painless oral ulcers, synovitis, splenomegaly, generalized adenopathy, Raynaud's phenomenon. | ↑ ANA, ↑ DS-DNA, ↓ $C_3$, polyclonal gammopathy on SPEP, ↑ ferritin. Pleural fluids with ↑ ANA, ↓ $C_3$. | Migratory ill-defined non-segmental infiltrates ± small pleural effusions. No consolidation or cavitation. |
| Aspiration pneumonia | Swallowing disorder 2° to CNS/GI disorder; impaired consciousness; recent aspiration 2° to dental, upper GI, or pulmonary procedure. | Unremarkable. | ↑ WBC, ↑ ESR. | Infiltrate usually involves superior segments of lower lobes (or posterior segments of upper lobes if aspiration occurred supine). Focal infiltrate initially, which may be followed in 7 days by cavitation/lung abscess. |

## UNILATERAL ILL-DEFINED INFILTRATES WITH EFFUSION



### Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| TB (primary) | Recent TB contact. | Unilateral lower lobe dullness related to size of pleural effusion. | PPD anergic. Exudative pleural effusion (pleural fluid with ↑ lymphocytes, ↑ glucose, ± RBCs). | Lower lobe infiltrate with small/moderate pleural effusion. No cavitation or apical infiltrates. Hilar adenopathy asymmetrical when present. |
| Nocardia | Fevers, night sweats, fatigue, ↓ cell-mediated immunity (e.g., HIV, organ transplant, PAP, immuno-suppressive therapy). | Unremarkable. | Normal/↑ WBC, ↑ ESR. Sputum with gram-positive AFB. | Dense large infiltrates. May cavitate and mimic TB, lymphoma, or squamous cell carcinoma. No calcification ± pleural effusion. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/ splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↓ $PO_4^{=}$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute/ convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Lymphangitic metastases | History of breast, thyroid, pancreas, cervical, prostate, or lung carcinoma. | Findings related to underlying malignancy. | Normal/ ↑ WBC, ↑ ESR. | Interstitial indistinct pulmonary infiltrates (may be reticulonodular) with lower lobe predominance Usually unilateral but may be bilateral. No consolidation or cavitation ± pleural effusions. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Pulmonary embolus/ infarct | Acute onset dyspnea/ pleuritic chest pain. History of lower extremity trauma, stasis or hypercoagulable disorder. | ↑ pulse/ respiratory rate. | ↑ fibrin split products and D-dimers ± ↑ total bilirubin. Bloody pleural effusion. ECG with RV strain/ P-pulmonale (large embolus). Positive V/Q scan and CT pulmonary angiogram. | Normal or show non-specific pleural-based infiltrates resembling atelectasis. Focal segmental/lobar hyperlucency (Westermark's sign) in some. "Hampton's hump" with infarct. Resolving infarcts ↓ in size but maintain shape/density ("melting ice cube"). |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, ↑$\alpha_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |

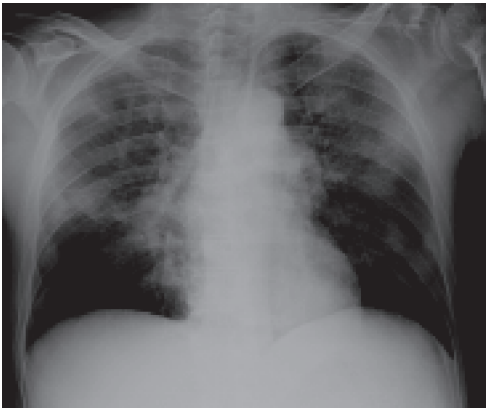
## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Bronchogenic carcinoma | Fever, ↓ appetite with weight loss, cough ± hemoptysis. Cough with copious clear/mucoid sputum in large cell anaplastic carcinoma. Increased risk in smokers, aluminum/uranium miners, cavitary lung disease (adenocarcinoma), previous radiation therapy from lymphoma/breast cancer. | Paraneoplastic syndromes especially with small (oat) cell/squamous cell carcinoma ± hypertrophic pulmonary osteoarthropathy. | Normal/↑ WBC, ↑ platelets, ↑ ESR, findings related to underlying malignancy, ± clubbing. | Small/squamous cell carcinomas present as central lesions/hilar masses. Adenocarcinoma/large cell anaplastic carcinomas are usually peripheral initially. "Tumor tendrils" extending into surrounding lung tissue is characteristic. No calcifications (may be present on chest CT). Cavitation with squamous cell carcinoma. ± pleural effusions. |
| Alveolar cell carcinoma | Fever, ↑ appetite with weight loss, night sweats. | ± dullness over lobe with large lower lobe lesions. | Positive cytology by BAL/lung biopsy. | Well/ill-defined circumscribed peripheral infiltrates ± air bronchograms. May be multifocal/multilobar. Hilar adenopathy present. Stranding to the hilum ("pleural tail" sign). ± pleural effusion if lower lobe infiltrate. No cavitation. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Metastatic carcinoma | History of breast, thyroid, renal cell, colon, pancreatic cancer or osteogenic sarcoma. | Findings related to underlying malignancy and, when present, to bone, hepatic, CNS metastases. | Secondary to effects of primary neoplasm, metastases, paraneoplastic syndrome. | Nodular lesions that vary in size. Metastatic lesions are usually well circumscribed with lower lobe predominance. Usually no bronchial obstruction (obstruction suggests colon, renal, or melanoma metastases). Usually no cavitation (except for squamous cell metastases). Calcification usually suggests osteosarcoma (rarely adenocarcinoma). Pleural effusion rare (except for breast cancer). |

## BILATERAL INFILTRATES WITHOUT EFFUSION



### Infectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Influenza (human, avian, swine) | Acute onset of fever, myalgias, headache, fatigue, sore throat, rhinorrhea, dry cough, ± pleuritic chest pain. | ↑ respiratory rate, cyanosis in severe cases. | ↓ WBC, ↓ platelets, few/no atypical lymphocytes, ↑ A-a gradient. Influenza in respiratory secretions by culture/viral FA panel. | Early normal/near normal appearance. (< 48 hours) Later (> 48 hours) diffuse patchy bilateral interstitial infiltrates. No focal/segmental infiltrates unless secondary bacterial pneumonia present. ± small pleural effusions. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| MERS | Acute onset of fever/ chills, headache, myalgias, dry cough ± N/V/D<br><br>Malaise; Hemoptysis | Early fulminant respiratory failure. | (N) WBC lymphopenia/ lymphocytosis, ↑ LDH<br>↑ LFTs<br>MERS-Cov in lower respiratory secretions. | Unilateral/bilateral interstitial, nodule dense infiltrate.<br><br>Consolidation common/± pleural effusions. |
| SARS | Acute onset of fever/ chills, headache myalgias, dry cough ± N/V/D.<br><br>Biphasic illness | ↑ respiratory rate, SOB in severe cases. | N/↓ WBC, lymphopenia, ↓ platelets, ↑ LDH, ↑ LFTs, ↓ $pO_2$, ↑ A-a gradient. SARS – CoV in respiratory secretions. | Bilateral symmetrical patchy infiltrates. Consolidation uncommon. No cavitation or effusion. |
| HSV-1 | Fever. Often presents in normal hosts as "failure to wean" from ventilator. | Unremarkable. | ↑ WBC, ↓ $pO_2$, ↑ A-a gradient. Cytology + for cytopathic effects (CPE) of HSV. | Minimal bilateral diffuse infiltrates without cavitation or effusion. |
| RSV | Recent URI contact, dry cough, wheezing. | Mild lower respiratory tract infection in normal host. Moderate/severe pneumonia in organ transplants. | Normal WBC; ↓ $pO_2$/↑ A-a gradient in severe RSV. RSV in respiratory secretions by culture/viral FA panel. | Near normal chest x-ray or bilateral symmetrical patchy infiltrates. Consolidation uncommon. No cavitation or effusion. |
| VZV | VZV pneumonia occurs 2–3 days after rash. ↑ risk with pregnancy, smoking. | Healing vesicles, dry cough. Mild pneumonia in normal hosts. Moderate/ severe pneumonia in organ transplants. | ↑ WBC, ↑ platelets, ↑ basophils; ↓ $pO_2$/↑ A-a gradient in severe chickenpox pneumonia. ↑ VZV titers. | Minimal diffuse fluffy interstitial infiltrates. Diffuse small calcifications may develop years later. No calcification of hilar nodes (in contrast to TB/ histoplasmosis). |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| CMV | ↓ cell-mediated immunity (HIV, organ transplants, immunosuppressive therapy). Increasing dyspnea over 1 week. | Fever ≤ 102°F. | ↓ $pO_2$, ↑ A-a gradient, ↑ LDH (PCP). PCP cysts or CMV "Cowdry Owl eye" inclusion bodies in respiratory secretions or transbronchial/ open lung biopsy. | Most HIV patients with PCP also have underlying CMV. Organ transplants with CMV usually do not have underlying PCP. |
| P (carinii) jiroveci (PCP) | ↓ cell-mediated immunity (e.g., HIV, immuno-suppressive therapy). Increasing dyspnea over 1 week. Chest pain with shortness of breath suggests pneumothorax. | ↓ breath sounds bilaterally. Other findings depend on size/location of pneumothorax (if present). | Normal/↑ WBC (left shift), ↑ lymphocytes, ↑ LDH. ↓ $pO_2$, ↓ $DL_{CO}$, ↑ A-a gradient. PCP cysts in sputum/ respiratory secretions. | Bilateral perihilar symmetrical patchy infiltrates ± pneumothorax. No calcification, cavitation, or pleural effusion. |
| TB (reactivation) | Fevers, night sweats, normal appetite with weight loss, cough ± hemoptysis. | ± bilateral apical dullness. | Normal WBC, ↑ platelets, ↑ ESR (≤ 70 mm/h). Positive PPD. AFB in sputum smear/ culture. | Slowly progressive bilateral infiltrates. No pleural effusion. Usually in apical segment of lower lobes or apical/ posterior segments of upper lobes. Calcifications common. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↑ $pO_4^=$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute/convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |
| Psittacosis | Recent bird contact with psittacine birds. Severe headache. | Fever/chills, ± relative bradycardia, ± Horder's spots on face, epistaxis, ± splenomegaly. Signs of consolidation common. | ↑/normal WBC, ↑ LFTs. Sputum with few PMNs. Positive C. psittaci serology. | Dense infiltrate. Consolidation common. Pleural effusion/cavitation rare. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Q fever | Recent contact with sheep or parturient cats. | Fever/chills, ± relative bradycardia, splenomegaly, ± hepatomegaly. | ↑/normal WBC, ↑ LFTs. Sputum with no bacteria/few PMNs (caution–biohazard). Acute Q fever with ↑ in phase II ELISA antigens. | Dense consolidation. Cavitation/pleural effusion rare. |
| Nosocomial pneumonia (hematogenous) | Fever/pulmonary symptoms ≥ 7 days in hospital. Increased risk with antecedent heart failure in previous 1–2 weeks. | Bilateral rales ± purulent respiratory secretions (tracheobronchitis). | ↑ WBC (left shift). Blood cultures positive for pulmonary pathogens. Respiratory secretions with WBCs ± cultures positive for P. aeruginosa, Acinetobacter, Enterobacter, Klebsiella, or Serratia (represents colonization, *not* lower respiratory tract/lung pathogens). Definitive diagnosis by lung biopsy/culture. | Bilateral symmetrical diffuse infiltrates. May be focal/ segmental in aspiration nosocomial pneumonia. ↑ lung volumes (vs. ARDS). Klebsiella cavitation in 3–5 days; P. aeruginosa cavitation in 72 hours. No pleural effusion. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Adult respiratory distress syndrome (ARDS) | Intubated on ventilator, multi-organ system failure. | ± rales. | ↑ WBC (left shift), normal ESR, ↓ $pO_2$, ↓ $D_LCO$, ↑ A-a gradient. | Bilateral fluffy infiltrates appearing ≥ 12 hours after profound hypoxemia. No cardiomegaly or pleural effusion. Reduced lung volumes (vs. nosocomial pneumonia or CHF). Bilateral consolidation ≥ 48 hours after appearance of infiltrates. |
| Goodpasture's syndrome | Often preceded by a URI. Most common in 20–30 year old adults. Fever, weight loss, fatigue, cough, hemoptysis, hematuria. | Findings secondary to iron deficiency anemia. | ↑ WBC, anemia, ↑ creatinine, urine with RBCs/RBC casts. Positive pANCA. Linear IgG pattern on alveolar/glomerular basement membrane. | Bilateral fine reticulonodular infiltrates predominantly in lower lobes. No cavitation. |
| Wegener's granulomatosis | Most common in middle-aged adults. Cough, fever, fatigue. | Findings of chronic sinusitis, bloody nasal discharge. | ↑ WBC, anemia, ↑ platelets, ↑ ESR, ↑ RF, negative ANA, proteinuria, hematuria. Positive cANCA. | Bilateral asymmetrical nodular infiltrates of varying size with irregular margins. Cavitation common. Inner lining of cavities irregular. Air-fluid levels rare. ± pleural effusions. No calcifications. |
| Pulmonary hemorrhage | History of closed chest trauma or hemorrhagic disorder. | ↑ WBC (left shift), ↑ pulse rate, ↑ respiratory rate. Signs of closed chest trauma. | Anemia plus findings secondary to underlying hemorrhagic disorder. | Localized or diffuse fluffy alveolar infiltrates. No cavitation, consolidation, or effusion. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Chronic renal failure | Chronic renal failure on dialysis. | Findings related to uremia. | Normal/↑ WBC (left shift) plus findings related to renal failure. | Bilateral symmetrical fluffy perihilar infiltrates (butterfly pattern) ± pleural effusions. No cardiomegaly (unlike CHF), but large pericardial effusion can mimic cardiomegaly. |
| Lung contusion | Recent closed chest trauma, chest pain. | Chest wall contusion over infiltrate. | ↑ WBC (left shift). | Patchy ill-defined infiltrate(s) ± rib fractures/pneumothorax in area of infiltrate. Infiltrate clears within 1 week. |
| Fat emboli | 1–2 days post-long bone fracture/ trauma. | ↑ respiratory rate. | Urinalysis with "Maltese crosses." | Bilateral predominantly peripheral lower lobe infiltrates. Usually clears within 1 week. |
| Loeffler's syndrome | Drug or parasitic exposure. | Unremarkable. | Normal WBC, ↑ eosinophilia, ↑ ESR. | Characteristic "reversed bat-wing" pattern (i.e., peripheral infiltrates). Upper lobe predominance. |
| Sarcoidosis (Stage III) | Dyspena, fatigue, nasal stuffiness. | Waxy/yellowish papules on face/ upper trunk. Funduscopic exam with "candle wax drippings." | ↑ ESR, normal LFTs, ↑ creatinine (if renal involvement), ↑ ACE levels, hypercalciuria, hypercalcemia, polyclonal gammopathy on SPEP. Anergic. | Bilateral nodular infiltrates of variable size without hilar adenopathy. Cavitation/ pleural effusion rare. |

## **Noninfectious Causes** (cont'd)

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Alveolar cell carcinoma | Fever, ↑ appetite with weight loss, night sweats. | ± dullness over lobe with large lower lobe lesions. | Positive cytology by BAL/lung biopsy. | Well/ill-defined circumscribed peripheral infiltrates ± air bronchograms. May be multifocal/multilobar. Hilar adenopathy present. Stranding to the hilum ("pleural tail" sign). ± pleural effusion if lower lobe infiltrate. No cavitation. |
| Metastatic carcinoma | History of breast, thyroid, renal cell, colon, pancreatic cancer or osteogenic sarcoma. | Findings related to underlying malignancy and, when present, to bone, hepatic, CNS metastases. | Secondary to effects of primary neoplasm, metastases, paraneoplastic syndrome. | Nodular lesions that vary in size. Metastatic lesions are usually well circumscribed with lower lobe predominance. Usually no bronchial obstruction (obstruction suggests colon, renal, or melanoma metastases). Usually no cavitation (except for squamous cell metastases). Calcification usually suggests osteosarcoma (rarely adenocarcinoma). Pleural effusion rare (except for breast cancer). |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, ↑$\alpha_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |

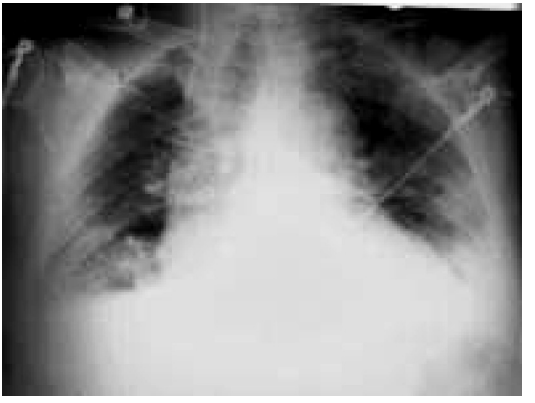
## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Leukostasis (AML) | Untreated acute myelogenous leukemia (AML). | Fever, sternal tenderness, petechiae, ecchymosis. | ↑ WBC (≥ 100 K/mm$^3$) with blasts in peripheral smear/bone marrow, ↓ platelets. | Diffuse symmetrical fluffy infiltrates without pleural effusion. |
| Drug-induced | Exposure to chemo-therapeutic agents (e.g., BCNU, busulfan, methotrexate, cyclophospham-ide, bleomycin) or other drugs (e.g., nitro-furantoin, sulfasalazine, amiodarone, opiates, cocaine). | Unremarkable. | Normal WBC ± ↑ eosinophilia, normal/↑ ESR/LFTs. Eosinophils in pleural effusion. | Bilateral coarse symmetrical patchy infiltrates/fibrosis ± pleural effusions. Hilar adenopathy only with drug-induced pseudolymphoma (secondary to dilantin). No cavitation. |
| Idiopathic pulmonary hemosiderosis (IPH) | Hemoptysis ± cough. | Findings of iron deficiency anemia. | Iron deficiency anemia. Hemosiderin in alveolar macrophages and urine. | Diffuse, bilateral ill-defined opacities or multiple "stellate" shaped infiltrates that clear between attacks. Recent hemorrhage may be superimposed on a fine reticular pattern that occurs after repeated bleeds. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Bronchiolitis obliterans with organizing pneumonia (BOOP) | Fever, dyspnea, cough. | Unremarkable. | ↑ WBC (left shift), ↑ LDH, ↓ $pO_2$, ↑ A-a gradient. | Classically bilateral patchy peripheral infiltrates. Often lower lobe predominance. No cavitation or pleural effusion. |
| Pulmonary alveolar proteinosis (PAP) | Asymptomatic if not infected with Nocardia. | Unremarkable. | Normal/↑ WBC, ↑ LDH. | Bilateral granular or peripheral infiltrates in butterfly pattern. No hilar adenopathy, cardiomegaly, or pleural effusion. |

## BILATERAL INFILTRATES WITH EFFUSION



## Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Legionella | Recent contact with Legionella containing water. Usually elderly. May have watery diarrhea, abdominal pain, mental confusion. | Fever/chills, relative bradycardia. Hepatic/splenic enlargement goes against the diagnosis. ↓ breath sounds if consolidation or pleural effusion. | ↑ WBC, ↑ SGOT/SGPT, ↑ $PO_4^{=}$, ↓ $Na^+$, ↑ CPK, ↑ ESR, ↑ CRP, ↑ ferritin levels, microscopic hematuria, L. pneumophila antigenuria (serotypes 01–06 only) may not be positive early. Mucoid/purulent sputum with few PMNs. Sputum culture for Legionella or sputum DFA (before therapy) is diagnostic. ↑ Legionella titer ≥ 1:256 or ≥ 4-fold rise between acute/convalescent titers. | Rapidly progressive asymmetrical infiltrates clue to Legionella. Consolidation and pleural effusion not uncommon. Cavitation rare. |

## **Infectious Causes** (cont'd)

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Hantavirus (HPS) | Subacute onset, shortness of breath, substernal chest discomfort. Improvement followed by rapid deterioration. | ↑ respiratory rate, cyanosis in severe cases. | ↓ WBC, ↓ platelets<br>↓ $pO_2$, ↑ A-a gradient.<br>↑ hantavirus titers. | Large pleural effusions. |
| MERS | Recent contact with MERS case or camel contact.<br><br>Acute onset of fever/chills, headache, myalgias, dry cough ± N/V/D, Malaise, ±/ hemoptysis | Early fulminant respiratory failure. | (N) WBC, relative lymphopenia, ↑ LDH<br>↑ LFTs<br>MERS-CoV in lower respiratory secretions. | Unilateral (early) or bilateral (late) interstitial, nodular dense infiltrates.<br><br>Recent contact with MERS case or camel contact.<br><br>Consolidation common ± pleural effusions. |
| Measles | Recent airborne exposure. | Measles rash, Koplik's spots. | Normal/↑ WBC (left shift), normal/↓ platelets, ↑ LFTs, ↑ CPK, normal/↓ $pO_2$. If ↓ $pO_2$, then ↑ A-a gradient.<br>↑ IgM measles titer.<br>Warthin-Finkeldey cells in respiratory secretions. | Bilateral diffuse fine reticulonodular infiltrates ± hilar adenopathy. Lower lobe predominance. Consolidation/ pleural effusion uncommon. |
| Strongyloides | Strongyloides exposure. 1/3 asymptomatic; 2/3 with fever, dyspnea, cough. Hyperinfection syndrome with abdominal pain, diarrhea ± GI bleed. | With hyperinfection syndrome, fever, ↓ BP, abdominal tenderness ± rebound, ± meningitis. | ↑ WBC (left shift), ↑ eosinophilia, ± anemia. Blood/CSF cultures positive for enteric gram-negative bacilli. Rhabditiform larvae in sputum/stool. | Diffuse hilar patchy infiltrates without consolidation or cavitation. Eosinophilic pleural effusion common. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Congestive heart failure | Coronary heart disease, valvular heart disease, cardiomyopathy. | No/low grade fevers, ↑ pulse/respiratory rate, positive jugular venous distension and hepatojugular reflex, cardiomegaly, $S_3$, ascites, hepatomegaly, pedal edema. | ↑ WBC (left shift), normal platelets, mildly ↑ SGOT/SGPT. | Cardiomegaly, pleural effusion (R > [R + L] > L). Kerley B lines with vascular redistribution to upper lobes. Typically bilateral rather than unilateral. |
| Chronic renal failure | Chronic renal failure on dialysis. | Findings related to uremia. | Normal/↑ WBC (left shift) plus findings related to renal failure. | Bilateral symmetrical fluffy perihilar infiltrates (butterfly pattern) ± pleural effusions. No cardiomegaly (unlike CHF), but large pericardial effusion can mimic cardiomegaly. |
| SLE | Fatigue, chest pain. History of SLE. | Fever/myalgias, alopecia, malar rash, "cytoid bodies" in retina, painless oral ulcers, synovitis, splenomegaly, generalized adenopathy, Raynaud's phenomenon. | ↑ ANA, ↑ DS-DNA, ↓ $C_3$, polyclonal gammopathy on SPEP, ↑ ferritin. Pleural fluids with ↑ ANA, ↓ $C_3$. | Migratory ill-defined non-segmental infiltrates. No signs of consolidation or cavitation. ± small pleural effusions. |

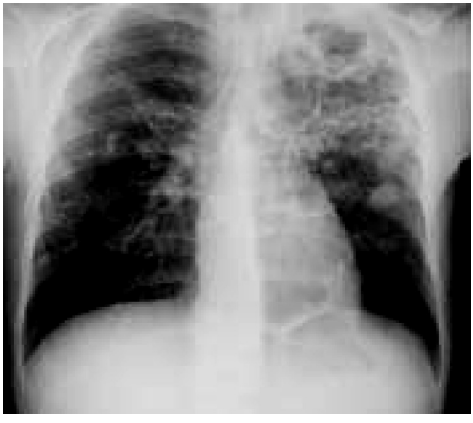
## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Goodpasture's Syndrome | Often preceded by a URI. Most common in 20–30 year old adults. Fever, weight loss, fatigue, cough, hemoptysis, hematuria. | Findings secondary to iron deficiency anemia. | ↑ WBC, anemia, ↑ creatinine, urine with RBCs/RBC casts. Positive pANCA. Linear IgG pattern on alveolar/ glomerular basement membrane. | Bilateral fine reticulonodular infiltrates predominantly in lower lobes. No cavitation. |
| Wegener's granulo-matosis | Most common in middle-aged adults. Cough, fever, fatigue. | Findings of chronic sinusitis, bloody nasal discharge. | ↑ WBC, anemia, ↑ platelets, ↑ ESR, ↑ RF, negative ANA, proteinuria, hematuria. Positive cANCA. | Bilateral asym-metrical nodular infiltrates of varying size with irregular margins. Cavitation common. Inner lining of cavities irregular. Air-fluid levels rare. ± pleural effusions. No calcifications. |
| Sarcoidosis (Stage III) | Dyspnea, fatigue, nasal stuffiness. | Waxy/yellowish papules on face/ upper trunk. Funduscopic exam with "candle wax drippings." | ↑ ESR, normal LFTs, ↑ creatinine (if renal involvement), ↑ ACE levels, hypercalciuria, hypercalcemia, polyclonal gammopathy on SPEP. Anergic. | Bilateral nodular infiltrates of variable size without hilar adenopathy. Cavitation/pleural effusion rare. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR, ↑ alkaline phosphatase, $\uparrow\alpha_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |
| Lymphangitic metastases | History of breast, thyroid, pancreas, cervical, prostate, or lung carcinoma. | Findings related to underlying malignancy. | Normal/ ↑ WBC, ↑ ESR. | Interstitial indistinct pulmonary infiltrates (may be reticulonodular) with lower lobe predominance Usually unilateral but may be bilateral. No consolidation or cavitation ± pleural effusions. |
| Drug-induced | Exposure to chemotherapeutic agents (e.g., BCNU, busulfan, methotrexate, cyclophosphamide, bleomycin) or other drugs (e.g., nitrofurantoin, sulfasalazine, amiodarone, opiates, cocaine). | Unremarkable. | Normal WBC ± ↑ eosinophilia, normal/↑ ESR/ LFTs. Eosinophils in pleural effusion. | Bilateral coarse symmetrical patchy infiltrates/fibrosis ± pleural effusions. Hilar adenopathy only with drug-induced pseudolymphoma (secondary to dilantin). No cavitation. |

## CAVITARY INFILTRATES (THICK-WALLED)



### Infectious Causes Based on Speed of Cavitation

| Speed of Cavitation | Causes |
|---|---|
| Very rapid cavitation (3 days) | S. aureus, P. aeruginosa |
| Rapid cavitation (5–7 days) | K. pneumoniae |
| Slow cavitation (> 7 days) | Pyogenic lung abscess, septic pulmonary emboli |
| Chronic cavitation | TB (reactivation), histoplasmosis (reactivation), sporotrichosis, melioidosis, nocardia, actinomycosis, Rhodococcus equi, amebic abscess, alveolar echinococcosis (hydatid cysts) |

## Infectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| S. aureus | Fever, cough, dyspnea. Recent/ concurrent influenza pneumonia. | ↓ breath sounds ± cyanosis. | ↑ WBC (left shift), ↓ $pO_2$, ↑ A-a gradient. Sputum positive for S. aureus. ↑ IgM influenza titers. | Multiple thick-walled cavitary lesions superimposed on normal looking lung fields or early minimal infiltrates of influenza. |
| P. aeruginosa | Nosocomial pneumonia usually on ventilator. Nearly always rapidly fatal. | Unremarkable. | ↑ WBC (left shift). Respiratory secretions culture ± for P. aeruginosa. Blood cultures positive for P. aeruginosa (hematogenous nosocomial pneumonia). | Bilateral diffuse infiltrates with rapid cavitation (≤ 72 hours). |
| Klebsiella pneumoniae | Nosocomial pneumonia or history of alcoholism in patient with community-acquired pneumonia. | Fever, chills, signs of alcoholic cirrhosis, signs of consolidation over involved lobe. | ↑ WBC, ↓ platelets, ↑ SGOT/SGPT (2° to alcoholism). "Red currant jelly" sputum with PMNs and plump gram-negative encapsulated bacilli. | "Bulging fissure" sign secondary to expanded lobar volume. Empyema rather than pleural effusion. Usually cavitation in 5–7 days (thick walled). |
| Pyogenic lung abscess | Recent aspiration. Fevers, chills, weight loss. Swallowing disorder secondary to CNS/ GI disorder. | Foul (putrid lung abscess) breath. | ↑ WBC, ↑ ESR. Sputum with normal oropharyngeal anaerobic flora in putrid lung abscess. | Thick-walled cavity in portion of lung dependent during aspiration (usually basilar segment of lower lobes if aspiration occurred supine). Cavitation occurs > 7 days. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Septic pulmonary emboli | Usually IV drug abuser with fever/chills. Tricuspid regurgitation murmur or recent OB/GYN surgical procedure. | Fever > 102°F. Tricuspid valve regurgitant murmur with cannon A waves in neck. | Blood cultures positive for acute bacterial endocarditis pathogens. | Multiple peripheral nodules of varying size. Lower lobe predominance. Cavitation > 7 days characteristic of septic pulmonary emboli. |
| TB (reactivation) | Fevers, night sweats, normal appetite with weight loss, cough ± hemoptysis. | ± bilateral apical dullness. | Normal WBC, ↑ platelets, ↑ ESR (≤ 70 mm/h). Positive PPD. AFB in sputum smear/culture. | Slowly progressive bilateral infiltrates. No pleural effusion. Usually in apical segment of lower lobes or apical/posterior segments of upper lobes. Calcifications common. |
| Histoplasmosis (reactivation) | Fever, night sweats, cough, weight loss, histoplasmosis exposure (river valleys of Central/Eastern United States). | ± E. nodosum; otherwise unremarkable. | Normal WBC, normal/↑ eosinophilia, anemia, ↑ platelets, PPD negative. Immunodiffusion test with positive H precipitin band (diagnostic of active/chronic histoplasmosis). | Unilateral/bilateral multiple patchy infiltrates with upper lobe predilection. Bilateral hilar adenopathy uncommon. Calcifications common. No pleural effusion. Chest x-ray resembles reactivation TB. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Sporotrichosis | Fever, cough, weight loss. ± hemoptysis. Antecedent lympho-cutaneous or skeletal sporotrichosis, rare. | Only if secondary to residual of lympho-cutaneous sporotrichosis, ± E. nodosum. | Normal WBC. No eosinophilia. | Unilateral > bilateral upper lobe nodular densities. Thick or thin-walled cavities. No hilar adenopathy. No pleural effusion. |
| Melioidosis | Past travel to Asia (usually > 10 years). Fever, cough, hemoptysis. ↑ risk of reactivation/ dissemination with DM, alcoholics, renal failure, leukemias/ lymphomas, steroids, immuno-suppressives. May occur in normal hosts. | Unremarkable. | ↑ WBC (left shift), anemia, ↑ ESR, PPD negative. GNBs with bipolar "safety pin" staining in sputum. Sputum/ blood cultures positive for B. (Pseudomonas) pseudomallei. | Resembles reactivation TB, but infiltrates nodular/ diffuse (septicemic) or cavitary (chronic) predominantly in middle/lower lung fields. ± air fluid level. No pleural effusion. |
| Nocardia | Fevers, night sweats, fatigue, ↓ cell-mediated immunity (e.g., HIV, organ transplants, PAP, immuno-suppressive therapy). | Unremarkable. | Normal/↑ WBC, ↑ ESR. Sputum with gram-positive AFB. | Dense large infiltrates. May cavitate and mimic TB, lymphoma, or squamous cell carcinoma. No calcification ± pleural effusion. |
| Actinomycosis | Recent dental work. | ± chest wall sinus tracts. | Normal/↑ WBC, ↑ ESR. Sputum with Gram-positive filamentous anaerobic bacilli. | Dense infiltrates extending to chest wall. No hilar adenopathy. Cavitation ± pleural effusion rare. |

## Infectious Causes (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Rhodococcus equi | Insidious onset of fever, dyspnea, chest pain, ± hemoptysis. Immuno-suppressed patients with ↓ cell-mediated immunity or exposure to cattle, horses, pigs. | Unremarkable. | Normal/↑ WBC. Sputum/pleural fluid with gram-positive pleomorphic weakly acid-fast bacilli. Sputum, pleural fluid, blood cultures positive for R. equi. | Segmental infiltrate with upper lobe predominance ± cavitation. Air-fluid levels and pleural effusion common. |
| Amebic cysts | Hepatic amebic abscess. Remote history of usually mild amebic dysentery. | ± hepato-megaly. | Normal WBC and ESR. ↑ E. histolytica HI titers. | Well-circumscribed cavitary lesions adjacent to right diaphragm. ± calcifications. Sympathetic pleural effusion above hepatic amebic abscess. |
| Alveolar echinoco-ccosis (hydatid cysts) | Symptoms related to cyst size/ location: 1/3 asymptomatic; 2/3 with fever, malaise, chest pain ± hemoptysis. RUQ abdominal pain may occur. | Hepatomegaly common. | Normal/↑ WBC, no eosinophilia, ↑ alkaline phosphate/ SGPT with hepatic cysts. Abdominal ultrasound/CT with calcified hepatic irregularly shaped cysts ("Swiss cheese" calcification characteristic). ↑ E. multilocularis IHA titers. | RLL usual location (hepatic cysts penetrate diaphragm into RLL). Nodules are 70% solitary, 30% multiple. Pleural effusion rare. Endocyst membrane on surface of cyst fluid ("water lilly" sign) is characteristic. |

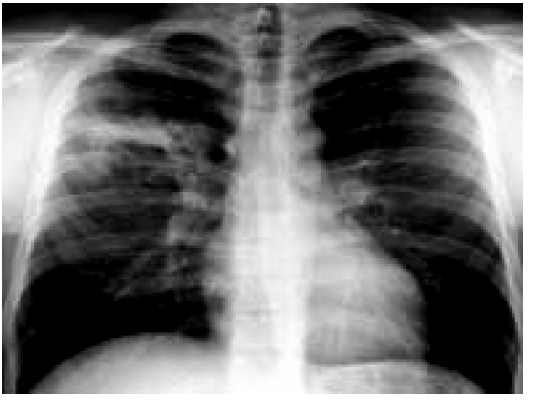
## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Wegener's granulomatosis | Most common in middle-aged adults. Cough, fever, fatigue. | Findings of chronic sinusitis, bloody nasal discharge. | ↑ WBC, anemia, ↑ platelets, ↑ ESR, ↑ RF, negative ANA, proteinuria, hematuria. Positive cANCA. | Bilateral asymmetrical nodular infiltrates of varying size with irregular margins. Cavitation common. Inner lining of cavities irregular. Air-fluid levels rare. ± pleural effusions. No calcifications. |
| Squamous cell carcinoma | Long-term smoking history. | Clubbing, hypertrophic pulmonary osteoarthropathy ± findings 2° to superior vena caval syndrome and CNS/bone metastases. | ↑ $Ca^{++}$ (without bone metastases). | Unilateral perihilar mass lesion. Cavitation common. No pleural effusion. |
| Lymphoma | Fever, ↓ appetite with weight loss, night sweats, fatigue. | Adenopathy ± splenomegaly. | Normal WBC, ↑ basophils, ↑ eosinophilia, ↓ lymphocytes, ↑ platelets, ↑ ESR ↑ alkaline phosphatase, ↑$\propto_{1,2}$ globulins on SPEP. | Unilateral or asymmetrical bilateral hilar adenopathy. Lung infiltrate may appear contiguous with hilar adenopathy. No clear channel between mediastinum and hilar nodes. Small pleural effusions rare. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Metastatic carcinoma | History of breast, thyroid, renal cell, colon, pancreatic cancer or osteogenic sarcoma. | Findings related to underlying malignancy and, when present, to bone, hepatic, CNS metastases. | Secondary to effects of primary neoplasm, metastases, paraneoplastic syndrome. | Nodular lesions that vary in size. Metastatic lesions are usually well-circumscribed with lower lobe predominance. Usually no bronchial obstruction (obstruction suggests colon, renal, or melanoma metastases). Usually no cavitation (except for squamous cell metastases). Calcification usually suggests osteosarcoma (rarely adenocarcinoma). Pleural effusion rare (except for breast cancer). |
| Rheumatoid nodules | Usually in severe rheumatoid arthritis (RA); ± history of silicosis. | Findings secondary to RA. Rheumatoid nodules on exterior surfaces of arms. | Normal WBC, ↑ ESR, ↑ ANA, ↑ RF (high titer). Pleural fluid with ↓ glucose. | Lung nodules are round and well-circumscribed, predominantly in lower lobes and typically superimposed on interstitial lung disease ("rheumatoid lung"). Cavitation is common. ± pulmonary fibrosis, pleural effusion. Silicosis + RA nodules = Caplan's syndrome. |

## CAVITARY INFILTRATES (THIN-WALLED)



### Infectious Causes

| | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| **Causes** | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Atypical TB | Often occurs in setting of previous lung disease. | Unremarkable. | Normal WBC, ↑ ESR. Weakly positive PPD. Positive sputum AFB/ culture. | Multiple cavitary lesions ± calcifications usually involving both lungs. Resembles reactivation TB except that cavities are thin-walled. No pleural effusion. |
| Coccidiomycosis (reactivation) | Previous exposure in endemic coccidiomycosis areas (e.g., Southwest USA). Asymptomatic. | ± E. nodosum. | Normal WBC. Eosinophilia acutely but not in chronic phase, and eosinophils in pleural fluid. CF IgG titer ≥ 1:32 indicates active disease. | Thick/thin walled cavities (< 3 cm) usually in anterior segments of lower lobes ± calcifications/ bilateral hilar adenopathy. Air-fluid levels rare unless secondarily infected. Pleural effusion rare. |

## **Infectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Paragonimiasis | Ingestion of fresh-water crabs/ crayfish. Acute symptoms (< 6 months): fevers, abdominal pain, diarrhea followed by episodes of pleuritic chest pain. Chronic symptoms (> 6 months): fevers, night sweats, cough ± hemoptysis. Asymptomatic in some. | Wheezing, ± urticaria (acutely). | ↑ WBC, eosinophilia. Eosinophils in pleural fluid. Sputum with Charot-Leyden crystals. Sputum/feces with operculated P. Westermani eggs. | Cavitary patchy or well-defined infiltrates predominantly in mid-lung fields. Hydropneumothorax common. Calcifications and pleural effusion common. |
| Sporotrichosis | Fever, cough, weight loss. ± hemoptysis. Antecedent lymphocutaneous or skeletal sporotrichosis, rare. | Only if secondary to residual of lympho-cutaneous sporotrichosis, ± E. nodosum. | Normal WBC. No eosinophilia. | Unilateral > bilateral upper lobe nodular densities. Thick or thin-walled cavities. No hilar adenopathy. No pleural effusion. |
| Pneumatoceles | Common in S. aureus pneumonia in children. Fever, cough, dyspnea. ± antecedent influenza. | Unremarkable unless pneumatocele ruptures, then signs of pneumothorax. | ↑ WBC (left shift), ↓ $pO_2$ (secondary to influenza). | Multiple thin-walled cavities in areas of S. aureus pneumonia. Common in children; rare in adults. |

## Noninfectious Causes

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | History | Physical | Laboratory | Chest X-Ray |
| Emphysema (blebs/cyst) | Long history of smoking. Rupture of apical bleb common in males > 30 years. Pneumonia rare in severe emphysema (vs. chronic bronchitis) but may occur early in unaffected areas of lung. | Asthenic "pink puffers." Barrel chest. Diaphragmatic excursions < 2 cm. | Normal WBC, ↓ $pO_2$. | ↓ lung markings ("vanishing lung") ± blebs. Hyperlucent lungs with upper lobe predominance. Flattened diaphragms, vertically elongated cardiac silhouette, ↑ retrocardiac and retrosternal airspaces. No infiltrates or pleural effusions. (In upper lobe emphysema, no vascular redistribution to upper lobes with CHF). |
| Bronchogenic cyst | Congenital anomaly. Usually asymptomatic. Cough if symptomatic. | Unremarkable unless secondarily infected, then signs 2° to mediastinal abscess. | Normal WBC/ESR. | Circumscribed cystic lesion originates in lung but appears high in mediastinum. If filled with fluid, appears as solitary tumor. If near the trachea, may rupture into bronchus/trachea and cyst may contain air. If communicates openly with bronchus, appears as thin-walled cavitary nodule. If infected, presents as mediastinal abscess. |
| Cystic bronchiectasis | Recurrent pulmonary infections with purulent sputum ± hemoptysis. | Unremarkable unless dextrocardia with sinusitis (Kartagener's syndrome). | ↑ WBC, normal ESR. | Bilateral large cystic lucencies at lung bases. Upper lobes relatively spared (unless secondary chronic aspiration). Thickened bronchial markings at bases. Bronchiectasis of cystic fibrosis predominantly involves upper lobes. |

## **Noninfectious Causes** (cont'd)

| Causes | Features (may have some, none, or all) | | | |
|---|---|---|---|---|
| | **History** | **Physical** | **Laboratory** | **Chest X-Ray** |
| Sequestered lung | Usually asymptomatic. Productive cough ± hemoptysis if communicates with bronchus or if infected. | Unremarkable. | Normal WBC, ↑ ESR. | Solid nodule unless communicates with bronchus, then thin-walled cavity ± air fluid levels. Usually posterior based segment of lower lobes (LLL > RLL). If > 3 cm, presents as mass lesion. |
| Histiocytosis X (eosinophilic granuloma, Langerhan's cell histiocytosis) | Patients usually 20–40 years. Usually asymptomatic. Fever, cough, dyspnea in some. Diabetes insipidus rare. | Hepatosplenomegaly, skin lesions, hemoptysis (rare). | Normal WBC, eosinophilia. | Pneumothorax superimposed on diffuse pulmonary fibrosis. Cystic bone lesions. Usually mid/upper lung fields with nodules/thin-walled cysts or infiltrates. No hilar adenopathy or pleural effusion. |

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Chapter 9

# Infectious Disease Differential Diagnosis

**Cheston B. Cunha, MD**

**Table 9.1. Fever Curves**

| Finding | Causes |
|---|---|
| Morning (am) temperature spikes | Infectious: TB, typhoid fever, Whipple's disease<br>Noninfectious: PAN |
| Relative tachycardia | Infectious: gas gangrene, myocarditis (Coxsackie, RMSF, typhus, diptheria, trichinosis, VLM, influenza)<br>Noninfectious: Hyperthyroidism, hypoxia, cardiac arrhythmias, anxiety, pulmonary emboli |
| Relative bradycardia | Infectious: typhoid fever, typhus, leptospirosis, Legionnaire's disease, Q fever, psittacosis, RMSF, babesiosis, ehrlichiosis/anaplasmosis, yellow fever, dengue fever, arboviral hemorrhagic fevers<br>Noninfectious: drug fever, CNS lesions, β-blockers, verapamil, diltiazem, lymphoma, factitious fever |
| Single fever spikes | Infectious: Transient bacteremia<br>Noninfectious: Blood/blood product transfusions |
| Double quotidian fevers | Infectious: kala-azar, right sided GC ABE, miliary TB, mixed malarial infections<br>Noninfectious: adult Still's disease, antipyretics |
| Camelback fever pattern | Infectious: Colorado tick fever, dengue fever, leptospirosis, brucellosis, LCM, yellow fever, poliomyelitis, smallpox, rat-bite fever (Spirillum minus), chikungunya fever, rift valley fever, african hemorrhagic fevers (Marburg, Ebola, Lassa, etc), echovirus (echo 9), ehrlichiosis/ anaplasmosis<br>Noninfectious: antipyretics |

### Fever with chills/rigors

Classically, chills/rigors are associated with some infections, diseases, e.g., influenza, bacteremia, malaria, but rare/mild with typhoid fever. Prominent/sustained rigors argues against the diagnosis of typhoid fever.

### Fever with night sweats

Night sweats may be present with some chronic infectious diseases, e.g., abscesses, TB, SBE and various malignancies, e.g., lymphomas, leukemia. Other causes include certain medications, e.g., monoclonal antibody therapy (rituximab), HIV drugs. Night sweats are not a feature of rheumatic/inflammatory disorders.

**Table 9.2. General Appearance Abnormalities**

| Finding | Causes |
|---|---|
| Hypotension/ shock | Infectious: anthrax, plague, typhus, ***GI sources***: colon (perforation, colitis, abscess); ***GU sources***: cystitis (only in SLE, DM, alcoholism, multiple myeloma, Vibrio vulnificus, CLL, steroids); obstruction: relative (BPH), unilateral (partial), or bilateral/ ureteral (partial/total); kidney (acute pyelonephritis, renal abscess, perinephric abscess, renal calculi); prostate (acute prostatitis, prostatic abscess). ***Other sources***: CVC infection, TSS (S. aureus, group A streptococci, C. sordellii), dengue fever, SARS, HPS, influenza (human, avian, swine), CAP with decreased/absent splenic function, or severe cardiopulmonary disease, influenza/ILI with CA-MRSA (PVL+)<br><br>Noninfectious: myocardial infarction, pulmonary embolism, acute pancreatitis, relative adrenal insufficiency, GI bleed, overzealous diuresis, inadequate volume replacement or hypotonic fluid replacement, aortic dissection, abdominal aneurysm rupture, rectus sheath hematoma |
| Soft tissue crepitance | Infectious: mixed aerobic/anaerobic infection*<br><br>Noninfectious: subcutaneous emphysema, recent surgery in area of crepitance |
| Bullae (vesicles) | Infectious: gas gangrene (hemorrhagic), S. aureus > group A streptococci, V. vulnificus (hemorrhagic), necrotizing fasciitis, bullous impetigo, HSV, VZV, smallpox<br><br>Noninfectious: pemphigus, pemphigoid, dermatitis herpetiformis, TEN, porphyria, contact dermatitis, E. multiforme, DM, barbiturates |
| Generalized edema/nephrotic syndrome | Infectious: malaria (P. malariae), trichinosis, VZV, yellow fever, influenza A, HBV, HIV, EBV, CMV, 2° syphilis, leprosy<br><br>Noninfectious: drugs, lymphomas, thiamine deficiency (wet beri-beri), kwashiorkor, post-streptococcal glomerulonephritis, DM, PAN, Henoch-Schönlein purpura, SLE, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, myxedema, sickle cell disease, amyloidosis, $\alpha$-1 antitrypsin deficiency, nail-patella syndrome, Wegener's granulomatosis, sarcoidosis, renal vein thrombosis |
| Erythroderma | Infectious: human T-cell leukemia virus 1 (HTLV-1), TSS, scarlet fever, dengue fever, chikungunya fever<br><br>Noninfectious: psoriasis, lymphoma, atopic dermatitis, contact dermatitis, exfoliative dermatitis, drugs, ichthyosis, erythroleukemia, pityriasis, dermatomyositis, Kawasaki's disease, Hodgkin's lymphoma |
| Hyper-pigmentation | Infectious: kala-azar, Whipple's disease, histoplasmosis<br><br>Noninfectious: hemochromatosis, PBC, Addison's disease, drugs – brown (bleomycin), blue/gray (busulfan, fluorouracil, chlorpromazine), purple/gray (amiodarone), blue/gray (minocycline) |

* Versus gas gangrene (minimal/no gas on muscle auscultation).

**Table 9.2. General Appearance Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Jaundice | Infectious: yellow fever, EBV, leptospirosis, ascariasis (in bile/pancreatic duct), viral hemorrhagic fevers, viral hepatitis<br>Noninfectious: hepatobiliary malignancy, benign biliary obstruction, PBC, cirrhosis, hemolytic anemias, alcoholic hepatitis, drugs, Gilbert's syndrome, pancreatic carcinoma |
| Vitiligo | Infectious: leprosy, yaws, pinta, HIV<br>Noninfectious: DM, hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis |
| Lizard/elephant skin | Infectious: onchocerciasis<br>Noninfectious: ichthyosis |
| Urticaria | Infectious: strongyloides, dracunculiasis, HBV, F. hepatica, schistosomal dermatitis<br>Noninfectious: insect bites/stings, drugs, malignancies, cholinergic urticaria, serum sickness, urticarial vasculitis, cryoglobulinemia, systemic mastocytosis, Schnitzler's syndrome |
| Rash (only below waist) | Infectious: Parvovirus B19 (stocking/glove)<br>Noninfectious: Henoch-Schönlein purpura (HSP) |

**Table 9.3. Head Abnormalities**

| Finding | Causes |
|---|---|
| Prematurely gray hair | Infectious: HIV<br>Noninfectious: smoking, pernicious anemia |
| Temporal muscle wasting | Infectious: HIV<br>Noninfectious: myotonic dystrophy |
| Facial swelling (edema) | Infectious: arboviral hemorrhagic fevers, trichinosis, leprosy, EEE, onchocerciasis<br>Noninfectious: angioneurotic edema, nephrotic syndrome, acute glomerulonephritis, leukemic infiltrates, amyloidosis |
| Severe seborrheic dermatitis | Infectious: HIV<br>Noninfectious: CGD |
| Facial red spots | Infectious: psittacosis (Horder's spots)<br>Noninfectious: Campbell de Morgan spots |

**Table 9.3. Head Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Localized alopecia | Infectious: leprosy, Tinea capitis, smallpox, blastomycosis, VZV, TB (cutaneous)<br>Noninfectious: SLE, DM, scleroderma, common variable immune deficiency (CVID) |
| Generalized alopecia | Infectious: post-malaria, post-typhoid fever, post-kala-azar, post-yellow fever, 2° syphilis, HIV<br>Noninfectious: nutritional deficiencies, drugs, hyperthyroidism |
| Total/partial eyebrow loss | Infectious: leprosy, syphilis<br>Noninfectious: iatrogenic, hereditary, hypothyroidism, hypopituitarism |
| Long eyelashes | Infectious: kala-azar, trypanosomiasis<br>Noninfectious: hereditary, drugs, HIV drugs |
| Lacrimal gland enlargement<br>*unilateral* | Infectious: Chagas' disease<br>Noninfectious: malignancies |
| *bilateral* | Infectious: TB<br>Noninfectious: Sjogren's syndrome, RA, SLE, sarcoidosis |
| Facial erythema | Infectious: facial cellulitis, erysipelas, TB (lupus vulgaris), arboviral hemorrhagic fevers<br>Noninfectious: dermatomyositis, drugs, rosacea, carcinoid syndrome, SLE |
| Parotid enlargement | Infectious: mumps, Chagas' disease, rat bite fever (Streptobacillus moniliformis), melioidosis, CMV, EBV, LCM, adenovirus, Coxsackie A<br>Noninfectious: Sjogren's syndrome, sarcoidosis, cirrhosis |
| Scalp nodules | Infectious: myiasis, onchocerciasis<br>Noninfectious: bony exostoses, malignancies, benign cysts, pyogenic granuloma, Kimura's disease |

**Table 9.4. Eye Abnormalities**

| Finding | Causes |
|---|---|
| Bilateral upper lid edema | Infectious: EBV (Hoagland's sign)<br>Noninfectious: bilateral eye irritation |
| Bilateral lid edema | Infectious: trichinosis, meningococcemia, adenovirus<br>Noninfectious: Wegener's granulomatosis |

**Table 9.4. Eye Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Heliotrope eyelid discoloration | Infectious: cholera (early), influenza A (severe) |
| | Noninfectious: dermatomyositis |
| Periorbital edema | |
| *unilateral* | Infectious: Chagas' disease, loiasis, gnathostomiasis, sparganosis |
| | Noninfectious: insect bites, unilateral eye irritation |
| *bilateral* | Infectious: RMSF, trichinosis, tularemia, dengue fever |
| | Noninfectious: allergies, Insect bites, TNF-receptor-1-associated periodic syndrome (TRAPS), dermatomyositis |
| Argyll-Robertson pupils | Infectious: syphilis |
| | Noninfectious: sarcoidosis |
| Iritis | Infectious: onchocerciasis, 2° syphilis, relapsing fever, leprosy |
| | Noninfectious: SLE, dermatomyositis, Behçet's syndrome, Reiter's syndrome, RA |
| Conjunctivitis | |
| *unilateral* | Infectious: TB, HSV, tularemia, adult inclusion conjunctivitis, Chagas' disease, LGV, CSD, loiasis, ocular myiasis, diphtheria, adenovirus (types 8, 19) |
| | Noninfectious: SLE, eye irritation |
| *bilateral* | Infectious: TSS, measles, rubella, meningococcemia, gonorrhea, adenovirus (type 3), plague, RMSF, sparganosis, LGV, listeria, relapsing fever, pertussis, influenza, microsporidia, HHV-6, arboviral hemorrhagic fevers, dengue hemorrhagic fever |
| | Noninfectious: Kawasaki's disease, Reiter's syndrome, Steven-Johnson syndrome, adult Still's disease, eye irritation |
| Hemorrhagic conjunctivitis | |
| *unilateral* | Infectious: adenovirus (type 8, 19) |
| | Noninfectious: trauma |
| *bilateral* | Infectious: trichinosis, pertussis, leptospirosis, Coxsackie A (type 24), adenovirus (type 11), enterovirus (type 70), arboviral hemorrhagic fevers |
| | Noninfectious: trauma |
| Subconjunctival hemorrhage | Infectious: SBE, trichinosis, meningococcemia, pertussis, leptospirosis, RMSF |
| | Noninfectious: severe anemia, Kawasaki's disease |
| Conjunctival suffusion | Infectious: RMSF, leptospirosis, relapsing fever, ehrlichiosis, HPS, influenza (human, avian), arboviral hemorrhagic fevers, St.LE |
| | Noninfectious: bilateral eye irritation |

**Table 9.4. Eye Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Episcleritis | Infectious: TB, leprosy, 2° syphilis, Lyme disease<br>Noninfectious: sarcoidosis, RA, adult Still's disease, SLE, PAN, TA, RE |
| Scleral nodules | Infectious: loiasis, sparganosis, leprosy, tularemia, TB<br>Noninfectious: RA, vitamin A deficiency (Bitot's spots), sarcoidosis |
| Dry eyes | Infectious: measles<br>Noninfectious: vitamin A deficiency, SLE, Sjogren's syndrome, RA, sarcoidosis |
| Watery eyes | Infectious: bacterial conjunctivitis, adenovirus<br>Noninfectious: PAN, allergenic conjunctivitis |
| Uveitis | Infectious: TB, histoplasmosis, leprosy, syphilis, malaria, HSV, VZV, EBV, TSS, typhus, LGV, CMV, African trypanosomiasis, brucellosis, leptospirosis, RMSF, CSD<br>Noninfectious: adult Still's disease, SLE, PAN, sarcoidosis, Behçet's syndrome, Reiter's syndrome, RA, relapsing polychondritis, ankylosing spondylitis, Kawasaki's disease, Wegener's granulomatosis |
| Corneal haziness | Infectious: adenovirus, leprosy, trachoma, onchocerciasis<br>Noninfectious: vitamin A deficiency, cataracts |
| Keratitis | Infectious: HSV, congenital syphilis, acanthamoeba, TB, toxoplasmosis, histoplasmosis, CMV, trachoma, microsporidia, nocardia, leprosy, onchocerciasis, meliodosis<br>Noninfectious: Behçet's syndrome, Reiter's syndrome, Steven-Johnson syndrome, vitamin A deficiency |
| Corneal ulcers | Infectious: HSV, listeria, acanthamoeba, tularemia, shigella, RMSF<br>Noninfectious: trauma, Wegener's granulomatosis |
| Endophthalmitis | Infectious: TB, candida, aspergillus, toxocara, serratia, S. pneumoniae<br>Noninfectious: retinoblastoma |
| Chorioretinitis | Infectious: toxoplasmosis, CMV, onchocerciasis, congenital syphilis, histoplasmosis, TB, WNE, coccidiomycosis, leptospirosis, chikungunya fever<br>Noninfectious: sarcoidosis, SLE, PAN |
| Cytoid bodies (cotton wool spots) | Infectious: CSD, HIV, CMV, SBE<br>Noninfectious: SLE, adult Still's disease, PAN, atrial myxoma, Wegener's granulomatosis, TA |

**Table 9.4. Eye Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Roth spots | Infectious: SBE, psittacosis, RMSF, malaria<br>Noninfectious: PAN, SLE, DM, severe anemia, leukemia, cholesterol emboli syndrome, atrial myxoma, TA, Takayasu's arteritis |
| Periphlebitis (candle wax drippings) | Infectious: CMV, leptospirosis (Weil's syndrome)<br>Noninfectious: sarcoidosis |

**Table 9.5. Ear Abnormalities**

| Finding | Causes |
|---|---|
| Acute deafness | Infectious: ABM, mumps (aseptic meningitis), RMSF, typhus, brucellosis, Lassa fever<br>Noninfectious: sound/barotrauma |
| External ear lesions | Infectious: cutaneous leishmaniasis (Chiclero ulcer), leprosy, Kaposi's sarcoma<br>Noninfectious: relapsing polychondritis, eczema, carcinoma, contact dermatitis, sarcoidosis, SLE, gout (tophi), keloids, actinic keratosis |

**Table 9.6. Nasal Abnormalities**

| Finding | Causes |
|---|---|
| Purple nose tip/ hyperpigmented | Infectious: Kaposi's sarcoma, TB (Bazin's erythema induratum), chikungunya fever ("Chik sign")<br>Noninfectious: vasculitis, lymphoma, drugs, sarcoidosis |
| Nose tip gangrene | Infectious: Staphylococcus aureus ABE (emboli)<br>Noninfectious: SLE, vasculitis |
| Epistaxis | Infectious: psittacosis, typhoid fever, nasal diphtheria, Colorado tick fever, TBRF, influenza, dengue hemorrhagic fever, arboviral hemorrhagic fevers, acute renal failure, leprosy, leptospirosis, VZV, TB, rhinosporidium, mucocutaneous leishmaniasis<br>Noninfectious: Local trauma, sinus malignancies, von Willebrand's disease, polycythemia vera, Waldenstrom's macroglobulinemia, relapsing polychondritis |
| Nasal septal perforation | Infectious: leprosy, 2° syphilis, mucocutaneous leishmaniasis, blastomycosis, pinta, yaws<br>Noninfectious: cocaine, lethal midline granuloma, Wegener's granulomatosis, miasis |

**Table 9.7. Mouth Abnormalities**

| Finding | Causes |
|---|---|
| Trismus | Infectious: tetanus |
| | Noninfectious: temporomandibular joint dislocation/arthritis, trigeminal neuralgia |
| Herpes labialis | Infectious: HSV, pneumococcal pneumonia, meningococcal meningitis, malaria |
| | Noninfectious: contact dermatitis (may mimic H. labialis) |
| Angular chelitis | Infectious: 2° syphilis, HIV |
| | Noninfectious: riboflavin deficiency, trauma, contact dermatitis, anemia |
| Gingivitis | Infectious: trench mouth |
| | Noninfectious: Wegener's granulomatosis |
| Tongue tenderness | Infectious: relapsing fever |
| | Noninfectious: vitamin deficiencies, pernicious anemia |
| Tongue ulcers | Infectious: histoplasmosis, HSV, syphilis |
| | Noninfectious: aphthous ulcers, chemotherapy, radiation therapy |
| Leukoplakia | Infectious: HIV (hairy), syphilis |
| | Noninfectious: lichen planus |
| Oral ulcers *solitary* | Infectious: syphilis, CMV, histoplasmosis, TB, Leishmania braziliensis |
| | Noninfectious: squamous cell carcinoma, Behçet's syndrome, Wegener's granulomatosis |
| *multiple* | Infectious: HSV, HFM disease, herpangina, brucellosis, Lassa fever, African tick bite fever, chickunguniya fever |
| | Noninfectious: SLE*, celiac disease, aphthous ulcers, squamous cell carcinoma, Behçet's syndrome, FAPA syndrome*, hyper IgE (Job's) syndrome E. multiforme, RE, cyclic neutropenia, hyper IgD syndrome, Sweet's syndrome |
| Frenal ulcer | Infectious: pertussis |
| | Noninfectious: trauma |
| Palatal petechiae | Infectious: Group A streptococci, EBV, CMV, HSV, VZV, toxoplasmosis, rubella, HIV, tularemia |
| | Noninfectious: thrombocytopenia (2° to any cause), platelet dysfunction disorders, DIC, Ehlers-Danlos syndrome, Marfan's syndrome |

* Painless ulcers

**Table 9.7. Mouth Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Palatal perforation | Infectious: congenital syphilis, myiasis |
| | Noninfectious: Post-surgical, midline granuloma, cocaine |
| Palatal vesicles | Infectious: ***Anterior*:** HSV, VZV, hand-foot-mouth disease (Coxsackie A). ***Posterior*:** herpangina (Coxsackie A) |
| | Noninfectious: bullous pemphigus, Steven-Johnson syndrome (drug-induced) |
| Uvular edema | Infectious: Group A streptococci |
| | Noninfectious: Franklin's disease, drugs, angioneurotic edema |
| Crimson crescents | Infectious: chronic fatigue syndrome (CFS), HIV |
| | Noninfectious: None |
| Tonsillar membranes | Infectious: diphtheria, Arcanobacterium hemolyticum |
| | Noninfectious: None |
| Tonsillar ulcers | Infectious: tularemia (oropharyngeal), 1° syphilis, Vincent's angina, TB |
| | Noninfectious: carcinoma, T-cell lymphoma, AML |
| Hoarseness | Infectious: laryngeal TB, C. pneumoniae, respiratory viruses, pertussis |
| | Noninfectious: recurrent laryngeal nerve paralysis, laryngeal cancer |

**Table 9.8. Neck Abnormalities***

| Finding | Causes |
|---|---|
| Enlarged greater auricular nerve | Infectious: leprosy |
| | Noninfectious: none |
| Bull neck | Infectious: diphtheria, mumps, Ludwig's angina, pertussis, group A streptococcal suppurative lymphangitis |
| | Noninfectious: angioneurotic edema, subcutaneous emphysema |
| Jugular vein tenderness | Infectious: suppurative jugular thrombophlebitis (Lemierre's syndrome) |
| | Noninfectious: thrombophlebitis |
| Neck sinus tract | Infectious: actinomycosis, TB, atypical TB |
| | Noninfectious: branchial cleft cyst, CGD |
| Superior vena cava syndrome | Infectious: actinomycosis |
| | Noninfectious: lymphoma, squamous cell carcinoma |

* See Table 9.13 for cervical adenopathy (p. 488).

**Table 9.9. Chest Abnormalities**

| Finding | Causes |
|---|---|
| Shoulder tenderness | Infectious: subdiaphragmatic abscess, septic arthritis (shoulder) |
| | Noninfectious: squamous cell carcinoma (Pancoast's tumor), bursitis |
| Sternal tenderness | Infectious: sternal osteomyelitis (post-open heart surgery) |
| | Noninfectious: metastatic carcinoma, pre-leukemia, acute leukemia, myeloproliferative disorder, trauma |
| Costochondral tenderness | Infectious: costochondritis (Coxsackie B) |
| | Noninfectious: trauma, plasmacytoma |
| Trapezius tenderness | Infectious: subdiaphragmatic abscess |
| | Noninfectious: fibromyalgia |
| Chest wall sinuses | Infectious: TB, actinomycosis, blastomycosis, abscess, M. fortuitum-chelonei (post-breast implant surgery), sternal osteomyelitis (post-sternotomy) |
| | Noninfectious: bronchogenic carcinoma |
| Spontaneous pneumothorax | Infectious: TB, PCP, Legionnaire's disease, lung abscess, pertussis |
| | Noninfectious: histiocytosis X (eosinophilic granuloma, Langerhan's cell histiocytosis), osteogenic sarcoma, emphysema, ARDS |
| Diffuse wheezing | Infectious: RSV, influenza, HMPV, HBOV, C. pneumoniae, M. pneumoniae, acute shistosomiasis (S. mansoni > S. haematobium) |
| | Noninfectious: pulmonary emboli, LVF, asthma, Churg-Strauss granulomatosis, carcinoid syndrome, asthmatic bronchitis, angioedema |
| Chest dullness | |
| *consolidation* | Infectious: bacterial pneumonia, psittacosis, nocardia, Q fever |
| | Noninfectious: large cell carcinoma |
| *pleural effusion* | Infectious: group A streptococci, tularemia, H. influenzae, 1° TB |
| | Noninfectious: Meig's syndrome, pancreatitis, CHF, malignancies, pulmonary embolism |

**Table 9.10. Back Abnormalities**

| Finding | Causes |
|---|---|
| Spinal tenderness | Infectious: vertebral osteomyelitis, typhoid fever, TB, brucellosis, SBE |
| | Noninfectious: malignancies, multiple myeloma |
| D'espine's sign | Infectious: bilateral pneumonia (consolidation), TB |
| | Noninfectious: sarcoidosis, large cell carcinoma, lymphoma |
| Unilateral CVA tenderness | Infectious: pyelonephritis, renal/perinephric abscess |
| | Noninfectious: trauma |

**Table 9.11. Heart Abnormalities**

| Finding | Causes |
|---|---|
| Tachycardia | Infectious: myocarditis (Coxsackie, RMSF, typhus, diphtheria, trichinosis, Toxocara canis/cati (VLM), influenza, dengue), gas gangrene<br>Noninfectious: hypovolemia, hypoxia, anxiety, hyperthyroidism, MI, pulmonary embolism, CHF, Kawasaki's disease, substance withdrawal, myocarditis (idiopathic giant cell) |
| Heart block<br>*Acute* | Infectious: Lyme disease, ABE with paravalvular/septal abscess, diptheria, myocarditis (Coxsackie, influenza, RMSF)<br>Noninfectious: acute (inferior) MI, drugs, myocarditis (idiopathic giant cell) |
| *Chronic* | Infectious: Chagas' disease<br>Noninfectious: AV nodal ablation, sarcoidosis, Lev's/Lenegre's disease |
| Pericardial effusion | Infectious: viral pericarditis, TB pericarditis, dengue<br>Noninfectious: SLE, uremia, malignancy |
| Heart murmur | Infectious: SBE, 3° syphilis<br>Noninfectious: valvular heart disease, severe anemia, Takayasu's arteritis, SLE (Libman-Sacks), endomyocardial fibroelastosis, atrial myxoma, marantic endocarditis |

**Table 9.12. Abdominal Abnormalities**

| Finding | Causes |
|---|---|
| Abdominal wall tenderness | Infectious: leptospirosis, abdominal wall cellulitis/abscess, trichinosis<br>Noninfectious: trauma, rectus sheath hematoma |
| Abdominal wall sinus tract | Infectious: TB, abscess, ameboma, actinomycosis<br>Noninfectious: carcinomas |
| Rose spots | Infectious: typhoid fever, shigella, trichinosis, rat bite fever, brucellosis, leptospirosis<br>Noninfectious: Campbell de Morgan spots |
| Abdominal tenderness (2° to pancreatitis) | Infectious: Coxsackie virus, echovirus, mumps, ascariasis, EBV, CMV, HBV, HSV, VZV, HIV<br>Noninfectious: EtOH, cholelithiasis (+ common pancreatitis duct), tauma, post-ERCP, hyperlipidemia (types I, IV, V), hypertriglyceridemia, TPN, hypercalcemia, SLE, PAN, posterior penetrating duodenal ulcer, drugs (steroids, azathioprine, diuretics, furosemide, thiazides, L-asparaginase, valproic acid, pentamidine) |

**Table 9.12. Abdominal Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Right upper quadrant tenderness | Infectious: cholangitis, cholecystitis, pylephlebitis, splenic flexure diverticulitis, emphysematous cholecystitis (Clostridia sp.), hepatic abscess (amebic, echinococcal, bacterial), right lower lobe CAP, brucellosis, leptospirosis, typhoid fever, viral hepatitis, dengue, malaria<br>Noninfectious: burns, post-partum, ptosed right kidney, acute pancreatitis, Kawasaki's disease, cholesterol emboli syndrome, acalculous cholecystitis PAN, SLE, total parenteral nutrition, ceftriaxone (pseudocholelithiasis) |
| Right upper quadrant tympany | Infectious: peritonitis (2° to organ perforation)<br>Noninfectious: post-abdominal surgery |
| Right upper quadrant mass | Infectious: bacterial abscess, echinococcal cysts, amebic abscess<br>Noninfectious: ptosed right kidney, Reidel's lobe, hepatoma, malignancies, distended gallbladder (Couvoisier's sign) |
| Right lower quadrant tenderness | Infectious: shigella, typhoid fever, typhoidal EBV, typhoidal tularemia, parvovirus B19, TB, ameboma, typhlitis, actinomycetoma, pseudoappendicitis (scarlet fever), Legionnaires' disease, yersinia, campylobacter, measles (pre-eruptive), RMSF, PID, syphilis (luetic crisis), brucellosis<br>Noninfectious: appendicitis, RE, ectopic pregnancy, diverticulitis, hyper IgE (Job's) syndrome, DM crisis, porphyria, pancreatitis, SLE |
| Left upper abdominal quadrant tenderness (splenic tenderness) | Infectious: SBE, brucellosis, typhoid fever, malaria, splenic abscess, EBV, CMV, HHV-6<br>Noninfectious: splenic infarct |
| Abdominal wall nodules | Infectious: leprosy<br>Noninfectious: lipomas, panniculitis, metastatic disease, sarcoidosis |
| Perubilical purpura (thumbprint sign) | Infectious: strongyloides (hyperinfection syndrome)<br>Noninfectious: retroperitoneal hemorrhage (Cullen's sign) |
| Hepatomegaly | Infectious: viral hepatitis, bacterial liver abscess, amebic abscess, ehrlichiosis, babesiosis, brucellosis, leptospirosis (Weil's syndrome), arboviral hemorrhagic fevers, typhus, typhoid fever, malaria, Q fever, EBV, CMV, HIV, Castleman's disease (MCD) |

**Table 9.12. Abdominal Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| | Noninfectious: alcoholic cirrhosis, cholangiocarcinoma, carcinoma of pancreas, constrictive pericarditis, pericholangitis, veno-occlusive disease, autoimmune hepatitis, α-1antitrypsin deficiency, cystic fibrosis, fatty liver, hemangiomas, jejunoileal bypass, Reye's syndrome, multiple myeloma, hepatocellular carcinoma, metastatic carcinoma*, parenteral hyperalimentation (TPN) |
| Splenomegaly | Infectious: ***Mildly enlarged spleen:*** malaria, kala-azar, dengue, SBE, ehrlichiosis, babesiosis, typhoid fever, typhus, leptospirosis (Weil's syndrome), viral hepatitis, EBV, CMV, relapsing fever, syphilis, toxoplasmosis, psittacosis, brucellosis, Q fever, CSD, schistosomiasis, RE, trypanosomiasis, histoplasmosis, TB, splenic abscess, HIV, hydatid cysts, colorado tick fever; Castleman's disease (MCD), ***Moderately enlarged spleen:*** malaria, kala-azar; Castleman's disease (MCD), ***Massively enlarged spleen:*** malaria, kala-azar, Castleman's disease (MCD)<br><br>Noninfectious: ***Mildly enlarged spleen:*** SLE, sarcoidosis, Felty's syndrome, hemochromatosis, Wilson's disease, Budd-Chiari syndrome, megaloblastic anemia, iron deficiency anemia, systemic mastocytosis, angioblastic lymophadenopathy, splenic cysts, splenic trauma/hemorrhage, histiocytosis X (Langerhan's eosinophilic granuloma), hyperthyroidism, serum sickness, amyloidosis, berylliosis, Kawasaki's disease<br>***Moderately enlarged spleen:*** portal hypertension, hemolytic anemias, myeloproliferative disorders, CLL, Gaucher's disease, Niemann-Pick disease; ***Massively enlarged spleen:*** CML, hairy cell leukemia, lymphoma, myelofibrosis |
| Hepatosple-nomegaly | Infectious: malaria, typhoid fever, toxocara (visceral larval migrans), psittacosis, brucellosis, trypanosomiasis, kala-azar, 2° syphilis, EBV, CMV, acute HIV, schistosomiasis, toxoplasmosis, relapsing fever, RMSF, typhus, CSD, histoplasmosis, TB, dengue, babesiosis, ehrlichiosis, Q fever, Castleman's disease (MCD)<br><br>Noninfectious: hypernephroma, CGD, hyper IgD syndrome, sarcoidosis |
| Ascites | Infectious: TB peritonitis, shistosomiasis, filariasis, spontaneous bacterial peritonitis, dengue, Whipple's disease<br><br>Noninfectious: malignancies, Budd-Chiari syndrome, tricuspid regurgitation, constrictive pericarditis, inferior vena cava syndrome, FMF, Henoch-Schönlein purpura, SLE, portal hypertension, pancreatic/bile ascites, CHF, Meig's syndrome |

* Usually from lung, colon, pancreas, kidney, breast, stomach, or esophagus.

**Table 9.13. Lymph Node Abnormalities**

| Finding | Causes |
|---|---|
| Preauricular adenopathy | Infectious: ipsilateral conjunctivitis, tularemia, anterior scalp infections, rat bite fever (Spirillum minus) |
| | Noninfectious: lymphoma |
| Occipital adenopathy | Infectious: posterior scalp infections, CSD, rubella |
| | Noninfectious: lymphoma |
| Anterior cervical adenopathy | Infectious: group A streptococcal pharyngitis, viral pharyngitis, mouth/dental infections, TB (scrofula), HHV-6, toxoplasmosis, CSD, brucellosis |
| | Noninfectious: head/neck cancer, Kawasaki's disease, lymphoma, SLE, Kikuchi's disease, Rosai-Dorfman disease |
| Posterior cervical adenopathy<br>*unilateral* | Infectious: toxoplasmosis, African trypanosomiasis (Winterbottom's sign) |
| | Noninfectious: posterior scalp infection, Kawasaki's disease, lymphoma, Kikuchi's disease, Rosai-Dorfman disease |
| *bilateral* | Infectious: EBV, HHV-6, CMV, Chagas' disease, HAV |
| | Noninfectious: lymphoma, Kawasaki's disease, Rosai-Dorfman disease, hyper IgD syndrome, sarcoidosis |
| Supraclavicular adenopathy | Infectious: TB, CSD |
| | Noninfectious: intra-abdominal malignancy (Virchow's sign), Kikuchi's disease |
| Infraclavicular adenopathy | Infectious: African trypanosomiasis, CSD |
| | Noninfectious: lymphoma |
| Epitrochlear adenopathy | Infectious: 2° syphilis, CSD, brucellosis |
| | Noninfectious: sarcoidosis, IVDA |
| Axillary adenopathy | Infectious: CFS (usually left), CSD, B. malayi, rat bite fever (Spirillum minus), brucellosis |
| | Noninfectious: lymphoma, CLL, sarcoidosis, Schnitzler's syndrome |
| Ulcer-node syndromes | Infectious: ***Ulcer > node:*** anthrax, rickettsial fevers (except RMSF), sporotrichosis, cutaneous leishmaniasis (new world). ***Node = ulcer:*** 1° syphilis, chancroid, tularemia (ulceroglandular), rat bite fever (Spirillum minus). ***Node > ulcer:*** syphilis, LGV, chancroid, HSV-2 |
| | Noninfectious: lymphoma |
| Periumbilical nodule | Infectious: intra-abdominal infection |
| | Noninfectious: malignancy (Sister Joseph's sign) |

**Table 9.13. Lymph Node Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Inguinal adenopathy | Infectious: lower extremity infections, bubonic plague, rat bite fever (Spirillum minus), filariasis, leprosy, tularemia, CSD |
| *unilateral* | Noninfectious: intra-abdominal malignancy, bilateral lower extremity infection, IVDA |
| *bilateral* | Infectious: any infection causing generalized adenopathy, B. malayi, HSV-2, syphilis, LGV |
| | Noninfectious: any disorder causing generalized adenopathy, Schnitzler's syndrome |
| Generalized lymphadenopathy | Infectious: TB, EBV, HHV-6, CMV, rubella, measles, toxoplasmosis, CSD, LGV, brucellosis, group A streptococci, 2° syphilis, HIV, kala-azar (African), trypanosomiasis, arboviral hemorrhagic fevers, Whipple's disease, Castleman's disease (MCD) |
| | Noninfectious: SLE, RA, adult Still's disease, pseudolymphoma (Dilantin), Kikuchi's disease, Gaucher's disease, sarcoidosis, serum sickness, hyperthyroidism, ALL, CLL, Kimura's disease |

**Table 9.14. Genitourinary Abnormalities**

| Finding | Causes |
|---|---|
| Epididymoorchitis | Infectious: mumps, TB, blastomycosis, melioidosis, brucellosis, leptospirosis, EBV, W. bancrofti, Coxsackie A/B, S. hematobium, LCM, GC, C. trachomatis (young adults), P. aeruginosa (elderly adults), Colorado tick fever, rat bite fever (Spirillum minus), relapsing fever |
| | Noninfectious: lymphoma, SLE, PAN, sarcoidosis, FMF, TNF-receptor-1-associated periodic syndrome (TRAPS), trauma, torsion, malignancy |
| Scrotal enlargement | Infectious: mumps, W. bancrofti (not B. malayi), Fournier's gangrene |
| | Noninfectious: hydrocele, testicular torsion |
| Groin mass | Infectious: onchocerciasis (hanging groins), TB, W. bancrofti, shistosomiasis |
| | Noninfectious: lymphoma |
| Perirectal fistula | Infectious: peri-rectal abscess, actinomycosis, LGV |
| | Noninfectious: RE, malignancies |
| Perirectal ulcer | Infectious: HSV, amebiasis cutis, 1° syphilis |
| | Noninfectious: malignancy |
| Genital ulcers | Infectious: Syphilis (1°), HSV, Chancroid, LCV, Chikungunya fever, TB |
| | Noninfectious: Biçhet's syndrome, RE, malignancies |
| Prostate enlargement/ tenderness | Infectious: prostatitis, prostatic abscess* |
| | Noninfectious: BPH |

* Acute: aerobic GNB, VSE/VRE, Ureoplasma urealyticum, C. trachomatis, B. fragilis (post-transrectal biopsy). Chronic: TB, histoplasmosis, blastomycosis, aspergillus, candida, cryptococcus, meliodosis.

**Table 9.15. Extremity Abnormalities**

| Finding | Causes |
|---|---|
| Digital gangrene | Infectious: SBE, S. aureus bacteremia/ABE (emboli), meningococcemia, RMSF, typhus<br>Noninfectious: SLE, vasculitis, peripheral vascular disease |
| Splinter hemorrhages | Infectious: SBE, ABE, trichinosis<br>Noninfectious: trauma, atrial myxoma, acute leukemia, RA, scurvy, mitral stenosis, severe anemia |
| Clubbing | Infectious: SBE, lung abscess, TB<br>Noninfectious: ulcerative colitis (UC), Crohn's disease (RE), cirrhosis, cyanoic congenital heart disease, bronchogenic carcinoma, PBC, celiac disease, hyperthyroidism, hyperparathyroidism, bronchiectasis, hereditary |
| Dactylitis | Infectious: kala-azar, 2° syphilis, TB<br>Noninfectious: sarcoidosis, sickle cell disease, gout, psoriatic arthritis |
| Tender fingertips | Infectious: SBE, typhoid fever<br>Noninfectious: SLE, vasculitis, radial artery occlusion |
| Lymphangitis | Infectious: group A streptococci, B. malayi, onchocerciasis, melioidosis<br>Noninfectious: IVDA |
| Nodular lymphangitis | Infectious: sporotrichosis, atypical TB, Erysipelothrix rhusiopathiae, kala-azar, coccidiomycosis, histoplasmosis, blastomycosis, nocardia, Pseudoallescheria boydii, cryptococcus, anthrax, group A streptococci, tularemia<br>Noninfectious: ganglion cyst (wrist/hand only) |
| Painless purple palm/sole lesions | Infectious: ABE (Janeway lesions)<br>Noninfectious: trauma |
| Carpal tunnel syndrome | Infectious: TB, leprosy<br>Noninfectious: cirrhosis, RA, scleroderma, SLE, DM, hypothyroidism, sarcoidosis, multiple myeloma, amyloidosis |
| Verrucous hand/arm lesions | Infectious: TB, leprosy, syphilis, sporotrichosis, kala-azar, bartonellosis (verruga peruana)<br>Noninfectious: squamous cell carcinoma, sarcoidosis |
| Edema of the dorsum of hand/foot | Infectious: RMSF, TSS, loiasis, dengue fever, chikungunya fever<br>Noninfectious: trauma, PMR, Kawasaki's disease |

**Table 9.15. Extremity Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Wrist swelling | Infectious: loiasis, septic arthritis, parvovirus $B_{19}$, rubella, chikungunya fever<br>Noninfectious: RA |
| Arthritis (septic/reactive) | Infectious: septic arthritis, rat bite fever (Streptobacillus moniliformis), Lyme disease, LGV, brucellosis, GC, parvovirus B19, shigella, yersinia, salmonella, campylobacter, Clostridium difficile, mumps, rubella, dengue fever, HIV, HBV, Whipple's disease<br>Noninfectious: FMF, RA, pseudogout, SLE, hyper IgD syndrome, lymphoma, Reiter's syndrome, post-streptococcal RF, Poncet's disease, JRA |
| Papular axillary lesions | Infectious: hydraadenitis suppurativa, 2° syphilis, yaws, blastomycosis<br>Noninfectious: chronic contact dermatitis, acanthosis nigricans, Fox-Fordyce disease, seborrheic dermatitis |
| Tenosynovitis | Infectious: GC (acute), TB (chronic), atypical TB (acute/chronic)<br>Noninfectious: rheumatic diseases |
| Thigh tenderness (bilateral, anterior) | Infectious: bacteremia (Louria's sign), leptospirosis, ehrlichiosis, endocarditis, parvovirus $B_{19}$<br>Noninfectious: myositis, vasculitis, sickle cell crisis |
| Calf tenderness | Infectious: RMSF<br>Noninfectious: myositis |
| Tender muscles | Infectious: trichinosis<br>Noninfectious: myositis |
| Thrombophlebitis | Infectious: psittacosis, campylobacter<br>Noninfectious: Behçet's disease, malignancy |
| Verrucous foot/leg lesions | Infectious: TB, cutaneous leishmaniasis, paracoccoidomycosis, sporotrichosis, leprosy, 2° syphilis, mycetoma<br>Noninfectious: lichen planus, squamous cell carcinoma |
| Foot/leg ulcers | Infectious: M. ulcerans (Buruli ulcer may be anywhere), yaws, cutaneous diphtheria, cutaneous leishmaniasis, TB, rat bite fever (Spirillum minus)<br>Noninfectious: sickle cell (medial malleolar ulcers), DM (only sole of foot/between toes), peripheral vascular disease |
| Leg edema *unilateral* | Infectious: onchocerciasis, B. malayi (below knee)<br>Noninfectious: malignancy, Milroy's disease |

**Table 9.15. Extremity Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| *bilateral* | Infectious: elephantiasis (chronic recurrent erysipelas), Chagas' disease<br>Noninfectious: lymphatic obstruction (2° to abdominal/pelvic malignancy), congenital yellow nail syndrome |
| Nodular arm/leg lesions | Infectious: TB (Bazin's erythema induratum), filariasis, sporotrichosis, cutaneos leishmaniasis, atypical TB, leprosy, HIV<br>Noninfectious: erythema nodosum, PAN, thrombophlebitis, panniculitis, nodular vasculitis, Wegener's granulomatosis, Sweet's syndrome, myiasis |
| Palpable purpura | Infectious: meningococcemia, RMSF<br>Noninfectious: vasculitis, cryoglobulinemia, Gardner-Diamond syndrome, Sweet's syndrome |
| Eschar | Infectious: ecthyma gangrenosum, typhus, rickettsial spotted fevers (except RMSF, rickettsial pox), anthrax, cutaneous diphtheria, African tick bite fever (multiple eschars)<br>Noninfectious: burns, drugs, recluse spider bite |
| Scleroderma (wood hard skin lesions) | Infectious: actinomycosis<br>Noninfectious: malignancies, DM |
| Hyperpigmented shins | Infectious: onchocerciasis<br>Noninfectious: DM (dermopathy) |
| Cutaneous cold abscesses | Infectious: TB, atypical TB<br>Noninfectious: hyper IgE (Job's) syndrome, CGD |
| Purple nodules | Infectious: disseminated cryptococcus, aspergillus, candida, trypanosomiasis, Kaposi's sarcoma, HIV<br>Noninfectious: leukemia, lymphoma, melanoma |
| Painful leg nodules | Infectious: Kaposi's sarcoma<br>Noninfectious: erythema nodosum, superficial thrombophlebitis, PAN, panniculitis, osteogenic sarcoma |
| Migratory rashes | Infectious: hookworms, dracunculiasis, loiasis, gnathostomiasis, strongyloidiasis, sparganosis<br>Noninfectious: myiasis |
| Rash of palms/soles | Infectious: syphilis, RMSF, EBV, scarlet fever, echo 9, smallpox, monkeypox, chickenpox, rat bite fever (Streptobacillus moniliformis), HFM, orf, E. multiforme (M. pneumoniae, HSV)<br>Noninfectious: drug rashes, E. multiforme (drugs) |

**Table 9.15. Extremity Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Rash (purpuric) of hands/feet | Infectious: parvovirus B19, VZV, EBV, CMV, HHV-6, HHV-7, HBV, Coxsackie, rubella<br>Noninfectious: trauma |
| Erythema nodosum | Infectious: TB, group A streptococci, EBV, LGV, psittacosis, coccidiomycosis, blastomycosis, histoplasmosis, CSD, yersinia, campylobacter<br>Noninfectious: UC, RE, drugs, sarcoidosis, lymphoma, SLE |
| Erythema multiforme | Infectious: HSV, M. pneumoniae, Coxsackie B<br>Noninfectious: drugs |
| Plantar hyperkeratoses | Infectious: 3° syphilis, yaws, pinta, HIV, tungiasis<br>Noninfectious: Reiter's syndrome, arsenic |
| Desquamation of hands/feet | Infectious: erysipelas, scarlet fever, TSS, severe infections, yaws, leptospirosis, influenza, measles, arboviral hemorrhagic fevers, chickungunya fever, dengue fever (palms/soles)<br>Noninfectious: Kawasaki's disease, post-edematous states, radiation therapy, vitamin A excess, pellagra, drugs |

**Table 9.16. Neurological Abnormalities**

| Finding | Causes |
|---|---|
| Mental confusion/ encephalopathy (acute) | Infectious: legionnaire's disease, HSV, HHV-6, RMSF, scrub typhus (R. tsutsu-gamuschi) listeria, mycoplasma meningoencephalitis, amebic meningitis, trichinosis, brain abscess, anthrax, brucellosis, SBE, ABE, HIV, viral encephalitis, CSD, Whipple's disease, Q fever, Colorado tick fever, chikungunya fever, meliodosis<br>Noninfectious: Wernicke's encephalopathy, toxic/metabolic disorders, Behçet's syndrome, SLE, alcoholism, drugs, CHF, chronic renal failure, hepatic encephalopathy, brain tumor, CNS metastases, meningeal carcinomatosis, celiac disease, cefepime, ciprofloxacin > levofloxacin |
| Nuchal rigidity | Infectious: meningitis (bacterial, fungal, TB, viral)<br>Noninfectious: meningismus, cervical arthritis |
| General muscle rigidity | Infectious: trichinosis, tetanus, rabies, viral encephalitis, brucellosis<br>Noninfectious: malignancies, malignant neuroleptic syndrome, strychnine poisoning, Parkinson's disease |
| Transient deafness | Infectious: RMSF, mediterranean spotted fever, murine typhus, S. pneumoniae ABM, S. suis ABM, H. influenzae ABM, mumps, measles, VZV (Ramsey-Hunt Syndrome), EEE, congenital syphilis, brucellosis, Lassa fever<br>Noninfectious: trauma, Susac's syndrome |

**Table 9.16. Neurological Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Cranial nerve (CN) abnormalities<br>*unilateral* | Infectious: 6th CN palsy (TB meningitis, N. meningitidis), 7th CN palsy (see Bell's palsy), TBRF, 8th CN palsy (N. meningitidis)<br>Noninfectious: 7th CN palsy (neurosarcoidosis, meningeal carcinomatosis), 2nd, 6th CN palsy (Wegener's granulomatosis) |
| *bilateral* | Infectious: 6th CN palsy (TB)<br>Noninfectious: meningeal carcinomatosis |
| Optic nerve atrophy | Infectious: 3° syphilis, TB, toxoplasmosis, mumps, measles, rubella<br>Noninfectious: sickle cell disease, severe anemia, polycythemia vera, drugs, sarcoidosis, TA, Behçet's syndrome, SLE, PAN, MS, glaucoma |
| Bell's Palsy | Infectious: Lyme disease, HSV-1, VZV (Ramsay-Hunt syndrome), HIV, St.LE, CSD, mumps, EBV infectious mononucleosis, Mycoplasma pneumoniae, syphilis, otitis media, bacterial meningitis, leprosy<br>Noninfectious: sarcoidosis, multiple sclerosis, Guillain-Barre syndrome, B-cell lymphoma, Wegener's granulamatosis, pontine lesions (infarct, tumors, demyelinative lesions), tumor compressing the facial nerve, sphenoid ridge mengiomas, acoustic neuromas, neurofibromatosis (type 2), fibrous dysplasia, osteopetrosis, Paget's disease, scleroderma, Melkersson-Rosenthal syndrome, trauma, drugs (vincristine, HBV vaccination), idiopathic |
| Anisocoria | Infectious: TB, 3° syphilis, VZV, meningitis, encephalitis, botulism, diphtheria<br>Noninfectious: DM, toxins, cavernous sinus thrombosis, glaucoma, brain tumor, intracranial aneurysm |
| Papilledema | Infectious: meningitis (bacterial, fungal, TB, viral, etc.)<br>Noninfectious: pseudotumor cerebri, hypercarbia, brain tumor, DM, subarachnoid bleed, SLE, drugs, central retinal artery occlusion, cavernous sinus thrombosis, hypertensive encephalopathy |
| Mononeuritis multiplex | Infectious: leprosy, Lyme disease, HIV<br>Noninfectious: DM, amyloidosis, sarcoidosis, lymphomatoid granulomatosis, vasculitis |
| Transverse myelitis | Infectious: HIV, HTLV-1, EBV, CMV, VZV, HSV, polio, rabies, TB, EV 71, epidural abscess, typhus, brucellosis, shistosomiasis, Lyme disease, syphilis, toxoplasmosis, M. pneumoniae<br>Noninfectious: MS, malignancies, vaccines, SLE, sarcoidosis |
| Guillain-Barré syndrome | Infectious: influenza, Campylobacter jejuni, CMV, EBV, VZV, M. pneumoniae, EV 71, brucellosis<br>Noninfectious: influenza vaccine |
| Flaccid paralysis (acute) | Infectious: polio, WNE, CMV, VZV, rabies, botulism, JE, EV 71, EV D68, Powassan encephalitis (PE), chikungunya fever, brucellosis<br>Noninfectious: CVA, tick bite paralysis, hypocalcemic periodic paralysis |

**Table 9.16. Neurological Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Hemiplegia/ hemiparesis | Infectious: SBE, subdural empyema, brain abscess, JE, brucellosis, post-VZV<br>Noninfectious: TIA, CVA, malignancies, CNS vasculitis, migraine, GCA/TA, SLE, neurosarcoidosis, birth control pills, protein C/S, factor V Leiden deficiency |

**Table 9.17. WBC Abnormalities**

| Finding | Causes |
|---|---|
| Leukocytosis | Infectious: most acute infections<br>Noninfectious: most acute noninfectious disease disorders, any major stress, steroids, drug fever, daptomycin |
| Leukopenia | Infectious: miliary TB, typhoid/enteric fever, malaria, babesiosis dengue, chickungunya fever, tularemia, brucellosis, kala-azar, psittacosis, viral hepatitis, EBV, CMV, HHV-6, VZV, influenza, Colorado tick fever, Campylobacter histoplasmosis, relapsing fever, WNE, VEE, ehrlichiosis/anaplasmosis, SARS<br>Noninfectious: drugs, pre/acute leukemias, Felty's syndrome, Gaucher's disease, splenomegaly, pernicious anemia, SLE, cyclic neutropenia, severe combined immunodeficiency disease (SCID), Chediak-Higashi syndrome, Kikuchi's disease, sarcoidosis |
| Relative lymphocytosis | Infectious: Whipple's disease, acute infection (convalescence), TB, brucellosis, pertussis, tularemia, 2° syphilis, histoplasmosis, EBV, CMV, HHV-6, mumps, viral hepatitis, rubella, VZV, kala-azar, toxoplasmosis, RMSF, chickungunya fever, typhoid/enteric fever (non-S. typhi > S. typhi), MERS<br>Noninfectious: ALL, CLL, lymphomas, carcinomas, multiple myeloma, RA, Hashimoto's thyroiditis, myxedema, adrenal insufficiency, thyrotoxicosis, vasculitis, Dilantin (DPH), p-aminosalicylic acid (PAS), serum sickness |
| Relative lymphopenia | Infectious: CMV, HHV-6, HHV-8, HIV, miliary TB, Legionella, typhoid/enteric fever (S. typhi > non-S. typhi), Q fever, brucellosis, SARS, malaria, babesiosis, influenza (human, avian, swine), RMSF, histoplasmosis, dengue fever, chickungunya fever, ehrlichiosis, parvovirus B19, HPS, WNE, viral hepatitis (early), Whipple's disease, MERS<br>Noninfectious: cytoxic drugs, steroids, sarcoidosis, SLE, lymphoma, RA, radiation, Wiskott-Aldrich syndrome, severe combine immunodeficiency disease (SCID), common variable immune deficiency (CVID), Di George's syndrome, Nezelof's syndrome, intestinal lymphangiectasia, ataxia-telangiectasia, constrictive pericarditis, tricuspid regurgitation, Kawasaki's disease, idiopathic $CD_4$ cytopenia, acute/chronic renal failure, hemodialysis, myasthenia gravis, celiac disease, cirrhosis, coronary bypass, Wegener's granulomatosis, CHF, acute pancreatitis, carcinomas (terminal) |

**Table 9.17. WBC Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Monocytosis | Infectious: TB, SBE, RMSF, diphtheria, histoplasmosis, brucellosis, pertussis, kala-azar, 2° syphilis, malaria, typhoid/enteric fever, babesiosis, EBV, CMV, influenza A, recovery from chronic infection<br>Noninfectious: sarcoidosis, myeloproliferative disorders (↑ pre-AML), lymphomas, Gaucher's disease, RE, UC, celiac disease, RA, SLE, PAN, TA, hyposplenism, post-splenectomy |
| Atypical lymphocytes† | Infectious: EBV*, CMV*, HHV-6, Castleman's disease (MCD), viral hepatitis, mumps, measles, rubella, VZV, toxoplasmosis, brucellosis, HSV, arboviral hemorrhagic fevers, malaria, dengue, babesiosis, ehrlichiosis/anaplasmosis<br>Noninfectious: drug fever, Kikuchi's disease |
| Immunoblasts | Infectious: HPS<br>Noninfectious: lymphomas |
| Eosinophilia | Infectious: trichinosis, echinococcosis, fascioliasis, paragonimiasis, taeniasis, Strongyloides stercoralis, hookworm, filariasis, schistosomiasis, Toxocara canis/cati (VLM), histoplasmosis, coccidioidomycosis, filariasis ascariasis, gnathostomiasis, angiostrongyliasis, cysticercosis, Isospora belli, Dientamoeba fragilis, scarlet fever<br>Noninfectious: drug fever, asthma, dermatitis herpetiformis, pemphigus vulgaris, eczema, hay fever/allergic rhinitis, psoriasis, atopic dermatitis, mycosis fungoides, myeloproliferative disorders (MPDs), polycythemia vera, CML, eosinophilic leukemia, eosinophilic gastritis, acute leukemias, sickle cell anemia, lymphomas, malignancies, Churg-Strauss granulomatosis, urticaria, hyper IgE syndrome (Job's syndrome), Sweet's syndrome, bronchopulmonary aspergillosis (BPA), angioneurotic edema, serum sickness, eosinophilia-myalgia syndrome, dermatomyositis, PAN, allergic vasculitis, Loffler's syndrome, pulmonary infiltrates eosinophilia (PIE) syndrome, Loffler's endocarditis, Addison's disease, sarcoidosis, Wegener's granulomatosis, Goodpasture's syndrome, UC, RE, Wiskott-Aldrich syndrome, IgA deficiency, allergic vasculitis, Kimura's disease, peritoneal dialysis, radiation |
| Eosmopenin | Infectious: typhoid fever<br>Noninfectious: steroids, immunosupressive |
| Basophilia | Infectious: smallpox, chickenpox (VZV)<br>Noninfectious: pre-leukemias, acute leukemias, lymphomas, myeloproliferative disorders (MPDs), post-splenectomy |
| WBC inclusions | Infectious: ehrlichiosis/anaplasmosis (morula: HGA > HME)<br>Noninfectious: staining artifacts |

* May have > 20% atypical lymphocytes.

† Not seen with malignancies. Abnormal lymphocytes (morphologically monotonous) seen with leukemias.

**Table 9.18. RBC Abnormalities**

| Finding | Causes |
|---|---|
| Schistocytes (microangiopathic hemolytic anemia) | Infectious: meningococcemia (DIC)<br>Noninfectious: DIC (due to any cause), TTP, hemolytic uremic syndrome (HUS), "Waring Blender" syndrome (prosthetic valve), malignant hypertension |
| Spherocytes | Infectious: gas gangrene, Castleman's disease (MCD)<br>Noninfectious: autoimmune hemolytic anemias, hereditary spherocytosis, severe transfusion reactions, severe burns, cirrhosis |
| Target cells | Infectious: none<br>Noninfectious: post-splenectomy, iron deficiency anemia, cirrhosis, hemoglobulin S or C, thalassemia |
| RBC inclusions | Infectious: malaria (ring forms, RBC pigment), babesiosis (ring forms, no RBC pigment, "Maltese crosses"/tetrads)<br>Noninfectious: Cabot's rings (severe hemolytic anemia, pernicious anemia), Heinz bodies (GGPD deficiency, drug induced, hereditary anemias), Pappenheimer bodies (thalassemia, sideroblastic anemias, lead poisoning), artifacts |
| Howell-Jolly bodies† | Infectious: fulimant pneumococcal sepsis<br>Noninfectious: asplenia/hyposplenism*, congenital asplenia, splenectomy, splenic infarcts, splenic neoplasms, megaloblastic anemias, thalassemia "Maltese Crosses", steroids |
| Hemophagocytosis | Infectious: HIV, HSV, EBV, CMV, adenovirus, parvovirus B19, malaria, babesiosis, toxoplasmosis, kala-azar, histoplasmosis, cryptococcosis, disseminated candidiasis, typhoid/enteric fever, syphilis, listeria, SBE, Q fever, leprosy, TB, brucellosis, Castleman's disease (MCD)<br>Noninfectious: histiocytosis X (eosinophilic granuloma, Langerhan's cell histiocytosis), myeloproliferative disorders (MPDs), SLE, sarcoidosis, RA, lymphomas, acute leukemias, multiple myeloma, Chediak-Higashi syndrome, Dilantin (DPH), familial hemophagocytic histiocytosis |
| Anemia (acute) | Infectious: Oroya fever, gas gangrene, malaria, babesiosis, CMV<br>Noninfectious: ITP, "Waring blender" syndrome (prosthetic heart valve), hemorrhagic/necrotic pancreatitis, hemorrage, drug induced |

* Chronic alcoholism, amyloidosis, chronic active hepatitis, IgA deficiency, intestinal lymphangectasia, myeloproliferative disorders, Waldenstrom's macroglobulinemia, NHL, celiac disease, RA, UC, thyroiditis, systemic mastocytosis, sickle cell disease, Fanconi's syndrome, Sezary's syndrome.

† Also "pitted/pocked" RBCs.

**Table 9.19. Platelet Abnormalities**

| Finding | Causes |
|---|---|
| Thrombocytopenia | Infectious: acute/severe bacterial infections, measles, rubella, dengue, arboviral, hemorrhagic fevers, EBV, CMV, VZV, mumps, influenza (human, avian, swine), typhus, RMSF, WNE, ehrlichiosis, diphtheria, malaria, babesiosis, trypanosomiasis, TSS, histoplasmosis, kala-azar, HIV, miliary TB, relapsing fever, HPS, brucellosis, Campylobacter, SARS, MERS<br>Noninfectious: drugs, DIC, fat emboli syndrome, TTP, ITP, hemolytic uremic syndrome (HUS), pre/acute/leukemias, lymphomas, carcinomas, myeloproliferative disorders (MPDs), multiple myeloma, Gaucher's disease, cirrhosis, hemodialysis |
| Thrombocytosis | Infectious: TB, chronic infections (e.g., osteomyelitis, abscess), SBE, Q fever, M. pneumoniae<br>Noninfectious: Malignancies, myeloproliferative disorders, post-splenectomy, lymphomas, Wegener's granulomatosis, vasculitis, TA, PAN, Kawasaki's disease, anemia (nemolytic, iron deficiency) fosfomycin, miconazole, ceftriaxone, oral cephalosporins, carbapenems, β-lactam/β-lactamase inhibitor combinations, iron therapy |

**Table 9.20. Pancytopenia**

| Finding | Causes |
|---|---|
| Pancytopenia | Infectious: miliary TB, brucellosis, histoplasmosis, ehrlichiosis/anaplasmosis, parvovirus B19, HBV, CMV, EBV, HIV<br>Noninfectious: myeloproliferative disorders (MPDs), drugs, malignancies, Chediak-Higashi syndrome, megaloblastic anemias, Gaucher's disease, hypersplenism, sarcoidosis, SLE, paroxysmal nocturnal hemoglobinuria (PNH), myelophistic anemias, leukemias, lymphoma |

**Table 9.21. Serum Test Abnormalities**

| Finding | Causes |
|---|---|
| Erythrocyte Sedimentation Rate (ESR)<br>*highly elevated (≥100 mm/hr)* | Infectious: SBE, osteomyelitis, abscess, CAP (Leginnaire's disease, Q fever, S. pneumoniae), non-pulmonary TB, babesiosis<br>Noninfectious: malignancies, rheumatic disorders, vasculitis, drug fever, PMR/GCA, uremia/chronic renal failure, cirrhosis, Kawasaki's disease, Sweet's syndrome, pulmonary emboli/infarction |
| *low/subnormal* | Infectious: trichinosis, CFS, ehrlichiosis/anaplasmosis<br>Noninfectious: severe anemia, cachexia, massive hepatic necrosis, DIC, polycythemia vera, sickle cell anemia, CHF |
| SPEP (polyclonal gammopathy) | Infectious: HIV, malaria, kala-azar, LGV, rat bite fever, Toxocara canis/cati (VLM), Q fever (chronic), Castleman's disease (MCD)<br>Noninfectious: SLE, PAN, cirrhosis, CAH, sarcoidosis, atrial myxoma, Takayasu's arteritis, Rosai-Dorfman disease |

**Table 9.21. Serum Test Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| SPEP (monoclonal gammopathy) | Infectious: CMV, kala-azar, typhoid fever, Castleman's disease (MCD)<br>Noninfectious: multiple myeloma, Waldenström's macroglobulinemia, Schnitzler's syndrome, MGUS |
| ↑ ferritin levels† *acute* | Infectious: legionnaires' disease, WNE, EBV, CMV, toxoplasmosis, MSSA/MRSA ABE, malaria, babesiosis, ehlichiosis/anaplasmosis, arboviral hemorrhagic fevers<br>Noninfectious: Kawasaki's disease, Rosai-Dorfman disease, hemophagocytic syndrome (due to any cause) |
| *chronic* | Infectious: HIV, TB, filariasis<br>Noninfectious: Malignancies (preleukemias, lymphomas, multiple myeloma, hepatomas, liver/CNS metastases), myeloproliferative disorders (MPDs), RA, adult Still's disease, SLE, TA, Kawasaki's disease, chronic renal failure, hemodialysis, liver transplants, hemochromatosis, cirrhosis, $\alpha$-1 antitrypsin deficiency, CAH, (MAS), chronic HCV, cholestatic jaundice, macrophage activation syndrome sickle cell anemia, multiple blood transfusions, anemia of chronic disease |
| ↑ cold agglutinins | Infectious: Mycoplasma pneumoniae, EBV, CMV, mumps, measles, malaria, Coxsackie, Q fever, HIV, HCV, influenza, adenovirus, trypanosomiasis<br>Noninfectious: lymphomas, CLL, CML, multiple myeloma, Waldenstrom's macroglobulinemia, cold agglutinin disease, paroxysmal nocturnal hemoglobinuria (PNH), SLE, Rosai-Dorfman disease |
| Monospot test (false +) | Infectious: CMV, HSV, HHV-6, malaria, dengue, babesiosis, toxoplasmosis, brucellosis, Mediterranean spotted fever (MSF), rubella, mumps, viral hepatitis, Lyme disease, HIV<br>Noninfectious: SLE, sarcoidosis, AML, drugs, idiopathic |
| ↑ Lactate dehydrogenase (LDH) | Infectious: malaria, babesiosis, ehrlichiosis/anaplasmosis, viridans streptococcal SBE, amebic liver abscess, PCP, histoplasmosis, disseminated TB, toxoplasmosis, HPS, oroya fever, gas gangrene, viral myocarditis, rubella, measles, viral hepatitis, CAP/NP, dengue, arboviral hemorrhagic fevers, trichinosis, SARS, MERS, adenovirus, CMV, EBV, influenza (human, avian, swine)<br>Noninfectious: hemolyzed blood, hemolytic anemia, malignancies, pernicious anemia, megablastic anemia, pulmonary emboli, MI, renal infarction, muscle injury, liver injury, DIC, SLE pneumonitis, adult Still's disease, "Waring blender" syndrome (prosthetic heart valve), hemorrhagic/necrotic pancreatitis |

**Table 9.21. Serum Test Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| ↑ Procalcitonin levels (PCT) | Infectious: bacterial pneumonias (CAP, NHAP, NP), bacteremias (gram – > gram +), TB, ABM, fungal pneumonias (except PCP), viral hepatitis, toxoplasmosis, osteomyelitis, SBE*, malaria (P. falciparum)<br>Noninfectious: renal insufficiency, alcoholic hepatitis, lung cancer (small cell), thyroid cancer, surgery, trauma, burns, cardiogenic shock, Goodpasture's syndrome shock, GVHD, peritoneal dialysis (PD), hypotension, hemorrhagic/necrotic pancreatitis, normal variant (elderly) BMT, febrile neutropenia, drug fever, immunosuppression/steroids, $OKT_3$ therapy |
| ↑ Lactate | Infections: sepsis (bacterial), septic shock, malaria, cholera<br>Noninfectious: cardiogenic shock, hypovolemic shock, hypoperfusion, hypoxia, respiratory insufficiency/failure, renal insufficiency, hepatic insufficiency, hemorrhage, Ringer's lactate, metabolic acidosis ( ↑ anion gap), seizures, pulmonary emboli, diabetes mellitus, malignancies (leukemias, lymphomas, solid tumors), drugs (salicylates, methanol, ethylene glycol, INH, cyanide, metformin, acetaminophen, lactulose, ethanol, theophylline, niacin, cocaine, methemoglobinemia, severe anemia, carbon monoxide, short bowel syndrome (jejunoileal bypass) |
| ↑ Teichoic acid antibody titer (≥1:4) | Infections: MSSA/MRSA ABE, MSSA/MRSA abscesses, MSSA/MRSA osteomyelitis (chronic/acute)<br>Noninfectious: none |

| Fingal serum tests | Candida | Aspergillus | Histoplasmos | Blastomycosis | PCP | Cryptococcus | Fusaria | Zygomycetes |
|---|---|---|---|---|---|---|---|---|
| β 1, 3 D–glucan§ (BG) | + | + | + | – | + | – | + | – |
| Aspergillus galacto-mannan (AG) | – | + | + | – | – | – | + | – |

* Viridans streptococci.

† Not an acute phase reactant when highly/persistently ↑ > 2 × normal.

§ False + BG with P. aeruginosa bacteremia, fungal derived antibiotics (amoxicillin/clavulanate, piperacillin/tazobactam), platelet transfusions, IVIG, HD (with cellulose membranes), high serum protein levels (albumin).

**Table 9.22. Liver Test Abnormalities**

| Finding | Causes |
|---|---|
| ↑ Alkaline phosphatase (AP)<br>*mildly elevated* | Infectious: legionnaires' disease, viral hepatitis, liver abscess, EBV, CMV, Q fever, syphilis (2° or tertiary), TSS, hepatic candidiasis, clonorchiasis, ehrlichiosis/anaplasmosis, diphtheria, malaria, trypanosomiasis, histoplasmosis, HIV, miliary TB, relapsing fever, HPS |
| | Noninfectious: drugs, DIC, fat emboli syndrome, TTP, ITP, hemolytic uremic syndrome, pre/acute/leukemias, lymphomas, carcinomas, myeloproliferative disorders (MPDs), multiple myeloma, Gaucher's disease, cirrhosis, post-hepatic obstruction, alcoholic hepatitis, pregnancy, bone growth (children), osteomalacia, rickets, hyperthyroidism, UC, drug fever, hepatoma, liver metastases, lymphoma, Erdheim-Cheste disease (ECD), mastocytosis Schnitzler's syndrome TA, normal variant (elderly) |
| *moderately/highly elevated* | Infectious: liver abscess |
| | Noninfectious: PBC, post-hepatic obstruction, post-necrotic cirrhosis, Paget's disease, osteogenic sarcoma, hepatoma, TA, bone fractures, tigecycline |
| ↑ Serum transaminases (SGOT/AST, SGPT/ALT)<br>*mildly elevated* | Infectious: legionnaires' disease, psittacosis, Q fever, relapsing fever, brucellosis, TSS, RMSF, babesiosis, ehrlichiosis/anaplasmosis, liver abscess, syphilis (2° or tertiary), shigellosis, clonorchiasis, EBV, CMV, HSV-1, VZV (disseminated), HHV-6, anicteric viral hepatitis, gonococcemia, malaria, gram-negative bacteremia, adenovirus, dengue |
| | Noninfectious: drug fever, alcoholic cirrhosis, (SGOT/AST 2:1 SGPT/ALT) CHF, infarction (myocardial, cerebral, pulmonary), pancreatitis, intrahepatic cholestasis, sickle cell disease, amyloidosis, delirium tremens, intravascular hemolysis, UC, eosinophilia-myalgia syndrome, Kawasaki's disease, adult Still's disease |
| *highly elevated* | Infectious: viral hepatitis, HSV hepatitis, yellow fever, arboviral hemorrhagic fevers |
| | Noninfectious: shock liver, rhabdomyolysis (SGOT/AST 2:1 SGPT/ALT), exercise, drugs (statins INH, RIF) |
| ↑ Total bilirubin | Infectious: legionnaires' disease, gonococcemia, liver abscess, viral hepatitis, EBV, CMV, pneumococcal bacteremia, malaria |
| | Noninfectious: hemolysis, Gilbert's syndrome, cirrhosis, alcoholic hepatitis, carcinoma (pancreatic, biliary), choledocholithiasis, amyloidosis, sickle cell disease, Rotor's syndrome, $\alpha$-1 antitrypsin deficiency, hepatic vein thrombosis, autoimmune (lupoid) hepatitis, hemachromatosis |
| ↑ GGT (GGTP) | Infectious: acute viral hepatitis, EBV |
| | Noninfectious: cirrhosis, alcoholic hepatitis, PBC, fatty liver, CAH, hepatoma, liver metastases, pancreatitis (acute), myocardial infarction (acute), breast cancer, lung cancer, prostate cancer, melanoma, hypernephroma (RCC), obstructive jaundice, cholestasis, CAH |

**Table 9.23. Rheumatic Test Abnormalities**

| Finding | Causes |
|---|---|
| ↑ Rheumatoid factors (RF) | Infectious: SBE, TB, syphilis, kala-azar, EBV, typhoid/enteric fever, HBV, HCV, chickungunya fever, malaria<br>Noninfectious: cirrhosis, CAH, ITP, silicosis, asbestosis, asthma, Wegener's granulomatosis, pulmonary fibrosis, Behçet's disease, SLE, RA, Sjögren's, dermatomyositis, sarcoidosis, PBC, B-cell malignancies, normal variant |
| ↑ Anti-nuclear antibody titers (ANA) | Infectious: HIV, EBV, CMV, TB, SBE, leprosy, kala-azar, malaria<br>Noninfectious: SLE, scleroderma, MCTD, CREST syndrome, RA, autoimmune (lupoid) hepatitis, CAH, dermatomyositis, subacute thyroiditis, ITP, PBC, multiple sclerosis, sarcoidosis, Wegener's granulomatosis, myasthenia gravis, ESRD on HD, normal variant (elderly) |
| ↑ Double stranded DNA (DS-DNA) | Infectious: CMV, EBV<br>Noninfectious: SLE, RA, CAH, PBC |
| ↑ Angiotensin-converting enzyme levels (ACE) | Infectious: TB, leprosy, coccidiomycosis, viral hepatitis<br>Noninfectious: sarcoidosis, allergic alveolitis, hyperparathyroidism hyperthyroidism, PBC, Gaucher's disease, DM, ESRD, amyloidosis, multiple myeloma, lymphoma, cirrhosis, psoriasis, silicosis, asbestosis, berylliosis |
| ↑ c-ANCA | Infectious: viridans streptococcal SBE, S. bovis SBE, chromomycosis, aspergillosis, amebiasis, legionnaires' disease, leptospirosis, HIV<br>Noninfectious: crescentic GMN, microscopic polyangitis (MPA), Sweet's syndrome, PAN, UC, RE, SLE, Churg-Strauss granulomatosis, Wegener's granulomatosis, HSP, TA, Kawasaki's disease, sarcoidosis |
| ↑ Anti-smooth muscle antibodies (ASM) | Infectious: Q fever, HCV (chronic), EBV, typhoid/enteric fever<br>Noninfectious: autoimmune (lupoid) hepatitis, Wilson's disease, PBC, TA, normal variant (elderly) |

**Table 9.24. Urinary Abnormalities**

| Finding | Causes |
|---|---|
| Pyuria*§ | Infectious: TB, leptospirosis, brucellosis, TSS, diphtheria, candida, GC, trichomonas, cystitis, pyelonephritis, prostatitis, acute urethral syndrome, partially treated UTI, medullary abscess, chlamydia/mycoplasma NGU, balanitis, acute appendicitis, St.LE.<br>Noninfectious: interstitial nephritis, urethral irritation/inflammation, strenuous exercise, SLE, calculi, bladder tumors, chronic interstitial cystitis, RE, diverticulitis, Kawasaki's disease, sarcoidosis |

* Gross pus suggests ruptured renal abscess.
§ WBC casts suggest SLE, nephritis, or acute pyelonephritis.

**Table 9.24. Urinary Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Hematuria<br>*gross* | Infectious: ABE (renal septic emboli), malaria (P. falciparum), yellow fever, adenoviral cystitis (type 11), BKV (transplants) |
| | Noninfectious: renal malignancy, bladder malignancy, BPH, papillary necrosis (DM), trauma |
| *microscopic* | Infectious: SBE, renal TB, schistosomiasis (S. hematobium), S. saprophyticus, HPS, legionnaire's disease, Q fever, BKV (transplants), EBV |
| | Noninfectious: trauma, BPH, prostatitis, malignancy, malignant hypertension, PAN, drug reactions, calculi, urethral stricture, renal vein thrombosis, hydronephrosis, polycystic kidney disease, malakoplakia, strenuous exercise, renal infarction, sarcoidosis |
| Proteinuria | Infectious: TB, HBV, syphilis, malaria (black water fever), brucellosis, SBE, chronic pyelonephritis, leprosy, shistosomiasis, any acute infection |
| | Noninfectious: post-streptococcal GMN, malignant hypertension, ATN, amyloidosis, sickle cell disease, polycystic kidneys, scleroderma, sarcoidosis, PAN, Wegener's granulomatosis, Goodpasture's syndrome, multiple myeloma, lymphomas, RCC, renal trauma, strenuous exercise |
| Urinary pH<br>*alkaline* | Infectious: Corynebacterium urealyticum, Klebsiella (rare), Proteus, providencia, S. saprophyticus, Ureaplasma urealyticum |
| | Noninfectious: systemic alkalosis, postprandial "alkaline tide," alkalinization therapy, old urine, vegetarian diet |
| *acidic* | Infectious: TB |
| | Noninfectious: acidification therapy, systemic acidosis, ketosis |
| ↓ Specific gravity (1.023 – 1.030) | Infectious: pyelonephritis† |
| | Noninfectious: diabetes insipidus, tubo-interstitial renal diseases, sickle cell disease |
| Nitrite positive | Infectious: most uropathogens** |
| | Noninfectious: none |
| Leukocyte esterase†‡ | Infectious: acute cystitis, acute pyelonephritis |
| | Noninfectious: inflammation anywhere in the upper/lower GU tract |

† Cystitis is associated with a normal specific gravity. The transient decrease in specific gravity of pyelonephritis corrects to normal following effective treatment.

** Negative urinary nitrite occurs with group B streptococci, group D enterococci, (VSE/VRE) S. saprophyticus, S. aureus, Acinetobacter sp., Gardnerella sp., Corynebacterium urealyticum, Burkholderia sp., Pseudomonas sp., Candida sp.

‡ ≥ 5 WBCs/hpf = positive.

**Table 9.24. Urinary Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| Eosinophiluria‡ | Infectious: Shistosoma hematobium<br>Noninfectious: cholesterol emboli syndrome, HSP, drug induced interstital nephritis, renal allograft rejection |
| Myoglobinuria (2° to rhabdomyolysis) | Infectious: legionnaires' disease, gas gangrene, leptospirosis, Vibrio vulnificus, listeria, S. aureus, group A streptococci, group B streptococci, S. pneumoniae, tularemia, typhoid/enteric fever, echovirus, Coxsackie, influenza, adenovirus, EBV, CMV, HSV, VZV, HIV<br>Noninfectious: crush injury, excessive exercise, MI, seizures, malignant hyperthermia, dermatomyositis, burns, polymyositis, SLE, diabetic ketoacidosis, McArdle's syndrome, drugs (statins, alcohol, cocaine, heroin, PCP, neuroleptics, amphetamines, ethylene glycol) |
| Chyluria | Infectious: W. bancrofti<br>Noninfectious: abdominal or chest lymphatic obstruction |

‡ ≥ 5 WBCs = positive.

**Table 9.25. Pleural Fluid Abnormalities**

| Pleural Fluid | Causes |
|---|---|
| ↓ Glucose | Infectious: TB, bacterial, cryptococcosis, coccidiomycosis, mycoplasma, empyema<br>Noninfectious: carcinoma, rheumatoid lung, lymphoma, esophageal rupture, parapneumonic effusion |
| ↑ Protein | Infectious: TB<br>Noninfectious: carcinoma, lymphoma, rheumatoid lung |
| ↑ Amylase | Infectious: None<br>Noninfectious: pancreatitis/pseudocyst, adenocarcinoma, esophageal rupture |
| Extracellular debris | Infectious: abscesses, anaerobic empyema<br>Noninfectious: rheumatoid lung |
| PMNs | Infectious: bacteria, cryptococcosis, coccidiomycosis, empyema, TB (early)<br>Noninfectious: pancreatitis, subdiaphragmatic abscess (sympathetic effusion), CHF, idiopathic |
| Lymphocytes | Infectious: TB<br>Noninfectious: carcinoma, lymphoma, rheumatoid lung, SLE |

**Table 9.26. CSF Abnormalities**

| Finding | Causes |
|---|---|
| RBCs in CSF | Infectious: listeria, leptospirosis†, TB, amebic meningoencephalitis, HSV, anthrax meningitis<br>Noninfectious: traumatic tap, CNS bleed/tumor |
| Purulent CSF with negative Gram stain | Infectious: Neisseria meningitidis, Streptococcus pneumoniae<br>Noninfectious: none |
| CSF with negative Gram stain and predominantly PMNs/decreased glucose | Infectious: PTBM, listeria, HSV, TB (early), parameningeal infection, emboli secondary to SBE, amebic meningoencephalitis, CNS syphilis (early)<br>Noninfectious: sarcoidosis, adult Still's disease, posterior-fossa syndrome/ intracranial hemorrhage |
| CSF with negative Gram stain and predominantly *lymphocytes/ normal glucose* | Infectious: PTBM, viral meningitis, Lyme disease, HIV, leptospirosis†, RMSF, parameningeal infection, TB, fungi, parasitic meningitis<br>Noninfectious: sarcoidosis, meningeal carcinomatosis |
| *lymphocytes/ decreased glucose* | Infectious: PTBM, CNS TB, CNS fungi, LCM, mumps, enteroviral meningitis, listeria, leptospirosis†, syphilis<br>Noninfectious: neurosarcoidosis, meningeal carcinomatosis |
| ↑ CSF lactic acid levels | Infectious: **< 4 nm/L**, Not acute bacterial meningitis (ABM); **< 4–6 nm/L**, TB, RBCs, HSV, partially treated bacterial meningitis (PTBM), parameningeal infections;<br>**> 6 nm/L**, acute bacterial meningitis (ABM), cerebral malaria (severe)<br>Noninfectious: **< 6 nm/L**, neurosarcoidosis, CNS SLE, cerebral anoxia, hepatic encephalopathy; meningeal carcinomatosis; CNS lymphomas, CNS tumor, intracranial hemorrhage, post-craniotomy with EVD |
| Highly ↑ CSF Protein | Infectious: brain abscess, CNS TB (with subarachnoid block), viral meningitis, viral encephalitis<br>Noninfectious: brain tumor, MS, demyelinating CNS diseases |
| ↑ CSF adenosine deaminase (ADA) levels | Infectious: CNS TB, listeria, ABM, neurobrucellosis<br>Noninfectious: SAH, CNS malignancy |
| CSF plasma cells | Infectious: CNS TB, WNE, VZV, HIV, neuroborreliosis, neurosyphilis<br>Noninfectious: CNS lymphoma, MS, CNS myeloma, ADEM |

† Leptospirosis is the only infectious disease with the CSF bilirubin > serum bilirubin.

**Table 9.26. CSF Abnormalities** (cont'd)

| Finding | Causes |
|---|---|
| CSF eosinophils | Infectious: coccidioidomycosis, neurocysticercosis, gnathostomiasis, angiostrongyliasis, baylisascariasis, shistosomiasis, paragonamiasis, Toxocariasis canis/cati (VLM)<br>Noninfectious: CNS lymphomas, CNS leukemias, V-A/VP shunts, myelography (contrast material), CNS vasculitis, drugs (NSAIDs, TMP–SMX), intrathecal drugs |

**Table 9.27. CSF Diagnostic Criteria for EVD associated ABM**

**EVD Associated ABM**

- Highly elevated CSF lactic acid level (> 6 nmol/L)

  *plus*

- Marked CSF pleocytosis (> 50 WBCs/hpf)

  *plus*

- Positive CSF Gram stain (with *same morphology* as the cultured neuropathogen)

  *plus*

- Positive CSF culture with (*same morphology* as the Gram stain of the neuropathogen)

**EVD Associated Pseudomeningitis**

- < 4 CSF Diagnostic Criteria for EVD Associated ABM

  Noninfections: CNS malignancy, ICH, SAH, post-craniotomy, brain trauma

LA = CSF lactic acid
ABM = acute bacterial meningitis
EVD = external-ventricular drain

# Chapter 10

# Antibiotic Pearls & Pitfalls

**Burke A. Cunha, MD**

## PENICILLIN

- *Penicillin is expensive* because it is made by a single manufacturer.
- There are very few uses for parenteral penicillin therapy today.
- PRSP has been associated with TMP–SMX and macrolides, *not penicillin.*

## AMPICILLIN

- Unless treating serious systemic infections due to E. faecalis (VSE), *avoid using ampicillin. Ampicillin use results in increased E. coli resistance.*
- Remember ampicillin is the preferred drug to treat serious systemic infections caused by VSE but is *ineffective against nearly all E. faecium (VRE).*
- Because susceptibility is in part "concentration dependent," *do not assume that susceptibilities of ampicillin or amoxicillin are the same.* On a same-dose basis, amoxicillin achieves twice the concentrations of ampicillin in body fluids (e.g., middle ear fluid, sinus fluid, bronchial fluid, urine).
- Remember that *unlike ampicillin, amoxicillin is infrequently associated with oral thrush or irritative diarrhea.*
- *Amoxicillin 1 gm (PO) q8h* can be used in ampicillin IV-to-PO switch programs since this dose *provides levels comparable to parenteral (IM) ampicillin.*

## AMOXICILLIN/CLAVULANIC ACID

- Clavulanic acid is a beta-lactamase inhibitor which, when added to amoxicillin, restores its activity against beta-lactamase—producing strains of H. influenzae.
- The *newer preparations of amoxicillin/clavulanic acid result in less gastrointestinal symptoms and diarrhea* compared to older preparations with more clavulanate.
- *Ineffective against PRSP due to alterations in PBPs which are not β-lactamase mediated.*

## ORAL ANTI-STAPHYLOCOCCAL PENICILLINS

- *Do not rely on oral anti-staphylococcal penicillins* such as dicloxacillin for methicillin-sensitive S. aureus (MSSA) infections since they *are erratically/poorly absorbed and not consistently effective*. When treating MSSA infections orally, a first generation cephalosporin (e.g., cephalexin) is preferable.
- *Dicloxacillin is poorly tolerated due to its metallic taste and belching.*

## ORAL ANTI-PSEUDOMONAL PENICILLINS

- *Avoid using indanyl carbenicillin for P. aeruginosa UTI's due to the rapid development of resistance with P. aeruginosa*. Use other oral anti-P. aeruginosa agents for P. aeruginosa lower UTI's, e.g., doxycycline, levofloxacin, or fosfomycin.

## PARENTERAL FIRST-GENERATION CEPHALOSPORINS

- *Cefazolin has limited activity against H. influenzae.*
- Cefazolin remains *preferred therapy for skin infections due to group A streptococci or MSSA.*
- For treatment of biliary tract infections, cefazolin is active against E. coli and Klebsiella pneumoniae but is *not active against E. faecalis* (VSE).
- *Cefazolin remains useful prophylaxis for cardiothoracic procedures in hospitals with low prevalence of MRSA.*

## ORAL FIRST-GENERATION CEPHALOSPORINS

- *Cephalexin suboptimal for respiratory tract infections* i.e., H. influenzae a likely pathogen (otitis media, sinusitis, AECB, community-acquired pneumonia) *since 1st GCs have limited H. influenzae activity.*
- For IV-to-PO switch programs and *cephalexin 1gm (PO) q6h approximates the serum concentrations of parenteral (IM) cefazolin.*
- Oral 3rd GCs do not have the same degree of anti-S. aureus MSSA activity as cephalexin.

## PARENTERAL SECOND-GENERATION CEPHALOSPORINS

- Cefoxitin and cefotetan are useful for intra-abdominal infections.
- *Cefuroxime* offers no advantage for bacterial URIs over doxycycline, respiratory quinolones, or 3rd GCs and *does not prevent CNS "seeding" by S. pneumoniae or H. influenzae bacteremia secondary to CAP.*

## ORAL SECOND-GENERATION CEPHALOSPORINS

- *Oral second generation cephalosporins* include cefaclor, cefprozil, and cefuroxime are *used primarily to treat URIs.*
- *Cefaclor has limited ability to penetrate into respiratory secretions* limiting its efficacy in URIs.
- Among the oral second generation cephalosporins, *cefprozil has the greatest degree of penetration into respiratory secretions.*

## PARENTERAL THIRD-GENERATION CEPHALOSPORINS

- *Except for cefoperazone,* 1st, 2nd, 3rd *generation cephalosporins have no anti-E. faecalis* (VSE) *activity.*
- *Except for ceftriaxone,* third generation cephalosporins predispose to C. difficile diarrhea. *Ceftriaxone is associated with non-C. difficile diarrhea* related to changes in colonic flora.
- Be aware that *ceftriaxone is associated with pseudo-biliary lithiasis.* Patients developing right upper quadrant pain on ceftriaxone should be suspected as having drug-induced pseudo-biliary lithiasis.
- *For CNS infections give third generation cephalosporins in "meningeal doses."*
- *The only third-generation cephalosporin associated with resistance is ceftazidime e.g., P. aeruginosa.*
- *Ceftazidime predisposes to MDR P. aeruginosa, and increases MRSA prevalence.*
- *Ceftazidime associated with ESBL K. pneumoniae, E. coli, or Enterobacter agglomerans.*
- *Ceftazidime little anti-MSSA activity.*
- 3rd GCs *without* anti-B. fragilis activity are *ceftazidime and ceftriaxone.*
- 3rd GCs *without* significant anti-P. aeruginosa activity are *cefotaxime, ceftizoxime, and ceftriaxone.*

## ORAL THIRD-GENERATION CEPHALOSPORINS

- Cefdinir, cefditoren, cefixime, cefpodoxime and ceftibuten are used for their aerobic anti-GNB activity.
- *The only 3rd GC with good anti-MSSA activity is cefpodoxime.*

## PARENTERAL FOURTH-GENERATION CEPHALOSPORIN (CEFEPIME)

- Cefepime (4th GC) is *an anti-Pseudomonal cephalosporin* that is often active against ceftazidime resistant P. aeruginosa strains.
- For *P. aeruginosa* and MDRO GNBs use high dose cefepime, i.e., 2 gm (IV) q8h.

## PARENTERAL ANTI-MRSA CEPHALOSPORIN (CEFTAROLINE)

- Ceftaroline is the *only cephalosporin active in vivo against both MSSA and MRSA.*
- Ceftaroline is useful for cSSIs and MSSA/MRSA bacteremias

## MONOBACTAMS (AZTHREONAM)

- *Aztreonam has no gram-positive activity.*
- Although structurally similar to the beta-lactams, *aztreonam is safe in penicillin-allergic patients.*

## CARBAPENEMS (IMIPENEM, MEROPENEM, ERTAPENEM, DORIPENEM)

- *Avoid imipenem in patients with seizures/CNS disorders* since imipenem may cause seizures. Also, *renal insufficiency increases imipenem's seizure potential.*
- Meropenem doesn't cause seizures in those with or without seizure disorders or with normal or decreased renal function.
- *All carbapenems have anti-pseudomonal activity except for ertapenem.*
- *Ertapenem has no anti-enterococcal activity*, important in biliary/UTIs.
- Avoid IV bolus injections/rapid infusions of doripenem, ertapenem or imipenem. *Only meropenem may be administered as an IV bolus,* important in septic shock.

## BETA-LACTAMASE INHIBITOR COMBINATIONS

- *Some strains of MDR Acinetobacter baumannii are susceptible only to sulbactam/ampicillin.*
- *Tazobactam does not enhance the anti-pseudomonal activity of piperacillin.*
- Ceftazidime/avibactam and ceftolozane/tazobactam are effective for MDR GNB UTIs and urosepsis. Active against KPCs, but not metallo-beta-lactamases.
- Ceftazidime/avibactam and ceftolozone/tazobactam have some B. fragilis activity, but for cIAIs, should be used together with metronidazole.

## TETRACYCLINES (DOXYCYCLINE, MINOCYCLINE)

- *While MRSA may be susceptible to doxycycline in vitro, in vivo it frequently fails or the clinical response is delayed/incomplete. Minocycline IV/PO for MSSA/MRSA is more effective than doxycycline.*
- *Doxycycline has good CSF penetration and is often used for oral therapy of neuroborreliosis.*
- *At urinary concentrations, doxcycline is effective against P. aeruginosa CAB/lower UTIs, i.e.,* high urine levels > 300 mcg/mL *However, in vitro testing will report P. aeruginosa resistant to doxycycline.*
- For nearly all non-viral zoonotic infections, *doxycycline is effective except for babesiosis.*
- *Oral minocycline is useful to treat serious systemic infections due to MSSA/MRSA i.e., ABE, osteomyelitis, meningitis, etc.*

## CHLORAMPHENICOL

- Chloramphenicol is *one of few drugs that can be given orally to treat acute bacterial meningitis* due to susceptible organisms.
- *Chloramphenical is the only antibiotic that when given orally results in higher serum concentrations than when given at the same dose intravenously.*
- *Avoid chloramphenical for the treatment of hepatobiliary infections and UTIs since chloramphenicol is excreted into the bile as an inactivate metabolite, and urinary levels are low.*
- Remember, *aplastic anemia is a rare idiosyncratic side effect associated with oral/ topical therapy but not IV therapy.*

- Chloramphenicol-induced aplastic anemia is an idiosyncratic reaction and *serial CBCs are unhelpful in predicting/avoiding aplastic anemia.*
- Serial *CBCs may be obtained to monitor dose-related side effects (anemia)* not idiosyncratic side effects (aplastic anemia).
- *Prolonged chloramphenicol therapy may cause sequential, dose-related suppression of bone marrow elements. Suppressed blood elements return in reverse sequence when chloramphenicol is discontinued.*
- *Vacualization on bone marrow biopsy* specimens in patients receiving chloramphenicol *is a manifestation of chloramphenicol effect, not aplastic anemia.*
- *Chloramphenicol is effective for E. faecium (VRE) systemic infections.*

## CLINDAMYCIN

- *Clindamycin misses approximately 15% of coagulase-negative S. epidermidis (CoNS),* the most common pathogen in foreign body/implant-related infections.
- *Clindamycin is one of the few antibiotics able to penetrate/dissolve staphylococcal biofilms.* Clindamycin may be useful adjunctively in treating foreign body associated infections when the prosthetic device cannot be removed.
- The *incidence of C. difficile diarrhea is greater with PO > IV clindamycin.*
- Clindamycin is not active against group D enterococci (VSE/VRE).
- With CA-MRSA, *inducible clindamycin resistance (MLS(B)) should be suspected if erythromycin is resistant and clindamycin is susceptible.* The "D test" will confirm clindamycin resistance.
- Clindamycin anti-toxin properties may be useful in severe GAS infections, e.g., necrotizing fasciitis.

## AMINOGLYCOSIDES (GENTAMICIN, TOBRAMYCIN, AMIKACIN)

- Among aminoglycosides, *gentamicin has the most anti-gram-positive coccal activity.*
- *Amikacin has the highest degree of P. aeruginosa activity.*
- Gentamicin and tobramycin have 6 loci that may be inactivated by acetylating, acetylating and phosphorylating enzymes. Amikacin has only 1 locus that may be attacked by these enzymes, making P. aeruginosa resistance less likely.

- *Avoid aminoglycoside monotherapy in the treatment of nosocomial pneumonia since aminoglycoside activity is diminished in the presence of tissue hypoxia, WBC debris and local acidosis, which are prominent in nosocomial pneumonia.*
- *Avoid administering aminoglycosides via nebulizer since aerosolized aminoglycosides may predispose to resistance.*
- *Avoid administering aminoglycosides in split-daily doses.* A single daily dose is optimal since aminoglycosides obey "concentration-dependent" killing kinetics.
- When aminoglycosides are given to *patients with renal insufficiency, begin with the usual initial dose, then decrease the maintenance dose in proportion to the degree of renal dysfunction* based on the creatinine clearance.
- *If aminoglycosides are being used for synergy, use half the therapeutic dose* (synergy dose).
- *Aminoglycosides given on a once-daily basis optimize aminoglycoside antibacterial killing while minimizing nephrotoxic potential and eliminate the need for aminoglycoside levels.*
- *Aminoglycoside ototoxicity may occur with extremely high/prolonged peak levels.* Episodic elevated peak levels are not associated with ototoxicity.
- When aminoglycosides are given on a once-daily basis, renal tubular cells have sufficient time between dosing intervals to decrease intracellular levels and thus avoid nephrotoxicity.
- *Do not assess aminoglycoside nephrotoxicity based on serum creatinines.* Aminoglycoside nephrotoxicity is best *assessed by indicators of renal tubular damage such as urinary renal cast counts.*
- *Limiting aminoglycoside therapy to 2 weeks with split-daily dosing minimizes the risk for aminoglycoside nephrotoxicity.*
- *Aminoglycosides are suboptimal for P. aeruginosa.* Other antibiotics (e.g., meropenem, doripenem, cefepime) are preferred.
- *Aminoglycosides appear to be active against streptococci by in-vitro* susceptibility testing, but *aminoglycosides have no inherent activity against streptococci,* i.e., groups A, B, C, G, D.
- Aminoglycosides (e.g., gentamicin) are *only active against group D enterococci (E faecalis, VSE) when combined with penicillin or vancomycin.*
- *Avoid, if possible, using aminoglycosides for peritoneal lavage* since the peritoneum provides a very large cross-sectional area for drug absorption, *increasing the risk for neuromuscular blockade/respiratory arrest.*
- For *CNS infections, aminoglycosides must be administered intrathecally* (I.T.) since they do not cross the blood brain barrier in sufficient concentrations to be therapeutic.

## TMP–SMX

- Remember, *TMP–SMX has the same spectrum as ceftriaxone* (i.e., no P. aeruginosa coverage).
- *Avoid using TMP–SMX to treat serious systemic K. pneumoniae infections.* K. pneumoniae isolates that are sensitive to TMP–SMX *in-vitro* are often ineffective *in-vivo*.
- *In patients with hypersensitivity reactions to TMP–SMX, it is always the sulfa component, not the TMP component, which is responsible.* If continued treatment is desired with TMP–SMX, therapy may be completed with the TMP component alone.
- *Although TMP–SMX is inactive against most streptococci, it is an excellent antibiotic against MSSA.*
- *TMP–SMX is active against CA-MRSA* but is suboptimal *against HA-MRSA and CO-MRSA.*
- For the *treatment of hydradenitis suppurativa due to MSSA, TMP–SMX is preferred* antibiotic because of its ability to penetrate deep into infected sebaceous glands.
- For aerobic GNB bacteremias (other than P. aeruginosa), use TMP–SMX 10 mg/kg/day (IV/PO) given in 4 equally divided doses q6h.
- *For CNS penetration and the treatment of unusual organisms (e.g., PCP), use TMP–SMX at dose of 20 mg/kg/day (IV/PO) given in 4 equally divided doses q6h.*
- *Avoid TMP–SMX in the treatment of respiratory tract infections since it is associated with S. pneumoniae resistance.*

## QUINOLONES (CIPROFLOXACIN, OFLOXACIN, LEVOFLOXACIN, MOXIFLOXACIN)

- *Levofloxacin at a dose of 750 mg IV/PO is preferred to ciprofloxacin for treatment of serious systemic P. aeruginosa infections.*
- *With the exception of ciprofloxacin, quinolones do not lower the seizure threshold/cause seizures.*
- *Moxifloxacin is the only quinolone with a hepatobiliary mode of excretion; dose does not need to be modified and renal insufficiency but concentrations in the urine for lower UTIs may be subaptimal.*
- *For meningococcal prophylaxis, quinolones are equally effective* (quinolones penetrate well into respiratory secretions/have a high degree of anti-meningococcal activity).

- The "*respiratory quinolones*", e.g., moxifloxacin, levofloxacin have a high degree of bioavailability which makes them *ideal to treat systemic infections PO or as part of IV to PO switch therapy*. Respiratory quinolones have anti-TB activity (an option in treating MDR TB).
- *Ciprofloxacin has less activity against S. pneumoniae and S. aureus than moxifloxacin or levofloxacin*.
- Quinolones have some degree of anti-*E. faecalis* (VSE) but have no *E. faecium* (VRE) activity. *Among the quinolones, moxifloxacin has the highest degree of anti-VSE activity.*

## NITROFURANTOIN

- *Nitrofurantoin is an ideal oral agent to treat cystitis.*
- *If the CrCL < 30 ml/min, nitrofurantoin may not be effective for lower UTIs/CAB.*
- If re-emptive treatment of CAB is desired in immunocompromised hosts, e.g., diabetics, SLE, myeloma, CLL, steroids, neutropenia, *nitrofurantoin is an ideal oral agent and is active against the usual CAB uropathogens, i.e., coliforms and group D enterococci (VSE/VRE).*
- Nitrofurantoin is active *against all aerobic GNB uropathogens except P. aeruginosa, Serratia marcesens, and Proteus sp.*

## VANCOMYCIN

- If vancomycin is combined with a nephrotoxic drug and nephrotoxicity occurs, it *should be ascribed to the nephrotoxic drug* and not vancomycin.
- Vancomycin is a "*concentration-dependent*" drug (with MSSA/MRSA with MICs > 1 mcg/ml), but a "*time dependent*" drug (with MSSA/MRSA MICs < 1 mcg/ml).
- Other drugs preferable to vancomycin to treat cSSIs and bacteremias/ABE due to MSSA.
- *No need for vancomycin levels for usual vancomycin dosing.* However, vancomycin levels may be useful in patients with unusually high volume of distribution ($V_d$) (e.g., edema/ascites, trauma, burns).
- Vancomycin "tolerance" is *common among staphylococci and enterococci*.
- Vancomycin is *alone inadequate for* E faecalis (VSE) bacteremia/SBE. Add gentamicin for optimal VSE activity.
- Vancomycin *may cause cell wall thickening* ("permeability-mediated" resistance) manifested by ↑ MICs.
- Because of its large molecular size, *vancomycin does not penetrate well into* synovial fluid.
- *Vancomycin IV predisposes to VRE*, but PO vancomycin does *not*.

## OXAZOLIDINONES (LINEZOLID, TEDIZOLID)

- Linezolid is highly active against the major gram-positive pathogens, including MSSA, MRSA, VSE, and VRE.
- Linezolid is *equally efficacious when administered PO or IV.*
- Unlike vancomycin, *linezolid does not increase E. faecium* (VRE) prevalence.
- Because linezolid is eliminated by hepatic mechanisms, no dosing adjustment is necessary in renal insufficiency.
- Tedizolid, like linezolid, may be given IV/PO.
- Once daily dosing IV/PO effective with tedizolid ($t_{½}$ = 11 hrs).
- Linezolid is *one of the few PO antibiotics that can be used to treat CNS infections.*

## QUINUPRISTIN/DALFOPRISTIN

- Quinupristin/dalfopristin is active against E. faecium (VRE) but *not E. faecalis (VSE).*
- Quinupristin/dalfopristin is highly effective against MSSA and MRSA.

## LIPOPEPTIDE (DAPTOMYCIN)

- Daptomycin is more *active against MSSA/MRSA than* VSE/VRE (mean MSSA/MRSA MICs = 0.5 mcg/ml vs. mean VSE/VRE MICs = 1.0 mcg/ml). *If daptomycin is used to treat VSE/VRE, a higher dose is recommend (dose for MSSA/MRSA bacteremia: 6 mg/kg/day dose for VSE/VRE bacteremia: 12 mg/kg/day).*
- Daptomycin is *inactivated by calcium in alveolar surfactant fluid* and should *not* be used for pneumonias, but useful for septic pulmonary emboli or lung abscesses.
- Following vancomycin therapeutic failures with MSSA/MRSA bacteremias/ABE, *daptomycin resistance may occur during therapy.*
- *An initial dose of gentamicin may increase intracellular entry/effectiveness of daptomycin* when treating MSSA/MRSA infections.

## TIGECYCLINE

- Tigecycline may be given safely to patients with penicillin or sulfa drug allergy but *avoid in patients with tetracycline allergy*.
- Tigecycline (hepatobiliary elimination) does *not need to be adjusted in renal insufficiency*.
- With A. baumannii only, Etesting shows falsely high MICs with tigecycline.
- Tigecycline is highly active against *MDR K. pneumoniae* and may be the *only antibiotic effective against such strains*.
- Tigecycline is one of only two antibiotics effective against the nearly pan-resistant strains of NDM-1.

## MACROLIDES (ERYTHROMYCIN, AZITHROMYCIN, CLARITHROMYCIN)

- *Macrolides have been largely responsible for PRSP and MDRSP*. Use instead doxycycline or a "respiratory quinolone."
- IV erythromycin lactobionate is the macrolide *most* likely to be associated with QTc prolongation. Macrolides with *lower serum levels* (e.g., azithromycin) are not associated with QTc prolongation.
- Macrolides may cause an "irritative" diarrhea, but *not* C. difficile diarrhea.
- Erythromycin estolate may cause cholestatic jaundice in adults, but not in children.
- Due to widespread group A streptococci and MSSA resistance to macrolides, *avoid* macrolides for the treatment of skin/soft tissue infections.

## METRONIDAZOLE

- Metronidazole (IV) is *preferred therapy* for *C. difficile colitis*.
- Metronidazole (PO) *frequently fails and is inferior to PO vancomycin* for *C. difficile diarrhea*.
- A underecognized/untoward effect of metronidazole (PO) use for *C. difficile diarrhea* is *increased VRE* prevalence.
- Metronidazole has a long serum half life ($t_{1/2}$) of approximately 7 hr which permits *once daily dosing*, i.e., 1 g (IV) q24h. Except for *C. difficile colitis*, there is little rationale for dosing metronidazole 500 mg (IV) on a q6 or q8h basis.

- Metronidazole is *one of the few hepatically eliminated antibiotics that requires a dosing adjustment in severe renal insufficiency* (CrCl < 10 ml/min.).
- *Don't combine metronidazole and moxifloxacin* for intraabdominal infections (no rationale for double B. fragilis coverage).

## LIPOGLYCOPEPTIDES (TELEVANCIN, ORITAVANCIN, DALBAVANCIN)

- Lipoglycopeptides are useful for cSSIs due to MSSA/MRSA.
- Lipoglycopeptides with long $t_{1/2}$ permits infrequent dosing, e.g., telavancin ($t_{1/2}$ = 8 hrs) q 24 hrs dosing; oritavancin ($t_{1/2}$ = 245 hrs) single dose; dalbavancin ($t_{1/2}$ = 346 hrs) q weekly dosing.
- Telavancin is not removed by HD (protein binding = 90%), but *like some other antibiotics, may have decreased efficacy with CrCl < 50 ml/min.*
- *Falsely elevated INR, PT, PTT may occur with telavancin.*

## FOSFOMYCIN

- Fosfomycin is highly active against *most* MDR GNS uropathogens (including VSE/VRE) and may be used *orally* to treat lower UTIs/CAB due to susceptible organisms.
- *Fosfomycin is one of the few oral antibiotics effective against most MDR GNB uropathogens.* Misses some strains of MDR *Enterobacter sp., Klebsiella pneumoniae, Acinetobacter sp., and P. aeruginosa.*
- *Longer fosfomycin treatment courses may be needed to eradicate some MDR GNB uropathogens.*
- *Achieves high urinary concentrations which minimizes the potential for GNB resistance.*
- *Synergistic with quinolones against MDR GNBs.*
- Fosfomycin penetrates the inflamed and non-inflamed prostate in therapeutic concentrations.
- Fosfomycin is one of the few oral antibiotics useful to treat acute (inflamed prostate) prostatitis and chronic (non-inflamed) prostatitis due to MDR GNB.
- Dose of fosfomycin for chronic prostatitis due to MDR GNB may need to be higher than usual, e.g., (PO) q72h.
- Duration of fosfomycin therapy in chronic prostatitis (due to MDR GNB) may need to be prolonged (weeks – months).
- As with other antibiotics used for the treatment of chronic prostatitis, fosfomycin therapy (high dose/prolonged therapy) may fail in the setting of prostate cancer, radioactive prostate seeds, or prostatic calcifications.

- If prostatic calcifications are present, they should if possible be removed (TURP). If prostatic calcifications cannot be resected, fosfomycin (high dose/prolonged) may be effective with doxycycline is added to the regimen.
- Fosfomycin urinary concentrations are > 1200 mcg/ml after a 3 gm (PO) dose. Urine levels > 200 mcg/ml for > 48 hours.
- Fosfomycin is less active than GNB against VSE/VRE (MICs = 48 – 64 mcg/ml).

## COLISTIN AND POLYMYXIN B

- *Colistin and Polymyxin B have same spectrum of activity, but differ in activity, e.g., polymyxin B has greater activity against P. aeruginosa than colistin.*
- Colistin and Polymyxin B and colistin are active against most aerobic GNBs but no activity *against Proteus, Providencia, Morganella, Serratia, or B. cepacia.*
- *Colistin is one of the very few antibiotics effective against the nearly pan-resistant NDM-1 strains.*
- *Colistin an antibiotic for GNBs that may be given at each HD (q48h).* HD dose: 2 mg/kg (IV) q48h (no post-HD dose needed).

## NITAZOXANIDE

- Nitazoxanide is active against anaerobic bacteria, e.g., C. difficile, H. pylori and B. fragilis.
- Oral nitazoxanide is more effective against C. difficile than metronidazole for either C. difficile diarrhea or C. difficile colitis.
- Nitazoxanide is effective against B, fragilis strains with decreased susceptibility/ resistance to metronidazole.
- Nitazoxanide has no activity against aerobic Gram positive and GNB.
- Nitazoxanide has some activity against viral pathogens, e.g., norovirus, rotavirus, adenovirus.

# Chapter 11

# Antimicrobial Drug Summaries

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**This section contains prescribing information pertinent to the clinical use of antimicrobial agents in adults, as compiled from a variety of sources.** ***Antimicrobial agents for pediatric infectious diseases are described in Chapter 7***. The information provided is not exhaustive, and the reader is referred to other drug information references and the manufacturer's product literature for further information. Clinical use of the information provided and any consequences that may arise from its use are the responsibilities of the prescribing physician. The authors, editors, and publisher do not warrant or guarantee the information contained in this section, and do not assume and expressly disclaim any liability for errors or omissions or any consequences that may occur from such. **The use of any drug should be preceded by careful review of the package insert, which provides indications and dosing approved by the U.S. Food and Drug Administration. This information can be obtained on the website provided at the end of the reference list for each drug summary.**

All orally administered antibiotics should be taken with food unless otherwise specified (included after usual oral dose)

Drugs are listed alphabetically by generic name; trade names follow in parentheses. To search by trade name, consult the index. Each drug summary contains the following information:

**Usual dose. Represents the usual dose to treat most susceptible infections in adult patients with normal hepatic and renal function.** Dosing for special situations is listed under the comments section; additional information can be found in Chapters 2, 4, 5 and the manufacturer's product literature. Loading doses for doxycycline, fluconazole, itraconazole, voriconazole, caspofungin, and other antimicrobials are described in either the usual dose or comments section. **Meningeal doses of antimicrobials used for CNS infection are described at the end of the comments section.**

**Peak serum levels.** Refers to the peak serum concentrations (mcg/ml) after the usual dose is administered. Peak serum level is useful in calculating the "kill ratios," the ratio of peak serum level to minimum inhibitory concentration (MIC) of the organism. **The higher the "kill ratio," the more effective the "dose dependent" antimicrobial is likely to be against a particular organism.**

**Bioavailability.** Refers to the percentage of the dose reaching the systemic circulation from the site of administration (PO or IM). **For PO antibiotics, bioavailability refers to the percentage of dose**

**adsorbed from the GI tract**. For IV antibiotics, "not applicable" appears next to bioavailability, since the entire dose reaches the systemic circulation. Antibiotics with high bioavailability (> 90%) are ideal for IV to PO switch therapy.

**Excreted unchanged.** Refers to the percentage of drug excreted unchanged, and **provides an indirect measure of drug concentration in the urine/feces. Antibiotics excreted unchanged in the urine in low concentration are unlikely to be useful for urinary tract infections.**

**Serum half-life (normal/ESRD).** The serum half-life ($\mathbf{t_{½}}$) is the time (in hours) in which serum concentration falls by 50%. **Serum half-life is useful in determining dosing interval**. If the half-life of drugs eliminated by the kidneys is prolonged in end-stage renal disease (ESRD), then the total daily dose is reduced in proportion to the degree of renal dysfunction. If the half-life in ESRD is similar to the normal half-life, then the total daily dose does not change.

**Plasma protein binding.** Expressed as the **percentage of drug reversibly bound to serum albumin. It is the unbound (free) portion of a drug that equilibrates with tissues and imparts antimicrobial activity. Plasma protein binding is not typically a factor in antimicrobial effectiveness unless binding exceeds 95%**. Decreases in serum albumin (nephrotic syndrome, liver disease) or competition for protein binding from other drugs or endogenously produced substances (uremia, hyperbilirubinemia) will increase the percentage of free drug available for antimicrobial activity, and may require a decrease in dosage. Increases in serum binding proteins (trauma, surgery, critical illness) will decrease the percentage of free drug available for antimicrobial activity, and may require an increase in dosage.

**Volume of distribution ($\mathbf{V_d}$).** Represents the apparent volume into which the drug is distributed, and is calculated as the amount of drug in the body divided by the serum concentration (in liters/kilogram). $V_d$ is related to total body water distribution ($V_d$ $H_2O$ = 0.7 L/kg). Hydrophilic (water soluble) drugs are restricted to extracellular fluid and have a $V_d \leq 0.7$ L/kg. In contrast, **hydrophobic (highly lipid soluble) drugs penetrate most fluids/tissues of the body and have a large $\mathbf{V_d}$**. Drugs that are concentrated in certain tissues (e.g., liver) can have a $V_d$ greatly exceeding total body water. $V_d$ is affected by organ profusion, membrane diffusion/permeability, lipid solubility, protein binding, and state of equilibrium between body compartments. **For hydrophilic drugs, increases in $\mathbf{V_d}$ may occur with burns, heart failure, dialysis, sepsis, cirrhosis, or mechanical ventilation**; decreases in $V_d$ may occur with trauma, hemorrhage, pancreatitis (early), or GI fluid losses. Increases in $V_d$ may require an increase in total daily drug dose for antimicrobial effectiveness; decreases in $V_d$ may require a decrease in drug dose. **In addition to drug distribution, $\mathbf{V_d}$ reflects binding avidity to cholesterol membranes and concentration within organ tissues (e.g., liver).**

**Mode of elimination.** Refers to the primary route of inactivation/excretion of the antibiotic, which **impacts dosing adjustments in renal/hepatic failure.**

**Dosage adjustments.** Each grid provides dosing adjustments based on renal and hepatic function. **In renal insufficiency** (*for **renally eliminated antibiotics***), **the *initial dose* is the *same* as with normal renal function**; but the ***maintenance dose is decreased ~ ↓ CrCl*** (see antibiotic drug summaries for specific dosing recommendations). **Antimicrobial dosing for hemodialysis (HD)/peritoneal dialysis (PD) patients (between HD/PD) is the same as a CrCl < 10 mL/min. Some antimicrobial agents require a supplemental dose immediately after hemodialysis (post–HD)/peritoneal dialysis (post–PD)**. Following the post–HD or post–PD supplemental dose, antimicrobial dosing should resume as for a CrCl < 10 mL/min. "No change" indicates no change from the usual dose. "Avoid" indicates the drug should be avoided in the setting described. "None" indicates no supplemental dose is required. "No information" indicates there are insufficient data from which to make a dosing recommendation.

**Dosing recommendations are based on pharmacokinetic data, published studies, and experience**. CVVH dosing recommendations represent general guidelines, since antibiotic removal is dependent on area/type of filter, ultrafiltration rates, and sieving coefficients; replacement dosing should be individualized and guided by serum levels, if possible. **Creatinine clearance (CrCl) is used to gauge the degree of renal insufficiency, and can be estimated by the following calculation: CrCl (mL/min) = [(140 – age) × weight (kg)] / [72 × serum creatinine (mg/dL)]. The calculated value is multiplied by 0.85 for females**. It is important to recognize that due to age-dependent decline in renal function, elderly patients with "normal" serum creatinines may have low CrCls requiring dosage adjustments. (For example, a 70-year-old, 50-kg female with a serum creatinine of 1.2 mg/dL has an estimated CrCl of 34 mL/min.)

Slow extended daily dialysis (SLEDD) is now being used in some critical care patients. It is less likely to remove molecules > 1000 Daltons as compared to CVVH. Assuming a dialysate flow rate of 100 mL/min and a blood flow rate of 200 mL/min clearances during dialysis are about 82-98 mL/min using a Fresenius AV600 polysulfone hemodialyzer. However increasing the flow rate to 300 mL/min increases the clearance during dialysis to 170 mL/min. Therefore, doses during SLEDD may be the same as for normal renal function. **Clearances for SLEDD are comparable to CVVH except over a shorter period, so when no information is available, dosage adjustments can be made as for CVVH**. If needed, post-SLEDD doses should be given depending on the antibiotic.

"Antiretroviral Dosage Adjustment" grids indicate recommended dosage adjustments when protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitor (NNRTIs) are combined or used in conjunction with rifampin or rifabutin.

**Drug interactions. Refers to common/important drug-drug interactions**, compiled from various sources. If a specific drug interaction is well-documented (e.g., antibiotic × with lovastatin), than other drugs from the same drug class (e.g., atorvastatin) may also be listed, based on theoretical considerations. Drug interactions may occur as a consequence of altered absorption (e.g., metal ion chelation of tetracycline), altered distribution (e.g., sulfonamide displacement of barbiturates from serum albumin), altered excretion (e.g., probenecid competition with penicillin for active transport in the kidney), altered metabolism (e.g., rifampin–induced hepatic P-450 metabolism of theophylline/warfarin; chloramphenicol inhibition of phenytoin metabolism).

**Adverse side effects.** Common/important side effects are indicated.

**Allergic potential.** Described as low or high. **Refers to the likelihood of a hypersensitivity reaction** to a particular antimicrobial.

**Safety in pregnancy.** Designated by the U.S. Food and Drug Administration's (USFDA) use-in-**pregnancy letter code** (Table 11.3).

**Comments.** Includes other useful information for each antimicrobial agent.

**Cerebrospinal fluid penetration.** Expressed as a **percentage relative to serum concentration**. If an antimicrobial is used for CNS infections, the meningeal dose is indicated directly above CSF penetration. No meningeal dose is given if CSF penetration is inadequate for treatment of meningitis due to susceptible organisms.

**Biliary tract penetration.** Expressed as a percentage relative to peak serum concentrations. Percentages > 100% reflect concentrations within the biliary system. This information is useful for estimating biliary tract concentrations.

**Table 11.1 Selected Substrates, Inhibitors, and Inducers of Cytochrome P450 Isoenzymes**

| | Substrates | Inhibitors | Inducers |
|---|---|---|---|
| CYP1A2 | None | Erythromycin | None |
| CYP2C9 | None | Erythromycin, INH, Metronidazole, Oritavancin | TMX-SMX, RIF |
| CYP3A4 | Isavuconazole | Erythromycin, Isavuconazole | Oritavancin |
| OATI | Oseltamivir, Cidofovir | None | None |
| PGP | Quinolones, Itraconazole | Isavuconazole | RIF |

OAT-1 = organic anion transporter-1; TMP–SMX = trimethoprim sulfamethoxazole; RIF = rifampin; INH = isoniazid.

**Table 11.2 Antibiotics and Cytochrome P450 Isoenzymes**

| Antibiotics that are not involved in CYP450 system | Antibiotics that are involved in CYP450 system either as inducer or inhibitor |
|---|---|
| Tigecycline, daptomycin, clindamycin, linezolid, vancomycin, minocycline, cephalosporins, carbapenems, nitrofurantoin, colistin, penicillins, oxacillin, aztreonam, moxifloxacin, aminoglycosides, tedizolid, telavancin, dalbavancin, ceftolozane/tazobactam, ceftazidime/avibactam | Nafcillin, quinupristin/dalfopristin, macrolides, telithromycin, fluoroquinolones (except moxifloxacin), azoles, rifampin, INH, TMP–SMX, tetracycline, doxycycline, metronidazole, chloramphenicol, oritavancin |

**Table 11.3 USFDA Use-in-Pregnancy Letter Code**

| Category | Interpretation |
|---|---|
| A | **Controlled studies show no risk.** Adequate, well-controlled studies in pregnant women have not shown a risk to the fetus in any trimester of pregnancy. |
| B | **No evidence of risk in humans.** Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility. |
| C | **Risk cannot be ruled out.** Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking. There is a chance of fetal harm if the drug is administered during pregnancy, but potential benefit from use of the drug may outweigh potential risk. |
| D | **Positive evidence of risk.** Studies in humans or investigational or post-marketing data have demonstrated fetal risk. Nevertheless, potential benefit from use of the drug may outweigh potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective. |

**Table 11.3 USFDA Use-in-Pregnancy Letter Code** (Cont'd)

| Category | Interpretation |
|---|---|
| X | **Contraindicated in pregnancy.** Studies in animals or humans or investigational or post-marketing reports have demonstrated positive evidence of fetal abnormalities or risk which clearly outweigh any possible benefit to the patient. |

**Lipid-Associated Formulations of Amphotericin B.** There are 3 licensed lipid-associated formulations of amphotericin B (LFAB) (Table 11.4). Although closely related in some ways, these formulations have distinct properties and must be understood separately. The principal advantage of the LFAB over amphotericin B deoxycholate (AMBD) is greater safety. In general, the rates of both acute infection-related toxicities (fever, chills, etc.) and chronic therapy-associated toxicities (principally nephrotoxicity) are reduced with LFAB. However, the LFAB can produce all of the toxicities of AMBD (and in selected patients, LFAB have been more toxic than AMBD). Overall, (L-Amb) (AmBisome) and ABLC (Abelcet) appear to be safer than ABCD (Amphotec, Amphocil). Whichever formulation is selected for therapy, it is important to specify its name carefully when prescribing. The phrase "lipid amphotericin B" should be avoided due to its imprecision. Patients who are tolerating one formulation may develop all the standard infusion-related toxicities if switched inadvertently to a new formulation. In general (and in contrast to the usual preference for generic names), use of trade names is the clearest way to specify the choice of drug in this category. In this handbook, the phrase "lipid-associated formulation of amphotericin B" suggests use of any of the 3 formulations. The issues surrounding the selection of an LFAB for an individual patient are summarized in Table 11.4 (see comments).

**Table 11.4 Lipid-Associated Formulations of Amphotericin B**

| Generic name (abbreviation) | Trade names | Licensed (IV) dosages in the United States | Comments |
|---|---|---|---|
| Amphotericin B lipid complex (ABLC) | Abelcet | 5 mg/kg/d | Reliable choice; long history of use. |
| Liposomal amphotericin B (L-Amb) | AmBisome | 3 mg/kg/d (empiric therapy)<br>3–5 mg/kg/d (systemic fungal infections)<br>6 mg/kg/d (cryptococcal meningitis in HIV patients) | Reliable choice; best studied (L-Amb); well-supported dosing recommendations by indication; probably the least nephrotoxic; good data to support increasing the dose safely. |
| Amphotericin B colloidal dispersion, amphotericin B cholesteryl sulfate complex (ABCD) | Amphotec, Amphocil | 3–4 mg/kg/d | Infusion-related toxicities have limited its use. |

## Abacavir (Ziagen) ABC

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 300 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 3 mcg/mL*
*Bioavailability: 83%*
*Excreted unchanged (urine): 1.2%*
*Serum half-life (normal/ESRD): 1.5/8 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 0.86 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild hepatic insufficiency | 200 mg (PO) q12h |
| Moderate—severe hepatic insufficiency | Avoid |

**Drug Interactions:** Methadone (↑ methadone clearance with abacavir 600 mg bid); ethanol (↑ abacavir serum levels/half-life and may ↑ toxicity).
**Adverse Effects:** *Abacavir may cause severe hypersensitivity reactions which may be fatal (see comments); usually during the first 4–6 weeks of therapy;* Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Discontinue abacavir as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, never restart abacavir or any other abacavir-containing product. Report cases of hypersensitivity syndrome to Abacavir Hypersensitivity Registry at 1-800-270-0425. Drug fever/rash, abdominal pain/diarrhea, nausea, vomiting, anorexia, bad dreams/ sleep disorders, weakness, headache, ↑ SGOT/ SGPT, hyperglycemia, hypertriglyceridemia, lactic acidosis with hepatic steatosis (rare, but potentially life-threatening toxicity with use of NRTI's).
**Allergic Potential:** High (~5%)
**Safety in Pregnancy:** C
**Comments:** Discontinue abacavir and *do not restart in patients with signs/symptoms of hypersensitivity reaction*, which may include fever, rash, fatigue, nausea, vomiting, diarrhea, abdominal pain, anorexia, respiratory symptoms. Ethanol increases abacavir levels by 41%. When combined with didanosine rapid emergence of cross resistance via mutations to K65R, L74V, Y11F, and M184V occurs leading to failure of drug efficacy. Use with caution in patients with serious risk of coronary disease.
**Cerebrospinal Fluid Penetration:** 27–33%

**REFERENCES:**

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Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy. A randomized trial. JAMA 288:207–15, 2002.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral society — USA panel. JAMA 308:387–402, 2012.
Website: www.pdr.net

## Abacavir + Lamivudine (Epzicom) ABC/3TC

**Drug Class:** HIV NRTI combination.
**Usual Dose:** Epzicom tablet = abacavir 600 mg + lamivudine 300 mg. Usual dose: 1 tablet q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 4.06/2.04 mcg/L*
*Bioavailability: 86/86%*
*Excreted unchanged (urine): 1.2/71%*
*Serum half-life (normal/ESRD): (1.5/8)/(5-7/20) hrs*
*Plasma protein binding: 50/36%*
*Volume of distribution ($V_d$): 0.86/1.3 L/kg*
**Primary Mode of Elimination:** Hepatic/Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Mild hepatic insufficiency | Contraindicated |
| Moderate—severe hepatic insufficiency | Contraindicated |

**Drug Interactions:** Methadone (↑ methadone clearance with abacavir 600 mg bid); ethanol (↑ abacavir serum levels/half-life; may ↑ toxicity); didanosine, zalcitabine (↑ risk of pancreatitis); TMP–SMX (↑ lamivudine levels); zidovudine (↑ zidovudine levels).
**Adverse Effects: Abacavir may cause severe hypersensitivity reactions that may be fatal (see comments), usually during the first 4–6 weeks of therapy;** Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Discontinue Abacavir as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue Abacavir if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, NEVER restart Abacavir or any other abacavir-containing product. Drug fever, rash, abdominal pain, diarrhea, nausea, vomiting, anorexia, anemia, leukopenia, photophobia, depression, insomnia, weakness, headache,

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

cough, nasal complaints, dizziness, peripheral neuropathy, myalgias, ↑ AST/ALT, hyperglycemia, hypertriglyceridemia, pancreatitis, lactic acidosis with hepatic steatosis (rare, but potentially life-threatening toxicity with the NRTI's). Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretrovital therapy.

**Allergic Potential:** High (~5%)/Low

**Safety in Pregnancy:** C

**Comments:** In patients with signs/symptoms of hypersensitivity reactions discontinue and do not restart, which may include fever, rash, fatigue, nausea, vomiting, diarrhea, abdominal pain, anorexia, respiratory symptoms. **Potential cross resistance with didanosine.** When combined with didanosine rapid emergence of cross resistance via mutations to K65R, L74V, Y115F, and M184V occurs leading to failure of drug efficacy. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV and have discontinued epivir. Hepatic function should be monitored closely for at least several months in patients who discontinue epivir.

**Cerebrospinal Fluid Penetration:** 27–33/15%

**REFERENCES:**

Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. http://aidsinfo.nih.gov/ConsentFiles/AdultandAdolescentGL.pdf, 2012.

Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Abacavir + Lamivudine + Zidovudine (Trizivir) ABC/3TC/ZDV

**Drug Class:** HIV NRTI combination.

**Usual Dose:** Trizivir tablet = abacavir 300 mg + lamivudine 150 mg + zidovudine 300 mg. Usual dose = 1 tablet (PO) q12h.

**Pharmacokinetic Parameters:**

*Peak serum level: 3/1.5/1.2 mcg/mL*

*Bioavailability: 86/86/64%*

*Excreted unchanged (urine): 1.2/90/16%*

*Serum half-life (normal/ESRD): [1.5/6/1.1] / 8/20/2.2] hrs*

*Plasma protein binding: 50/36/20%*

*Volume of distribution ($V_d$): 0.86/1.3/1.6 L/kg*

**Primary Mode of Elimination:** Hepatic/Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | Avoid |
| Post–HD or Post–PD | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Moderate—severe hepatic insufficiency | Avoid |

**Drug Interactions:** Amprenavir, atovaquone (↑ zidovudine levels); clarithromycin (↓ zidovudine levels); cidofovir (↑ zidovudine levels, flu-like symptoms); doxorubicin (neutropenia); stavudine (antagonistic to zidovudine; avoid combination); TMP–SMX (↑ lamivudine and zidovudine levels); zalcitabine (↓ lamivudine levels). May exacerbate neutropenia in combination with gangcyclovir.

**Adverse Effects:** *Abacavir may cause severe/fatal rash/hypersensitivity reaction;* Patients who carry the HLA-B*5701 allere are at high risk

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

for experiencing a hypersensitivity reaction to abacavir. Discontinue abacavir as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, never restart abacavir or any other abacavir-containing product. Most common (> 5%): nausea, vomiting, diarrhea, anorexia, insomnia, fever/chills, headache, malaise/fatigue. Others (less common): peripheral neuropathy, myopathy, steatosis, pancreatitis. Lab abnormalities: anemia, leukopenia, mild hyperglycemia, ↑ LFTs, ↑ CPK, ↑ aldolase, hypertriglyceridemia. Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.

**Allergic Potential:** High (~5%)

**Safety in Pregnancy:** C

**Comments:** Avoid in patients with CrCl < 50 mL/min. HBV hepatitis may relapse if lamivudine is discontinued.

**REFERENCES:**

McDowell JA, Lou Y, Symonds WS, et al. Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 44:2061–7, 2000.

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Acyclovir (Zovirax)

**Drug Class:** Antiviral (see comments).

**Usual Dose:**

**HSV-1/2:** Herpes labialis: 400 mg (PO) 5x/day × 5 days. Genital herpes: *Initial therapy.* 200 mg (PO) 5x/day × 10 days. *Recurrent/intermittent therapy* (< 6 episodes/year): 200 mg (PO) 5x/day × 5 days. *Chronic suppressive therapy* (> 6 episodes/year): 400 mg (PO) q12h × 1 year. Mucosal/genital herpes: 5 mg/kg (IV) q8h × 7 days or 400 mg (PO) 5x/day × 7 days. Nosocomial pneumonia 5 mg/kg (IV) q8h × 10 days or 400 mg (PO) 5x/day × 7 days. Meningitis/encephalitis: 10 mg/kg (IV) q8h × 10 days*. PO not recommended. *Severe HSV encephalitis may require 14–21 days.

**VZV:** Chickenpox: 10 mg/kg (IV) q8h × 5 days or 800 mg (PO) q6h × 5 days. VZV pneumonia: 5–10 mg/kg (IV) q8h × 10 days (normal hosts) 10 mg/kg (IV) q8h × 10 days (compromised hosts). Herpes zoster (shingles): *Dermatomal/Disseminated*: 10 mg/kg (IV) q8h × 7–10 days or 800 mg (PO) 5x/day × 7–10 days.

VZV meningitis/encephalitis: 10 mg/kg (IV) q8h × 10 days. PO not recommended.

**Pharmacokinetic Parameters:**

*Peak serum level: 7.7 mcg/mL*
*Bioavailability: 30%*
*Excreted unchanged (urine): 70%*
*Serum half-life (normal/ESRD): 3/5 hrs*
*Plasma protein binding: 30%*
*Volume of distribution ($V_d$): 0.7 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments* for HSV/VZV**

| | |
|---|---|
| CrCl 10–25 mL/min | No change/ 800 mg (IV/PO) q8h |
| CrCl < 10 mL/min | 400 mg (IV/PO) q12h/ 800 mg (IV/PO) q12h |

| | |
|---|---|
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 5 mg/kg(IV) q24h/ 10 mg/kg(IV) q24h 400 mg (PO) q8h/ 800 mg (PO) q8h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Cimetidine, probenecid, theophylline (↑ acyclovir levels); nephrotoxic drugs (↑ nephrotoxicity); zidovudine (lethargy); theophylline (↑ levels).
**Adverse Effects:** Seizures/tremors (dose related), encephalopathy, crystalluria, ATN. HUS (only with HIV) Base dose on ideal body weight in the elderly to minimize adverse effects.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** $Na^+$ content = 4 mEq/g. CSF levels may be increased with probenecid.
***Highly active against HSV and VZV. Some activity against CMV. No activity against EBV, RSV or adenoviruses.***

Meningeal dose = HSV or VZV encephalitis dose.
**Cerebrospinal Fluid Penetration:** 20%

**REFERENCES:**

Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. J Infect Dis 190:1374–81, 2004.
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Website: www.pdr.net

## Adefovir dipivoxil (Hepsera)

**Drug Class:** HBV antiviral.
**Usual Dose:** 10 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 18 ng/mL*
*Bioavailability: 59%*
*Excreted unchanged (urine): 45%*
*Serum half-life (normal/ESRD): 7.5/9 hrs*
*Plasma protein binding: 4%*
*Volume of distribution ($V_d$): 0.4 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl ≥ 50 mL/min | 10 mg (PO) q24h |
| CrCl 20–50 mL/min | 10 mg (PO) q48h |
| CrCl 10–20 mL/min | 10 mg (PO) q72h |
| Hemodialysis | 10 mg (PO) q7days |
| Post–HD or PD dose | 10 mg (PO) |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CVVH/CVVHD/ CVVHDF dose | 10 mg (PO) q72h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** No significant interaction with lamivudine, TMP–SMX, acetaminophen, ibuprofen.
**Adverse Effects:** Asthenia, headache, abdominal pain, nausea, flatulence, diarrhea, dyspepsia.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** May be taken with or without food. Does not inhibit CP450 isoenzymes. Do not discontinue abruptly to avoid exacerbation of HBV hepatitis.
**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**
Buti M, Esteban R. Adefovir dipivoxil. Drugs of Today 39:127–35, 2003.
Cundy KC, Burditch-Crovo P, Walker RE, et al. Clinical pharmacokinetics of adefovir in human HIV-1 infected patients. Antimicrob Agents Chemother 35:2401–2405, 1995.
Lu H, Geng DY, Shen F, et al. Optimization of adefovir dipivoxil therapy in chronic hepatitis B according to baseline predictors and on-treatment HBV DNA: a 5-Year prospective study. Virol J 8:444, 2011.
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Website: www.pdr.net

## Amantadine (Symmetrel)

**Drug Class:** Antiviral (influenza).
**Usual Dose:** 200 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 0.5 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 16/192 hrs*
*Plasma protein binding: 67%*
*Volume of distribution ($V_d$): 6.6 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | 100 mg (PO) q24h |
| CrCl 15–30 mL/min | 100 mg (PO) q48h |
| CrCl < 15 mL/min | 200 mg (PO) q week |
| Post–HD | None |
| Post–PD | None |
| CVVH/CVVHD/ CVVHDF dose | 100 mg (PO) q48h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Alcohol (↑ CNS effects); benztropine, trihexyphenidyl (↑ interacting drug effect: dry mouth, ataxia); CNS stimulants (additive stimulation); digoxin (↑ digoxin levels); trimethoprim (↑ amantadine and trimethoprim levels); scopolamine (↑ scopolamine effect: blurred vision, slurred speech, toxic psychosis).
**Adverse Effects:** Confusion/delusions, insomnia, dysarthria, ataxia, anticholinergic effects (blurry vision, dry mouth, orthostatic hypotension, urinary retention, constipation), livedo reticularis, may ↑ $QT_c$ interval.
**Allergic Potential:** Low
**Safety in Pregnancy:** C

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Comments:** May precipitate heart failure. Avoid co-administration with anticholinergics, MAO inhibitors, or antihistamines. Resistant to amantadine, widespread may improve peripheral airway function/oxygenation in ventilated patients with severe influenza (human, avian, swine). ***Highly active against influenza A. No activity against other viruses*.**

**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges = 15%
Inflamed meninges = 20%

**REFERENCES:**
Cunha BA, Amantadine may be lifesaving in severe influenza A. Clin Infect Dis 43:1372–3, 2006.
Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. Lancet 355:827–5, 2000.
Jackson RJ, Cooper KL, Tappenden P, et al. Oseltamivir, zanamivir and amantadine in the prevention of influenza: A systematic review. J Infect 62:14–25, 2011.
Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: A multicenter study from Japan of the 2002–2003 influenza season. Clin Infect Dis 40:1309–16, 2005.
Keyers LA, Karl M, Nafziger AN, et al. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. Arch Intern Med 160:1485–8, 2000.
Website: www.pdr.net

## Amikacin (Amikin)

**Drug Class:** Aminoglycoside.
**Usual Dose:** 1 gm or 15 mg/kg (IV) q24h (preferred to q12h dosing).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level 65–75 mcg/mL (q24h dosing): 20–30 mcg/mL (q12h dosing)*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 95%*
*Serum half-life (normal/ESRD): 2/50 hrs*
*Plasma protein binding: < 5%*
*Volume of distribution ($V_d$): 0.25 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 500 mg (IV) q24h<br>or 7.5 mg/kg (IV) q24h |
| CrCl 10–50 mL/min | 500 mg (IV) q48h<br>or 7.5 mg/kg (IV) q48h |
| CrCl < 10 mL/min | 250 mg (IV) q48h<br>or 3.75 mg/kg (IV) q48h |
| Post–HD dose | 500 mg (IV)<br>or 7.5 mg/kg (IV) |
| Post–HFHD dose | 500 mg (IV)<br>or 7.5 mg/kg (IV) |
| Post–PD dose | 250 mg (IV)<br>or 3.75 mg/kg (IV) |
| CVVH/CVVHD/<br>CVVHDF dose | 500 mg (IV) q48h<br>or 7.5 mg/kg (IV) |
| Moderate—severe<br>hepatic insufficiency | No change |

**Drug Interactions:** Amphotericin B, cephalothin, cyclosporine, enflurane, methoxyflurane, NSAIDs, polymyxin B, radiographic contrast, vancomycin (↑ nephrotoxicity); cis-platinum (↑ nephrotoxicity, ↑ ototoxicity); loop diuretics (↑ ototoxicity); neuromuscular blocking agents (↑ apnea, prolonged paralysis); non-polarizing muscle relaxants (↑ apnea).
**Adverse Effects:** Neuromuscular blockade with rapid infusion/absorption. Nephrotoxicity only with prolonged/extremely high serum trough levels; may cause reversible non-oliguric

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

renal failure (ATN). Ototoxicity associated with prolonged/extremely high peak serum levels (usually irreversible): Cochlear toxicity (1/3 of ototoxicity) manifests as decreased high frequency hearing, but deafness is unusual. Vestibular toxicity (2/3 of ototoxicity) develops before ototoxicity (typically manifests as tinnitus).

**Allergic Potential:** Low

**Safety in Pregnancy:** D

**Comments: Synergy dose:** 500 mg (IV) q24h or 7.5 mg/kg (IV) q24h. **Single daily dosing virtually eliminates nephrotoxic/ototoxic potential**. Incompatible with solutions containing β-lactams, erythromycin, chloramphenicol, furosemide, sodium bicarbonate. IV infusion should be given slowly over 30 minutes. May be given IM. Intraperitoneal infusion ↑ risk of neuromuscular blockade. Avoid intratracheal/aerosolized intrapulmonary instillation, which may predispose to antibiotic resistance. $V_d$ increases with edema/ascites, trauma, burns, cystic fibrosis; may require ↑ dose. $V_d$ decreases with dehydration, obesity; may require ↓ dose. **Renal cast counts are the best indicator of aminoglycoside nephrotoxicity, not serum creatinine**. Dialysis removes ~ 50% of amikacin from serum. **CAPD dose:** 10–20 mg/L in dialysate (IP) with each exchange.

**Therapeutic Serum Concentrations** (for therapeutic efficacy, *not toxicity*): Peak (q24h/q12h dosing): 65–75/20–30 mcg/mL
Trough (q24h/q12h dosing): 0/4–8 mcg/mL

**Intrathecal (IT) dose:** 10–40 mg (IT) q24h.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 15%
Inflamed meninges = 20%

**Bile Penetration:** 30%

**REFERENCES:**

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Website: www.pdr.net

## Amoxicillin (Amoxil, A-cillin, Polymox, Trimox, Wymox)

**Drug Class:** Aminopenicillin.

**Usual Dose:** 1 gm (PO) q8h.

**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 14 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 60%*
*Serum half-life (normal/ESRD): 1.3/16 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.26 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 500 mg (PO) q8h |
| CrCl 10–50 mL/min | 500 mg (PO) q12h |
| CrCl < 10 mL/min | 500 mg (PO) q24h |
| Post–HD or post–PD | 500 mg |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (PO) q24h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Allopurinol (↑ risk of rash).
**Adverse Effects:** Drug fever/rash, ↑ SGOT/SGPT.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** ↑ risk of rash with EBV infectious mononucleosis. No irritative diarrhea with 1 gm (PO) q8h dose due to nearly complete proximal GI absorption. **2 gm amoxicillin effective against most strains of PRSP**.

**Cerebrospinal Fluid Penetration:**
Non-inflamed/Inflamed meninges = 1%/8%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**

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Website: www.pdr.net

## Amoxicillin/Clavulanic Acid (Augmentin)

**Drug Class:** Aminopenicillin/β-lactamase inhibitor.
**Usual Dose:** 500/125 mg (PO) q8h or 875/125 mg (PO) q12h for severe infections or respiratory tract infections.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 10.0/2.2 mcg/mL*
*Bioavailability: 90/60%*
*Excreted unchanged (urine): 80/40%*
*Serum half-life (normal/ESRD): [1.3/16]/[½] hrs*
*Plasma protein binding: 18/25%*
*Volume of distribution ($V_d$): 0.26/0.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 500 mg q8h)

| | |
|---|---|
| CrCl 10–50 mL/min | 500/125 mg (PO) q12h |
| CrCl < 10 mL/min | 250/125 mg (PO) q24h |
| Post–HD dose | 250/125 mg (PO) |
| Post–PD dose | 250/125 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 500/125 mg (PO) q24h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Allopurinol (↑ risk of rash).
**Adverse Effects:** Drug fever/rash, diarrhea, ↑ SGOT/SGPT. Rash potential same as ampicillin.
**Resistance Potential:** Low
Allergic Potential: High
**Safety in Pregnancy:** B
**Comments:** ↑ risk of rash with EBV infectious mononucleosis. **875/125 mg formulation should not be used in patients with CrCl < 30 mL/min.**

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 1%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**

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Website: www.pdr.net

## Amoxicillin/Clavulanic Acid ES-600 (Augmentin ES-600)

**Drug Class:** Aminopenicillin/β-lactamase inhibitor.
**Usual Dose:** 90 mg/kg/day oral suspension in 2 divided doses (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 15.7/1.7 mcg/mL*
*Bioavailability: 90/60%*
*Excreted unchanged (urine): 70/40%*
*Serum half-life (normal/ESRD): [1.4/16]/[1.1/2] hrs*
*Plasma protein binding: 18%/25%*
*Volume of distribution ($V_d$): 0.26/0.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | Avoid |
| Moderate—severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Allopurinol (↑ risk of rash).
**Adverse Effects:** Drug fever/rash, diarrhea, ↑ SGOT/SGPT. Rash potential same as ampicillin.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** 5 mL contains 600 mg amoxicillin and 42.9 mg clavulanatic acid. Take with meals to minimize GI upset. **Do not substitute 400 mg or 200 mg/5 mL formulation for ES-600.** Contains phenylalanine. May cause false + BG.
***Volume of ES-600 to provide 90 mg/kg/day:***

| Weight | Volume (q12h) | Weight | Volume (q12h) |
|---|---|---|---|
| 8 kg | 3.0 mL | 24 kg | 9.0 mL |
| 12 kg | 4.5 mL | 28 kg | 10.5 mL |
| 16 kg | 6.0 mL | 32 kg | 12.0 mL |
| 20 kg | 7.5 mL | 36 kg | 13.5 mL |

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 1%

**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**
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Website: www.pdr.net

## Amoxicillin/Clavulanic Acid XR (Augmentin XR)

**Drug Class:** Aminopenicillin/β-lactamase inhibitor.
**Usual Dose:** 2000/125 mg (2 tablets) (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 17/2 mcg/mL*
*Bioavailability: 90/60%*
*Excreted unchanged (urine): 70/40%*
*Serum half-life (normal/ESRD): [1.3/16]/[½] hrs*
*Plasma protein binding: 18/25%*
*Volume of distribution ($V_d$): 0.26/0.3 L/kg*
**Primary Mode of Elimination:** Renal

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | No change |
| CrCl < 30 mL/min | Avoid |
| Post–HD/PD dose | Avoid |
| CVVH/CVVHD/ CVVHDF dose | Avoid |
| Moderate—severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Allopurinol (↑ risk of rash); may ↓ effectiveness of oral contraceptives.
**Adverse Effects:** Drug fever, rash, diarrhea, ↑ SGOT/SGPT, nausea, abdominal pain.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Amoxicillin/clavulanic acid XR is a time-released formulation. Do not crush tablets. Take with food to increase absorption. XR formulation contains a different ratio of amoxicillin/clavulanic acid so other formulations cannot be interchanged. 2 tablets (1000/62.5 mg per tablet) 2000/125 mg per dose. May cause false + BG.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 1%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**

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Website: www.pdr.net

## Amphotericin B (Fungizone)

**Drug Class:** Antifungal.
**Usual Dose:** 0.5–0.8 mg/kg (IV) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 1–2 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 15/48 days*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 4 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| Post–HD or post–PD | None |
| Post–HFHD dose | No change |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Adrenocorticoids (hypokalemia); aminoglycosides, cyclosporine, polymyxin B (↑ nephrotoxicity); digoxin (↑ digitalis toxicity due to hypokalemia); flucytosine (↑ flucytosine levels if amphotericin B produces renal dysfunction); neuromuscular blocking agents (↑ neuromuscular blockade due to hypokalemia).
**Adverse Effects:** Fevers/chills, flushing thrombophlebitis, bradycardia, seizures, hypotension, distal renal tubular acidosis (↓ $K^+$/↓ $Mg^{++}$), anemia, pancreatitis. If renal

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

insufficiency is secondary to amphotericin, either ↓ daily dose by 50%, give dose every other day, or switch to an amphotericin lipid formulation.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Higher doses (1–1.5 mg/kg q24h) may be needed in life-threatening situations but are nephrotoxic and should only be administered under expert supervision. Do not co-administer in same IV with other drugs. Give by slow IV infusion over 2 hours initially. Aggressive hydration (1–2 liters/d) may reduce nephrotoxicity. **Test dose unnecessary.** Amphotericin B with granulocyte colony stimulating factor (GCSF) may result in ARDS. Amphotericin B with pentamidine may cause acute tubular necrosis in HIV patients. **Fevers/chills may be reduced by meperidine, aspirin, NSAIDs, hydrocortisone or acetamino-phen, if given 30–60 minutes before infusion. Bladder irrigation dose:** 50 mg/L until cultures are negative.

***Highly active against Candida (↓ susceptibility to C. glabrata, C. krusei), Cryptococcus, Histoplasmosis, Blastomycosis, Sporotrichosis, Penicillum marneffei, Paracoccidiomycosis, Coccidiomycosis. Some activity against Fusarium, Naegleria, Leishmania, Malassezia or Mucor. No activity against C. lusitaniae, Pseudoallescheria/Scedosporium or Trichosporon.***

**Meningeal dose** = usual dose plus 0.5 mg 3–5x/week (IT) via Ommaya reservoir.

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Amphotericin B Lipid Complex (Abelcet) ABLC

**Drug Class:** Antifungal (see p. 525).
**Usual Dose:** 5 mg/kg (IV) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 1.7 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 173/173 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 131 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD/PD dose | None |
| Post–HFHD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Adrenocorticoids (hypokalemia); aminoglycosides, cyclosporine, polymyxin B (↑ nephrotoxicity); digoxin (↑ digitalis toxicity due to hypokalemia); flucytosine (↑ flucytosine effect); neuromuscular blocking agents (↑ neuromuscular blockade due to hypokalemia).
**Adverse Effects:** Fevers/chills, flushing thrombophlebitis, bradycardia, seizures, hypotension, distal renal tubular acidosis (↓ $K^+$/↓ $Mg^{++}$), anemia. Fewer/less severe side effects and less nephrotoxicity than amphotericin B. Renal toxicity is dose-dependent (use caution).
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** See p. 525. Useful in patients unable to tolerate amphotericin B or in patients with amphotericin B nephrotoxicity. Infuse at 2.5 mg/kg/hr.
***Highly active against Candida* (↓ susceptibility to *C. glabrata, C. krusei*), *Cryptococcus, Histoplasmosis, Blastomycosis, Sporotrichosis, Penicillum marneffei, Paracoccidiomycosis, Coccidiomycosis. Some activity against Fusarium, Naegleria, Leishmania, Malassezia or Mucor. No activity against C. lusitaniae, Pseudoallescheria/Scedosporium or Trichosporon.***

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Amphotericin B Liposomal (AmBisome)

**Drug Class:** Antifungal (see p. 525).
**Usual Dose:** 3–6 mg/kg (IV) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 17–83 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 153 hrs/no data*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 131 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD/PD dose | None |
| Post–HFHD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Adrenocorticoids (hypokalemia); aminoglycosides, cyclosporine, polymyxin B (↑ nephrotoxicity); digoxin (↑ digitalis toxicity due to hypokalemia); flucytosine (↑ flucytosine effect); neuromuscular blocking agents (↑ neuromuscular blockade due to hypokalemia).
**Adverse Effect:** Fevers/chills, flushing, thrombohlebitis, bradycardia, seizures, hypotension, distal renal tubular acidosis (↓ K*/ ↓ Mg**), anemia.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** See p. 525. Less nephrotoxicity than amphotericin B and other amphotericin lipid preparations. **Empiric therapy of fungemia dose:** 3 mg/kg (IV) q24h can be used. **Suspected/known Aspergillus dose:** 5 mg/kg (IV) q24h. **Cryptococcal meningitis dose:** 6 mg/kg (IV) q24h. ***Highly active against Candida (↓ susceptibility to C. glabrata, C. krusei), Cryptococcus, Histoplasmosis, Blastomycosis, Sporotrichosis, Penicillum marneffei, Paracoccidiomycosis, Coccidiomycosis. Some activity against Fusarium, Naegleria, Leishmania, Malassezia or Mucor. No activity against C. lusitaniae, Pseudoallescheria/Scedosporium or Trichosporon.***

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 369:1519–1527, 2007.
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Miceli MH, Diaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infectious Diseases 11:142–151, 2011.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine (Baltimore) 89:236–244, 2010.
Website: www.pdr.net

## Amphotericin B Cholesteryl Sulfate Complex (Amphotec), ABCD (amphotericin B colloidal dispersion)

**Drug Class:** Antifungal (see p. 525).
**Usual Dose:** 3–4 mg/kg (IV) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 2.9 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 39/29 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 4 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD/PD dose | None |
| Post–HFHD dose | None |
| CVVH/CVVHD/CVVHDF dose | None |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Adrenocorticoids (hypokalemia); aminoglycosides, cyclosporine, polymyxin B (↑ nephrotoxicity); digoxin (↑ digitalis toxicity due to hypokalemia); flucytosine (↑ flucytosine effect); neuromuscular blocking agents (↑ neuromuscular blockade due to hypokalemia).
**Adverse Effects:** Fevers/chills, flushing, thrombophlebitis, bradycardia, seizures, hypotension, distal renal tubular acidosis (↓ $K^+$/↓ $Mg^{++}$), anemia. Fewer/less severe side effects/less nephrotoxicity vs. amphotericin B.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** See p. 525. Reconstitute in sterile water, not dextrose, saline or bacteriostatic water. Do not co-administer with in same IV line with other drugs. Give by slow IV infusion over 2 hours (1 mg/kg/hr). Test dose unnecessary.
***Highly active against Candida* (↓ susceptibility to *C. glabrata C. krusei*), *Cryptococcus, Histoplasmosis, Blastomycosis, Sporotrichosis, Penicillum marneffei, Paracoccidiomycosis, Coccidiomycosis. Some activity against Fusarium, Naegleria, Leishmania, Malassezia or Mucor. No activity against C. lusitaniae, Pseudoallescheria/Scedosporium or Trichosporon.***

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. Medicine (Baltimore) 89:236–244, 2010.
Website: www.pdr.net

## Ampicillin (various)

**Drug Class:** Aminopenicillin.
**Usual Dose:** 2 gm (IV) q4h, 500 mg (PO) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190.)
**Resistance Potential:** High (MSSA, aerobic GNBs)

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Pharmacokinetic Parameters:**
*Peak serum level: 48 (IV)/5 (PO) mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 0.8/10 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.25 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 1 gm (IV) q4h<br>500 mg (PO) q6h |
| CrCl 10–50 mL/min | 1 gm (IV) q8h<br>250 mg (PO) q8h |
| CrCl < 10 mL/min | 1 gm (IV) q12h 250 mg (PO) q12h |
| Post–HD dose | 1 gm (IV)<br>500 mg (PO) |
| Post–PD dose | 1 gm (IV)<br>250 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 1 gm (IV) q8h<br>250 mg (PO) q12h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Allopurinol (↑ frequency of rash); warfarin (↑ INR).
**Adverse Effects:** Drug fever/rash, nausea, GI upset, irritative diarrhea, ↑ SGOT/SGPT, ↑ incidence of rash vs. penicillin (in patients with EBV, HIV, lymphocytic leukemias, or allopurinol), C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing amphotericin B, heparin, corticosteroids, erythromycin, aminoglycosides, or metronidazole.
$Na^+$ content = 2.9 mEq/g.
Meningeal dose = 2 gm (IV) q4h.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**
Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant Enterococcus faecium. Antimicrob Agents Chemother. 56:838–844, 2012.
Wright AJ. The penicillins. Mayo Clin Proc 74:290–307, 1999.
Website: www.pdr.net

## Ampicillin/Sulbactam (Unasyn)

**Drug Class:** Aminopenicillin/β-lactamase inhibitor.
**Usual Dose:** 1.5–3 gm (IV) q6h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low (pseudoresistance with E. coli/Klebsiella)
**Pharmacokinetic Parameters:**
*Peak serum level: 109-150/48-88 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80/80%*
*Serum half-life (normal/ESRD): [1/9]/[1/9] hrs*
*Plasma protein binding: 28/38%*
*Volume of distribution ($V_d$): 0.25/0.38 L/kg*
**Primary Mode of Elimination:** Renal/hepatic
**Dosage Adjustments*** (based on 3 gm (IV) q6h)

| | |
|---|---|
| CrCl 30–80 mL/min | 1.5 gm (IV) q6h |
| CrCl 15–30 mL/min | 1.5 gm (IV) q12h |
| CrCl < 15 mL/min | 1.5 gm (IV) q24h |
| Post–HD dose | 1.5 gm (IV) |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 1.5–3 gm (IV) q12h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Probenecid (↑ ampicillin/ sulbactam levels); allopurinol (↑ rash).
**Adverse Effects:** Drug fever/rash, ↑ SGOT/SGPT, hemolytic anemia, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: Mild/moderate infection dose:** 1.5 gm (IV) q6h.
**Meningeal dose:** 4.5 gm (IV) q6h (for susceptible strains of MDR Acinetobacter baumanii meningitis).

**Cerebrospinal Fluid Penetration:** 30%
**Bile Penetration:** 900%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**

Itokazu GS, Danziger LH. Ampicillin-sulbactam and ticarcillin-clavulanic acid: A comparison of their in vitro activity and review of their clinical efficacy. Pharmacotherapy 11:382–414, 1991.

Jain R, Danziger LH. Multidrug-resistant Acinetobacter infections: an emerging challenge to clinicians. Ann Pharmacother 38:1449–59, 2004.

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Swenson JM, Killgore GE, Tenover FC. Antimicrobial susceptibility testing of Acinetobacter spp. by NCCLS broth microdilution and disk diffusion methods. J Clin Microbiol 42:5102–8, 2004.

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Wright AJ. The penicillins. Mayo Clin Proc 73:290–307, 1999.

Website: www.pdr.net

## Amprenavir (Agenerase) APV

**Drug Class:** HIV protease inhibitor.
**Usual Adult Dose:** 1200 mg (PO) q12h (capsules) or 1400 mg (PO) q12h (solution); age 13–16 years < 50 kg or pediatrics 4–12 years: 20 mg/kg (PO) q12h (capsules) or 1.5 ml/kg (PO) q12h (15 mg/mL solution). Maximum dose 2400 mg/d (capsules), 2800 mg/d (oral solution).
**Pharmacokinetic Parameters:**
*Peak serum level: 7.6 mcg/mL*
*Bioavailability: No data*
*Excreted unchanged (urine): 1%*
*Serum half-life (normal/ESRD): 7-10/7-10 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 6.1 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 10 mL/min | No change |
| CrCl < 10 mL/min | No change (avoid solution) |
| Post-HD/PD dose | No change |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | 450 mg (PO) q12h (capsules) |
| Severe hepatic insufficiency | 300 mg (PO) q12h (capsules) |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Delavirdine | Avoid |
| Didanosine buffered solution | Take amprenavir 1 hour before or after |
| Efavirenz | No data |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Indinavir | No data |
| Lopinavir/ritonavir | May ↓ lopinavir levels |
| Nelfinavir | No data |
| Nevirapine | No data |
| Ritonavir | Limited data for amprenavir 600 mg q12h + ritonavir 100 mg q12h (or amprenavir 1200 mg q24h + ritonavir 200 mg q24h) |
| Saquinavir | No data |
| Rifampin | Avoid |
| Rifabutin | Rifabutin 150 mg q24h or 300 mg 2–3x/week |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); bepridil, cisapride, ergotamine, statins, benzodiazepines, St. John's wort, pimozide, sildenafil, methadone (avoid if possible); carbamazepine, phenobarbital, phenytoin (may ↓ amprenavir levels, monitor anticonvulsant levels); $H_2$ blockers, proton pump inhibitors (↓ amprenavir levels).

**Adverse Effects:** Rash, Stevens-Johnson Syndrome (rare), GI upset, headache, depression, taste perversion, diarrhea, perioral paresthesias, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ cholesterol/triglycerides (evaluate risk for coronary disease/pancreatitis), fat redistribution, ↑ SGOT/SGPT, possible increased bleeding in hemophilia.

**Allergic Potential:** High. Amprenavir is a sulfonamide; use with caution in sulfa allergy

**Safety in Pregnancy:** C

**Comments:** Can be taken with or without food, but avoid high fat meals (may ↓ absorption). High vitamin E content. Capsules and solution are not interchangeable on a mg per mg basis. Decrease dosage in moderate or severe liver disease; use with caution. Oral solution contains propylene glycol: avoid in pregnancy, hepatic/renal failure, patients taking disulfiram or metronidazole, or children < 4 years old. Effective antiretroviral therapy consists of three antiretrovirals (same/different classes)

GlaxoSmithKline discontinued production and sale of amprenavir in the United States in order to focus on production of the amprenavir prodrug, fosamprenavir. This action was not taken because of concerns about safety or efficacy of amprenavir. Amprenavir may continue to be available in some countries outside the United States.

**REFERENCES:**

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Anidulafungin (Eraxis, Ecalta)

**Drug Class:** Echinocandin antifungal.
**Usual Dose:** 200 mg (IV) × 1 dose, then 100 mg (IV) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 4.2 mg/L (100/50 mg dose)/7.2 mg/L (200/100 mg dose)*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): < 1%*
*Serum half-life (normal/ESRD): 40–50 hours/ 40–50 hours*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): 30–50L*
**Primary Mode of Elimination:** Fecal (30%)
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** No significant interactions.
**Adverse Effects:** ↑ SGOT/SGPT/GGTP/alkaline phosphatase. Histamine-related reactions (rash, urticaria, pruritus, fever, dyspnea and hypotension) if infusion > 1.1 mg/min.
**Allergic Potential:** Histamine-related symptoms
**Safety in Pregnancy:** C
**Comments:** Not an inducer, inhibitor, or substrate of CYP450 system. Rate of infusion should not exceed 1.1 mg/min. Incompatible with other drugs. Do not infuse with other medications. Use reconstituted vials within 24 hours. Infusion solution should be stored at 25°C/77°F.

***Highly active against Candida albicans, non-albicans Candida (↓ susceptibility to C. parasilosis).***
***Some activity against Aspergillus.***
***No activity against Cryptococcus, Fusarium, Pseudoallescheria/Scedosporium, Trichosporon, Rhodotorula or Mucor.***

**Cerebrospinal Fluid Penetration:** No data

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Atazanavir (Reyataz) ATV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** 300 mg (PO) q24h with ritonavir 100 mg (PO) q24h or 400 mg (PO) q24h with food if unable to tolerate ritonavir.
**Treatment Experienced Patients:** 300 mg with ritonavir 100 mg once daily with food.

**Pharmacokinetic Parameters:**
*Peak serum level: 3152 ng/mL; with ritonavir: 5233 ng/mL*
*Bioavailability: No data*
*Excreted unchanged (urine) (urine/feces): 7%/20%*
*Serum half-life (normal/ESRD): 6.5 hrs; with ritonavir: 8.6 hrs/no data*
*Plasma protein binding: 86%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD or PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | 300 mg (PO) q24h without ritonavir |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Delavirdine | No data |
| Didanosine | Give atazanavir 2 hrs before didanosine with food |
| Efavirenz | Treatment naive: atazanavir 400 mg q24h + ritonavir 100 mg q24h + efavirenz 600 mg q24h<br>Treatment experienced: not recommended |
| Indinavir | Avoid combination |
| Nevirapine | No data |
| Ritonavir | Atazanavir 300 mg/d + ritonavir 100 mg/d as single daily dose with food |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Saquinavir | ↑ saquinavir (soft-gel) levels; no information |
| Rifampin | Avoid |
| Rifabutin | 150 mg q48h or 3x/week |

**Drug Interactions:** Antacids or buffered medications (↓ atazanavir levels; give atazanavir 2 hours before or 1 hour after); $H_2$-receptor blockers (↓ atazanavir levels). In treatment-naïve patients taking an $H_2$-receptor antagonist, give either atazanavir 400 mg once daily with food at least 2 hours before and at least 10 hours after the $H_2$-receptor antagonist, or give atazanavir 300 mg once daily with ritonavir 100 mg once daily with food, without the need for separation from the $H_2$-receptor antagonist. In treatment-experienced patients, give atazanavir 300 mg once daily with ritonavir 100 mg once daily with food at least 2 hours before and at least 10 hours after the $H_2$-receptor antagonist); antiarrhythmics (↑ amiodarone, systemic lidocaine, quinidine levels; prolongs PR interval; monitor antiarrhythmic levels); antidepressants (↑ tricyclic antidepressant levels; monitor levels); calcium channel blockers (↑ calcium channel blocker levels, ↑ PR interval; ↓ diltiazem dose by 50%; use with caution; consider ECG monitoring); clarithromycin (↑ clarithromycin and atazanavir levels; consider 50% dose reduction; consider alternate agent for infections not caused by MAI); cyclosporine, sirolimus, tacrolimus (↑ immunosuppressant levels; monitor levels); ethinyl estradiol, norethindrone (↑ oral contraceptive levels; use lowest effective oral contraceptive dose); lovastatin, simvastatin (↑ risk of myopathy, rhabdomyolysis; avoid combination); sildenafil (↑ sildenafil levels; do not give more than 25 mg q48h); tadalafil (max. 10 mg/72 hours); vardenafil (max. 2.5 mg/72 hours); St. John's wort (avoid combination); warfarin (↑ warfarin levels; monitor INR); tenofovir (tenofovir reduces systemic exposure to atazanavir).

**Contraindications: atazanavir include cisapride, pimozide, rifampin, irinotecan, midazolam, triazolam, lovastatin, simvastatin, bepridil, some ergot derivatives, indinavir, PPIs, St. John's wort, rifapentine, boceprevir.**

**Adverse Effects:** Abdominal pain, nausea, vomiting, headache, diarrhea, asthenia, anorexia, and dizziness.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Monitor LFTs in patients with HBV, HCV. Take 400 mg (two 200-mg capsules) once daily with food. Bioavailability is enhanced with food. Monitor LFTs in patients with HBV, HCV. In moderate liver disease reduce dose to 200 mg once daily. It is not recommended in patients with severe liver impairment.

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Atovaquone (Mepron)

**Drug Class:** Antiprotozoal.
**Usual Dose: PCP treatment dose:** 750 mg (PO) q12h. **PCP prophylaxis dose:** 1500 mg (PO) q24h
**Pharmacokinetic Parameters:**
*Peak serum level: 12–24 mcg/mL*
*Bioavailability: 30% (47% with food; food ↑ bioavailability by 2-fold)*
*Excreted unchanged (feces): 94%*
*Serum half-life (normal/ESRD): 2.9/2.9 days*
*Plasma protein binding: 99.9%*
*Volume of distribution ($V_d$): 0.6 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 80 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Rifabutin, rifampin (↓ atovaquone effect); zidovudine (↑ zidovudine levels). Rifampin decreases atovaquone levels by 50%.
**Adverse Effects:** Rash, nausea, vomiting, diarrhea, headache, drowsiness, dizziness, fever, anemia, leukopenia, ↑ SGOT/SGPT, ↑ amylase.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments: Active against T. gondii, PCP, Plasmodia, and Babesia**.
**Cerebrospinal Fluid Penetration:** < 1%

**REFERENCES:**

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Website: www.pdr.net

## Atovaquone + Proguanil (Malarone)

**Drug Class:** Antimalarial.
**Usual Dose:** Malaria prophylaxis: 1 tablet (250 mg/100 mg) (PO) q24h for 2 days before entering endemic area, daily during exposure, and daily

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

× 1 week post-exposure. Malaria treatment: 4 tablets (1000 mg/400 mg) (PO) as single dose × 3 days.

**Pharmacokinetic Parameters:**
*Peak serum level: 38 mcg/mL*
*Bioavailability: 23/90%*
*Excreted unchanged (feces): 94/50%*
*Serum half-life (normal/ESRD):*
*[60/60]/[21/no data] hrs*
*Plasma protein binding: 99/75%*
*Volume of distribution ($V_d$): 3.5/42 L/kg*

**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | No change |
| CrCl 10–30 mL/min | Avoid (for prophylaxis) |
| CrCl < 10 mL/min | Avoid (for prophylaxis) |
| Post–HD/PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Chloroquine (↑ incidence of mouth ulcers); metoclopramide, rifabutin, rifampin, tetracycline (↓ atovaquone + proguanil effect); ritonavir (↑ or ↓ atovaquone + proguanil effect); typhoid vaccine (↓ typhoid vaccine effect).
**Adverse Effects:** Rash, headache, drowsiness, dizziness, nausea, vomiting, diarrhea, fever, anemia, leukopenia, ↑SGOT/↑SGPT, ↑ amylase,
**Allergic Potential:** Low
**Safety in Pregnancy:** C

**Comments:** Malarone tablet = 250 mg atovaquone + 100 mg proguanil. **Effective against chloroquine sensitive/resistant strains of P. falciparum, but not P. ovale, P. vivax, or P. malariae**. Dosage may be decreased in patients with diarrhea. Take with food/milk.

**Cerebrospinal Fluid Penetration:** < 1%

**REFERENCES:**

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Website: www.pdr.net

## Azithromycin (Zithromax)

**Drug Class:** Macrolide (Azolide).
**Usual Dose:** 500 mg (IV/PO) × 1 dose, then 250 mg (IV/PO) q24h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** High (S. pneumoniae, GAS, MSSA)

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Pharmacokinetic Parameters:**
*Peak serum level: 1.1 (IV)/0.2 (PO) mcg/mL*
*Bioavailability: 35%*
*Excreted unchanged (urine): 6%*
*Serum half-life (normal/ESRD): 68/68 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 31 L/kg*

**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | Use with caution |
| Post–HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Amiodarone, carbamazepine, cisapride, clozapine, corticosteroids, midazolam, triazolam, valproic acid (not studied/not reported); cyclosporine (↑ cyclosporine levels with toxicity); digoxin (↑ digoxin levels); pimozide (may ↑ QT interval, torsade de pointes).
**Adverse Effects: ↑ incidence cardiac/ non-cardiac sudden deaths after 5 days of therapy.** Nausea, GI upset, non-C. difficile diarrhea. May ↑ $QT_c$ interval.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Bioavailability is decreased by food. C. trachomatis urethritis dose: 1 gm (PO) × 1 dose.
**N. gonorrhoea urethritis dose:** 2 gm (PO) × 1 dose.
**MAI prophylaxis dose:** 1200 mg (PO) weekly.
**MAI therapy dose:** 600 mg (PO) q24h.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** > 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 519)

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Aztreonam (Azactam)

**Drug Class:** Monobactam.
**Usual Dose:** 2 gm (IV) q8h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 204 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 60–70%*
*Serum half-life (normal/ESRD): 1.7/7 hrs*
*Plasma protein binding: 56%*
*Volume of distribution ($V_d$): 0.2 L/kg*

**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 2 gm IV q8h)

| | |
|---|---|
| CrCl 10–50 mL/min | 1 gm (IV) q8h |
| CrCl < 10 mL/min | 500 mg (IV) q8h |
| Post–HD dose | 500 mg (IV) |
| Post–PD dose | 500 mg (IV) |
| CVVH/CVVHD/ CVVHDF dose | 1–2 gm (IV) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** None.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing vancomycin or metronidazole. **No cross allergenicity with penicillins, β-lactams; safe to use in penicillin allergic patients.**
**CAPD dose:** 1 gm (IP), then 250 mg/L of dialysate (IP) with each exchange.

Meningeal dose = 2 gm (IV) q6h.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 40%
**Bile Penetration:** 300%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Capreomycin (Capastat)

**Drug Class:** Anti–TB drug.
**Usual Dose:** 1 gm (IM) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 30 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 50%*
*Serum half-life (normal/ESRD): 5/30 hrs*
*Plasma protein binding: No data*
*Volume of distribution ($V_d$): 0.4 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 500 mg (IM) q24h |
| CrCl 10–50 mL/min | 500 mg (IM) q48h |
| CrCl < 10 mL/min | 500 mg (IM) q72h |
| Post–HD dose | 500 mg (IM) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (IM) q48h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Eosinophilia, leukopenia, drug fever/rash, ototoxicity (vestibular), nephrotoxicity (glomerular/tubular).
**Allergic Potential:** Moderate
**Safety in Pregnancy:** C
**Comments:** Pain/phlebitis at IM injection site. Additive toxicity with aminoglycosides/viomycin.

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**
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Website: www.pdr.net

## Caspofungin (Cancidas)

**Drug Class:** Echinocandin antifungal.
**Usual Dose:** ***Loading Dose*** 70 mg (IV) × 1 dose, then ***Maintenance Dose*:** 50 mg (IV) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level:*
*70 mg: 12.1* (single dose)*/14.83 mcg/mL* (multiple dose)
*50 mg: 7.6/8.7 mcg/mL* (multiple dose)
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 1.4%*
*Serum half-life (normal/ESRD): 10/10 hrs*
*Plasma protein binding: 97%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | None |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Moderate hepatic insufficiency | 35 mg (IV) q24h (maintenance dose after 70 mg (IV) loading dose) |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Carbamazepine, rifampin, dexamethasone, efavirenz, nelfinavir, nevirapine, phenytoin (↓ caspofungin levels; ↑ caspofungin maintenance dose to 70 mg/day); cyclosporine (↑ caspofungin levels, ↑ SGOT/SGPT; co-administration is discouraged unless careful monitoring can be ensured and unless the benefit of caspofungin outweighs the risk of hepatotoxicity); tacrolimus (↓ tacrolimus levels, ↑ SGOT/SGPT).
**Adverse Effects:** Drug fever/rash.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Administer by slow IV infusion over 1 hour; do not give IV bolus. Do not mix/co-infuse with glucose solutions.
**Highly-resistant organisms dose: 70 mg (IV) q24h. Esophageal candidiasis dose:** begin therapy with 50 mg dose.
***Highly active against Candida albicans and non*-albicans *Candida, Hansenula. Some activity against C. parapsilosis, Aspergillus. No activity against Cryptococcus, Fusarium, Pseudoallescheria/Scedosporium, Rhodotorula, Trichosporon, or Mucor.***

**Cerebrospinal Fluid Penetration:** 20%

**REFERENCES:**

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Website: www.pdr.net

## Cefaclor (Ceclor)

**Drug Class:** 2nd generation oral cephalosporin.
**Usual Dose:** 500 mg (PO) q8h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 13 mcg/mL*
*Bioavailability: 80%*
*Excreted unchanged (urine): 60–85%*
*Serum half-life (normal/ESRD): 0.8/3 hrs*
*Plasma protein binding: 25%*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Volume of distribution ($V_d$): 0.30 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | 250 mg (PO) q8h |
| Post–HD dose | 250 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Limited penetration into respiratory secretions. **Ceclor CD 500 mg (PO) q12h is equivalent to cefaclor 250 mg (PO) q8h, not cefaclor 500 mg (PO) q8h. Ceclor CD 500 mg (PO) q12h is equivalent to 250 mg (PO) q8h of cefaclor.**

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 60%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

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Website: www.pdr.net

## Cefadroxil (Duricef, Ultracef)

**Drug Class:** 1st generation oral cephalosporin.
**Usual Dose:** 1000 mg (PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 16 mcg/mL*
*Bioavailability: 99%*
*Excreted unchanged (urine): 85%*
*Serum half-life (normal/ESRD): 0.5/22 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.31 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–25 mL/min | 500 mg (PO) q24h |
| CrCl < 10 mL/min | 500 mg (PO) q36h |
| Post–HD dose | 500 mg (PO) |
| Post–PD dose | 250 mg (PO) |
| CVVH/CVVHD/CVVHDF dose | 500 mg (PO) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Penetrates oral/respiratory secretions well.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 20%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**
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Website: www.pdr.net

## Cefamandole (Mandol)

**Drug Class:** 2nd generation cephalosporin.
**Usual Dose:** 2 gm (IV) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp.191-197)
**Resistance Potential:** High (H. influenzae, Enterobacter sp.)
**Pharmacokinetic Parameters:**
*Peak serum level: 240 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 85%*
*Serum half-life (normal/ESRD): 1/11 hrs*
*Plasma protein binding: 76%*
*Volume of distribution ($V_d$): 0.29 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 1 gm (IV) q6h |
| CrCl 10–50 mL/min | 1 gm (IV) q6h |
| CrCl < 10 mL/min | 1 gm (IV) q12h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CVVH/CVVHD/ CVVHDF dose | 1 gm (IV) q6h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Alcohol (disulfiram-like reaction); antiplatelet agents, heparin, thrombolytics, warfarin (↑ risk of bleeding).
**Adverse Effects:** Drug fever/rash, ↑ INR.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions with $Mg^{++}$ or $Ca^{++}$. **Contains MTT side chain, but no increase in clinical bleeding.**

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 300%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**
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Gentry LO, Zeluff BJ, Cooley DA. Antibiotic prophylaxis in open-heart surgery: A comparison of cefamandole, cefuroxime, and cefazolin. Ann Thorac Surg 46:167–71, 1988.
Website: www.pdr.net

## Cefazolin (Ancef, Kefzol)

**Drug Class:** 1st generation cephalosporin.
**Usual Dose:** 1 gm (IV) q8h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 185 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 96%*
*Serum half-life (normal/ESRD): 1.8/40 hrs*
*Plasma protein binding: 85%*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 35–55 mL/min | 1 gm (IV) q12h |
| CrCl 10–35 mL/min | 500 mg (IV) q12h |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl < 10 mL/min | 500 mg (IV) q24h |
| Post–HD dose | 1 gm (IV) |
| Post–HFHD dose | 2 gm (IV) |
| Post–PD dose | 500 mg (IV) |
| CVVH/CVVHD/CVVHDF dose | 500 mg (IV) q12h |
| HD q 48–72h dose | 2 gm (IV) q HD* |
| Moderate—severe hepatic insufficiency | No change |

*Give at end of HD.

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, AIHA.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing erythromycin, aminoglycosides, cimetidine, theophylline.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetrations:** 300%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**

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Website: www.pdr.net

## Cefdinir (Omnicef)

**Drug Class:** 3rd generation oral cephalosporin.
**Usual Dose:** 600 mg (PO) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 2.9 mcg/mL*
*Bioavailability: 16% (tab) / 25%(suspension)*
*Excreted unchanged (urine): 11–18%*
*Serum half-life (normal/ESRD): 1.7/3 hrs*
*Plasma protein binding: 70%*
*Volume of distribution ($V_d$): 0.35 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 300 mg (PO) q24h |
| Post–HD dose | 300 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | 300 mg (PO) q24h |
| Moderate—severe hepatic insufficiency | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Probenecid (↑ cefdinir levels).
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Good activity against bacterial respiratory pathogens. Available as capsules or suspension. **CAP dose:** 300 mg (PO) q12h; **Other respiratory infections dose:** 600 mg (PO) q24h.

**Cerebrospinal Fluid Penetration:** < 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**
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Website: www.pdr.net

## Cefditoren (Spectracef)

**Drug Class:** 3rd generation oral cephalosporin.
**Usual Dose:** 400 mg (PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 1.8 mcg/mL*
*Bioavailability: 16%*
*Excreted unchanged (urine): 20%*
*Serum half-life (normal/ESRD): 1.5/5 hrs*
*Plasma protein binding: 88%*
*Volume of distribution ($V_d$): 0.13 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 30–50 mL/min | 200 mg (PO) q12h |
| CrCl < 30 mL/min | 200 mg (PO) q24h |
| Post–HD dose | 200 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | 200 mg (PO) q24h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** $H_2$ receptor antagonists, $Al^{++}$, $Mg^{++}$) antacids (↓ absorption of cefditoren); Probenecid (↓ elimination of cefditoren).
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Serum concentrations increased ~ 50% if taken without food. ↑ elimination of carnitine; do not use in carnitine deficiency or hereditary carnitine metabolism disorder. **Contains Na+ caseinate; avoid in patients with casein hypersensitivity.**

**Cerebrospinal Fluid Penetration:** < 1%
**Bile Penetration:** 200%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**
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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Wellington K, Curran MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. Drugs 64:2597–618, 2004.
Website: www.pdr.net

## Cefepime (Maxipime)

**Drug Class:** 4th generation cephalosporin.
**Usual Dose:** 2 gm (IV) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 163 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80%*
*Serum half-life (normal/ESRD): 2.2/18 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.29 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–60 mL/min | 2 gm (IV) q12h |
| CrCl 10–30 mL/min | 2 gm (IV) q24h |
| CrCl < 10 mL/min | 1 gm (IV) q24h |
| Post–HD dose | 2 gm (IV) |
| Post–HFHD dose | 2 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CAPD | 2 gm (IV) q48h |
| CVVH/CVVHD/ CVVHDF dose | 1 gm (IV) q12h |
| HD q 48–72h dose | 2 gm (IV) q HD* |
| Moderate—severe hepatic insufficiency | No change |

*Give at end of HD.

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis. **Neurotoxicity, particularly with doses not adjusted for renal function. Neurotoxic manifestations include encephalopathy, non-convulsive status epilecticus, and myoclonus.**
**Allergic Potential:** Moderate
**Safety in Pregnancy:** B
**Comments:** For ESBL + Enterobacteriaceae (MIC 4–8 mcg/mL, proven serious systemic P. aeruginosa infections, febrile neutropenia, or cystic fibrosis, use 2 gm (IV) q8h. For aerobic GNB bacteremias use 2 gm (IV) q12h.

Meningeal dose = 2 gm (IV) q8h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 15%
**Bile Penetration:** 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**


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Website: www.pdr.net


"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Cefixime (Suprax)

**Drug Class:** 3rd generation oral cephalosporin.
**Usual Dose:** 400 mg (PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 3.7 mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 50%*
*Serum half-life (normal/ESRD): 3.1/11 hrs*
*Plasma protein binding: 65%*
*Volume of distribution ($V_d$): 0.1 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 20–50 mL/min | 400 mg (PO) q24h |
| CrCl < 20 mL/min | 200 mg (PO) q24h |
| Post–HD dose | 400 mg (PO) |
| Post–PD dose | 200 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 200 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Carbamazepine (↑ carbamazepine levels).
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B

**Comments: PRNG dose:** 400 mg (PO) × 1 dose. Also useful for quinolone-resistant GC.
**Little/no activity against S. aureus (MSSA).**

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 800%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

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Website: www.pdr.net

## Cefoperazone (Cefobid)

**Drug Class:** 3rd generation cephalosporin.
**Usual Dose:** 2 gm (IV) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 240 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 20%*
*Serum half-life (normal/ESRD): 2.4/2.4 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 0.17 L/kg*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 1 gm (IV) q12h |

**Drug Interactions:** Alcohol (disulfiram-like reaction); antiplatelet agents, heparin, thrombolytics, warfarin (↑ risk of bleeding).
**Adverse Effects:** Drug fever/rash. ↑ **INR due to MTT side chain, but no increase in clinical bleeding. Prophylactic vitamin K unnecessary.**
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments: One of the few antibiotics to penetrate into an obstructed biliary tract.** May be administered IM. **Concentration dependent serum half life.**

Meningeal dose = 2 gm (IV) q8h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 1200% (also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

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Website: www.pdr.net

## Cefotaxime (Claforan)

**Drug Class:** 3rd generation cephalosporin.
**Usual Dose:** 2 gm (IV) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 214 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 20–36%; 15–25% excreted as active metabolite*
*Serum half-life (normal/ESRD): 1/15 hrs*
*Plasma protein binding: 37%*
*Volume of distribution ($V_d$): 0.25 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 1 gm (IV) q12h |
| CrCl < 10 mL/min | 1 gm (IV) q24h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CVVH/CVVHD/ CVVHDF dose | 2 gm (IV) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** Moderate
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing sodium bicarbonate, metronidazole, or aminoglycosides. **Desacetyl metabolite** ($t_{1/2}$ = 1.5 hrs) **synergistic with cefotaxime against S. aureus/B. fragilis.**

Meningeal dose = 3 gm (IV) q6h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 75%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

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Website: www.pdr.net

## Cefotetan (Cefotan)

**Drug Class:** 2nd generation cephalosporin (Cephamycin).
**Usual Dose:** 2 gm (IV) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 237 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 50–80%*
*Serum half-life (normal/ESRD): 4/10 hrs*
*Plasma protein binding: 88%*
*Volume of distribution ($V_d$): 0.17 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–80 mL/min | 2 gm (IV) q12h |
| CrCl 10–30 mL/min | 2 gm (IV) q24h |
| CrCl < 10 mL/min | 2 gm (IV) q48h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CVVH/CVVHD/ CVVHDF dose | 750 mg (IV) q12h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Alcohol (disulfiram-like reaction); antiplatelet agents, heparin, thrombolytics, warfarin (↑ risk of bleeding).
**Adverse Effects:** Drug fever/rash, hemolytic anemia, C. difficile diarrhea/colitis. ↑ **INR due to MTT side chain, but no increase in clinical bleeding.**
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Less effective than cefoxitin against B. fragilis D.O.T strains.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 20% (also see ***Antibiotic Pearls & Pitfalls*** p. 510).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**
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Stroncek D, Procter JL, Johnson J. Drug-induced hemolysis: cefotetan-dependent hemolytic anemia mimicking an acute intravascular immune transfusion reaction. Am J Hematol 64:67–70, 2000.
Website: www.pdr.net

## Cefoxitin (Mefoxin)

**Drug Class:** 2nd generation cephalosporin (Cephamycin).
**Usual Dose:** 2 gm (IV) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 221 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 85%*
*Serum half-life (normal/ESRD): 1/21 hrs*
*Plasma protein binding: 75%*
*Volume of distribution ($V_d$): 0.12 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–50 mL/min | 2 gm (IV) q12h |
| CrCl 10–30 mL/min | 1 gm (IV) q12h |
| CrCl < 10 mL/min | 1 gm (IV) q24h |
| Post–HD dose | 2 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CVVH/CVVHD/CVVHDF dose | 2 gm (IV) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments: Effective against B. fragilis, including D.O.T.** strains (B. distasonis, B. ovatus, B. thetaiotaomicron).

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 250%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**
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Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
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Marshall WF Blair JE. The cephalosporins. Mayo Clin Proc 74:187–95, 1999.
Website: www.pdr.net

## Cefpodoxime (Vantin)

**Drug Class:** 3rd generation oral cephalosporin.
**Usual Dose:** 200 mg (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 2.3 mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 30%*
*Serum half-life (normal/ESRD): 2.3/9.8 hrs*
*Plasma protein binding: 21–33%*
*Volume of distribution ($V_d$): 0.9 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–80 mL/min | No change |
| CrCl < 30 mL/min | 200 mg (PO) q24h |
| Post–HD dose | 200 mg (PO) |
| Post–PD dose | 200 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 200 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis pulmonary infiltrates with eosinophilia, ↑ SGOT/SGPT.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Only oral 3rd generation cephalosporin active against S. aureus (MSSA).
**PPNG dose**: 400 mg (PO) × 1 dose.
**cSSSI dose**: 400 mg (PO) q12h.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 100%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**
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Schatz BS, Karavokiros KT, Taeubel MA, et al. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, cefixime, and ceftibuten. Ann Pharmacother 30:258–68, 1996.
Website: www.pdr.net

## Cefprozil (Cefzil)

**Drug Class:** 2nd generation oral cephalosporin.
**Usual Dose:** 500 mg (PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 10 mcg/mL*
*Bioavailability: 95%*
*Excreted unchanged (urine): 60%*
*Serum half-life (normal/ESRD): 1.3/5.9 hrs*
*Plasma protein binding: 36%*
*Volume of distribution ($V_d$): 0.23 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 250 mg (PO) q12h |
| Post–HD dose | 500 mg (PO) |
| Post–PD dose | 250 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (PO) q24h |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Penetrates oral/respiratory secretions well. No resistance.

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

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Gainer RB 2nd. Cefprozil: A new cephalosporin; its use in various clinical trials. South Med J 88:338–46, 1995.
Marshall WF Blair JE. The cephalosporins. Mayo Clin Proc 74:187–95, 1999.
Schatz BS, Karavokiros KT, Taeubel MA, et al. Comparison of cefprozil, cefpodoxime, proxetil, loracarbef, cefixime, and ceftibuten. Ann Pharmacother 30:258–68, 1996.
Website: www.pdr.net

## Ceftaroline fosamil (Teflaro)

**Drug class:** Anti-MRSA cephalosporin
**Usual dose:** 600 mg (IV) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level:* 19 mcg/mL
*Bioavailability:* not applicable
*Excreted unchanged:* 64%
*Serum half-life (normal/ESRD):* 2.7 hours / 6.16 hours
*Plasma protein binding:* 20%
*Volume of distribution ($V_d$):* 20.3 L/kg

**Primary Mode of Elimination:** Renal
**Drug Interactions:** None.
**Adverse Reactions:** C. difficile, diarrhea, nausea, vomiting, allergic reactions, rash, constipation,

| | |
|---|---|
| CrCl[a] > 50 | No change |
| CrCl > 30 to ≤ 50 | 400 mg (IV) (over 1 hour) q12h |
| CrCl ≥ 15 to ≤ 30 | 300 mg (IV) (over 1 hour) q12h |
| ESRD on HD* | 200 mg (IV) (over 1 hour) q12h[c] |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

* should be administered after HD on hemodialysis days.

↑SGOT/↑SGPT hypokalemia, direct Coombs test, phlebitis.
**Safety in Pregnancy:** B
**Comments:** The only cephalosporin effective against MRSA *in vivo*. Not an inducer, inhibitor or substrate of CYP450 system. Infuse over 1 hour.

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

Biek D, Critchley IA, Riccobene TA, et al. Ceftaroline fosamil: a novel broad-spectrum cephalosporin with expanded anti-Gram-positive activity. J Antimicrob Chemother 65:9–16, 2010.
Casapao AM, Steed ME, Levine DP, et al. Ceftaroline fosamil for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection. Expert Opin Pharmacother 13:1177–1186, 2012.
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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 51:641–650; 2010.
File TM Jr, Low DE, Edckburg PB, et al. Efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 51:1395–1405, 2011.
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Poon H, Chang MH, Fung HB. Ceftaroline fosamil: a cephalosporin with activity against methicillin-resistant Staphylococcus aureus. Clin Ther 34:743–765, 2012.
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Watkins RR. Successful treatment of osetomyelitis from methicillin-resistant Staphylococcus aureus with ceftaroline. Infectious Disease in Clinical Practice 21:1;48–49, 2013.
Zainah H, Vazquez JA. Use of ceftaroline in complicated methicillin-resistant Staphylococcus aureus bacteremia. Infectious Disease in Clinical Practice 21:1;58–60, 2013.
Website: www.pdr.net

## Ceftazidime (Fortaz, Tazicef, Tazidime)

**Drug Class:** 3rd generation cephalosporin.
**Usual Dose:** 2 gm (IV) q8h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** High (P. aeruginosa, Klebsiella pneumoniae; ↑ prevalence of MRSA)
**Pharmacokinetic Parameters:**
*Peak serum level: 170 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80–90%*
*Serum half-life (normal/ESRD): 1.9/21 hrs*
*Plasma protein binding: 10%*
*Volume of distribution ($V_d$): 0.36 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–80 mL/min | 2 gm (IV) q12h |
| CrCl 10–30 mL/min | 2 gm (IV) q24h |
| CrCl < 10 mL/min | 1 gm (IV) q48h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 500 mg (IV) |
| CVVH/CVVHD/ CVVHDF dose | 2 gm (IV) q12h |
| HD q48–72h dose | 2 gm (IV) q HD* |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

*Give at end of HD.

**Drug Interactions:** None.
**Adverse Effects:** Phlebitis, drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing vancomycin or aminoglycosides. ***Use increases MRSA prevalence and P. aeruginosa resistance. Potent inducer of Klebsiella/Enterobacter/E. coli ESBLs.***
**CAPD dose:** 125 mg/L of dialysate (I.P.) with each exchange.

Meningeal dose = 2 gm (IV) q8h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 20%
**Bile Penetration:** 50%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

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Owens JC, Jr, Ambrose PG, Quintiliani R. Ceftazidime to cefepime formulary switch: Pharmacodynamic rationale. Conn Med 61:225–7, 1997.

Rains CP, Bryson HM, Peters DH. Ceftazidime: An update of its antibacterial activity, pharmacokinetic properties, and therapeutic efficacy. Drugs 49:577–617, 1995.

Website: www.pdr.net

## Ceftazidime/Avibactam (Avycaz)

**Drug Class:** Antipseudomal cephalosporin/β-lactamase inhibitor
**Usual Dose:** 2.5 gm (IV) q8h
**Spectrum:** (see ***Susceptibility Profiles*** pp 191-197)
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak Serum level: 170 mcg/ml/15 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged: 80–90%/85%*
*Serum half-life (normal/ESRD): [1.9h/21 h]/ [2.0h/22.82 h]*
*Plasma protein binding: 10%/8.2%*
*Volume of distribution ($V_d$): 0.36 L/kg/0.32 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 31–50 mL/min | 1.25 gm (IV) q8h |
| CrCl 16–30 mL/min | 0.94 gm (IV) q12h |
| CrCl 6–15 mL/min | 0.94 gm (IV) q24h |
| CrCl < 5 mL/min | 0.94 gm (IV) q48h |
| Post–HD dose | 0.94 gm (IV) q48h |
| Post-PD dose | No data |
| CVVH dose | No data |
| Hepatic insufficiency | No change |

**Drug Interactions:** None
**Adverse Effects:** Headache, dizziness, insomnia, constipation, diarrhea, abdominal pain, nausea, vomiting, ↑ SGOT/SGPT, drug fever/rash, phlebitis, hypersensitivity reactions, C. difficile diarrhea/colitis.
**Allergic Potential:**
**Safety in Pregnancy:** B

**Comments:** Avibactam is a novel, non-β-lactam, β-lactamase inhibitor, which acts a reversible inhibitor (compared to irreversible action of other β-lactamase inhibitors) and has an expanded spectrum of β-lactamase inhibition including: class A (includes Klebsiella pneumoniae carbapenemase-KPC), class C, some class D. Avibactam's spectrum does not include class B β-lactamase (metalloenzymes). Use of avibactam with ceftazidime restores susceptibility against ceftazidime-nonsusceptible organisms. Active against multi-drug resistant Gram negative organisms, including P. aeruginosa, ESBL producing pathogens, and CRE. Infuse slowly over 2 hours.
For complicated intra-abdominal infections (cIAI), caftazidime/avibactam must be used in combination with metronidazole.

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**

Ehmann DE, Jahic H, Ross PL, et al. Kinetics of avibactam inhibition against Class A, C, and D beta-lactamases. J Biol Chem. 288:27960-27971, 2013.

Keepers TR, Gomez M, Celeri C, et al. Bactericidal activity, absence of serum effect, and time-kill kinetics of ceftazidime-avibactam against beta-lactamase-producing Enterobacteriaceae and Pseudomonas aeruginosa. Antimicrob Agents Chemother. 58:5297-5305, 2014.

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Website: www.pdr.net

## Ceftibuten (Cedax)

**Drug Class:** 3rd generation oral cephalosporin.
**Usual Dose:** 400 mg (PO) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 18 mcg/mL*
*Bioavailability: 80%*
*Excreted unchanged: 56% (urine); 39% (fecal) Serum half-life (normal/ESRD): 2.4/22 hrs*
*Plasma protein binding: 65%*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–50 mL/min | 200 mg (PO) q24h |
| CrCl < 30 mL/min | 100 mg (PO) q24h |
| Post–HD dose | 400 mg (PO) |
| Post–PD dose | 200 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 200 mg (PO) q24h |

| | |
|---|---|
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Little/no activity against S. aureus/S. pneumoniae.
**Cerebrospinal Fluid Penetration:** < 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

Andrews JW, Wise R, Baldwin DR, et al. Concentrations of ceftibuten in plasma and the respiratory tract following a single 400 mg oral dose. Int J Antimicrob Agents 5:141–144, 1995.
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Website: www.pdr.net

## Ceftizoxime (Cefizox)

**Drug Class:** 3rd generation cephalosporin.
Usual Dose: 2 gm (IV) q8h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
Pharmacokinetic Parameters:
*Peak serum level: 132 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 1.7/35 hrs*
*Plasma protein binding: 30%*
*Volume of distribution ($V_d$): 0.32 L/kg*
**Primary Mode of Elimination:** Renal
Dosage Adjustments*

| | |
|---|---|
| CrCl 50–80 mL/min | 1 gm (IV) q8h |
| CrCl 10–50 mL/min | 1 gm (IV) q12h |
| CrCl < 10 mL/min | 1 gm (IV) q24h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 1 gm (IV) |
| CVVH/CVVHD/CVVHDF dose | 1 gm (IV) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
Allergic Potential: High
Safety in Pregnancy: B
**Comments: PRNG dose: 500 mg (IM) × 1 dose.**

Meningeal dose = 3 gm (IV) q6h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 50%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

Klein NC, Cunha BA. Third-generation cephalosporins. Med Clin North Am 79:705–19, 1995.
Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
Marshall WF, Blair JE. The cephalosporins. Mayo Clin Proc 74:187–95, 1999.
Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ceftolozane/Tazobactam (Zerbaxa)

**Drug Class:** Anti-pseudomonal cephalosporin/β-lactamase inhibitor.
Usual Dose: 1.5 gm (IV) q8h
**Spectrum:** (see ***Susceptibility Profiles*** pp. 194–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 74.4/34 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 95/80%*
*Serum half-life (normal/ESRD):*
*Plasma protein binding: 16-21%/30%*
*Volume of distribution ($V_d$): 0.21 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments**

| | |
|---|---|
| CrCl 30–50 mL/min | 750 mg (IV) q8h |
| CrCl 15–29 mL/min | 375 mg (IV) q8h |
| HD dose | LD of 750 mg (IV) × 1 dose, 150 mg (IV) q8h (on HD days, administer immediately following HD |
| PD dose | No data |
| CVVH/CVVHD/ CVVHDF dose | No data |
| Moderate-severe hepatic insufficiency | No change |

**Drug Interactions:** No significant interactions are anticipated between ceftolozane/tazobactam and substrates, inhibitors and inducers of cytochrome P450 enzymes

**Adverse Effects:** Drug fever/rash, nausea, diarrhea, headache, insomnia, constipation, C. difficile diarrhea/colitis, mild transient ↑) SGOT/SGPT, hypotension, ↑ platelets (thrombocytosis), anemia.
**Allergic Potential:**
**Safety in Pregnancy:** Category B
**Comments:** Useful for MDR Gram Negative pathogens, including P. aeruginosa and ESBL producing pathogens. Ineffective against CRE. For treating cIAI, must add Metronidazole 500 mg (IV) q8h.

(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**

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Miller B, Hershberger E, Benziger D, et al. Pharmacokinetics and safety of intravenous ceftolozane/tazobactam in healthy adult subjects following single and multiple ascending doses. Antimicrob Agents Chemo 56:3086-3091, 2012.

Sorbera M, Chung E, Ho CW, et al. Ceftolozane/tazobactam: a new option in the treatment of complicated gram-negative infections. P & T 39:825-832, 2014.

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Website: www.pdr.net

## Ceftriaxone (Rocephin)

**Drug Class:** 3rd generation cephalosporin.
**Usual Dose:** 1–2 gm (IV) q24h (see comments).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 151–257 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine/feces): 33–67%*
*Serum half-life (normal/ESRD): 8/16 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 0.08–0.3 L/kg*
**Primary Mode of Elimination:** Renal/hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–HFHD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change (max dose: 2 gm/d) |

**Drug Interactions:** May cause intravascular precipitation when co-administered with calcium-containing solutions/products.
**Adverse Effects:** Drug fever/rash, non-C. difficile diarrhea, pseudobiliary lithiasis, hemolytic anemia, may interfere with platelet aggregation, thrombocytosis.
**Allergic Potential:** High
**Safety in Pregnancy:** B. **Avoid near term in 3rd trimester** (↑ incidence of kernicterus in newborns)

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 500%
(also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**


Araz N, Okan V, Demirci M, et al. Pseudolithiasis due to ceftriaxone treatment for meningitis in children: report of 8 cases. Tohoku J Exp Med 211:285–290, 2007.

Borg R, Dotevall L, Hagberg L, et al. Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. Scand J Infect Dis 37:449–454, 2005.

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Dietrich ES, Bieser U, Frank U, et al. Ceftriaxone versus other cephalosporins for perioperative antibiotic prophylaxis: a meta analysis of 43 randomized controlled trials. Chemotherapy 48:49–56, 2002.

Faella F, Pagliano P, Fusco U, Attanasio V, Conte M. Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: a case series including penicillin-resistant strains. Clin Micrbiol Infect 12:391–4, 2006.

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File TM Jr. Clinical implications and treatment of multiresistant Streptococcus pneumoniae pneumonia. Clin Microbiol Infect 12:31–41, 2006.

File TM Jr, Low DE, Edckburg PB, et al. Efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis 51:1395–1405, 2011.

Freeman CD, Nightingale CH, Nicolau DP, et al. Serum bactericidal activity of ceftriaxone plus metronidazole against common intra-abdominal pathogens. Am J Hosp Pharm 51:1782–7, 1994.

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Klein NC, Cunha BA. Third generation cephalosporins. Med Clin North Am 79:705–19, 1995.

Lamb HM, Ormrod D, Scott LJ, et al. Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. Drugs 62:1041–89, 2002.


"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. Diagn Microbiol Infect Dis 57:13S–18S, 2007.
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Savaris RF, Teixeria LM, Torres TG, et al. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 110:53–60, 2007.
Shelburne SA 3rd, Greenburg SB, Aslam S, et al. Successful ceftriaxone therapy of endocarditis due to penicillin non-susceptible viridans streptococci. J Infect 54:e108–e110, 2007.
Woodfield JC, Van Rij AM, Pettigrew RA, et al. A comparison of the prophylactic efficacy of ceftriaxone and cefotaxime in abdominal surgery. Am J Surg 185:45–9, 2003.
Website: www.pdr.net

## Cefuroxime (Kefurox, Zinacef, Ceftin)

**Drug Class:** 2nd generation IV/oral cephalosporin.
**Usual Dose:** 1.5 gm (IV) q8h; 500 mg (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 100 (IV)/7 (PO) mcg/mL*
*Bioavailability:* 52%
*Excreted unchanged (urine): 89%*
*Serum half-life (normal/ESRD): 1.2/17 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 0.15 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 20 –80 mL/min | No change |
| CrCl 10–20 mL/min | 750 mg (IV) q12h 500 mg (PO) q12h |
| CrCl < 10 mL/min | 750 mg (IV) q24h 250 mg (PO) q24h |
| Post–HD dose | 750 mg (IV) 250 mg (PO) |
| Post–PD dose | 750 mg (IV) 250 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 1 gm (IV) q12h 500 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Oral preparation penetrates oral/respiratory secretions well. **PPNG dose:** 1 gm (IM) × 1 dose. **Ineffective for H. influenzae meningitis prophylaxis or therapy.**

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

Alvarez-Sala JL, Kardos P, Martinez-Beltran, et al. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents and Chemother 50:1762–67, 2006.
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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clin Ther 24:1134–47, 2002.
Gentry LO, Zeluff BJ, Cooley DA. Antibiotic prophylaxis in open-heart surgery: A comparison of cefamandole, cefuroxime, and cefazolin. Ann Thorac Surg 46:167–71, 1988.
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Perry Cm, Brogden RN. Cefuroxime axetil. A review of its antibacterial activity, pharmacokinetic properties, and therapeutic efficacy. Drugs 52:125–58, 1996.
Website: www.pdr.net

## Cephalexin (Keflex)

**Drug Class:** 1st generation oral cephalosporin.
**Usual Dose:** 500 mg (PO) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 18 mcg/mL*
*Bioavailability: 99%*
*Excreted unchanged (urine): > 90%*
*Serum half-life (normal/ESRD): 0.7/16 hrs*
*Plasma protein binding: 10%*
*Volume of distribution ($V_d$): 0.35 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 500 mg (PO) q12h |
| CrCl < 10 mL/min | 500 mg (PO) q24h |
| Post–HD dose | 500 mg (PO) |
| Post–PD dose | 250 mg (PO) |
| CVVH/CVVHD/CVVHDF dose | 250 mg (PO) q8h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Highly active against S. aureus (MSSA) and Group A streptococci. **Limited activity against H. influenzae.**

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 200%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**

Chow M, Quintiliani R, Cunha BA, et al. Pharmacokinetics of high dose oral cephalosporins. J Pharmacol 19:185–194, 1979.
Cunha BA. Cephalexin remains the preferred antibiotic for uncomplicated cellulitis: revisited. J Chemo. 26:65-66, 2014.
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Cunha BA. Oral antibiotic therapy of serious systemic infections. Med Clin N Am 90:1197–1222, 2006.
Marshall WF Blair JE. The cephalosporins. Mayo Clin Proc 74:187–95, 1999.
Smith GH. Oral cephalosporins in perspective. DICP 24:45–51, 1990.
Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Chloramphenicol (Chloromycetin)

**Drug Class:** No specific class.
**Usual Dose:** 500 mg (IV/PO) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 9 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 10%*
*Serum half-life (normal/ESRD): 2.5/3 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 1 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD dose | 500 mg (IV/PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Barbiturates (↑ barbiturate effect, ↓ chloramphenicol effect); cyclophosphamide (↑ cyclophosphamide toxicity); cyanocobalamin, iron (↓ response to interacting drug); warfarin (↑ INR); phenytoin (↑ phenytoin toxicity); rifabutin, rifampin (↓ chloramphenicol levels); sulfonylureas (↑ sulfonylurea effect, hypoglycemia).
**Adverse Effects:**
Dose–related bone marrow suppression
Reversible. Bone marrow aspirate shows vacuolated WBCs ("chloramphenicol effect," not toxicity). Does not precede aplastic anemia

Idiosyncratic bone marrow toxicity
Irreversible aplastic anemia. May occur after only one dose; monitoring with serial CBCs is useless. Very rare. Usually associated with IM, intraocular, or oral administration. Rarely, if ever, with IV chloramphenicol.
**Allergic Potential:** Low
**Safety in Pregnancy:** A
**Comments:** Incompatible in solutions containing diphenylhydantoin, methylprednisone, aminophylline, ampicillin, gentamicin, erythromycin, vancomycin. **Dose-related marrow suppression is common, and reversible.** Hepatic toxicity related to prolonged/high doses (> 4 gm/d). **Oral administration results in higher serum levels than IV administration.** Do not administer IM. Chloramphenicol is inactivated in bile. **Urinary concentrations are therapeutically ineffective.**

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 90%
Inflamed meninges = 90%
**Bile Penetration:** 0%
(also see ***Antibiotic Pearls & Pitfalls*** p. 513).

**REFERENCES:**

Ariyal A, Basnyat B, Koirala S, et al. Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomized, controlled trial. Lancet Infect Dis 11:445–454, 2011.
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Feder HM Jr, Osier C, Maderazo EG. Chloramphenicol: A review of its use in clinical practice. Rev Infect Dis 3:479–91, 1981.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Kasten MJ. Clindamycin, metronidazole, and chloramphenicol. Mayo Clin Proc 74:825–33, 1999.
Safdar A, Bryan CS, Stinson S, et al. Prosthetic valve endocarditis due to vancomycin-resistant Enterococcus faecium: treatment with chloramphenicol plus minocycline. Clin Infect Dis 34:61–3, 2002.
Smilack JD, Wilson WE, Cocerill FR 3rd. Tetracycline, chloramphenicol, erythromycin, clindamycin, and metronidazole. Mayo Clin Proc 66:1270–80, 1991.
Wareham DW, Wilson P. Chloramphenicol in the 21st century. Hosp Med 63:157–61, 2002.
Website: www.pdr.net

## Cidofovir (Vistide)

**Drug class:** HSV, CMV (see comments).
**Usual dose:** 5 mg/kg (IV) weekly for 2 weeks, then 5 mg/kg every 2 weeks (for CMV retinitis in HIV patients, patients must have all of the following: SrCr < 1.5 mg/dL, CrCl > 55 mL/min, urine protein < 100 mg/dL).
**Pharmacokinetic Parameters:**
*Peak serum level: 19.6 mcg/mL*
*Bioavailability: not applicable*
*Excreted unchanged: 1%*
*Serum half-life (normal/ESRD): 2.2 h/no data*
*Plasma protein binding: 6%*
*Volume of distribution ($V_d$): 0.54 l/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| Cr increase of 0.3–0.4 mg/dL above baseline | 3 mg/kg (IV) (see usual dose for duration) |
| Cr increase of ≥ 0.5 mg/dL or + 3 proteinuria | Discontinue cidofovir |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Amphotericin B, aminoglycosides, foscarnet, pentamidine, tenofovir, zidovudine (↑ nephrotoxicity).
**Adverse Effects:** Nephrotoxicity; neutropenia; nausea, vomiting associated with probenecid, take with food; metabolic acidosis; decreased intraocular pressure; anterior uveitis and iritis.
**Contraindications:** if CrCl < 55 ml/min.
**Allergic Potential:** Low for cidofovir, high for probenecid.
**Safety in Pregnancy:** C
**Comments:** All patients should receive probenecid (2 g (PO) 3 hours before infusion start, then 1 g at 2 and again at 8 hours after completion of cidofovir infusion, take with food to minimize nausea and vomiting) and hydration with at least 1 L of normal saline with each dose of cidofovir; infuse over 1 hour; monitor neutrophils, growth factor support may be needed; contraindicated in severe hypersensitivity to probenecid or other sulfa drugs; direct ocular injection is contraindicated; effective contraception required for male and female patients. ***Highly active against CMV and HSV. Some activity against BK virus, JC virus, VZV, and adenoviruses. No activity against HHV-6, EBV, RSV, or influenza viruses.***

**Cerebrospinal Fluid Penetration:** < 1%

**REFERENCES:**

Ganguly N, Clough LA, Dubois LK, et al. Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogenic hematopoietic stem cell transplantation: a retrospective analysis of an algorithmic approach. Transpl Infect Dis 12:406–411, 2010.
Hua DK, Howard K, Craig JC, et al. Cost-effectiveness of cidofovir treatment of polyomavirus nephropathy in kidney transplant recipients. Transplantation 27:188–94, 2012.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Lurrain NS, Chou S. Antiviral drug resistance of human cytomegalovirus, Clin Microbiol Rev 23:689–712, 2010.
Pallet N, Burgard M, Quamouss O, et al. Cidofovir may be deleterious in BK virus-associated nephropathy. Transplantation 89:1542–1544, 2010.
Website: www.pdr.net

## Ciprofloxacin (Cipro)

**Drug Class:** Fluoroquinolone.
**Usual Dose:** 400 mg (IV) q12h; 500–750 mg (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** High (S. pneumoniae, E. coli, P. aeruginosa; ↑ prevalence of MRSA)
**Pharmacokinetic Parameters:**
*Peak serum level: 4.6 (IV)/2.9 (PO) mcg/mL*
*Bioavailability: 70%*
*Excreted unchanged (urine): 70%*
*Serum half-life (normal/ESRD): 4/8 hrs*
*Plasma protein binding: 20–40%*
*Volume of distribution ($V_d$): 2.5 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–50 mL/min | 400 mg (IV) q12h 500 mg (PO) q12h |
| CrCl < 30 mL/min | 400 mg (IV) q24h 500 mg (PO) q24h |
| Post–HD dose | 200–400 mg (IV) 250–500 mg (PO) |
| Post–PD dose | 200–400 mg (IV) 250–500 mg (PO) |
| CVVH/CVVHD/CVVHDF dose | 400 mg (IV) q12h 250 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$ antacids, citrate/citric acid, dairy products (↓ absorption of ciprofloxacin only if taken together); caffeine, cyclosporine, theophylline (↑ interacting drug levels); cimetidine (↑ ciprofloxacin levels); foscarnet (↑ risk of seizures); oral hypoglycemics (slight ↑ or ↓ in blood glucose); NSAIDs (may ↑ risk of seizures/CNS stimulation); phenytoin (↑ or ↓ phenytoin levels); probenecid (↑ ciprofloxacin levels); warfarin (↑ INR).
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis, headache, dizziness, insomnia, malaise, delirium, encephalopathy, seizures. FQ use has an increased risk of tendinitis/tendon rupture. Risk in highest in the elderly, those on steroids, and those with heart, lung or renal transplants. Peripheral neuropathy may occur early and may be permanent. May ↑ $QT_c$. Vitamins C and E (↓ ciprofloxacin levels).
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Enteral feeding decreases ciprofloxacin absorption ≥ 30%. Use with caution in patients with severe renal insufficiency or seizure disorder. Administer 2 hours before or after $H_2$ antagonists, omeprazole, sucralfate, calcium, iron, zinc, multivitamins, or aluminum/magnesium containing medications. Administer ciprofloxacin (IV) as an intravenous infusion over 1 hour.
**Nosocomial pneumonia dose:**
400 mg (IV) q8h.
**↑ incidence of C. difficile diarrhea/colitis with PPIs (for patients on PPIs during FQ therapy, D/C PPIs or switch to $H_2$ blocker for duration of FQ therapy).**

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 10%
Inflamed meninges = 26%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**
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Howell MD, Novack V, Grgurich P, et aJ. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med 170:784–790, 2010.
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Linsky A, Gupta K, LawlerEV, et al. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 170:772–778, 2010.
Masadeh MM, Mhaidat NM, Alzoubi KH, et al. Ciprofloxacin-induced antibacterial activity is reversed by vitamin E and vitamin C. Curr Microbiol 64:457–62, 2012.
Miliani K, L'Heriteau, F, Lacave L, et al. Imipenem and ciprofloxacin consumption as factors associated with high incidence rates of resistance Pseudomonas aeruginosa in hospitals in northern France. J Hosp Infect 77:343–347, 2011.
Sanders CC. Ciprofloxacin: In vitro activity, mechanism of action, resistance. Rev Infect Dis 10:516–27, 1998.
Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomized, open-label and double-blind, placebo-controlled, non-inferiority trail. Lancet 4:484–90, 2012.
Website: www.pdr.net

## Ciprofloxacin Extended-Release (Cipro XR)

**Drug Class:** Fluoroquinolone.
**Usual Dose:** 500 mg or 1000 mg (PO) q24h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** High (S. pneumoniae, E. coli, P. aeruginosa; ↑ prevalence of MRSA)
**Pharmacokinetic Parameters (500/1000 mg):**
*Peak serum level: 1.59/3.11 mcg/mL*
*Bioavailability: 70%*
*Excreted unchanged (urine): 50–70%; 22% excreted as active metabolite*
*Serum half-life: 6.6/6.3 hrs*
*Plasma protein binding: 20–40%*
*Volume of distribution ($V_d$): 2.5 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | No change for 500 mg dose; reduce 1000 mg dose to 500 mg (PO) q24h |
| Post–HD/PD dose | 500 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | same as for CrCl < 30 mL/min |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$ antacids, citrate/citric acid, dairy products, didanosine (↓ absorption of ciprofloxacin only if taken together); caffeine, cyclosporine,

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

theophylline (↑ interacting drug levels); cimetidine (↑ ciprofloxacin levels); foscarnet (↑ risk of seizures); insulin, oral hypoglycemics (slight ↑ or ↓ in blood glucose); NSAIDs (may ↑ risk of seizures/CNS stimulation); phenytoin (↑ or ↓ phenytoin levels); probenecid (↑ ciprofloxacin levels); warfarin (↑ INR).

**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis, seizures. FQ use has an increased risk of tendinitis/tendon rupture. Risk in highest in the elderly, those on steroids, and those with heart, lung or renal transplants.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments: Uncomplicated UTI (acute cystitis) dose:** 500 mg (PO) q24h; **complicated UTI/acute uncomplicated pyelonephritis dose:** 1000 mg (PO) q24h. May be administered with or without food. Administer at least 2 hours before or 6 hours after $H_2$ antagonists, omeprazole, sucralfate, calcium, iron, zinc, multivitamins, or aluminum/magnesium containing medications.

**↑ incidence of C. difficile diarrhea/colitis with PPIs (for patients on PPIs during FQ therapy, D/C PPIs or switch to $H_2$ blocker for duration of FQ therapy).**

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 10%
Inflamed meninges = 26%

**Bile Penetration:** 3000%

(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

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Website: www.pdr.net

## Clarithromycin (Biaxin)

**Drug Class:** Macrolide.

**Usual Dose:** 500 mg (PO) q12h.

**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

**Resistance Potential:** High (S. pneumoniae, GAS, MSSA)

**Pharmacokinetic Parameters:**
*Peak serum level: 1–4 mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 20%*
*Serum half-life (normal/ESRD): 3–7/4 hrs*
*Plasma protein binding: 70%*
*Volume of distribution ($V_d$): 3 L/kg*

**Primary Mode of Elimination:** Hepatic

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 250 mg (PO) q12h |
| Post–HD dose | 500 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Amiodarone, procainamide, sotalol, astemizole, terfenadine, cisapride, pimozide (may ↑ QT interval, torsade de pointes); carbamazepine (↑ carbamazepine levels, nystagmus, nausea, vomiting, diarrhea); cimetidine, digoxin, ergot alkaloids, midazolam, triazolam, phenytoin, ritonavir, tacrolimus, valproic acid (↑ interacting drug levels); clozapine, corticosteroids (not studied); cyclosporine (↑ cyclosporine levels with toxicity); efavirenz (↓ clarithromycin levels); rifabutin, rifampin (↓ clarithromycin levels, ↑ interacting drug levels);

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

statins (↑ risk of rhabdomyolysis); theophylline (↑ theophylline levels, nausea, vomiting, seizures, apnea); warfarin (↑ INR); zidovudine (↓ zidovudine levels).

**Adverse Effects:** Nausea, vomiting, GI upset, **Non-*C. difficile* diarrhea,** abdominal pain. May ↑ $QT_c$; avoid with other medications that prolong the $QT_c$ interval and in patients with cardiac arrhythmias/heart block.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Peculiar "aluminum sand" taste sensation on swallowing.

**Cerebrospinal Fluid Penetration:** < 10%

**Bile Penetration:** 7000%

(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**

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Website: www.pdr.net

## Clarithromycin XL (Biaxin XL)

**Drug Class:** Macrolide.
**Usual Dose:** 1 gm (PO) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** High (S. pneumoniae, GAS, MSSA)
**Pharmacokinetic Parameters:**
*Peak serum level: 3 mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 20%; 10–15% excreted as active metabolite*
*Serum half-life (normal/ESRD): 4/4 hrs*
*Plasma protein binding: 70%*
*Volume of distribution ($V_d$): 3 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 500 mg (PO) q24h |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Amiodarone, procainamide, sotalol, astemizole, terfenadine, cisapride, pimozide (may ↑ QT interval, torsade de pointes); carbamazepine (↑ carbamazepine levels, nystagmus, nausea, vomiting, diarrhea); cimetidine, digoxin, ergot alkaloids, midazolam, triazolam, phenytoin, ritonavir, tacrolimus, valproic acid (↑ interacting drug levels); clozapine, corticosteroids (not studied); cyclosporine (↑ cyclosporine levels with toxicity); efavirenz (↓ clarithromycin levels); rifabutin, rifampin (↓ clarithromycin levels, ↑ interacting drug levels); statins (↑ risk of rhabdomyolysis); theophylline (↑ theophylline levels, nausea, vomiting, seizures, apnea); warfarin (↑ INR); zidovudine (↓ zidovudine levels).
**Adverse Effects:** Nausea, vomiting **Non-C. difficile diarrhea.** May ↑ $QT_c$; avoid with other medications that prolong the $QT_c$ interval and in patients with cardiac arrhythmias/heart block.
**Allergic Potential: Low**
**Safety in Pregnancy:** C
**Comments:** Two 500 mg tablets of XL preparation permits once daily dosing and decreases GI intolerance.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 7000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

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Website: www.pdr.net

## Clindamycin (Cleocin)

**Drug Class:** Lincosamide.
**Usual Dose:** 600 mg (IV) q8h; 150–300 mg (PO) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 2.5–10 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 10%; 3.6% excreted as active metabolite*
*Serum half-life (normal/ESRD): 2.4/4 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 1 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Muscle relaxants, neuromuscular blockers (↑ apnea, respiratory paralysis); kaolin (↓ clindamycin absorption); theophylline (↑ theophylline levels, seizures).
**Adverse Effects:** C. difficile diarrhea/colitis, neuromuscular blockade.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** ***Anti-spasmodics contraindicated in C. difficile diarrhea.*** C. difficile diarrhea more common with PO vs. IV clindamycin. ***Clindamycin misses some Peptostreptococci, Fusobacteria, non-perfringens Clostridia, and Prevotella.***
**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 300%
(also see ***Antibiotic Pearls & Pitfalls*** p. 513).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Colistin (Coly-Mycin M)

**Drug Class:** Cell membrane altering antibiotic.
**Usual Dose:** 5 mg/kg (IV) q8h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 5 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 9/13 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 0.09 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–49 mL/min | 3.5 mg/kg (IV) q24h |
| CrCl 10–29 mL/min | 2.5 mg/kg (IV) q24h |
| CrCl < 10 mL/min | 1.5 mg/kg (IV) q24h |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 2.5 mg/kg (IV) q48h |
| Mild hepatic insufficiency | No change |
| Moderate—severe hepatic insufficience | No change |

**Drug Interactions:** Neuromuscular blocking agents (↑ neuromuscular blockade); nephrotoxic drugs (↑ nephrotoxic potential).
**Adverse Effects:** Dose dependent/reversible nephrotoxic potential (acute tubular necrosis). Paresthesias, vertigo, dizziness, slurred speech, blurry vision, respiratory arrest.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** 1 mg = 12,500 U. Colistin (Polymyxin E) has **less nephrotoxic potential than previously thought. Useful for MDR P. aeruginosa and Acinetobacter species.** For P. aeruginosa or Acinetobacter meningitis *also give amikacin 10–40 mg (IT) q24h or colistin 10 mg (IT) q24h*. **Intrathecal colistin dose:** 10 mg (IT) Q24h. **Nebulizer dose:** 80 mg in saline q8h; for recurrent infection use 160 mg q8h (freshly prepare solution and use within 24 hours). If possible, avoid aerosolized colistin, which may result in pulmonary/systemic toxicity

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

due to the polymyxin E1 metabolite. **Continuous infusion dose:** give ½ of daily dose (IV) over 5–10 min, then give remaining ½ dose (in D5W or NS) 1 hour after initial dose over next 24 hours.

**Cerebrospinal Fluid Penetration:** < 25% (also see ***Antibiotic Pearls & Pitfalls*** p. 520).

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Website: www.pdr.net

## Cycloserine (Seromycin)

**Drug Class:** TB drug.
**Usual Dose:** 250 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 20 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 65%*
*Serum half-life (normal/ESRD): 10–25 hrs/no data*
*Plasma protein binding: No data*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl 10–50 mL/min | 250 mg (PO) q12–24h |
| CrCl < 10 mL/min | 250 mg (PO) q24h |
| Post–HD dose | None |
| Post–PD dose | 250 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Alcohol (seizures); ethambutol, ethionamide (drowsiness, dizziness); phenytoin (↑ phenytoin levels).
**Adverse Effects:** Peripheral neuropathy, seizures (dose related), psychosis/delirium.
Allergic Potential: Low
Safety in Pregnancy: C
**Comments:** Avoid in patients with seizures. Ethambutol, ethionamide, or ethanol may increase CNS toxicity.
Meningeal dose = usual dose.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 90%
Inflamed meninges = 90%

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Website: www.pdr.net

## Dalbavancin (Dalvance)

**Drug Class:** Lipoglycopeptide
**Usual Dose:** 1 gm (IV) × 1 dose, then 500 mg (IV) × 1 dose 7 days later.

**Spectrum:** (see ***Susceptibility Profiles*** pp. 198-202.
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 287 mcg/mL*
*Bioavailability not applicable*
*Excreted unchanged (urine/feces): 33%/20%*
*Serum half-life (nornal/ESRD): 346 h/376 h*
*Plasma protein binding: 93%*
*Volume of distribution ($V_d$): 0.1–0.19 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 750 mg (IV) then 325 mg (IV) 7 days later |
| Post–HD dose | No change |
| Post–PD dose | No change |
| CVVH dose | No data |
| Hepatic insufficiency | No change |

**Drug Interactions:** None
**Adverse Effects:** Headache, nausea, vomiting, diarrhea, rash, pruritus, increased AST/ALT, C. difficile.
**Allergic Potential:** Moderate
**Safety in Pregnancy:** C
**Comments:** Infuse slowly over 30 minutes to avoid "Red Man Syndrome"; hypersensitivity reactions (use caution if patient had previous hypersensitivity reaction to other glycopeptides, e.g. vancomycin).

(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Dapsone

**Drug Class:** Antiparasitic, anti-leprosy, anti-PCP drug.
**Usual Dose:** 100 mg (PO) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 1.8 mcg/mL*
*Bioavailability: 85%*
*Excreted unchanged (urine): 10%*
*Serum half-life (normal/ESRD): 25/30 hrs*
*Plasma protein binding: 80%*
*Volume of distribution ($V_d$): 1.2 L/kg*
**Primary Mode of Elimination:** Hepatic/renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No data |

**Drug Interactions:** Didanosine (↓ dapsone absorption); oral contraceptives (↓ oral contraceptive effect); pyrimethamine, zidovudine (↑ bone marrow suppression); rifabutin, rifampin (↓ dapsone levels); trimethoprim (↑ dapsone and trimethoprim levels, methemoglobinemia).
**Adverse Effects:** Drug fever/rash, nausea, vomiting, hemolytic anemia in G6PD deficiency, methemoglobinemia.
**Allergic Potential:** High
**Safety in Pregnancy:** C
**Comments: Useful in sulfa (SMX) allergic patients**. Avoid, if possible, in G6PD deficiency or hemoglobin M deficiency.
**PCP prophylaxis dose:** 100 mg (PO) q24h. **PCP therapy dose:** 100 mg (PO) q24h.

**Cerebrospinal Fluid Penetration:** < 50%

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Daptomycin (Cubicin)

**Drug Class:** Lipopeptide.
**Usual Dose:** Complicated skin/skin structure infections: 4 mg/kg (IV) q24h. Bacteremia, endocarditis: 6 mg/kg (IV) q24h. Bacteremia, endocarditis unresponsive to 6 mg/kg (IV) q24h × 3 days: 12 mg/kg (IV) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level:*
*4 mg/kg = 58 mcg/mL; 6 mg/kg = 99 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80%*
*Serum half-life (normal/ESRD): 8.1/29.8 hrs*
*Plasma protein binding: 92%*
*Volume of distribution ($V_d$): 0.096 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | No change |
| CrCl < 30 mL/min | 4 mg/kg (IV) q48h or 6 mg/kg (IV) q48h or 12 mg/kg (IV) q48h |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 8 mg/kg (IV) q48h |
| HD q 48–72h dose | 10 mg/kg (IV) q HD* |
| Moderate—severe hepatic insufficiency | No change |

*Give at end of HD.
**Drug Interactions:** Warfarin/statin (no significant interaction in small number of volunteers; consider temporary suspension of statins during daptomycin use).
**Adverse Effects:** Constipation, nausea, headache, peripheral neuropathy. Rarely, ↑ CPK; in clinical trials, same or less (0.2%) than comparators. Eosinophilic pneumonia (rare and reversible when drug discontinued). False-positive ↑ INR.
**Allergic Potential:** No data
**Safety in Pregnancy:** B
**Comments:** Concentration-dependent killing may be enhanced with an initial dose of gentamicin. Antecedent vancomycin (↑ cell wall thickness of staphylococci) predisposes to daptomycin resistance (penetration mediated resistance). ↑ daptomycin MICs with strains of *S. aureus* may be ↓ by adding a β–lactam (to ↑ cell wall permeability) for staphylococci add nafcillin to daptomycin; for enterococci add ampicillin to daptomycin. **High-dose daptomycin 12 mg/kg (IV) q24h has been used for MSSA/MRSA bacteremias/ABE unresponsive to other an-tistaphylococcal drugs without toxicity.** Post-antibiotic effect (PAE) up to 6 hours. For rapid effect or need to limit infusion volume, daptomycin ***may be given IV push over 5 minutes*** (500 mg dose given in 10 mL; 1 g dose given in 20 mL). Cannot be given IM.

**Cerebrospinal Fluid Penetration:** ~ 5%
(also see ***Antibiotic Pearls & Pitfalls*** p. 518).

**REFERENCES:**
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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Darunavir (Prezista) DRV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** Treatment naive / treatment experienced with no darunavir resistance-associated substitutions: 800 mg (PO) q24h with ritonavir 100 mg (PO) q24h. Treatment

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

experienced / genotyping not available: 600 mg (PO) q12h with ritonavir 100 mg (PO) q12h.

**Pharmacokinetic Parameters:**

*Peak serum level: 3578 ng/mL*
*Bioavailability: 37% (alone) 82% (with ritonavir)*
*Excreted unchanged: 41.2% (feces), 7.7% (urine)*
*Serum half-life (normal/ESRD): 15/15 hrs*
*Plasma protein binding: 95%*
*Volume of distribution ($V_d$): not studied*

**Primary Mode of Elimination:** Fecal/Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | No data |
| Post–HD dose | No change |
| Post–PD dose | No change |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild—moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Efavirenz | No data |
| Nevirapine | No change |
| Didanosine | 1 hour before or 1 hour after darunavir |
| Tenofovir | No change |
| Fosamprenavir | No change |
| Indinavir | No data |
| Lopinavir/ritonavir | Avoid |
| Saquinavir | Avoid |
| Rifabutin | 150 mg (PO) qod |

**Drug Interactions:** Indinavir, ketaconazole, nevirapine, tenofovir (↑ darunavir levels); lopinavir/ritonavir, saquinavir, efavirenz (↓ darunavir levels); concomitant administration of darunavir/ritonavir with agents highly-dependent on CYP3A for clearance, astemizole, cisapride, dihydroergotamine, ergonovine, ergotamine, methylergonovine, midazolam, pimozide, terfenadine, midazolam, triazolam (may ↓ darunavir levels and ↓ effectiveness); sildenafil, vardenafil, tadalafil (↑ PDE-5 inhibitors; sildenafil do not exceed 25 mg in 48 hrs, vardenafil do not exceed 2.5 mg in 72 hrs, or tadalafil do not exceed 10 mg in 72 hrs); clarithromycin (↑ $QT_c$).

**Adverse Effects:** Rash, diarrhea, nausea, headache, nasopharyngitis drug induced hepatitis. Use with caution in patients with preexisting liver disease. New-onset or exacerbations of pre-exisiting diabetes mellitus and hyperglycemia, and increased bleeding in hemophiliacs (class effect). Immune reconstitution syndrome.

**Contraindicated:** lovastatin, simvastatin, atorvastatin (> 20 mg/day), rifapentine, boceprevir, telaprevir.

**Allergic Potential:** High (see comments)

**Safety in Pregnancy:** C

**Comments:** Always take with food (increases AUC, Cmax by approximately 30%). Must be given with ritonavir to boost bioavailability. Darunavir contains a sulfonamide moiety (as do fosamprenavir and tipranavir); use with caution in patients with sulfonamide allergies. astemizole, terfenadine, ergot derivatives dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, triazolam, are contraindicated with darunavir. Phenobarbital, phenytoin, carbamazepine, or products containing

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

St. John's wort, rifampin. Lovostatin and simavastatin may be taken with caution.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

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Website: www.pdr.net

## Delavirdine (Rescriptor) DLV

**Drug Class:** HIV NNRTI (non-nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 400 mg (PO) q8h.
**Pharmacokinetic Parameters:**
*Peak serum level: 35 mcg/mL*
*Bioavailability: 85%*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 5.8 hrs/no data*
*Plasma protein binding: 98%*
*Volume of distribution ($V_d$): 0.5 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | Use with caution |
| Severe hepatic insufficiency | Use with caution |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Amprenavir | Increased agenerase levels |
| Efavirenz | No data |
| Indinavir | Indinavir 600 mg q8h |
| Lopinavir/ritonavir | No data |
| Nelfinavir | No information (monitor for neutropenia) |
| Nevirapine | No data |
| Ritonavir | Delavirdine: no change; ritonavir: No data |
| Saquinavir soft-gel | Saquinavir soft-gel 800 mg q8h (monitor transaminases) |
| Rifampin, rifabutin | Avoid |
| Statins | Avoid |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** With antiretrovirals adjust according to table above. Avoid in combination with rifabutin rifampin. Contraindicated with astemizole, terrenadine, Dihydroergotamine, ergonovine, ergotamine, methylergonovine, Cisapride, Pimozide, Alprazolam, midazolam, triazolam. Phenytoin may decrease delaviridine levels. Clarithromycin, dapsone nefedipine, warfarin cause increase in interacting drug levels. Sildenaril (do not exceed 25 mg in 48 hrs), tadalafil (max 10mg/72 hrs); vardenafil (max 2.5 mg/72hrs). St. John's wort substantially reduces delaviridine levels.

**Adverse Effects:** Drug fever/rash, Stevens–Johnson Syndrome (rare), headache, nausea/vomiting, diarrhea, ↑ SGOT/SGPT. May cause immune reconstitution syndrome.

**Allergic Potential:** High

**Safety in Pregnancy:** C

**Comments:** May be taken with or without food, but food decreases absorption by 20%. May disperse four 100-mg tablets in > 3 oz. water to produce slurry; 200-mg tablets should be taken as intact tablets and not used to make an oral solution. Separate dosing with ddl or antacids by 1 hour.

**Cerebrospinal Fluid Penetration:** 0.4%

**REFERENCES:**

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Website: www.pdr.net

## Didanosine EC (Videx) ddI

**Drug Class:** HIV NRTI nucleoside reverse transcriptase inhibitor.

**Usual Dose:** 400 mg (PO) q24h for > 60 kg; 250 (PO) q24h for < 60 kg.

**Pharmacokinetic Parameters:**

*Peak serum level: 29 mcg/mL*

*Bioavailability: 42%*

*Excreted unchanged (urine): 60%*

*Serum half-life (normal/ESRD): 1.6/4.1 hrs*

*Plasma protein binding: ≤ 5%*

*Volume of distribution ($V_d$): 1.1 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–59 mL/min | 125 mg (PO) q24h |
| CrCl < 10 mL/min | 125 mg (PO) q24h: > 60 kg Avoid: < 60 kg |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 150 mg (PO) q24h [100 mg (PO) q24h] |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Alcohol, lamivudine, pentamidine and valproic acid increase the risk of

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

pancreatitis. Patients on tenofovir should have didanosine dose reduced to 250 mg/24 hrs. Concomitant use with tenofovir increases risk of virologic failure. The appropriate dose of didanosine when taken with tenofovir has not been determined in patients with creatinine clearance of ≤ 60 ml/min. Peripheral neuropathy is enhanced by stavudine, INH, metronidazole, ntirofuantoin, vincristine and zalcitabine. Dapsone levels are dramatically reduced by powder form especially and increase risk of PCP. Decreases levels of cipro floxacin delavirdine, indinavir. Methadone will decrease didanosine levels. Coadministration of didanosine with ribavirin is not recommended.

**Adverse Effects:** Fatal and non-fatal pancreatitis have occured during therapy with didanosine used alone or in combination regimens. Tenofovir can increase this risk as well. Lactic acidosis and severe hepatomegaly with steatosis can also occur especially in pregnant women. Combination with stavuidine potentiates this risk and should be avoided especially in pregnancy and in patients with concomitant HCV/HBV. Other effects include diarrhea, peripheral neuropathy, rash and abdominal pain, anemia, leukopenia, alopecia. Depigmentation and optic neuritis have occured. Patients with underlying liver disease are at increased risk of hepatic toxicity.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

Avoid in pregnancy as it may cause fatal pancreatitis

**Comments:** Available as buffered powder for oral solution and enteric-coated extended-release capsules (Videx EC 400 mg PO q24h). Take 30 minutes before or 2 hours after meal (food decreases serum concentrations by 49%). Avoid in patients with alcoholic cirrhosis/history of pancreatitis. Use with caution in combination with tenofovir, which can potentiate risk of pancreatitis and require a significant dose reduction of ddI. Avoid use with ribavirin.

**Cerebrospinal Fluid Penetration:** 20%

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Website: www.pdr.net

## Dolutegravir (Tivicay) DTG

**Drug class:** HIV integrase strand transfer inhibitor (INSTI).

**Usual dose:**

Treatment-naïve or treatment experienced INSTI-naïve patients: 50 mg (PO) of q24h

Treatment-naïve or treatment experienced INSTI-naïve patients also on efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin: 50 mg (PO) of q12h

INSTI-experienced with certain INSTI-associated resistance stitutions or clinically suspected INSTI resistance: 50 mg (PO) q12h

**Pharmacokinetic Parameters:**

*Peak serum level: 3.6–4.1 mcg/L*

*Bioavailability: Not applicable*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Excreted unchanged: 53% feces and 31% urine*
*Serum half-life (normal/ESRD): 14h/14h*
*Plasma protein binding: 98.9%*
*Volume of distribution ($V_d$): 17.4 L/kg*
**Primary Mode of Elimination: Hepatic**
**Dosage Adjustments***

| | |
|---|---|
| CrCl <10 mL/min | No change |
| Post-HD dose | No data |
| Post-PO dose | No data |
| CVVH dose | No data |
| Moderate to severe hepatic insufficiency | Avoid (Child-Pugh C) |

**Drug Interactions:** Should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications; metabolized through UGT1A1 and to a lesser degree through CYP3A and also a substrate of UGT1A3, UGT1A9, BRCP and P-gp. Drugs that induce or inhibit these enzymes or transporters may affect dolutegravir levels; avoid concomitant oxcarbazepine, phenytoin, phenobarbital, carbamazepine, rifampin, St. John's wort; should not be used with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir; coadministration with nevirapine should be avoided because there are insufficient data to make dosing recommendations; combinations of antiretrovirals that do not include metabolic inducers should be considered where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
**Adverse Effects:** Insomnia, headache, diarrhea, increased SGOT/SGPT, lipase, bilirubin hyperglycemia, increased CPK
**Allergic Potential:** High.
**Safety in Pregnancy:** B
**Comments:** Coadministration with dufetilide in contraindicated; hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, discontinue dolutegravir if these occur; patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations; Safety not established in patients < 40 kg and < 12 yo

**REFERENCES:**

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Walmsely SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 369:1807–1818, 2013.
Website: www.pdr.net

## Doripenem (Doribax)

**Drug Class:** Carbapenem.
**Usual Dose:** 1 gm (IV) q8h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 23 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 40%*
*Serum half-life (normal/ESRD): 1/6.20 hrs*
*Plasma protein binding: 8.1%*
*Volume of distribution ($V_d$): 16.8 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–50 mL/min | 1 gm (IV) q12h |
| CrCl 10–30 mL/min | 500 mg (IV) q12h |
| CrCl < 10 mL/min | 500 mg (IV) q24h |
| Post–HD dose | 250 mg (IV) |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Post–HFHD dose | 500 mg (IV) |
| Post–PD dose | 500 mg (IV) |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (IV) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Valproic acid (↓ valproic acid levels).
**Adverse Effects:** Headache, nausea, diarrhea, rash, phlebitis, pneumonitis if administered by inhalation (do *not* give by inhalation).
**Allergic Potential:** Anaphylaxis (rare)
**Safety in Pregnancy:** B
**Comments: cSSSIs, cIAIs, or UTIs dose:** 500 mg (IV) q8h. Infuse over 1 hour. ***MDR P. aeruginosa, MDR Acinetobacter baumannii/ nosocomial pneumonia dose:*** 1 gm (IV) q8h. **For NP/VAP, infuse IV over 4 hours. Unlike meropenem, doripenem should not be used for meningitis.**

**Cerebrospinal Fluid Penetration:** < 1%
**Bile Penetration:** 117%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

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Wall GC, Nayima VA, Neumeister KM. Assessment of hypersensitivity reactions in patients receiving carbapenem antibiotics who report antibiotics a history of penicillin. J Chemo. 26:150-153, 2014.
Website: www.pdr.net

## Doxycycline (Vibramycin, Vibra-tabs)

**Drug Class:** 2nd generation IV/PO tetracycline.
**Usual Dose:** 100 mg (IV/PO) q12h or 200 mg (IV/PO) q24h (PI dose). For ***serious systemic infections***, begin with a ***Loading Regimen*****:** 200 mg (IV/PO) q12h × 3 days **(PK dose)**, then continue at same dose **or** decrease to ***Maintenance dose:*** 100 mg (IV/PO) q12h to complete therapy.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 100/200 mg = 4/8 mcg/mL*
*Bioavailability: 93%*
*Excreted unchanged (urine): 40%*
*Serum half-life (normal/ESRD): 18–22 hrs/18–22 hrs*
*Plasma protein binding: 82%*
*Volume of distribution ($V_d$): 0.75 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

PI = package insert
PK = pharmacokinetic dose

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD or PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Antacids, $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$, multivitamins, sucralfate (↓ doxycycline absorption); barbiturates, carbamazepine, phenytoin (↓ doxycycline half-life); bicarbonate (↓ doxycycline absorption, ↑ doxycycline clearance); warfarin (↑ INR).
**Adverse Effects:** Nausea if not taken with food. Phlebitis if given IV in inadequate volume. Avoid in pregnancy. ***Does not* ↑ *SGOT/SGPT.*** Photosensitivity rare.
**Allergic Potential:** Low
**Safety in Pregnancy:** D
**Comments:** Tetracycline susceptibilities do not predict doxycycline effectiveness against S. pneumoniae, MSSA, MRSA. Due to high urinary concentrations doxycycline IV/PO effective in treating lower UTIs due to GNBs, e.g., P. aeruginosa even those resistant by susceptibility testing (related to achievable serum concentrations).
Protective against C. difficile. Absorption minimally effected by iron, bismuth, milk, or antacids containing $Ca^{++}$, $Mg^{++}$, or $Al^{++}$. Serum half life increases with multiple doses. **For MSSA, MRSA use minocycline instead of doxycycline**

Meningeal dose = 200 mg (IV/PO) q12h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 25%
Inflamed meninges = 25%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 512).

**REFERENCES:**

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PI = package insert
PK = pharmacokinetic dose

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Volovitz B, Shkap R, Amir J, et al. Absence of tooth staining with doxycycline treatment in young children. Clin Pediatr 46:121–126, 2007.
Website: www.pdr.net

## Efavirenz (Sustiva) EFV

**Drug Class:** HIV NNRTI (non-nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 600 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 12.9 mcg/mL*
*Bioavailability: Increased with food*
*Excreted unchanged (urine): 14–34%*
*Serum half-life (normal/ESRD): 40–55 hrs/no data*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 60 mL/min | No change |
| Post–HD or PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Delavirdine | No data |
| Indinavir | Indinavir 1000 mg q8h |
| Lopinavir/ritonavir (l/r) | Consider l/r 533/133 mg q12h in PI-experienced patients |
| Nelfinavir | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Nevirapine | No data |
| Ritonavir | Ritonavir 600 mg q12h (500 mg q12h for intolerance) |
| Saquinavir | Avoid use as sole PI |
| Rifampin | No change |
| Rifabutin | Rifabutin 450–600 mg q24h or 600 mg 2–3x/week if not on protease inhibitor |
| Telaprevir increase telaprevie 1125 mg q7–9h | |
| Voriconazole: give efavirenz 300 mg q24h, voriconazole 400 mg q12h | |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); astemizole, terfenadine, cisapride, ergotamine, midazolam, carbamazepine, phenobarbital, phenytoin (monitor anticonvulsant levels; use with caution); verapamil, diltiazem (↓ calcium channel blocker levels) caspofungin, itraconazole, posaconazole (↓ anti fungal levels); methadone, clarithromycin (↓ interacting drug levels; titrate methadone dose to effect; consider using azithromycin instead of clarithromycin).
**Contraindications:** Triazolam, rifapentine, boceprevir.
**Adverse Effects:** Drug fever/rash, CNS symptoms (nightmares, dizziness, neuropsychiatric symptoms, difficulty concentrating, somnolence), ↑ SGOT/SGPT, E. multiforme/Stevens-Johnson Syndrome (rare), false positive cannabinoid test.
**Allergic Potential:** High
**Safety in Pregnancy:** D
**Comments:** Rash/CNS symptoms usually resolve spontaneously over 2–4 weeks. Take at bedtime. Avoid taking after high fat meals (levels ↑ 50%). 600-mg dose available as single tablet.

**Cerebrospinal Fluid Penetration:** 1%

**REFERENCES:**
Haas DW, Fessel WJ, Delapenha RA, et al. Therapy with efavirenz plus indinavir in patients with extensive prior nucleoside reverse-transcriptase inhibitor experience: A randomized, double-blind, placebo-controlled trial. J Infect Dis 183:392–400, 2001.
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Website: www.pdr.net

## Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate (Atripla) EFV/FTC/TDF

**Drug Class:** HIV
**Usual Dose:** 1 tablet (efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg) (PO) q24h on an empty stomach.
**Pharmacokinetic Parameters:**
*Peak serum level: 4.0/1.8 mcg/mL/296 ng/mL*
*Bioavailability: NR/93%/25%*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Excreted unchanged: < 1% unchanged and 14–30% as metabolites/86%/32%*
*Serum half-life (normal/ESRD): (40–55 hrs/~10 hrs on hemodialysis)/(10 hrs/extended)/(17 hrs/no data)*
*Plasma protein binding: 99/< 4/< 0.7%*
*Volume of distribution ($V_d$): NR/NR/1.2 L/kg*

**Primary Mode of Elimination:** Hepatic/Renal/Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | Avoid |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Mild hepatic insufficiency | No data |
| Moderate—severe hepatic insufficiency | No data |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Fosamprenavir/ritonavir | An additional 100 mg/day (300 mg total) of ritonavir is recommended when ATRIPLA is administered with fosamprenavir/ritonavir q24h. No change in ritonaviir dose when ATRIPLA is administered with fosamprenavir/ritonavir q12h |
| Atazanavir | Atazanavir 300 mg q24h Ritonavir 100 mg q12h |
| Indinavir | Indinavir 1000 mg q8h |
| Lopinavir/ritonavir | Increase lopinavir/ritonavir to 600/150 mg (3 tablets) q12h |
| Ritonavir | No data |
| Saquinavir | Avoid |
| Didanosine | Avoid |
| Rifabutin | Rifabutin 450–600 mg q24h or 600 mg 2–3x/week if not on protease inhibitor |
| Rifampin | No data |

**Drug Interactions:** Antiretrovirals, rifabutin (see dose adjustment grid above); astemizole, cisapride, ergotamine, methylergonovine, midazolam, triazolam, St John's Wort (↓ efavirenz levels), voriconazole (↓ voriconazole levels; avoid); caspofungin (↓ caspofungin levels); carbamazepine, phenytoin, phenobarbital (monitor anticonvulsant levels; use with caution; potential for ↓ efavirenz levels); statins (may ↓ statin levels); methadone, (↓ methadone levels); clarithromycin (may ↓ clarithromycin effectiveness, consider using azithromycin). Should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives. Significantly reduces voriconazole drug levels.

**Adverse Effects:** Dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. Psychiatric symptoms of depression suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and manic reactions. Mild to moderate skin rash, Steven's Johnson syndrome. Pancreatitis can occur. Increase in lipids and

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

cholesterol. Immune reconstitution Syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.
**Allergic Potential:** High
**Safety in Pregnancy:** D
**Comments:** Rash/CNS effects usually resolve in a few weeks. Take at bedtime on empty stomach. High fat meals can ↑ efavirenz by 50%. Use with caution in patients with history of seizures (↑ risk of convulsions). May cause false positive tests for cannabanoids.

**Cerebrospinal Fluid Penetration:** 1%

**REFERENCES:**

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Elvitegravir + Cobicistat + Emtricitabine + Tenofovir disoproxil fumarate (Stribild) EVG/COBI/FTC/TDF

**Drug class Antiretroviral agent:** HIV Integrase strand transfer inhibitor (elvitagravir 150 mg), pharmacokinetic enhancer (cobicistat 150 mg), and 2 nucleos(t)ide analog HIV-1 reverse transcriptase inhibitors (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg)
**Usual dose:** 1 tablet once daily with food

**Pharmacokinetic Parameters:**
*Peak serum level*: 1.7/1.1/1.9/0.45 mcg/mL
*Bioavailability*: Increased with food
*Excreted unchanged*: minimal for elvitegravir and cobicistat, ~ 100% for emtricitabine and tenofovir disoproxil fumarate
*Serum half-life (normal/ESRD)*: 9/3/12/11 (not recommended in renal failure)
*Plasma protein binding*: 98/98/4/0.7%
*Volume of distribution ($V_d$)*: No data
**Primary Mode of Elimination:** Hepatic (elvitegravir and cobicistat); Renal (emtricitabine and tenofovir disoproxil fumarate)
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | Avoid |
| Post-HD dose | Avoid |
| Post-PD dose | Avoid |
| CVVH dose | Avoid |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** Inhibitor of CYP3A, CYP2D6 and CYP2C9; and p-glycoprotein; metabolized by CYP3A and CYP2D6; antacids (may ↓ elvitegravir absorption).
**Contraindications:** nephrotoxic drugs
**Adverse Effects:** nausea, diarrhea, new onset/worsening of renal failure, decreased bone mineral density redistribution/accumulation of body fat, immune reconstitution syndrome, lactic acidosis and hepatomegaly
**Allergic Potential:** not available
**Safety in Pregnancy:** B
**Comments:** not approved for HIV patients co-infected with HBV

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Emtricitabine (Emtriva) FTC

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 200 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 1.8 mcg/mL*
*Bioavailability: 93%*
*Excreted unchanged (urine): 86%*
*Serum half-life (normal/ESRD): 10 hrs/extended*
*Plasma protein binding: 4%*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl ≥ 50 mL/min | 200 mg (PO) q24h |
| CrCl 30–49 mL/min | 200 mg (PO) q48h |
| CrCl 15–29 mL/min | 200 mg (PO) q72h |
| CrCl < 15 mL/min | 200 mg (PO) q96h |
| Post–HD dose | 200 mg (PO) |
| Post–PD dose | 200 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 200 mg (PO) q72h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** No significant interactions with indinavir, stavudine, zidovudine, famciclovir, tenofovir.
**Adverse Effects: Lactic acidosis hepatomegaly with steatosis, post-treatment exacerbation of hepatitis B.** Headache, diarrhea, nausea and rash as well as abdominal pain, fatigue, dizziness abnormal dreams. Rare cases of skin hyperpigmentation on palms and soles. Immune reconstitution syndrome may occur.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** May be taken with or without food. Does not inhibit CYP450 enzymes. Mean intracellular half-live of 39 hours. Potential cross-resistance to lamivudine and zalcitabine. Low affinity for DNA polymerase-gamma. Should not be coadministered with drugs containing lamivudine.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**
Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. Drugs 64:2075–82, 2004.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Emtricitabine + Tenofovir disoproxil fumarate (Truvada) FTC/TDF

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor) + nucleotide analogue.
**Usual Dose:** One tablet (PO) q24h (each tablet contains 200 mg of emtricitabine + 300 mg of tenofovir).
**Pharmacokinetic Parameters:**
*Peak serum level: 1.8/0.3 mcg/L*
*Bioavailability: 93%/27% if fasting (39% with high fat meal)*
*Excreted unchanged (urine): 86/32%*
*Serum half-life (normal/ESRD): (10 hrs/ extended)/(17 hrs/no data)*
*Plasma protein binding: 4/0.7–7.2%*
*Volume of distribution ($V_d$):* no data/*1.3 L/kg*
**Primary Mode of Elimination:** Renal/Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl ≥ 50 mL/min | No change |
| CrCl 30–49 mL/min | One capsule (PO) q48h |
| CrCl 15–29 mL/min | Avoid |
| CrCl < 15 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/ CVVHDF dose | Avoid |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** No significant interactions with indinavir, stavudine, zidovudine, famciclovir, lamivudine, lopinavir/ritonavir, efavirenz, methadone, oral contraceptives. Tenofovir ↑ didanosine levels which may result in severe pancreatitis. Tenofovir reduces systemic exposure to atazanavir; whenever the two are co-administered, the recommended dose of atazanavir is 300 mg once daily with ritonavir 100 mg once daily. Atazanavir may increase tenofovir levels. Avoid coadministration with didanosine.
**Adverse Effects:** Headache, diarrhea, nausea, vomiting, GI upset, rash, lactic acidosis with hepatic steatosis (rare but potentially life-threatening with NRTI's). Decreases bone mineral density. May result in flare of hepatitis after stopping medication in patients with chronic hepatitis B infection. Cases of osteomalacia and renal tubular acidosis have occurred. Renal dysfunction is more common in diabetic patients. Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.
**Allergic Potential:** Low
**Safety in Pregnancy:** B

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Comments:** May be taken with or without food. Does not inhibit CYP450 enzymes. Mean intracellular half-life with emtricitabine is 39 hours. Potential cross-resistance to lamivudine, zalcitabine, abacavir, didanosine. Low affinity for DNA polymerase-gamma.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. Drugs 64:2075–82, 2004.

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Website: www.pdr.net

## Emtricitabine/Rilpivirine/Tenofovir (Complera) FTC/RPV/TDF

**Drug Class:** HIV 2 NRTI/1 NNRTI.

**Usual Dose:** 1 tablet (PO) q24h (contains 200 mg emtricitabine, 25 mg rilpivirine, 300 mg tenofovir).

**Pharmacokinetic Parameters:**

*Peak serum level: 1.8/1/0.3 mcg/L*

*Bioavailability: 93/No data/25%*

*Excreted unchanged: 86/1/75%*

*Serum half-life (normal): 10/50/17 hrs*

*Plasma protein binding: unknown/99/1%*

*Volume of distribution ($V_d$): no data/no data/no data*

**Primary Mode of Elimination:** Renal/hepatic/renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | Avoid |
| Post-HD dose | Avoid |
| Post-PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Mild—moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No data |

**Drug Interactions:** Do not administer with other NNRTIs. Antacid and H2 blockers should be separated. Any drug that induces or inhibits CYP3A has the potential to increase or decrease rilpivirine levels and should only be used if benefit outweighs risk, clarithromycin (↓ clarithromycin levels).

**Contraindications: carbamazepine, oxycarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, proton pump inhibitors, dexamethasone** (except single dose), **St. John's Wort.**

**Adverse Effects:** Nausea, diarrhea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, rash, **lactic acidosis/severe hepatomegaly with steatosis and post-treatment acute exacerbation of hepatitis B**, immune reconstitution syndrome, fat redistribution syndrome.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Monitor BMD in patients at risk for pathological fractures. *Not approved for patients co-infected with HBV and HIV.*

**Cerebrospinal Fluid Penetration:** No data

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Enfuvirtide (Fuzeon) ENF, T20

**Drug Class:** HIV fusion inhibitor.
**Usual Dose:** 90 mg (SC) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 4.9 mcg/mL*
*Bioavailability: 84.3%*
*Serum half-life (normal/ESRD): 3.8 hrs/no data*
*Plasma protein binding: 92%*
*Volume of distribution ($V_d$): 5.5 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 35 mL/min | No change |
| CrCl < 35 mL/min | No change |
| Post–HD dose | No change |
| Post–PD dose | No change |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** No clinically significant interactions with other antiretrovirals. Does not inhibit CYP450 enzymes.
**Adverse Effects:** Local injection site reactions are common. Diarrhea, nausea, fatigue may occur. Laboratory abnormalities include mild/transient eosinophilia. Pneumonia may occur, but cause is unclear and may not be due to drug therapy. Pancreatitis, myalgia, conjunctivitis (rare).
Allergic Potential: Hypersensitivity reactions may occur, including fever, chills, hypotension, rash, ↑ serum transaminases. Do not rechallenge following a hypersensitivity reaction
**Safety in Pregnancy:** B
**Comments:** Enfuvirtide interferes with entry of HIV-1 into cells by blocking fusion of HIV-1 and $CD_4$ cellular membranes by binding to HR1 in the gp41 subunit of the HIV-1 envelope glycoprotein. Additive/synergistic with NRTI's, NNRTI's, and PI's, and no cross resistance to other antiretrovirals in cell culture. Reconstitute in 1.1 mL of sterile water. SC injection should be given into upper arm, anterior thigh, or abdomen. Rotate injection sites; do not inject into moles, scars, bruises. After reconstitution, use immediately or refrigerate and use within 24 hours (no preservatives added).

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Leen C, Wat C, Nieforth K. Pharmacokinetics of enfuvirtide in a patient with impaired renal function. Clin Infect Dis 4:339–55, 2004.

Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Entecavir (Baraclude)

**Drug Class:** HBV nucleoside analogue.
**Usual Dose:** 0.5 mg (PO) q24h; 1 mg (PO) q24h for lamivudine-refractory patients or with decompensated liver disease. (Take without food)
**Pharmacokinetic Parameters:**
*Peak serum level: 4.2 ng/mL (for 0.5 mg dose)*
*Bioavailability: Similar for tablet and oral solution*
*Excreted unchanged (urine): 62–73%*
*Serum half-life (normal/ESRD): 128–139 hrs*
*Plasma protein binding: No information*
*Volume of distribution ($V_d$): No information*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 0.5 mg dose)

| | |
|---|---|
| CrCl > 50 mL/min | No change |
| CrCl 30–50 mL/min | 0.25 mg (PO) q24h |
| CrCl 10–30 mL/min | 0.15 mg (PO) q24h |
| CrCl < 10 mL/min | 0.05 mg (PO) q24h |
| Post-HD | 0.05 mg (PO or 0.5 mg (PO) q week) |
| Post–PD | 0.05 mg (PO) |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Cyclosporin, tacrolimus (may ↑ entecavir levels).
**Adverse Effects:** Fatigue, headache, upper respiratory tract infection, upper abdominal pain, ↑ ALT, cough, nausea.
**Allergic Potential:** No information
**Safety in Pregnancy:** C
**Comments:** Used to treat chronic HBV. Effective in lamivudine-resistant patients. Available as tablets and oral solution.

**REFERENCES:**


Honkoop P, De Man RA. Entecavir: a potent new antiviral drug for hepatitis B. Expert Opin Investig Drugs 12:683–8, 2003.

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Website: www.pdr.net


"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ertapenem (Invanz)

**Drug Class:** Carbapenem.
**Usual Dose:** 1 gm (IV/IM) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 150 mcg/mL*
*Bioavailability: 90% (IM)*
*Excreted unchanged (urine): 40%; 40% excreted as active metabolite*
*Serum half-life (normal/ESRD): 4/14 hrs*
*Plasma protein binding: 95%*
*Volume of distribution ($V_d$): 0.12 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–80 mL/min | No change |
| CrCl < 30 mL/min | 500 mg (IV) q24h |
| Post–HD dose | If dosed < 6 h prior to HD, give 150 mg (IV) |
| Post–PD dose | No information |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (IV) q24h |
| Moderate – Severe hepatic insufficiency | No change |

* If dosed > 6 h prior to HD, no Post–HD needed.

**Drug Interactions:** Not a substrate/inhibitor of cytochrome P-450 enzymes; probenecid (↓ clearance of ertapenem). Valproic acid (↓ seizure threshold).
**Adverse Effects:** Mild headache, infrequent nausea or diarrhea. No seizures. Probenecid (↓ clearance of ertapenem).
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Concentration-dependent protein binding. Compared to imipenem or meropenem, **ertapenem has little activity against VSE, Acinetobacter or P. aeruginosa.** For deep muscle (IM) injection, mix 1 gm with 3.2 mL of 1% lidocaine. **Probably safe to use in penicillin allergic patients**.

**Cerebrospinal Fluid Penetration:** 5–20%
**Bile Penetration:** 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Erythromycin lactobionate, base (various)

**Drug Class:** Macrolide.

**Usual Dose:** 1 gm (IV) q6h; 500 mg (PO) q6h (Take without food).

**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

**Resistance Potential:** High (S. pneumoniae, GAS, MSSA)

**Pharmacokinetic Parameters:**

*Peak serum level: 12 (IV);1.2 (PO) mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 5%; 5% exerted as active metabolite*
*Serum half-life (normal/ESRD): 1.4/5.4 hrs*
*Plasma protein binding: 80%*
*Volume of distribution ($V_d$): 0.5 L/kg*

**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Amiodarone, procainamide, sotalol, astemizole, terfenadine, cisapride, pimozide (↑ QTc); carbamazepine (↑ carbamazepine levels, nystagmus, nausea, vomiting, diarrhea; avoid combination); cimetidine, digoxin, ergot alkaloids, felodipine, midazolam, triazolam, phenytoin, ritonavir, tacrolimus, valproic acid (↑ interacting drug levels); clozapine (↑ clozapine levels; CNS toxicity); corticosteroids (↑ corticosteroid effect ); cyclosporine (↑ cyclosporine levels with toxicity); efavirenz (↓ erythromycin levels); rifabutin, rifampin (↓ erythromycin levels, ↑ interacting drug levels); statins (↑ risk of rhabdomyolysis); theophylline (↑ theophylline levels, nausea, vomiting, seizures, apnea); warfarin (↑ INR); zidovudine (↓ zidovudine levels).

**Adverse Effects:** Nausea, vomiting, GI upset, irritative diarrhea, abdominal pain, phlebitis. May ↑ $QT_c$; avoid with other medications that prolong the $QT_c$ interval and in patients with cardiac arrhythmias/heart block.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Do not mix erythromycin with B/C vitamins, glucose solutions, cephalothin, tetracycline, chloramphenicol, heparin, or warfarin. Increases GI motility and $QT_c$ interval.

**Limited anti-Legionella activity.**

**S. pneumoniae resistance prevalent.**

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**


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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ethambutol (Myambutol) EMB

**Drug Class:** TB drug.
**Usual Dose:** 15 mg/kg (PO) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 2–5 mcg/mL*
*Bioavailability: 80%*
*Excreted unchanged (urine): 50%*
*Serum half-life (normal/ESRD): 4/10 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 2 L/kg*
**Primary Mode of Elimination:** Renal/hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 15 mg/kg (PO) 3×/ week |
| CrCl 15–30 mL/min | 15 mg/kg (PO) q36h |
| Post-HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 15 mg/kg (PO) q36h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Aluminum salts, didanosine buffer (↓ ethambutol and interacting drug absorption).
**Adverse Effects:** Drug fever/rash, ↓ visual acuity, central scotomata, color blindness (red-green), metallic taste, mental confusion, peripheral neuropathy, ↑ uric acid.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Optic neuritis may occur with high doses (≥ 15 mg/kg/day). **TB D.O.T. dose:** 4 gm (PO) 2 × /week or 3 gm (PO) 3 × / week. **MAI dose:** 15 mg/kg (PO) q24h (with azithromycin 500 mg [PO] q24h).

Meningeal dose = 25 mg/kg (PO) q24h.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 40%

**REFERENCES:**

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Van Scoy RE, Wilkowske CJ. Antituberculous agents. Mayo Clin Proc 67:179–87, 1992.
Website: www.pdr.net

## Ethionamide (Trecator)

**Drug Class:** TB drug.
**Usual Dose:** 500 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 5 mcg/mL*
*Bioavailability: 99%*
*Excreted unchanged (urine): 1%*
*Serum half-life (normal/ESRD): 2/9 hrs*
*Plasma protein binding: 30%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Renal/hepatic

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 40 mL/min | No change |
| Post-HD/PD dose | No information |
| CVVH/CVVHD/ CVVHDF dose | No information |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 500 mg (PO) q24h |

**Drug Interactions:** Cycloserine (↑ neurologic toxicity); ethambutol (↑ GI distress, neuritis, hepatotoxicity); INH (peripheral neuritis, hepatotoxicity); pyrazinamide, rifampin (hepatotoxicity).
**Adverse Effects:** ↑ SGOT/SGPT, headache, nausea/vomiting, abdominal pain, tremor, olfactory abnormalities, alopecia, gynecomastia, hypoglycemia, impotence, neurotoxicity (central/peripheral neuropathy).
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Additive toxicity with thiacetazone

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:** 100%

**REFERENCES:**
Davidson PT, Le HQ. Drug treatment of tuberculosis 1992. Drugs 43:651–73, 1992.
[No authors listed.] Drugs for tuberculosis. Med Lett Drugs Ther 35:99–101, 1993.
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Website: www.pdr.net

## Etravirine (Intelence) ETR

**Drug Class:** HIV NNRTI.
**Usual Dose:** 200 mg (PO) q12h (take with meals).
**Pharmacokinetic Parameters:**
*Peak serum level: 2.97 mcg/mL*
*Bioavailability: no data*
*Excreted unchanged: 0%*
*Serum half-life (normal/ESRD): 41/41 hrs*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | No change |
| Post-HD dose | None |
| Post-PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | use with caution |

**Drug Interactions:** Do not administer with drugs that are inducers, inhibitors or substrates of CYP 3A4, 2C9 and/or 2C19 (tipranavir/ritonavir, atazanavir/ritonavir, protease inhibitors without ritonavir and/or NNRTIs), clarithromycin (↓ clarithromycin levels), statins (↓ statin levels), atovaquone/proguanil (↓ atovaquone/proguanil levels).
**Contraindications:** carbamazepine, phenytoin, phenobarbital, St. John's wort, rifapentine, atazanavir, efavirenz, fosamprenavir, nevirapine, rilpivirine, tipranavir.
**Adverse Effects:** Rash, peripheral neuropathy, immune reconstitution syndrome, fat redistribution.
**Allergic Potential:** Low

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Safety in Pregnancy:** B
**Comments:** Severe, life-threatening and fatal skin reactions (Steven-Johnson Syndrome, toxic epidermal necrolysis, hypersensitivity reaction and erythema multiforme). Doesn't ↓ methadone levels. If etravirine given with ritonavir–boosted protease inhibitor, rifabutin is contraindicated. Otherwise rifabutin can be given at 300 mg q24h.

**REFERENCES:**

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

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## Famciclovir (Famvir)

**Drug Class:** HSV, VZV, HHV-6 Antiviral (see comments).
**Usual Dose:**
**HSV-1/2:** Herpes labialis: 500 mg (PO) q12h × 7 days. Genital herpes: *Initial therapy:* 1 g (PO) q12h × 1 day. *Recurrent/intermittent therapy* (< 6 episodes/year): normal host: 125 mg (PO) q12h × 5 days; HIV-positive: 500 mg (PO) q12h × 7 days. *Chronic suppressive therapy* (> 6 episodes/year): 250 mg (PO) q12h × 1 year. Meningitis/encephalitis: 500 mg (PO) q8h × 10 days.
**VZV:** Chickenpox: 500 mg (PO) q8h × 5 days. Herpes zoster (shingles) (dermatomal/disseminated): 500 mg (PO) q8h × 7–10 days. VZV Pneumonia: 500 mg (PO) q8h ×7–10 days.

**Pharmacokinetic Parameters:**
*Peak serum level: 3.3 mcg/mL*
*Bioavailability: 77%*
*Excreted unchanged (urine): 60%*
*Serum half-life (normal/ESRD): 2.5/13 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 1.1 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments for HSV/VZV*** (based on 250 mg [PO] q8h/500 mg [PO] q8h)

| | |
|---|---|
| CrCl 40–60 mL/min | No change/500 mg (PO) q12h |
| CrCl 20–40 mL/min | 125 mg (PO) q24h/ 500 mg (PO) q24h |
| CrCl < 20 mL/min | 125 mg (PO) q24h/ 250 mg (PO) q24h |
| Post–HD dose | 125 mg (PO)/ 250 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 125 mg (PO) q24h/ 500 mg (PO) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Digoxin (↑ digoxin levels).
**Adverse Effects:** Headache, seizures/tremors (dose related), nausea, diarrhea, renal insufficiency (dose related).
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** 99% converted to penciclovir in liver/GI tract. ***Highly active against HSV, VZV, and HHV-6. Some activity against CMV. No activity against EBV, RSV or adenoviruses.***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Meningeal dose = VZV dose.
**Cerebrospinal Fluid Penetration:** 50%

**REFERENCES:**

Luber AD, Flaherty JF Jr. Famciclovir for treatment of herpesvirus infections. Ann Pharmacother 30:978–85, 1996.

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## Fluconazole (Diflucan)

**Drug Class:** Antifungal.
**Usual Dose: *Loading Dose* (LD) = twice the maintenance dose × 1 dose** followed by the ***Maintenance Dose* (MD)**.

Candidemia:
LD = 800 mg (IV/PO) × 1 then
MD = 400 mg (IV/PO) q24h

Mucocutaneous Candidiasis:
LD = 400 mg (IV/PO) × 1 then
MD = 200 mg (IV/PO) q24h

Candida esophagitis:
LD = 200 mg (IV/PO) × 1 then
MD = 100 mg (IV/PO) q24h

Candiduria:
LD = 200 mg (IV/PO) × 1 then
MD = 100 mg (IV/PO) q24h

**Pharmacokinetic Parameters:**
*Peak serum level: 6.7 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 80%; 11% excreted as active metabolite*
*Serum half-life (normal/ESRD): 27/100 hrs*
*Plasma protein binding: 12%*
*Volume of distribution ($V_d$): 0.7 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | 100 mg (IV/PO) q24h |
| Post–HD dose | 200 mg (IV/PO) |
| Post–PD dose | 200 mg (IV/PO) |
| CVVH/CVVHD/CVVHDF dose | 200–400 mg (IV/PO) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Astemizole, cisapride, terfenadine, amiodarone (may ↑ QT interval, torsades de pointes); cyclosporine, oral hypoglycemics, tacrolimus, theophylline, zidovudine (↑ interacting drug levels with possible toxicity); hydrochlorothiazide (↑ fluconazole levels); phenytoin, rifabutin, rifampin (↓ fluconazole levels, ↑ interacting drug levels); warfarin (↑ INR).
**Adverse Effects:** Not hepatotoxic. ***Does not* ↑ *SGOT/SGPT even in high dose.*** Hypokalemia.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Not effective against most non-albicans Candida.
***Highly active against C. albicans, C. tropicalis, C. parasilosis, and C. lusitaniae. Moderately active against Cryptococcus, Histoplasmosis, Blastomycosis, Sporotrichosis, Penicillum marneffei, Paracoccidiomycosis and Coccidiomycosis. Some (dose dependent) activity against C. glabrata. No activity against C. krusei, C. guilliermondii, C. rugosa, Mucor, Fusarium, Pseudoallescheria/Scedosporium, Trichosporon, Malassezia, Hansenula,***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

***Geotrichum, Rhodotorula or Aspergillus.***

Meningeal dose = 400 mg (IV/PO) q24h.

**Cerebrospinal Fluid Penetration:**

Non-Inflamed meninges = 50–90%

Inflamed meninges = 50–90%

**REFERENCES:**


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Website: www.pdr.net


## Flucytosine (Ancobon) 5-FC

**Drug Class:** Antifungal.

**Usual Dose:** 25 mg/kg (PO) q6h.

**Pharmacokinetic Parameters:**

*Peak serum level: 3.5 mcg/ml*

*Bioavailability: 80%*

*Excreted unchanged (urine): 90%*

*Serum half-life (normal/ESRD): 4/85 hrs*

*Plasma protein binding: 4%*

*Volume of distribution ($V_d$): 0.6 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl 20–40 mL/min | 37.5 mg/kg (PO) q12h |
| CrCl 10–20 mL/min | 37.5 mg/kg (PO) q18h |
| CrCl < 10 mL/min | 37.5 mg/kg (PO) q24h |
| Post–HD dose | 37.5 mg/kg (PO) |
| Post–PD dose | 1 gm (PO) |
| CVVH/CVVHD/ CVVHDF dose | 37.5 mg/kg (PO) q18h |
| Moderate—severe insufficiency | No change |

**Drug Interactions:** Cytarabine (↓ flucytosine effect); zidovudine (neutropenia).
**Adverse Effects:** Leukopenia, anemia, thrombocytopenia, nausea, vomiting, abdominal pain, ↑ SGOT/SGPT, drug fever/rashes.
**Allergic Potential:** High
**Safety in Pregnancy:** C
**Comments: Always use in combination with amphotericin B** for cryptococcal meningitis.
***Highly active against Cryptococcus neoformans. Some activity against C. albicans. No activity against other yeasts/fungi.***

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 100%
Inflamed meninges = 100%

**REFERENCES:**

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Wintermeyer SM, Mahata MC. Stability of flucytosine in an extemporaneously compounded oral liquid. Am J Health Syst Pharm 53:407–9, 1996.
Website: www.pdr.net

## Fosamprenavir (Lexiva) FPV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** 1400 mg (PO) q24h plus ritonavir 200 mg (PO) q24h or 700 mg (PO) q12h plus ritonavir 100 mg (PO) q12h. For PI-experienced patients: 700 mg (PO) q12h plus ritonavir 100 mg (PO) q12h.

**Pharmacokinetic Parameters:**
*Peak serum level: 4.8 mcg/mL*
*Bioavailability: No data*
*Excreted unchanged (urine) (urine): 1%*
*Serum half-life (normal/ESRD): 7 hrs/no data*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 6.1 L/kg*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | No change |
| Post–HD or PD dose | No change |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild-moderate hepatic insufficiency (Child-Pugh score 5–8) | 700 mg (PO) q12h without ritonavir; 450 mg (PO) q12h with ritonavir |
| Severe hepatic insufficiency (Child-Pugh score 9–12) | 350 mg (PO) q12h without ritonavir; 300 mg (PO) q12h with ritonavir |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Didanosine | Administer didanosine 1 hour apart |
| Delavirdine | Avoid |
| Efavirenz | Fosamprenavir 700 mg q12h + ritonavir 100 mg q12h + efavirenz; fosamprenavir 1400 mg q24h + ritonavir 200 mg q24h + efavirenz; no data for fosamprenavir 1400 mg q12h + efavirenz |
| Indinavir | No data |
| Lopinavir/ritonavir | Avoid |
| Nelfinavir | No information |
| Nevirapine | Avoid |
| Saquinavir | No information |
| Rifampin | Avoid |
| Rifabutin | Reduce usual rifabutin dose by 50% (or 75% if given with fosamprenavir plus ritonavir; max. 150 mg q48h) |

**Drug Interactions:** Antiretrovirals (see dose adjustment grid, above). Contraindicated with: ergot derivatives, cisapride, midazolam, triazolam, pimozide, (flecainide and propafenone if administered with ritonavir). Dose reduction (of other drug): atorvastatin, rifabutin, sildenafil, vardenafil, ketoconazole, itraconazole. colchicine (↑ colchicine levels) Concentration monitoring (of other drug): amiodarone, systemic lidocaine, quinidine, warfarin (INR), tricyclic antidepressants, cyclosporin, tacrolimus, sirolimus. $H_2$ blockers and proton pump inhibitors interfere with absorption. Sildenafil (do not give > 25 mg/48 hrs); tadalafil (max. 10 mg/72 hrs); vardenafil (max. 2.5 mg/72 hrs). Clarithromycin (↑ QTc). May increase methadone effect/decrease methadone dose.
**Contraindications:** Rifapentine, telaprevir, do not coadminister with: rifampin, lovastatin, simvastatin, St. John's wort, delavirdine.
**Adverse Effects:** Rash, Stevens-Johnson Syndrome (rare), GI upset, headache, depression, diarrhea, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ cholesterol/triglycerides (evaluate risk for coronary disease/pancreatitis), fat redistribution, ↑ SGOT/SGPT, possible increased bleeding in hemophilia. Immune reconstitution syndrome.
**Allergic Potential:** High. Fosamprenavir is a sulfonamide; use with caution in patients with sulfonamide allergies
**Safety in Pregnancy:** C

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Comments:** Usually given in conjunction with ritonavir. May be taken with or without food. Fosamprenavir is a prodrug that is rapidly hydrolyzed to amprenavir by gut epithelium during absorption. Amprenavir inhibits CYP3A4. Fosamprenavir contains a sulfonamide moiety (as do darunavir and tipranavir). Fosamprenavir without ritonavir is no longer recommended in treatment naive patients due to increased development to resistance as well as cross-resistance to darunavir.

**REFERENCES:**

Blick G, Greiger-Zanlungo P, Gret S, et al. Long-term efficacy and safety of once- daily fosamprenavir 1400 mg boosted by ritonavir 100 mg: the BOLD100 study. Int J STD AIDS 23:18–22, 2012

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Foscarnet (Foscavir)

**Drug Class:** CMV, HHV-6 Antiviral (see comments).

**Usual Dose:** HSV: 40 mg/kg (IV) q12h × 2–3 weeks; CMV: *Induction Dose:* 90 mg/kg (IV) q12h × 2 weeks, then *Maintenance Dose:* 90–120 mg/kg (IV) q24h until cured. *Relapse/reinduction dose:* 120 mg/kg (IV) q24h × 2 weeks.

**Pharmacokinetic Parameters:**

*Peak serum level: 150 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 85%*
*Serum half-life (normal/ESRD): 2–4/25 hrs*
*Plasma protein binding: 17%*
*Volume of distribution ($V_d$): 0.5 L/kg*

**Primary Mode of Elimination:** Renal /hepatic

**Dosage Adjustments***

| Induction | |
|---|---|
| CrCl 50–80 mL/min | 40–50 mg/kg (IV) q8h |
| CrCl 20–50 mL/min | 20–30 mg/kg (IV) q8h |
| CrCl < 20 mL/min | Avoid |
| **Maintenance** | |
| CrCl 50–80 mL/min | 60–70 mg/kg (IV) q24h |
| CrCl 20–50 mL/min | 65–80 mg/kg (IV) q48h |
| CrCl < 20 mL/min | Avoid |
| Post–HD dose | 60 mg/kg (IV) |
| Post–HF HD dose | 60 mg/kg (IV) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | Induction: 20–30 mg/kg (IV) q8h; maintenance: 65–80 mg/kg (IV) q48h |
| Mod. hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

Infusion pump must be used. Adequate hydration is recommended to prevent renal toxicity

† Higher doses may be considered for early reinduction due to progression of CMV retinitis, and for patients showing excellent tolerance.

**Drug Interactions:** Ciprofloxacin (↑ risk of seizures); amphotericin B, aminoglycosides, cis-platinum, cyclosporine, ritonavir, saquinavir (↑ nephrotoxicity); pentamidine IV (severe hypocalcemia reported; do not combine); zidovudine (↑ incidence/severity of anemia).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Adverse Effects:** Major side effects include nephrotoxicity and tetany (from ↓ $Ca^{++}$). Others include anemia, nausea, vomiting, GI upset, headache, seizures, peripheral neuropathy, hallucinations, tremors, nephrogenic DI, ↓ $Ca^{++}$, ↓ $Mg^{++}$, ↓ $PO_4^{=}$, oral/genital ulcers.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Renal failure prevented/minimized by adequate hydration. Dilute with 150 cc normal saline per 1 gm foscarnet. Do not mix with other types of solutions. Administer by IV slow infusion ≤ 1 mg/kg/min using an infusion pump. ***Highly active against CMV and HHV-6. Some activity against EBV, HSV and VZV. No activity against RSV or adenoviruses.***

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 90%
Inflamed meninges = 100%

**REFERENCES:**

Mattes FM, Hainsworth EG, Geretti AM, et al.
A randomized, controlled trial comparing ganciclovir plus foscarnet (each at half dose) preemptive therapy of cytomegalovirus infection in transplant recipients. J Infect Dis 189:1355–61, 2004.
Website: www.pdr.net

## Fosfomycin (Monurol)

**Drug Class:** Urinary antibiotic.
**Usual Dose:** 3 gm (PO) q24h (Take without food)
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 26 mcg/ml*
*Bioavailability: 37%*
*Excreted unchanged (urine): 60%; 40% excreted as active metabolite*
*Serum half-life (normal/ESRD): 5.7/50 hrs*
*Plasma protein binding: 3%*
*Volume of distribution ($V_d$): 2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | Use with caution |
| Post–HD dose | 3 gm (PO) |
| Post–PD dose | 1 gm (PO) |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Antacids, metoclopramide (↓ fosfomycin effect).
**Adverse Effects:** Nausea, vomiting, diarrhea, GI upset, ↑ SGOT/SGPT, thrombocytosis.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments: Useful for GNB cystitis/CAB** also active aginst VSE/VRE. Treat cystitis as single dose in females. **One of the few oral antibiotics active against most strains of MDR P. aeruginosa, MDR Klebsiella pneumoniae, and MDR Acinetobacter baumanii in urine** (*cystitis/CAB*). Treatment of MDR GNB cystitis/CAB (change Foley *before* beginning therapy). Use 3 g (PO) q 3 days × 2–3 doses. For prostatitis due to MDR GNB, use fosfp,ucom 3 g (PO) q2 days × 30 days. Urine levels > 128 mcg/ml × 36–48 (see ***Antibiotic Pearls & Pitfalls.*** p. 520).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**
Auer S, Wojna A, Hell M. Oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli. Antimicrob Agents Chemother 54:4006–4008, 2010.
Dinh A, Salomon J, Bru JP, et al. Fosfomycin: efficacy against infections caused by multidrug-resistant bacteria. Scand J infect Dis 44:182–9, 2012.
Falagas ME, Kastoris AC, Kapaskelis AM, et al. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis 10:43–50, 2010.
Gardiner BJ, Mahony AA, Ellis AG. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clin Infect Dis 58:e101-105, 2014.
Liu HY, Lin HC, Lin YC, et al. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. J Microbiol Immunol Infect 44:364–368, 2011.
Livermore DM, Warner M, Mushtaq S, et al. What remains against carbapenem-resistant Enterbacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. In J Antimicrob Agents 37:415–419, 2011.
Pontikis K, Karaiskos I, Bastani S, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents 43:52-59, 2014.
Website: www.pdr.net

## Ganciclovir (Cytovene)

**Drug Class:** CMV, HSV, HHV-6 Antiviral (see comments), nucleoside inhibitor/analogue.
**Usual Dose:** ***Induction Dose:*** 5 mg/kg (IV) q12h × 2 weeks; ***Maintenance Dose:***
5 mg/kg (IV) q24h or 1 gm (PO) q8h.
**Pharmacokinetic Parameters:**
*Peak serum level: 8.3 (IV)/1.2 (PO) mcg/ml*
*Bioavailability: 5%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 3.6/28 hrs*
*Plasma protein binding: 1%*
*Volume of distribution ($V_d$): 0.74 L/kg*
**Primary Mode of Elimination:** Renal
Dosage Adjustments*

| | |
|---|---|
| CrCl 50–70 mL/min | 2.5 mg/kg (IV) q12h (induction); 2.5 mg/kg (IV) q24h (maintenance); 500 mg (PO) q8h |
| CrCl 25–50 mL/min | 2.5 mg/kg (IV) q24h (induction); 1.25 mg/kg (IV) q24h (maintenance); 500 mg (PO) q12h |
| CrCl 10–25 mL/min | 1.25 mg/kg (IV) q24h (induction); 0.625 mg/kg (IV) q24h (maintenance); 500 mg (PO) q24h |
| CrCl < 10 mL/min | 1.25 mg/kg (IV) 3x/week (induction); 0.625 mg/kg (IV) 3x/week (maintenance); 500 mg (PO) 3x/week |
| Post–HD dose | 1.25 mg/kg (IV) (induction); 0.625 mg/kg (IV) (maintenance); 500 mg (PO) |
| Post–PD dose | Same dose as Post–HD |
| CVVH/CVVHD/CVVHDF dose | Same dose as CrCl 50–70 mL/min |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Cytotoxic drugs (may produce additive toxicity: stomatitis, bone marrow depression, alopecia); imipenem (↑ risk of seizures); probenecid (↑ ganciclovir levels); zidovudine (↓ ganciclovir levels, ↑ zidovudine levels, possible neutropenia); didanosine (↑ didanosine levels); cyclosporine, amphotericin, (↑ nephrotoxicity); mycophenolate mofetil (↑ mycophenolate mofetil and ganciclovir levels in renal insufficiency); tenofovir (↑ tenofovir, ganciclovir levels).

**Adverse Effects:** Headaches, hallucinations, seizures/tremor (dose related), drug fever/rash, diarrhea, nausea/vomiting, GI upset, leukopenia, thrombocytopenia, anemia, retinal detachment. Ventricular arrhythmias (VT/torsades de pointes).

**Allergic Potential:** High

**Safety in Pregnancy:** C

**Comments:** *Induction* dose usually given IV. *Maintenance* dose may be given IV or PO. For PO therapy use valganciclovir (not PO ganciclovir). Reduce dose with neutropenia/thrombocytopenia. Bioavailability increased with food: 5% fasting; 6–9% with food; 28–31% with fatty food.

***Highly active against CMV, HHV-6, and HSV. Some activity against VZV, EBV, and adenoviruses. No activity against RSV***

Meningeal dose = usual dose.

**Cerebrospinal Fluid Penetration:** 70%

**REFERENCES:**

Jacobsen T, Sipointis N. Drug interactions and toxicities associated with the antiviral management of cytomegalovirus infection. Am J Health Syst Pharm 67:1417–1425, 2010.

Matthews T, Boehme R. Antiviral activity and mechanism of action of ganciclovir. Rev Infect Dis 10:490–4, 1988.

Singh N. Preemptive therapy for cytomegalovirus with oral ganciclovir after liver transplantation. Transplantation 73:1977–78, 2002.

Tayebi-Khosroshahi H, Makhdami N, Heris HK, et al. Universal prophylaxis with ganciclovir preparation is not necessary in all kidney allograft recipients. Transplant Proc 43:547–50, 2011

Tokimasa S, Hara J, Osugi Y, et al. Ganciclovir is effective for prophylaxis and treatment of human herpesvirus-6 in allogeneic stem cell transplantation. Bone Marrow Transplant 29:595–8, 2002.

Website: www.pdr.net

## Gentamicin (Garamycin)

**Drug Class:** Aminoglycoside.

**Usual Dose:** 240 mg or 5 mg/kg (IV) q24h (preferred over q8h dosing) (see comments).

**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).

**Resistance Potential:** High (P. aeruginosa, aerobic GNBs)

**Pharmacokinetic Parameters:**

*Peak serum levels: 4–8 mcg/ml (q8h dosing); 16–24 mcg/ml (q24h dosing)*

*Bioavailability: Not applicable*

*Excreted unchanged (urine): 95%*

*Serum half-life (normal/ESRD): 2.5/48 hrs*

*Plasma protein binding: < 5%*

*Volume of distribution ($V_d$): 0.3 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 120 mg (IV) q24h<br>or 2.5 mg/kg (IV) q24h |
| CrCl 10–50 mL/min | 120 mg (IV) q48h<br>or 2.5 mg/kg (IV) q48h |
| CrCl < 10 mL/min | 80 mg (IV) q48h<br>or 1.25 mg/kg (IV) q48h |
| Post–HD dose | 80 mg (IV)<br>or 1 mg/kg (IV) |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Post–PD dose | 40 mg (IV)<br>or 0.5 mg/kg (IV) |
| Post–HFHD dose | 120 mg (IV)<br>or 2.5 mg/kg |
| Post-dose | 120 mg (IV)<br>or 2.5 mg/kg (IV) |
| CVVH/CVVHD/<br>CVVHDF dose | 120 mg (IV) q48h<br>or 2.5 mg/kg (IV) |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Amphotericin B, cephalothin, cyclosporine, enflurane, methoxyflurane, NSAIDs, polymyxin B, radiographic contrast, vancomycin (↑ nephrotoxicity); cis-platinum (↑ nephrotoxicity, ↑ ototoxicity); loop diuretics (↑ ototoxicity); neuromuscular blocking agents, magnesium sulfate (↑ apnea, prolonged paralysis); non-polarizing muscle relaxants (↑ apnea).

**Adverse Effects:** Neuromuscular blockade with rapid infusion/absorption. Nephrotoxicity only with prolonged/extremely high serum trough levels; may cause reversible non-oliguric renal failure (ATN). Ototoxicity associated with prolonged/extremely high peak serum levels (usually irreversible): Cochlear toxicity (1/3 of ototoxicity) manifests as decreased high frequency hearing, but deafness is unusual. Vestibular toxicity (2/3 of ototoxicity) develops before ototoxicity, and typically manifests as tinnitus.

**Safety in Pregnancy:** D

**Comments: Synergy dose:** 2.5 mg/kg (IV) q24h or 120 mg (IV) q24h. **Single daily dosing virtually eliminates nephrotoxic/ototoxic potential**. Incompatible with solutions containing β-lactams, erythromycin, chloramphenicol, furosemide, sodium bicarbonate. IV infusion should be given slowly over 1 hour. **May be given IM. Avoid intraperitoneal infusion due to risk of neuromuscular blockade**. Avoid intratracheal/aerosolized intrapulmonary instillation, which predisposes to antibiotic resistance. $V_d$ increases with edema/ascites, trauma, burns, cystic fibrosis; may require ↑ dose. $V_d$ decreases with dehydration, obesity; may require ↓ dose. **Renal cast counts are the best indicator of aminoglycoside nephrotoxicity, not serum creatinine**. Dialysis removes ~ 1/3 of gentamicin from serum. **CAPD dose:** 2–4 mg/L dialysate (IP) with each exchange.

**Therapeutic Serum Concentrations** (for therapeutic efficacy, *not toxicity*):
Peak (q24h/q8h dosing) = 16–24/8–10 mcg/ml
Trough (q24h/q8h dosing) = 0/1–2 mcg/ml

**Intrathecal (IT) dose:** 5 mg (IT) q24h.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 0%
Inflamed meninges = 20%

**Bile Penetration:** 30%

(also see ***Antibiotic Pearls & Pitfalls*** p. 514).

**REFERENCES:**

Bruss JB. Lack of evidence associating nephrotoxicity with low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis. Clin Infect Dis 49:806, 2009.

Cosgrove SE,Vigliani GA, Campion M, et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 48:713–721, 2009.

Cunha BA. Aminoglycosides: Current role in antimicrobial therapy. Pharmacotherapy 8:334–50, 1988.

Edson RS, Terrell CL. The aminoglycosides. Mayo Clin Proc 74:519–28, 1999.

Freeman CD, Nicolau DP, Belliveau PP, et al. Once-daily dosing of aminoglycosides: Review and recommendations for clinical practice. J Antimicrob Chemother 39:677–86, 1997.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Krol V, Cunha BA, Schoch PE, Klein NC. Appropriateness of empiric gentamicin and vancomycin therapy for bacteremias in chronic dialysis outpatient units in the era of antibiotic resistance. J Chemother 18:490–3, 2006.
Munita JM, Arias CA, Murray BE. Enterococcus faecalis infective endocarditis: Is it time to abandon aminoglycosides? Clin Infect Dis 56:1269-1272, 2013.
Roushan MRH, Mohraz M, Hajiahmadi M, et al. Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. Clin Infect Dis 42:1075–1080, 2006.
Snydman, DR, McDermott LA, Jacobus NV. Evaluation of in vitro interaction of daptomycin with gentamicin or beta-lactam antibiotics against Staphylococcus aureus and Enterococci by FIC index and timed-kill curves. J Chemother 17:614–21, 2005.
Veinstein A, Venisse N, Badin J, et al. Gentamicin in hemodialyzed critical care patients: early dialysis after administration of a high dose should be considered. Antimicrob Agents Chemo 57:977-982, 2013.
Website: www.pdr.net

## Griseofulvin (Fulvicin, Grifulvin, Ultra, Gris-PEG, Grisactin)

**Drug Class:** Antifungal.
**Usual Dose:** 500 mg-1 gm (PO) q24h (microsize); 330–375 mg (PO) q24h (ultramicrosize).
**Pharmacokinetic Parameters:**
*Peak serum level: 1–2 mcg/mL*
*Bioavailability: 50%*
*Excreted unchanged (urine): 1%*
*Serum half-life (normal/ESRD): 9/22 hrs*
*Plasma protein binding: 84%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD or PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Alcohol (↑ griseofulvin toxicity); barbiturates (↓ griseofulvin levels); oral contraceptives, warfarin (↓ interacting drug levels).
**Adverse Effects:** Photosensitivity reactions, rash, headache, nausea, vomiting, diarrhea, angular stomatitis, glossitis, leukopenia.
Allergic Potential: Moderate
**Safety in Pregnancy:** C
**Comments:** May exacerbate SLE/acute intermittent porphyria. Take microsize griseofulvin with fatty meal to ↑ absorption to ~ 70%. Ultramicrosize griseofulvin is absorbed 1.5 times better than microsize griseofulvin.

**REFERENCES:**

Trepanier EF, Amsden GW. Current issues in onychomycosis. Ann Pharmacotherapy 32:204–14, 1998.
Website: www.pdr.net

## Imipenem/Cilastatin (Primaxin)

**Drug Class:** Carbapenem.
**Usual Dose:** 1 gm (IV) q6h (see comments).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Spectrum:** (see ***Susceptibility Profiles*** p. 198–202).
**Resistance Potential:** High (P. aeruginosa, ↑ prevalence of MRSA)
**Pharmacokinetic Parameters:**
*Peak serum level: 42–116 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 70%*
*Serum half-life (normal/ESRD): 1/4 hrs*
*Plasma protein binding: 20% / 40% (cilastatin)*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 40–70 mL/min | 500 mg (IV) q6h |
| CrCl 20–40 mL/min | 250 mg (IV) q8h |
| CrCl < 20 mL/min† | 250 mg (IV) q12h |
| Post–HD dose | 250 mg (IV) |
| Post–PD dose | 250 mg (IV) |
| CVVH/CVVHD/CVVHDF dose | 500 mg (IV) q8h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

† Avoid if CrCl ≤ 5 mL/min unless dialysis is instituted within 48 hours.

**Drug Interactions:** Cyclosporine (↑ cyclosporine levels); ganciclovir (↑ risk of seizures); probenecid (↑ imipenem levels); valproic acid (↓ seizure threshold).
**Adverse Effects:** Seizures, phlebitis.
**Allergic Potential:** Low
**Safety in Pregnancy:** C

**Comments:** Imipenem:cilastatin (1:1). Infuse 1 gm (IV) over 40–60 minutes. Imipenem is renally metabolized by dehydropeptidase I; cilastatin is an inhibitor of this enzyme, effectively preventing the metabolism of imipenem. Imipenem/cilastatin can be given IM (IM absorption: imipenem 75%; cilastatin 100%). ***Fully susceptible organisms dose: 500 mg (IV) q6h; Less susceptible organisms (e.g., P. aeruginosa) dose:*** *1 gm (IV) q6–8h*. Incompatible in solutions containing vancomycin or metronidazole. ***Seizures more likely in renal insufficiency/high doses (> 2 gm/d)***. Inhibits endotoxin release from gram-negative bacilli. **Very low incidence of cross reactions with β-lactams**.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 10%
Inflamed meninges = 15%
**Bile Penetration:** 1%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

Balfour JA, Bryson HM, Brogden RN. Imipenem/cilastatin: An update of its antibacterial activity, pharmacokinetics, and therapeutic efficacy in the treatment of serious infections. Drugs 51:99–136, 1996.

Barza M. Imipenem: First of a new class of beta-lactam antibiotics. Ann Intern Med 103:552–60, 1985.

Fish DN, Teitelbaum, I, Abraham E. Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. Antimicrobial Agents and Chemotherapy 49:2421–2428, 2005.

Garbino J, Villiger P, Caviezel A, et al. A randomized prospective study of cefepime plus metronidazole with imipenem-cilastatin in the treatment of intra-abdominal infections. Infection 35:161–166, 2007.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Helinger WC, Brewer NS. Carbapenems and monobactams: Imipenem, meropenem, and aztreonam. Mayo Clin Proc 74:420–34, 1999.
Lamoth F, Erard V, Asner S, et al. High imipenem blood concentrations associated with toxic encephalopathy in a patient with mild renal dysfunction. Int J Antimicrob Agents 34:386–388, 2009.
Lautenbach E, Weiner MG, Nachamkin I, et al. Imipenem resistance among Pseudomonas aeruginosa Isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. Infection Control and Hosp Epidemiol 27:893–900, 2006.
Maravi-Poma E, Gener J, Alvarez-Lerma F, et al. Spanish group for the study of septic complications in severe acute pancreatitis. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med 29:1974–80, 2003.
Miliani K, L'Heriteau F, Lacave L, et al. Imipenem and ciprofloxacin consumption as factors associated with high incidence rates of resistance Pseudomonas aeruginosa in hospitals in northern France. J Hosp Infect 77:343–347, 2011.
Saltoglu N, Dalkiran A, Tetiker T, et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin Microbiol Infect 16:1252–1257, 2010.
Website: www.pdr.net

## Indinavir (Crixivan) IDV

**Drug Class:** HIV protease inhibitor.
Usual Dose: 800 mg (PO) q8h or 800 mg (PO) q12h with ritonavir 100–200 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 252 mcg/mL*
*Bioavailability: 65% (77% with food)*
*Excreted unchanged (urine): < 20%*
*Serum half-life (normal/ESRD): 2 hrs/no data*
*Plasma protein binding: 60 %*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | 600 mg (PO) q8h |
| Severe hepatic insufficiency | 400 mg (PO) q8h |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Atazanavir | Avoid |
| Didanosine | Administer didanosine 1 hour apart |
| Delavirdine | Indinavir 600 mg q8h |
| Efavirenz | Indinavir 1000 mg q8h |
| Lopinavir/ritonavir | Indinavir 600 mg q12h |
| Nelfinavir | Limited data for indinavir 1200 mg q12h + nelfinavir 1250 mg q12h |
| Nevirapine | Indinavir 1000 mg q8h |
| Ritonavir | Indinavir 800 mg q12h + ritonavir 100–200 mg q12h |
| Saquinavir | No information |
| Rifampin | Avoid combination |
| Rifabutin | Indinavir 1000 mg q8h; rifabutin 150 mg q24h or 300 mg 2–3x/week |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); astemizole, terfenadine, benzodiazepines, cisapride, ergot alkaloids, statins, calcium channel blockers (↑ calcium channel blocker levels); carbamazepine, phenobarbital, phenytoin (↓ indinavir levels, ↑ anticonvulsant levels; monitor); tenofovir (↓ indinavir levels, ↑ tenofovir levels); clarithromycin, erythromycin, telithromycin (↑ indinavir and macrolide levels); didanosine (administer indinavir on empty stomach 1 hour apart); ethinyl estradiol, norethindrone (↑ interacting drug levels; no dosage adjustment); grapefruit juice (↓ indinavir levels); itraconazole, ketoconazole (↑ indinavir levels); sildenafil (↑ or ↓ sildenafil levels; do not exceed 25 mg in 48 hrs), tadalafil (max. 10 mg/72 hrs), vardenafil (max 2.5 mg/72 hrs); theophylline (↓ theophylline levels); fluticasone nasal spray (avoid concomitant use).

**Contraindications:** rifapentine, St. John's wort

**Adverse Effects:** Nephrolithiasis, nausea, vomiting, diarrhea, anemia, leukopenia, headache, insomnia, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ SGOT/SGPT, ↑ indirect bilirubin (2° to drug-induced Gilbert's syndrome; inconsequential), fat redistribution, lipid abnormalities (evaluate risk of coronary disease/pancreatitis), abdominal pain, night sweats, possible ↑ bleeding in hemophilia, dry skin, chelitis, paronychiae.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Renal stone formation may be prevented/minimized by adequate hydration (1–3 liters water daily); ↑ risk of nephrolithiasis with alcohol. Take 1 hour before or 2 hours after meals (may take with skim milk or low fat meal). Separate dosing with ddI by 1 hour.

**Cerebrospinal Fluid Penetration:** 16%

**REFERENCES:**

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Website: www.pdr.net

## Isavuconazole (Cresemba)

**Drug Class:** Azole antifungal

**Usual Dose: Loading dose:** 200 mg (IV) q8h × 48 hrs, then **Maintenance dose:** 200 mg (IV/PO) q24h.

**Pharmacokinetic Parameters:**

*Peak serum level: 1.85 – 2.56 mcg/ml*

*Bioavailability (IV/PO): 98%*

*Excreted unchanged:* no data

*Serum half-life (normal/ESRD):* IV $t_{½}$ = 76–104 hrs; PO $t_{½}$ = 56–77 hrs/no data

*Plasma protein binding: 98%*

*Volume of distribution ($V_d$): 4.4–7.7 L/kg*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | No change |
| Post–HD dose | No change |
| Post–PD dose | No change |
| CVVH dose | No change |
| Mild/Moderate Hepatic insufficiency | 200 mg (IV) q8h × 48 hrs, then 100 mg (IV/PO) q24h |
| Severe hepatic insufficiency | Avoid use |

**Drug Interactions:** CYP3A4 substrate; Concomitant use of CYP3A4 inhibitors and inducers is not recommended. No clinically relevant interactions with warfarin or cyclosporine.
**Adverse Effects:** Nausea, vomiting, diarrhea, pyrexia, headache, constipation, dyspnea, cough, febrile neutropenia, chills, fatigue, ↑ AST/ALT, hypokalemia, hypersensitivity reactions, infusion related reactions, and shortening of the QT interval.
**Allergic Potential:** Low (potential anaphylaxis/severe cutaneous reactions 1.9%)
**Safety in Pregnancy:** Unknown
**Comments:** Water soluble azole, which does not require cyclodextrin for IV solubility. Isavuconazonium, is a produg (water soluble) that is rapidly hydrolyzed in the blood, to the active moiety, isavuconazole (lipid soluble). Available as both IV and PO formulations. Only azole that does not prolong the QT interval. Following reconstitution, IV isavuconazonium may spontaneously hydrolyze and precipitate as insoluble isavuconazole; an inline filter is recommended to remove precipitates. ***Highly active against Candida albicans; non-albicans Candida, Aspergillus; Active against Cryptococcus; Some activity against Mucor, Zygomycetes.***

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** Good

**REFERENCES:**

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Schmitt-Hoffmann A, Roos B, Maares J, et al. Multiple-dose pharmacokinetics and safety of the new antifungal triazole BAL4815 after intravenous infusion and oral administration of its prodrug, BAL8557, in healthy volunteers. Antimicrob Agents Chemo. 50:286-293, 2006.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Thompson GR, 3rd, Wederhold NP. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole. Mycopathologia. 170:291-313, 2010.
Website: www.pdr.net

## Isoniazid (INH)

**Drug Class:** Anti–TB drug.
**Usual Dose:** 300 mg (PO) q24h or 5 mg/kg (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 7 mcg/ml*
*Bioavailability: 90%*
*Excreted unchanged (urine): 50–70%*
*Serum half-life (normal/ESRD): 1/1 hr*
*Plasma protein binding: 15%*
*Volume of distribution ($V_d$): 0.75 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | 300 mg |
| Post–PD dose | 300 mg |
| CVVH/CVVHD/CVVHDF dose | None |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Alcohol, rifampin (↑ risk of ↑ SGOT/SGPT); alfentanil (↑ duration of alfentanil effect); aluminum salts (↓ isoniazid absorption); carbamazepine, phenytoin (↑ interacting drug levels); itraconazole (↓ itraconazole levels); warfarin (↑ INR).
**Adverse Effects:** ↑ SGOT/SGPT, drug fever/rash, age-dependent hepatotoxicity (after age 60), drug-induced ANA/SLE, hemolytic anemia, neuropsychiatric changes in the elderly. Transient/reversible ↑ SGOT/SGPT frequently occur early (< 3 weeks) after INH use. If ↑ SGOT/SGPT, monitor levels twice weekly until levels peak, then monitor levels weekly until levels return to within normal range. D/C INH if ↑ SGOT/SGPT ≥ 10 × upper limit of normal. Fulminant hepatic failure (rare).
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Administer with 50 mg of pyridoxine daily to prevent peripheral neuropathy. Increased blood pressure/rash with tyramine–containing products, e.g., cheese/wine. ↑ hepatotoxicity in slow acetylators.
**Slow acetylator dose:** 150 mg (PO) q24h.
**TB D.O.T. dose:** 15 mg/kg or 900 mg (PO) 3x/week.

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 90%
Inflamed meninges = 90%

**REFERENCES:**

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Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: A meta-analysis. Clin Infect Dis 40:670–6, 2005.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

McIllerson H, Wash P, Burger A, et al. Determinants of rifampin, isoniazid, pyrazinamide and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother 50:1170–77, 2006.
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Van Scoy RE, Wilkowske CJ. Antituberculous agents. Mayo Clin Proc 67:179–87, 1992.
Website: www.pdr.net

## Itraconazole (Sporanox)

**Drug Class:** Antifungal.

**Usual Dose:** 200 mg (PO, capsules or solution, solution produces better absorption) q12h or q24h (Take without food). Depending on disease, due to enhanced drug delivery, IV therapy begins with 200 mg IV q12h × 2 days (4 doses) and then continues with only 200 mg (IV) q24h; PO follow-up to IV therapy for serious infection is at 200 mg PO q12h. Each IV dose should be infused over 1 hour (see comments).

**Pharmacokinetic Parameters:**

*Peak serum level: 2.8 mcg/ml*
*Bioavailability: 55% (capsules)/90% (solution)*
*Excreted unchanged (urine): 1%*
*Serum half-life (normal/ESRD): 21–64/35 hrs*
*Plasma protein binding: 99.8%*
*Volume of distribution ($V_d$): 10 L/kg*

**Primary Mode of Elimination:** Hepatic; metabolized predominantly by the cytochrome P450 3A4 isoenzyme system (CYP3A4)

**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | No change |
| CrCl < 30 mL/min | No change for (PO); avoid (IV) due to ↑ cyclodextrin |
| Post–HD dose | 100 mg (IV/PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change† |
| Severe hepatic insufficiency | Use with caution |

† ↑ ↑ $t_{1/2}$ of itraconazole in patients with hepatic insufficiency should be considered when given with medications metabolized by P450 isoenzymes. Also see Adverse Effects for information regarding patients who develop liver dysfunction.

**Drug Interactions:** *Itraconazole may* ↑ *plasma levels of:* alfentanil, buspirone, busulfan, carbamazepine, cisapride, cyclosporine, digoxin, dihydropyridines, docetaxel, dofetilide, methylprednisolone, oral hypoglycemics (↑ risk of hypoglycemia), pimozide, quinidine, rifabutin, saquinavir, sirolimus, tacrolimus, trimetrexate, verapamil, vinca alkaloids, warfarin; alprazolam, diazepam, midazolam, triazolam (↑ sedative/hypnotic effects); atorvastatin, lovastatin, simvastatin (↑ risk of rhabdomyolysis); indinavir, ritonavir, saquinavir; coadministration of oral midazolam, triazolam, lovastatin, or simvastatin with itraconazole is contraindicated; coadministration of cisapride, pimozide, quinidine, amiodarone, or dofetilide with itraconazole is contraindicated due to the risk of ↑ $QT_c$/life-threatening ventricular arrhythmias. *Decreased*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*itraconazole levels may occur with:* antacids, carbamazepine, $H_2$-receptor antagonists, isoniazid, nevirapine, phenobarbital, phenytoin, proton pump inhibitors, rifabutin, rifampin; coadministration of rifampin with itraconazole is not recommended. *Increased itraconazole levels may occur with:* clarithromycin, erythromycin, indinavir, ritonavir.

**Adverse Effects:** ≥ 2%: nausea, diarrhea, vomiting, headache, abdominal pain, bilirubinemia, rash, ↑ SGPT/SGOT, hypokalemia, ↑ serum creatinine. Rarely, itraconazole has been associated with serious hepatotoxicity (liver failure/death). If liver disease develops, discontinue treatment, perform liver function testing, and reevaluate risk/benefit of further treatment. Use itraconazole with caution in patients with ↑ liver enzymes, active liver disease, or previous drug-induced hepatotoxicity. Life-threatening ventricular arrhythmias/sudden death have occurred in patients using cisapride, pimozide, or quinidine concomitantly with itraconazole; coadministration of these drugs with itraconazole is contraindicated. Use itraconazole with caution in patients with ventricular dysfunction. IV itraconazole may cause transient, asymptomatic ↓ in ejection fraction for ≤ 12 hours. If CHF develops, consider discontinuation of itraconazole.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** ***Oral itraconazole*:** Requires gastric acidity for absorption. When antacids are required, administer ≥ 1 hour before or 2 hours after itraconazole capsules. Oral solution is better absorbed without food; capsules are better absorbed with food. Capsule bioavailability is food dependent: 40% fasting/90% postprandial. For oral therapy, bioavailability of 10 ml of solution without food = 100 mg capsule with food. Administer with a cola beverage in patients with achlorhydria or taking $H_2$-receptor antagonists/other gastric acid suppressors. While oral solution and capsules can be interchanged for treatment of systemic disease if adequate blood levels are achieved, oral solution produces more reliable blood levels and is definitely preferred for oral/esophageal candidiasis where the local effect of the solution on the infection seem helpful. ***IV itraconazole***: Hydroxypropyl-β-cyclodextrin stabilizer in IV formulation accumulates in renal failure. IV itraconazole should not be used in patients with CrCl < 30 mL/min; if possible, use the oral preparation. Infuse 60 ml of dilute solution (3.33 mg/ml = 200 mg itraconazole, pH ~ 4.8) IV over 60 minutes, using infusion set provided. After administration, flush the infusion set with 15–20 ml of normal saline injection. The compatibility of IV itraconazole with flush solutions other than normal saline is unknown. ***Highly active against C. albicans, non-albicans Candida, Cryptococcus, Histoplasmosis, Blastomycosis, Paracoccidiomycosis, Sporotrichosis. Active against dermatophytes. No activity against Pseudoallescheria/Scedosporium, Fusaria or Mucor.***

**Cerebrospinal Fluid Penetration:** < 10%

**Bile Penetration:** 3–18%

**REFERENCES:**

Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized controlled trial. Ann Intern Med 135:412–22, 2001.

Bruggemann RJM, Alffenaar JWC, Blijlevens NMA, et al. Clinical relevance of the pharmoacokinetic interactions of azole antifungal drugs with coadministered agents. Clin Infect Dis 48:1441–1458, 2009.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Conte JE Jr, Golden JA, Kipps J, et al. Intrapulmonary pharmacokinetics and pharmacodynamics of itraconazole and 14-hydroxyitraconazol steady state. Antimicrob Agents Chemother 48:3823–7, 2004.
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Website: www.pdr.net

## Ketoconazole (Nizoral)

**Drug Class:** Antifungal.
**Usual Dose:** 200 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 3.5 mcg/ml*
*Bioavailability: 82%*
*Excreted unchanged (urine): 2–4%*
*Serum half-life (normal/ESRD): 6/20 hrs*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): 2 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 40 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | Use with caution |
| Severe hepatic insufficiency | Avoid |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Astemizole, cisapride, terfenadine, amiodarone (may ↑ QT interval, torsades de pointes); carbamazepine, INH (↓ ketoconazole levels); cimetidine, famotidine, nizatidine, ranitidine, omeprazole, INH (↓ ketoconazole absorption); cyclosporine, digoxin, loratadine, tacrolimus (↑ interacting drug levels with possible toxicity); didanosine (↓ ketoconazole levels); midazolam, triazolam (↑ interacting drug levels, ↑ sedative effects); oral hypoglycemics (severe hypoglycemia); phenytoin, rifabutin, rifampin (↓ ketoconazole levels, ↑ interacting drug); statins (↑ statin levels; rhabdomyolysis reported); warfarin (↑ INR).

**Adverse Effects:** Nausea, vomiting, abdominal pain, pruritus.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Dose-dependent reduction in gonadal (androgenic) function. Decreased cortisol production with doses ≥ 800 mg/day, but **does not result in adrenal insufficiency**. Give oral doses with citric juices.

***Highly active against dermatophytes, Malassezia, Candida albicans. Some activity against Aspergillus, Coccidiomycosis, Paracoccidiomycosis, Histoplasmosis. No activity against Pseudoallescheria/ Scedosporium, Fusaria or Mucor.***

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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Website: www.pdr.net

## Lamivudine (Epivir) 3TC

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor); HBV antiviral.

**Usual Dose:** 150 mg (PO) q12h or 300 mg (PO) q24h (HIV); 100 mg (PO) q24h (HBV).

**Pharmacokinetic Parameters:**

*Peak serum level: 1.5 mcg/mL*
*Bioavailability: 86%*
*Excreted unchanged (urine): 71%*
*Serum half-life (normal/ESRD): 5–7/20 hrs*
*Plasma protein binding: 36%*
*Volume of distribution ($V_d$): 1.3 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments* (HIV/HBV dose)**

| | |
|---|---|
| CrCl 30–50 mL/min | 150 mg (PO) q24h /100 mg (PO), then 50 mg (PO) q24h |
| CrCl 15–30 mL/min | 100 mg (PO) q24h /100 mg (PO), then 25 mg (PO) q24h |
| CrCl 5–15 mL/min | 50 mg (PO) q24h /35 mg (PO), then 15 mg (PO) q24h |
| CrCl < 5 mL/min | 25 mg (PO) q24h /35 mg (PO), then 10 mg (PO) q24h |
| Post–HD dose | 25 mg (PO)/10 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 100 mg (PO) q24h /100 mg (PO), then 25 mg (PO) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Didanosine, zalcitabine (↑ risk of pancreatitis); TMP–SMX (↑ lamivudine levels); zidovudine + lamivudine not recommended.
**Adverse Effects:** Lamivudine tablets and oral solution used to treat HIV infection contain a higher dose of lamivudine than Epivir-HBV® tablets and oral solution used to treat chronic HBV. Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV and have discontinued lamivudine. Hepatic function should be monitored closely for at least several months in patients who discontinue lamivudine. Most common include headache, dizziness, malaise, nausea nasal congestion, cough, rash, neuropathy, leucopenia. Pancreatitis and or lactic acidosis with hepatic steatosis (rare but potentially life threatening toxicity with NRTI's). Immune reconstitution syndrome can occur.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Potential cross resistance with didanosine. Prevents development of AZT resistance and restores AZT susceptibility. May be taken with or without food. Although effective against HBV, lamivudine is no longer a first-line option because of the development of resistance in 70% of treated patients.

**Cerebrospinal Fluid Penetration:** 15%

**REFERENCES:**

Diaz-Brito V, Leon A, Knobel H, et al. Post-exposure prophylaxis for HIV-infection: a clinical trail comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. Antivir Ther 17:337–46, 2012.
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Website: www.pdr.net

## Lamivudine + Zidovudine (Combivir) 3TC/ZDV

**Drug Class:** HIV NRTIs combination.
**Usual Dose:** Combivir tablet = 150 mg lamivudine + 300 mg zidovudine. Usual dose = 1 tablet (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 2.6/1.2 mcg/mL*
*Bioavailability: 82/60%*
*Excreted unchanged (urine): 86/64%*
*Serum half-life (normal/ESRD): [6/1.1]/[20/2.2] hrs*
*Plasma protein binding: <36/<38%*
*Volume of distribution ($V_d$): 1.3/1.6 L/kg*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Primary Mode of Elimination:** Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | Avoid |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Moderate hepatic insufficiency | Avoid |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** Atovaquone (↑ zidovudine levels); stavudine (antagonist to stavudine; avoid combination); ganciclovir, doxorubicin (neutropenia); tipranavir (↓ zidovudine levels); TMP–SMX (↑ lamivudine and zidovudine levels); vinca alkaloids (neutropenia).

**Adverse Effects:** Zidovudine, has been associated with hematologic toxicity including neutropenia and severe anemia. Prolonged use of zidovudine has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV and have discontinued lamivudine. Nausea, vomiting, diarrhea, anorexia, insomnia fever/chills, headache, malaise/fatigue, peripheral neuropathy and pancreatitis. Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.

**Allergic Potential:** Low

**Safety in Pregnancy:** C.

**Cerebrospinal Fluid Penetration:**
Lamivudine = 12%; Zidovudine = 60%

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Website: www.pdr.net

## Leflunomide (Arava)

**Drug Class:** CMV antiviral.

**Usual Dose:** 100 mg/day (PO) × 3 days, then 20 mg (PO) q24h.

**Pharmacokinetic Parameters:**

*Peak serum level: 8 mcg/mL*
*Bioavailability: 80%*
*Excreted unchanged: 0%*
*Serum half-life (normal/ESRD): 14 days/no data*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): 0.13 L/kg*

**Primary Mode of Elimination:** Hepatic/renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 15–30 mL/min | Use with caution |
| CrCl < 15 mL/min | Use with caution |
| Post–HD dose | Use with caution |
| Post–PD dose | Use with caution |
| CVVH/CVVHD/CVVHDF dose | Use with caution |
| Moderate—severe hepatic insufficiency | Avoid if ↑ SGOT/SGPT > 2 × n or pre-existing liver disease |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** May inhibit CYP 2C9; rifampin (↑ levels of active metabolite, M1); hepatotoxic drugs.
**Adverse Effects:** Headache, nausea, diarrhea, hypertension; hepatotoxicity, bone marrow suppression, rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis, interstitial lung disease.
**Allergic Potential:** Low
**Safety in Pregnancy:** X
**Comments:** Alternate therapy of CMV infection after 1st line therapies fail; do not use with pre-existing liver disease; metabolized to active metabolite (M1); not recommended in patients with severe, uncontrolled infections, bone marrow dysplasia or severe immunodeficiency, prolonged administration leads to significant accumulation, (drug elimination procedure with cholestyramine described in PI). Screen for TB before starting leflunomide; avoid live vaccinations while on leflunomide; monitor LFT's and CBCs. ***Discontinue if*** **↑ *SGOT/SGPT* > 3 × n.**

**REFERENCES:**

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John GT, et al. Leflunomide therapy for cytomegalovirus disease in renal allograft recipients. Transplantation 77:1460–61, 2004.
Website: www.pdr.net

## Levofloxacin (Levaquin)

**Drug Class:** Respiratory quinolone.
**Usual Dose:** 500–750 mg (IV/PO) q24h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 5–8 mcg/ml*
*Bioavailability: 99%*
*Excreted unchanged (urine): 87%*
*Serum half-life (normal/ESRD): 7 hrs/40 hrs*
*Plasma protein binding: 30%*
*Volume of distribution ($V_d$): 1.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 750 mg/500 mg (IV/PO) q24h)

| | |
|---|---|
| CrCl > 50 mL/min | No change |
| CrCl 20–50 mL/min | 750 mg (IV/PO) q48h /500 mg (IV/PO), then 250 mg (IV/PO) q24h |
| CrCl < 20 mL/min | 750 mg (IV/PO), then 500 mg (IV/PO) q48h /500 mg (IV/PO), then 250 mg (IV/PO) q48h |
| HD/CAPD dose | 500 mg (IV/PO) q48h |
| Post–HD dose | None |
| Post–HFHD dose | 250 mg (IV/PO) |
| Post–PD dose | 250 mg (IV/PO) |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (IV/PO) q48h/250 mg (IV/PO) q24h |
| HD q 48–72h dose | 500 mg (IV/PO) q HD* |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

*Give at end of HD.

**Drug Interactions:** $Al^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$ antacids (↓ absorption of levofloxacin if taken together); NSAIDs (CNS stimulation); probenecid (↑ levofloxacin levels); warfarin (↑ INR).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Adverse Effects:** Headache, insomnia, delerium (rare) nausea, constipation, delirium (rare) C. difficile diarrhea/colitis. ***Does not cause seizures.*** FQ use has an increased risk of tendinitis/tendon rupture. Risk in highest in the elderly, those on steroids, and those with heart, lung, or renal transplants. Peripheral neuropathy may occur early and may be permanent.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Take 2 hours before or after aluminum/magnesium-containing antacids. Does not increase digoxin concentrations. May ↑ QTc interval, particularly in patients with predisposing conditions or medications e.g., amiodarone. **Acute bacterial sinusitis dose:** 750 mg (PO) q24h × 5 days. **CAP dose:** 750 mg (IV/PO) q24h × 5 days. **Nosocomial pneumonia dose:** 750 mg (IV/PO) q24h × 7–14 days. **cSSSI dose:** 750 mg (IV/PO) q24h × 7–14 days. **TB dose** (alternate drug in MDR TB regimen): 500 mg (PO) q24h. **Complicated UTI/ acute pylonephritis dose:** 750 mg (IV/PO) q24h × 5 days.
↑ **incidence of C. difficile diarrhea/colitis with PPIs (for patients on PPIs during FQ therapy, D/C PPIs or switch to $H_2$ blocker for duration of FQ therapy).**
Effective against oral anaerobes/above the waist but not anaerobes below the waist e.g. B. fragilis.

**Cerebrospinal Fluid Penetration:** 16%
**Bile Penetration:** 100%
(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

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Website: www.pdr.net

## Linezolid (Zyvox)

**Drug Class:** Oxazolidinone.
**Usual Dose:** 600 mg (IV/PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 15–21 mcg/ml*
*Bioavailability: 100% (IV and PO)*
*Excreted unchanged (urine): 30%*
*Serum half-life (normal/ESRD): 6.4/7.1 hrs*
*Plasma protein binding: 31%*
*Volume of distribution ($V_d$): 0.64 L/kg*
**Primary Mode of Elimination:** Hepatic/Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | 600 mg (IV/PO) |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Pseudoephedrine, tyramine-containing foods (↑ risk of hypertensive crisis); serotonergic agents, e.g., SSRIs, MAOIs, St. John's wort, ritonavir (↑ risk of serotonin syndrome). Serotonin syndrome: fever, delerium, hypertension, tremor/clonus, hyperreflexia.
**Adverse Effects:** Mild, readily reversible thrombocytopenia, anemia, or leukopenia may occur usually after ≥ 2 weeks of therapy. Lactic acidosis (rare), optic/peripheral neuropathy (> 28 days of therapy, rare). If used for > 4 weeks, **↑ risk of myelosuppression or blindness (irreversible) particularly in those with optic nerve disorders or glaucoma. Monitor visual function if symptomatic or therapy ≥ 2 weeks; monitor CBC weekly if therapy > 2 weeks.** Hypoglycemia may occur (> 7 days) with IV/PO linezolid.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** ***Ideal for IV-to-PO switch programs***. Unlike vancomycin, ***linezolid use does not increase VRE prevalence***. Unlike

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

quinupristin/dalfopristin, linezolid is active against E. faecalis (VSE). **Effective oral therapy for MRSA, MRSE, and E. faecium (VRE) infections.** *Alternate therapy for Nocardia and Listeria infections.*

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:** 70%
**Bile Penetration:** 200%
(also see ***Antibiotic Pearls & Pitfalls*** p. 517).

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Website: www.pdr.net

## Lopinavir + Ritonavir (Kaletra) LPV/RTV

**Drug Class:** HIV protease inhibitor combination.
**Usual Dose:** Therapy-naive: 400/100 mg q12h or 800/200 mg q24h (if <3 lopinavir resistance—associated substitutions).
**Pharmacokinetic Parameters:**
*Peak serum level: 9.6/≤ 1 mcg/mL*
*Bioavailability: No data*
*Excreted unchanged (urine): 3%*
*Serum half-life (normal/ESRD): 5–6/5–6 hrs*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): No data/ 0.44 L/kg*
**Primary Mode of Elimination:** Hepatic

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Fosamprenavir | Avoid |
| Delavirdine | No data |
| Efavirenz | Consider lopinavir/ ritonavir 500/125 mg q12h |
| Indinavir | Indinavir 600 mg q12h |
| Nelfinavir | Same as for efavirenz |
| Nevirapine | Same as for efavirenz |
| Rifabutin | Max. dose of rifabutin 150 mg qod or 3 times per week |
| Saquinavir | Saquinavir 1000 mg q12h |

**Drug Interactions:** Antiretrovirals, rifabutin, (see dose adjustment grid, above); Rifampin may reduce lopinavir levels leading to drug failure and should be avoided. Sidenafil, tadalafil, and virdenafil levels will be greatly increased and their dosage must be decreased. Antiarhythmics such as amiodarone, bepredil, lidocaine and quinidine may increase levels. Once daily dosing not recommended in pregnancy or for patients receiving efavirenz, nevirapine, fosamprenavir, nelfinavir, carbamazepine, phenytoin, or phenobarbital. Tacrolimus, cyclosporine and rapamycin levels can be altered leading to increased toxicity. Methadone levels may be decreased leading to withdrawal reactions. Fluticasone levels may increase leading to Cushing like syndrome, astemizole, terfenadine, benzodiazepines, cisapride, ergotamine, flecainide, pimozide, propafenone, rifampin, statins, tenofovir (↓ lopinavir levels, ↑ tenofovir levels). ↓ effectiveness of oral contraceptives. Insufficient data on other drug interactions listed for ritonavir alone. At end of drug interaction add lopinavir/resolution contains alcohol and can lead to a disulfram reaction when administered with metronidazole clarithromycin (↑ $QT_c$).

**Contraindications:** St. John's wort, boceprevir, telaprevir, rifapentine.

**Adverse Effects:** Diarrhea (very common), headache, nausea, vomiting, asthenia, ↑ SGOT/SGPT, hepatotoxicity, abdominal pain, pancreatitis, paresthesias, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ cholesterol/triglycerides (evaluate risk for coronary disease, pancreatitis), ↑ CPK, ↑ uric acid, fat redistribution, possible increased bleeding in hemophilia. Oral solution contains 42.4% alcohol. Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Tablet formulation does not require refrigeration and may be taken with or without food. With oral solution, Lopinavir serum concentrations with moderately fatty meals are increased 54%.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Loracarbef (Lorabid)

**Drug Class:** 2nd generation oral cephalosporin.
**Usual Dose:** 400 mg (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 191–197).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 14 mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 1.2/32 hrs*
*Plasma protein binding: 25%*
*Volume of distribution ($V_d$): 0.35 L/kg*

**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 200 mg (PO) q24h |
| CrCl < 10 mL/min | 200 mg (PO) q72h |
| Post–HD dose | 400 mg (PO) |
| Post–PD dose | 200 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 200 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Drug fever/rash, C. difficile diarrhea/colitis.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Take 1 hour before or 2 hours after meals. **CAP dose:** 400 mg (PO) q12h. **Sinusitis/ tonsillitis dose:** 200 mg (PO) q12h.

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 510).

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Maraviroc (Selzentry) MVC

**Drug Class:** HIV chemokine receptor 5 (CCR5) antagonist.
**Usual Dose:** 150 mg, 300 mg, or 600 mg (PO) q12h, depending on concomitant medications (see below), in CCR5-tropic HIV-1 isolates. (available in 150 mg and 300 mg tablets).
**Pharmacokinetic Parameters:**
*Peak serum level: 266–618 mcg/mL*
*Bioavailability: 23–33%*
*Excreted unchanged: 20% (urine); 76% (feces)*
*Serum half-life (normal/ESRD): 14–18 hrs/not studied*
*Plasma protein binding: 76%*
*Volume of distribution ($V_d$): 194 L*

**Primary Mode of Elimination:** Fecal/renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min with potent CYP3A4 inhibitor | 150 mg (PO) q12h |
| CrCl > 30 mL/min with potent CYP3A4 inducer but no inhibitor | 600 mg (PO) q12h |
| CrCl < 30 mL/min with potent CYP3A4 inducer or inhibitor | Avoid |
| CrCl < 30 mL/min without potent CYP3A4 inducer or inhibitor | 300 mg (PO) q12h |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No data |
| Moderate hepatic insufficiency with potent CYP3A4 inhibitor | Use with caution |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, telithromycin | 150 mg (PO) q12h |
| Tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide | 300 mg (PO) q12h |
| Efavirenz, rifampin, etravirine, carbamazepine, phenobarbital, phenytoin | 600 mg (PO) q12h |

**Drug Interactions:** Maraviroc is a substrate of CYP3A and P-glycoprotein and is likely to be modulated by inhibitors and inducers of these enzymes/transporters.
**Adverse Effects:** Hepatotoxicity has been reported. A systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE) prior to the development of hepatotoxicity may occur. Other Adverse Effects: cough, infection, upper respiratory tract infection, rash, pyrexia, dizziness, abdominal pain, musculoskeletal symptoms (joint/muscle pain). Orthostatic hypotension with severe renal insufficiency.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Indicated for treatment-experienced adult patients infected with only cellular chemokine receptor (CCR) 5-tropic HIV-1 virus detectable who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Used in combination with other antiretroviral agents.Phenotype test is needed to confirm infection with CCR5-tropic HIV-1 (also known as "R5 virus"). May increase risk of infection (especially HSV) and neoplasms.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

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Website: www.pdr.net

## Meropenem (Merrem/Meronem)

**Drug Class:** Carbapenem.
**Usual Dose:** 1 gm (IV) q8h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 49 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 70%*
*Serum half-life (normal/ESRD): 1/7 hrs*
*Plasma protein binding: 2%*
*Volume of distribution ($V_d$): 0.35 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 1 gm dose; for 500 mg dosing use half of dose shown in grid)

| | |
|---|---|
| CrCl 25–50 mL/min | 1 gm (IV) q12h |
| CrCl 10–25 mL/min | 500 mg (IV) q12h |
| CrCl < 10 mL/min | 500 mg (IV) q24h |
| Post–HD dose | 500 mg (IV) |
| Post–HFHD dose | 500 mg (IV) |
| Post–PD dose | 500 mg (IV) |
| CVVH/CVVHD/ CVVHDF dose | 1 gm (IV) q12h |
| HD q 48–72h dose | 2 gm (IV) q HD* |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

*Give at end of HD.

**Drug Interactions:** Probenecid (↑ meropenem half-life by 40%), Valproic acid (↓ seizure threshold).
**Adverse Effects:** Rarely, mild infusion site inflammation. No seizures. **No cross allergenicity with penicillins/β-lactams; safe to use in patients with a history of penicillin anaphylactic/other allergic reactions.**

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** ***MDR GNBs, cystic fibrosis/ meningitis dose:*** *2 gm (IV) q8h;* **uSSSIs or UTIs dose:** 500 mg (IV) q8h. Inhibits endotoxin release from gram-negative bacilli. **Meropenem is the *only carbapenem that may be given by IV bolus injection over 3–5 minutes***. $Na^+$Content = 3.92 mEq/g

Meningeal dose = 2 gm (IV) q8h.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 10%
Inflamed meninges = 15%
**Bile Penetration:**
Without obstruction = 75%
With obstruction = 40%
(also see ***Antibiotic Pearls & Pitfalls*** p. 511).

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Methenamine hippurate (Hiprex, Urex) Methenamine mandelate (Mandelamine)

**Drug Class:** Urinary antiseptic.
Usual Dose: 1 gm (PO) q6h (hippurate); 1 gm (PO) q6h (mandelate).
**Spectrum:** All gram + and gram – uropathogens.
**Resistance Potential:** None
Pharmacokinetic Parameters:
*Peak serum level: Not applicable*
*Bioavailability: 90%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 4 hrs/no data*
*Plasma protein binding: Not applicable*
*Volume of distribution ($V_d$): Not applicable*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | Avoid |
| CrCl 10–50 mL/min | Avoid |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** Acetazolamide, sodium bicarbonate, thiazide diuretics (↓ antibacterial effect if ↑ urinary pH ≥ 5.5).
**Adverse Effects:** GI upset.
Allergic Potential: Low
Safety in Pregnancy: C
**Comments:** Take with food to decrease GI upset. Effectiveness depends on maintaining an acid urine (pH ≤ 5.5) with acidifying agents (e.g., ascorbic acid). **Useful only for catheter-associated bacteriuria (CAB)**, not UTIs. **Forms formaldehyde in acid urine; resistance does not develop.**

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Website: www.pdr.net

## Metronidazole (Flagyl)

**Drug Class:** Nitroimidazole antiparasitic/antibiotic..
**Usual Dose:** 1 gm (IV) q24h **(PK dose):** 500 mg (IV/PO) q6–8h **(PI dose)** (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

PI = package insert
PK = pharmacokinetic dose

**Resistance Potential:** Low (H. pylori, Gardnerella, Prevotella)
**Pharmacokinetic Parameters:**
*Peak serum level: 26 (IV)/12 (PO) mcg/mL*
*Bioavailability: 100%*
*Excreted unchanged (urine): 20%*
*Serum half-life (normal/ESRD): 8/14 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.25–0.85 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | 500 mg (IV) q24h/ 250 mg (PO) q12h |
| Post–HD dose | 1 gm (IV) 500 mg (PO) |
| Post–PD dose | 1 gm (IV) 500 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 500 mg (IV/PO) q24h |

**Drug Interactions:** Alcohol (disulfiram-like reaction); disulfiram (acute toxic psychosis); warfarin (↑ INR); phenobarbital, phenytoin (↑ metronidazole metabolism).
**Adverse Effects:** Encephalopathy, metallic taste, aseptic meningitis, seizures, peripheral neuropathy. With oral formulation, nausea, vomiting, GI upset. May discolor urine brown.
**Allergic Potential:** Low
**Safety in Pregnancy:** B (avoid in 1st trimester)
**Comments:** For intra-abdominal/pelvic sepsis (**plus anti-aerobic GNB drug**). **q24h dosing is preferred to q6h/q8h dosing because of long half-life** ($t_{1/2}$ = 8 h).

**C. difficile diarrhea dose:** 250 mg (PO) q6h.
**C. difficile colitis dose:** 500 mg (IV/PO) q6-8h or 1 gm (IV) q24h.
**For severe C. difficile colitis, add anti-GNB coverage**, e.g., ertapenem or meropenem (for microscopic/macroscopic perforation/peritonitis).
**Use increases VRE prevalence.** ***Metronidazole misses some anerobes eg, Propionibacteria, Actinobacillus, Eikinella, and limited activity against Actinomyces, Mobiluncus and Clostridium ramosum.***

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 30%
Inflamed meninges = 100%
(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**

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PI = package insert
PK = pharmacokinetic

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Website: www.pdr.net

## Mezlocillin (Mezlin)

**Drug Class:** Anti-pseudomonal penicillin.
**Usual Dose:** 3 gm (IV) q6h.
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 300 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 65%*
*Serum half-life (normal/ESRD): 1.1/4 hrs*
*Plasma protein binding: 30%*
*Volume of distribution ($V_d$): 0.18 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 30 mL/min | No change |
| CrCl 10–30 mL/min | 3 gm (IV) q8h |
| CrCl < 10 mL/min | 2 gm (IV) q8h |
| Post–HD dose | 3 gm (IV) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 3 gm (IV) q8h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 3 gm (IV) q12h |

**Drug Interactions:** Aminoglycosides (inactivation of mezlocillin in renal failure); warfarin (↑ INR); oral contraceptives (↓ oral contraceptive effect); cefoxitin (↓ mezlocillin effect).
**Adverse Effects:** Drug fever/rash, E. multiforme/ Stevens–Johnson Syndrome, anaphylactic reactions (hypotension, laryngospasm, bronchospasm), hives; serum sickness. **Dose-dependent inhibition of platelet aggregation is minimal/absent** (usual dose is less than carbenicillin).
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Dose-dependent half-life ($t_{½}$). $Na^+$ content = 1.8 mEq/g.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 3000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**
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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Micafungin (Mycamine)

**Drug Class:** Echinocandin antifungal.
**Usual Dose:**
Candidemia:
100 mg (IV) q24h.
Esophageal candidiasis:
150 mg (IV) q24h.
Prophylaxis of candidal infections in stem cell transplants:
50 mg (IV) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 5.1 mcg/ml (50 mg); 11.2 mcg/ml (100 mg); 16.4 mcg/ml (150 mg)*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 11%*
*Serum half-life (normal/ESRD): 10–15 hrs/no change*
*Plasma protein binding: > 99%*
*Volume of distribution ($V_d$): 0.39 L/kg*
**Primary Mode of Elimination:** Liver
**Dosage Adjustments**

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild or Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Sirolimus AUC ↑ by 21% with no change in Cmax (monitor for sirolimus toxicity), nifedipine AUC, and Cmax ↑ by 18% and 42%, respectively (monitor for nifedipine toxicity).
**Adverse Effects:** Nausea, vomiting, leukopenia, anemia, thrombocytopenia, ↑ SGOT/SGPT, ↑ BUN/↑ creatinine, rash.
**Allergic Potential:** Low
**Safety in Pregnancy:** C

**Comments:** Administer by IV infusion over one hour—do not give as a bolus as more rapid infusions may result in more frequent histamine mediated reactions. Do not mix or co-use with other medications; flush intravenous line with 0.9% saline prior to infusion.
***Highly active against Candida albicans and non-albicans Candida (↓ susceptibility to C. parasilosis), and Hansenula.***
***Some activity against Aspergillus. No activity against Cryptococcus, Fusarium, Pseudoallescheria/Scedosporium, Trichosporon, Rhodotorula or Mucor.***
Most cost effective parenteral antifungal for empiric therapy of systemic Candida/Aspergillus infections.

**Cerebrospinal Fluid Penetration:** < 1%

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Minocycline (Minocin)

**Drug Class:** 2nd generation tetracycline.
**Usual Dose:** 100 mg (IV/PO) q12h or 200 mg (IV/PO) q24h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 4 mcg/mL*
*Bioavailability: 95%*
*Excreted unchanged (urine): 10%*
*Serum half-life (normal/ESRD): 15/18–69 hrs*
*Plasma protein binding: 75%*
*Volume of distribution ($V_d$): 1.5 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 100 mg (IV/PO) q24h |

**Drug Interactions:** Antacids, $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$, multivitamins, sucralfate (↓ minocycline absorption); isotretinoin (pseudotumor cerebri); warfarin (↑ INR).
**Adverse Effects:** Nausea, GI upset if not taken with food, hyperpigmentation of skin with prolonged use, vestibular toxicity (dizziness), photosensitivity (rare), drug induced SLE.
Allergic Potential: Low
Safety in Pregnancy: D
**Comments:** Infuse slowly over 1 hour. Also ***effective against Nocardia***.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Effective IV/PO against serious systemic MSSA/MRSA infections**, e.g., MSSA/MRSA ABE, osteomyelitis, or meningitis.
Tetracycline susceptibilities do not predict minocycline effectiveness against MSSA, MRSA, and Acinetobacter sp.
***Even if MSSA/MRSA susceptible to doxycycline, use minocycline more reliably effective.***
For neuroborreliosis minocycline may be preferable to doxycycline

Meningeal dose = usual dose
**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges = 50%
Inflamed meninges = 50%
**Bile Penetration:** 1000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 512).

**REFERENCES:**
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Website: www.pdr.net

## Moxifloxacin (Avelox)

**Drug Class:** Respiratory quinolone.
**Usual Dose:** 400 mg (IV/PO) q24h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 4.4 (IV)/4.5 (PO) mcg/mL*
*Bioavailability: 90%*
*Excreted unchanged (urine): 20%*
*Serum half-life (normal/ESRD): 12/12 hrs*
*Plasma protein binding: 50%*
*Volume of distribution ($V_d$): 2.2 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |

| | |
|---|---|
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** $Al^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$ antacids, citrate/citric acid, dairy products (↓ absorption of fluoroquinolones only if taken together); amiodarone, procainamide, sotalol (may ↑ $QT_c$ interval, torsade de pointes), rifampicin (↓ moxifloxacin levels).
**Adverse Effects:** C. difficile diarrhea/colitis. May ↑ $QT_c$ interval; avoid taking with medications, e.g., amiodarone that prolong the $QT_c$ interval, and in patients with cardiac arrhythmias/heart block. ***Does not cause seizures.*** FQ use has an increased risk of tendinitis/tendon rupture. Risk in highest in the elderly, those on steroids, and those with heart, lung or renal transplants. Peripheral neuropathy may occur early and may be permanent.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** ***Only quinolone with anti–B. fragilis activity*****. FQ with the highest activity against S. pneumoniae, VSE, and MSSA.** Metabolized to microbiologically-inactive glucuronide (M1)/sulfate (M2) conjugates. Take 4 hours before or 8 hours after calcium or magnesium containing antacids or didanosine. No interactions with oral hypoglycemics. C8-methoxy group increases activity and decreases resistance potential. **TB dose** (*alternate drug in MDR TB drug regimens*): 400 mg (PO) q24h. **↑ incidence of C. difficile diarrhea/colitis with PPIs (for patients on PPIs during FQ therapy, D/C PPIs or switch to $H_2$ blocker for duration of FQ therapy).**

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 93%
(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Nafcillin (Unipen)

**Drug Class:** Anti-staphylococcal (MSSA) penicillin.
**Usual Dose:** 2 gm (IV) q4h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Pharmacokinetic Parameters:**
*Peak serum level: 80 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 10–30%*
*Serum half-life (normal/ESRD): 0.5/4 hrs*
*Plasma protein binding: 90%*
*Volume of distribution ($V_d$): 0.24 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD/PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Cyclosporine (↓ cyclosporine levels); nifedipine, warfarin (↓ interacting drug effect).
**Adverse Effects:** Not hepatotoxic. Drug fever/rash, leukopenia, interstitial nephritis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: Avoid oral formulation** (not well absorbed/erratic serum levels).

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 20%
**Bile Penetration:** 100%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**

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Website: www.pdr.net

## Nelfinavir (Viracept) NFV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** 1250 mg (PO) q12h (two 625-mg tablets per dose) with meals, or five 250-mg tabs or 750 mg (three 250-mg tabs) (PO) q8h.
**Pharmacokinetic Parameters:**
*Peak serum level: 35 mcg/mL*
*Bioavailability: 20–80%*
*Excreted unchanged (urine): 1–2%*
*Serum half-life (normal/ESRD): 4 hrs/no data*
*Plasma protein binding: 98%*
*Volume of distribution ($V_d$): 5 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild hepatic insufficiency | No change |
| Moderate—severe hepatic insufficiency | Use with caution |

**Antiretroviral Dosage Adjzustments**

| | |
|---|---|
| Delavirdine | No data (monitor for neutropenia) |
| Efavirenz | No change |
| Indinavir | Limited data for nelfinavir 1250 mg q12h + indinavir 1200 mg q12h |
| Lopinavir/ritonavir | Nelfinavir 1000 mg q12h or lopinavir/r 600/150 mg q12h |
| Nevirapine | No data |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Ritonavir | No data |
| Saquinavir | Saquinavir 1200 mg q12h |
| Rifampin | Avoid |
| Rifabutin | Nelfinavir 1250 mg q12h; rifabutin 150 mg q24h or 300 mg 2–3x/ week |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); amiodarone, quinidine, astemizole, terfenadine, benzodiazepines, cisapride, ergot alkaloids, statins, St. John's wort (avoid if possible); carbamazepine, phenytoin, phenobarbital (↓ nelfinavir levels, ↑ anticonvulsant levels; monitor); caspofungin (↓ caspofungin levels, may ↓ caspofungin effect); clarithromycin, erythromycin, telithromycin (↑ nelfinavir and macrolide levels); didanosine (dosing conflict with food; give nelfinavir with food 2 hours before or 1 hour after didanosine); itraconazole, voriconazole, ketoconazole (↑ nelfinavir levels); lamivudine (↑ lamivudine levels); methadone (may require ↑ methadone dose); oral contraceptives, zidovudine (↓ zidovudine levels); sildenafil (↑ or ↓ sildenafil levels; do not exceed 25 mg in 48 hrs, tadalafil (max. 10 mg/72 hrs, vardenafil (max. 2.5 mg/72 hrs).

**Adverse Effects:** Impaired concentration, nausea, abdominal pain, secretory diarrhea, ↑ SGOT/SGPT, rash, ↑ cholesterol/triglycerides (evaluate risk for coronary disease/pancreatitis), fat redistribution, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), possible increased bleeding in hemophilia.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Take with food (absorption increased 300%). 625-mg tablet available.

**Cerebrospinal Fluid Penetration:** Undetectable

**REFERENCES:**

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Website: www.pdr.net

## Nevirapine (Viramune) NVP

**Drug Class:** HIV NNRTI (non-nucleoside reverse transcriptase inhibitor).

**Usual Dose:** 200 mg (PO) q24h × 2 weeks, then 200 mg (PO) q12h.

**Pharmacokinetic Parameters:**

*Peak serum level: 0.9–3.6 mcg/mL*

*Bioavailability: 90%*

*Excreted unchanged (urine): 5%*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Serum half-life (normal/ESRD): 40 hrs/no data*
*Plasma protein binding: 60%*
*Volume of distribution ($V_d$): 1.4 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 20 mL/min | Use with caution |
| Post–HD dose | 200 mg (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | Use with caution |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Delavirdine | No data |
| Efavirenz | No data |
| Indinavir | Indinavir 1000 mg q8h |
| Lopinavir/ritonavir (l/r) | Consider l/r 600/150 mg q12h in PI-experienced patients |
| Nelfinavir | No data |
| Ritonavir | No change |
| Saquinavir | No data |
| Rifampin | Avoid |
| Rifabutin | Use with caution |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); carbamazepine, phenobarbital, phenytoin (monitor anticonvulsant levels); caspofungin (↓ caspofungin levels), itraconazole (↓ itraconazole/↑ nevirapine levels), voriconazole (↑ nevirapine levels); ethinyl estradiol (↓ ethinyl estradiol levels; use additional/ alternative method); methadone (↓ methadone levels; titrate methadone dose to effect); tacrolimus (↓ tacrolimus levels) clarithromycin (↓ clarithromycin levels), rifapentine (avoid).
**Adverse Effects:** Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher $CD_4$ counts at initiation of therapy place patients at increased risk; women with $CD_4$ counts > 250 cells/$mm^3$, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with mevirapine use can occur in both genders, all $CD_4$ counts and at any time during treatment. Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson Syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart nevirapine following severe hepatic, skin or hypersensitivity reactions. Take out all the rest under adverse reactions.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Absorption not affected by food. Not to be used for post-exposure prophylaxis because of potential for fatal hepatitis.

**Cerebrospinal Fluid Penetration:** 45%

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Nitazoxanide (Alinia)

**Drug Class:** Antiprotozoal; anti-C. difficle antibiotic.
**Usual Dose:** 500 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 9.1–10.6 mcg/mL; tizoxanile/tizoxanile glucuronide (metabolites)*
*Bioavailability: No data*
*Excreted unchanged (urine): < 10%*
*Serum half-life (normal/ESRD): No data*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic (66%); renal (34%)
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | 250 mg (PO) q12h |
| CrCl < 10 mL/min | Use with caution |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild/moderate | No change |
| Mild hepatic insufficiency | No change |
| Moderate—severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Avoid in patients with hypersensitivity to salicylates.
**Adverse Effects:** Dizziness, headache, nausea/vomiting, abdominal pain, flu-like syndrome, yellow discoloration of sclera/urine.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments: Nitazoxanide concentrates in GI tract** but is not present in serum. Absorption greatly increased with food.
(↑ plasma levels of metabolites ~ 50%). Contains 1.4 gm sucrose/5 mL of reconstituted suspension.
***Preferred therapy for Cryptosporidia* and giardiasis. Also effective against *Cyclospora and Iospora*. Effective for C. difficile diarrhea/colitis (including metronidazole /vancomycin failures). Also useful for H. pylori or B. hominis and Norovirus diarrhea.**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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White CA Jr. Nitazoxanide: a new broad spectrum antiparasitic agent. Expert Rev Anti Infect Ther 2:43–9, 2004.
Website: www.pdr.net

## Nitrofurantoin (Macrodantin, Macrobid)

**Drug Class:** Urinary antiseptic.
**Usual Dose:** 100 mg (PO) q12h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 1 mcg/mL*
*Bioavailability: 80%*
*Excreted unchanged (urine): 25%*
*Serum half-life (normal/ESRD): 0.5/1 hrs*
*Plasma protein binding: 40%*
*Volume of distribution ($V_d$): 0.8 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 100 mg (PO) q12h |
| CrCl 30–50 mL/min | 100 mg (PO) q24h |
| CrCl < 30 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/ CVVHDF dose | Avoid |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Antacids, magnesium (↓ nitrofurantoin absorption); probenecid (↑ nitrofurantoin levels).
**Adverse Effects:**
Acute hypersensitivity reactions (reversible): pneumonitis, AIHA
Chronic reactions (irreversible): chronic hepatitis, peripheral neuropathy, interstitial fibrosis.
**Allergic Potential:** Moderate
**Safety in Pregnancy:** B
**Comments: For CAB/lower UTIs only. Useful for asymptomatic bacteriuria of pregnancy;** no transplacental transfer. Chronic toxicities associated with prolonged use/renal insufficiency. Optimal effectiveness if CrCl > 60 mL/min. Usually effective if CrCl > 30 mL/min. Avoid if CrCl < 30 mL/min. **Active against most aerobic GNB uropathogens (including many ESBL + strains), except P. aeruginosa, Serratia marcesens, and Proteus sp. Effective for VSE/VRE catheter associated bacteriuria (CAB)/lower UTIs**
(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**

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Website: www.pdr.net

## Ofloxacin (Oflox)

**Drug Class:** Quinolone.
**Usual Dose:** 400 mg (IV/PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 5.5–7.2 mcg/ml*
*Bioavailability: 95%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 6/40 hrs*
*Plasma protein binding: 32%*
*Volume of distribution ($V_d$): 2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 20–50 mL/min | 400 mg (IV/PO) q24h |
| CrCl < 20 mL/min | 200 mg (IV/PO) q24 |
| Post–HD dose | 200 mg (IV/PO) |
| Post–PD dose | 200 mg (IV/PO) |
| CVVH/CVVHD/ CVVHDF dose | 300 mg (IV/PO) q24h |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 400 mg (IV/PO) q24h |

**Drug Interactions:** $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$ antacids, citrate/citric acid, dairy products (↓ absorption of ofloxacin only if taken together); cimetidine (↑ ofloxacin levels); cyclosporine (↑ cyclosporine levels); NSAIDs (CNS stimulation); probenecid (↑ ofloxacin levels); warfarin (↑ INR).
**Adverse Effects:** Drug fever/rash, mild neuroexcitatory symptoms. C. difficile diarrhea/colitis. FQ use has an increased risk of tendinitis/tendon rupture. Risk in highest in the elderly, those on steroids, and those with heart, lung or renal transplants.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** $H_2$ antagonist increases half–life by ~ 30%. Levofloxacin has improved pharmacokinetics/pharmacodynamics and greater antimicrobial activity. Take ofloxacin 2 hours before or after calcium/magnesium containing antacids. **PPNG dose:** 400 mg (PO) × 1 dose. **NGU/cervicitis dose:** 300 mg (PO) q12h × 1 week.

**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:** 1500%
(also see ***Antibiotic Pearls & Pitfalls*** p. 516).

**REFERENCES:**
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Monk JP, Campoli-Richards DM. Ofloxacin: A review of its antibacterial activity, pharmacokinetics properties, and therapeutic use. Drugs 33:346–91, 1987.
Website: www.pdr.net

## Oritavancin (Orbactiv)

**Drug Class:** Lipoglycopeptide
**Usual Dose:** 1200 mg (IV) x 1 dose
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198-202)
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 138 mcgl ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine/feces): < 5%/< 1%*
*Serum half-life (normal/ESRD): 245 hr/No data*
*Plasma protein binding: 85%*
*Volume of distribution (Vd): 1.25 L/kg*
**Primary Mode of Elimination:** renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | No change (use with caution) |
| Post–HD dose | No change (use with caution) |
| Post–PD dose | No change (use with caution) |
| CVVH dose | No data |
| Hepatic insufficiency | No change |

**Drug Interactions:** ↑ warfarin levels, monitor INR. Oritavancin is a weak inhibitor of CYP2C19 & CYP2C9; it is a weak inducer of CYP3A4.
**Adverse Effects:** Dizziness, headache, nausea, vomiting, skin abscesses, diarrhea, C. difficile, phlebitis, increased AST/AL T, hypersensitivity reactions (monitor closely patients with known hypersensitivity to glycopeptides)
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Oritavancin artificially prolongs coagulation tests: activated clotting time (ACT); artificial effects last for 48 hours for PTT, 24 hours for PT and 24 hours for INR. Oritavancln is not removed during hemodialysis. Useful for VRE infections. Infuse slowly over 3 hours; if infusion reaction develops, slow the rate or interrupt infusion and then resume infusion upon resolution. *Use of unfractionated heparin is contraindicated for 48 hours after oritavancin administration.* ↑ incidence of osteomyelitis vs. vancomycin; institute alternate therapy if osteomyelitis is known or suspected osteomyelitis. Oritavancin may adhere to C. difficile spores, potentially preventing early inhibition of germinated cells; this may reduce the risk of recurrent C. difficile.

**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges = 1%
Inflamed meninges = 10%
(also see ***Antibiotic Pearls & Pitfalls*** P. 198)

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**

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Website: www.pdr.net

## Oseltemavir (Tamiflu)

**Drug class:** Neuraminidase inhibitor.

**Usual dose:** Treatment: 75 mg (PO) q12h × 5 days; Prophylaxis: 75 mg (PO) q24h × 10 days.

**Pharmacokinetic Parameters:**

*Peak serum level: 65.2 mcg/L*

*Bioavailability: 75%*

*Excreted unchanged: 1%*

*Serum half-life (normal/ESRD): 1–3 hours/no data*

*plasma protein binding: 42%*

*Volume of distribution ($V_d$): 23–26 L/kg*

**Primary Mode of Elimination:** Renal (oseltamivir carboxylate)

**Dosage Adjustments***

| | |
|---|---|
| CrCl > 60 mL/min | No adjustment |
| CrCl 30–60 mL/min | 30 mg (PO) q12h (treatment)<br>30 mg (PO) q24h (prophylaxis) |
| CrCl 10–30 mL/min | 30 mg (PO) q24h |
| Post-HD dose | 30 mg (PO) |
| Post-PD dose | 30 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 30 mg (PO) q24h (treatment)<br>30 mg (PO) q24h (prophylaxis) |
| Moderate—severe hepatic insufficiency | Use with caution |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Live attenuated influenza vaccine 2 weeks before or 2 days after oseltemavir.
**Adverse Effects:** nausea, vomiting, serious skin reactions, diplopia, visual disturbances, palpitations, atrial fibrillation, supraventricular/ventricular tachycardias neuropsychiatric events.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments: Begin prophylaxis within 3 days** of exposure.

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Website: www.pdr.net

## Oxacillin (Prostaphlin)

**Drug Class:** Anti-staphylococcal (MSSA) penicillin.
**Usual Dose:** 1–2 gm (IV) q4h.
Spectrum: (see ***Susceptibility Profiles*** p. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 43 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 39–66%*
*Serum half-life (normal/ESRD): 0.5/1 hrs*
*Plasma protein binding: 94%*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 2 gm q4h)

| | |
|---|---|
| CrCl 10–80 mL/min | No change |
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Cyclosporine (↓ cyclosporine levels); nifedipine, warfarin (↓ interacting drug effect).
**Adverse Effects:** Drug fever/rash, leukopenia, ↑ SGOT/SGPT, hepatitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: Avoid oral formulation** (not well absorbed/erratic serum levels).

Meningeal dose = 2 gm (IV) q4h.
**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges = 1%
Inflamed meninges = 10%
**Bile Penetration:** 25%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**REFERENCES:**
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Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
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Website: www.pdr.net

## Pegylated Interferon alfa-2a (Pegasys)

**Drug Class:** HCV antiviral.
**Usual Dose:** Pegasys: 180 mcg (SQ) once weekly × 48 weeks; Ribavirin: 500 mg (< 75 kg) or 800 mg (> 75 mg) (PO) q12h × 48 weeks (see comments).
**Pharmacokinetic Parameters:**
*Trough level: 16 ng/ml*
*Bioavailability: No data*
*Excreted unchanged (urine): No data*
*Serum half-life (normal/ESRD): 80/100–120 hrs*
*Plasma protein binding: No data*
*Volume of distribution ($V_d$): 8–12 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | Pegasys: 180 mcg (SQ); avoid ribavirin |
| CrCl < 10 mL/min | Pegasys: 135 mcg (SQ) q week; avoid ribavirin |
| Post–HD dose | Pegasys: 135 mcg (SQ) q week; avoid ribavirin |
| Post–PD dose | Pegasys: 135 mcg (SQ); avoid ribavirin |
| CVVH/CVVHD/CVVHDF dose | Avoid ribavirin |
| Moderate hepatic insufficiency | 135 mcg if ALT ↑; Avoid ribavirin |
| Severe hepatic insufficiency | Avoid |
| Moderate depression | ↓ Pegasys to 135 mcg (90 mcg in some); evaluate once weekly |
| Severe depression | Discontinue Pegasys; immediate psychiatric consult |

**Pegasys Adjustment for Hematologic Toxicity**

| | |
|---|---|
| Absolute neutrophil count < 750/mm$^3$ | ↓ Pegasys to 135 mcg |
| Absolute neutrophil count < 500/mm$^3$ | Discontinue Pegasys until neutrophils > 1000/mm$^3$. Reinstitute at 90 mcg and monitor neutrophil count |
| Platelets < 50,000/mm$^3$ | ↓ Pegasys to 90 mcg |
| Platelets < 25,000/mm$^3$ | Discontinue Pegasys |

**Ribavirin Adjustment for Hematologic Toxicity**

| | |
|---|---|
| Hgb < 10 gm/dL and no cardiac disease | ↓ Ribavirin to 600 mg/day† |
| Hgb < 8.5 gm/dL and no cardiac disease | Discontinue ribavirin |
| Hgb ≥ 2 gm/dL ↓ during 4-week treatment period and stable cardiac disease | ↓ Ribavirin to 600 mg/day* |
| Hgb < 12 gm/dL despite 4 weeks at reduced dose and stable cardiac disease | Discontinue ribavirin |

* One 200 mg tablet in a.m. and two 200 mg tablets in p.m.

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Inhibits CYP IA2. May ↑ theophylline levels.
**Adverse Effects:** Flu-like symptoms, serious neuropsychiatric disturbances, bone marrow toxicity, nausea/vomiting/diarrhea, alopecia, hypothyroidism, ARDS.
**Allergic Potential:** Low
**Safety in Pregnancy:** Pegasys: C (ribavirin: X; also avoid in partners of pregnant women)
**Comments:** Ribavirin dose with Pegasys for HCV (genotypes 2, 3) is 800 mg/d. The optimal ribavirin dose for HCV (genotype 1) has not been determined but 800–1400 mg/d has been used. Combination therapy is more effective than monotherapy. Avoid in autoimmune hepatitis and decompensated cirrhosis. Check CBC weekly. For genotypes 2 and 3, duration of therapy is 24 weeks and ribavirin dose is 400 mg (PO) bid (rather than q12h). Ribavirin should be taken with breakfast and dinner to ↑ bioavailability/↓ nausea. Ribavirin taken after dinner may cause insomnia. Ribavirin's long serum half-life allows q24h dosing, but ↑ nausea.

**Cerebrospinal Fluid Penetration:** No data
**Bile Penetration:** No data

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Website: www.pdr.net

## Pegylated Interferon alfa-2b (Peg-Intron)

**Drug Class:** HCV antiviral.
**Usual Dose:** See pp. 97–98.
Pharmacokinetic Parameters:
*Peak serum level: 30 IU/ml / 3680 ng/ml*
*Bioavailability: No data/64%*
*Excreted unchanged (urine): No data/17%*
*Serum half-life (normal/ESRD): [40 hrs/no data] / [298 hrs/no data]*
*Plasma protein binding: No data*
*Volume of distribution ($V_d$): 0.99 L/kg*
**Primary Mode of Elimination:** Renal/renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–50 mL/min | give 75% of Peg-Intron dose; avoid ribavirin |
| CrCl < 30 mL/min | give 50% of Peg-Intron dose; avoid ribavirin |
| Post–HD dose | Avoid ribavirin |
| Post–PD dose | Avoid ribavirin |
| CVVH/CVVHD/ CVVHDF dose | Avoid ribavirin |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Moderate hepatic insufficiency | None |
| Severe hepatic insufficiency | Avoid |
| Moderate depression | ↓ Peg-Intron by 50%; evaluate once weekly |
| Severe depression | Discontinue both drugs; immediate psychiatric consult |

**Dosage Adjustments for Hematologic Toxicity**

| | |
|---|---|
| Hgb < 10 gm/dL | ↓ ribavirin by 200 mg/day |
| Hgb < 8.5 gm/dL | Permanently discontinue both drugs |
| WBC < $1.5 \times 10^9$/L | ↓ Peg-Intron by 50% |
| WBC < $1.0 \times 10^9$/L | Permanently discontinue both drugs |
| Neutrophils < $0.75 \times 10^9$/L | ↓ Peg-Intron by 50% |
| Neutrophils < $0.5 \times 10^9$/L | Permanently discontinue both drugs |
| Platelets < $80 \times 10^9$/L | ↓ Peg-Intron by 50% |
| Platelets < $50 \times 10^9$/L | Permanently discontinue both drugs |
| Hgb ≥ 2 gm/dL ↓ during 4-week treatment period and stable cardiac disease | ↓ Peg-Intron by 50% and ribavirin by 200 mg/day |
| Hgb < 12 gm/dL despite ribavirin dose reduction | Permanently discontinue both drugs |

**Drug Interactions:** Nucleoside analogs: fatal/non-fatal lactic acidosis. May ↑ levels of theophylline. Overlapping toxicity with other bone marrow suppressants.
**Adverse Effects:** Hemolytic anemia, psychological effects, cytopenias, pulmonary symptoms, pancreatitis, hypersensitivity reactions, ↑ triglycerides, flu-like symptoms, nausea/vomiting, alopecia, rash, hypothyroidism.
**Allergic Potential:** Low
**Safety in Pregnancy:** Peg-Intron: C (ribavirin: X; also avoid in partners of pregnant women)
**Comments:** Avoid in autoimmune hepatitis. Check CBC pretreatment and at 2 and 4 weeks (must adjust doses for ↓ WBC, ↓ neutrophils, ↓ platelets, ↓ hemoglobin). Poorly tolerated in decompensated cirrhosis or recurrent hepatitis C after transplant. Be alert for severe depression/psychiatric changes.

**Cerebrospinal Fluid Penetration:** No data
**Bile Penetration:** No data

**REFERENCES:**

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Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 345:1452–7, 2001.
Wright TL. Treatment of patients with hepatitis C and cirrhosis. Hepatology 36:S185–91, 2002.
Website: www.pdr.net

## Penicillin G (various)

**Drug Class:** Natural penicillin.
**Usual Dose:** 2–4 mu (IV) q4h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 20–40 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80%*
*Serum half-life (normal/ESRD): 0.5/5.1 hrs*
*Plasma protein binding: 60%*
*Volume of distribution ($V_d$): 0.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 2–4 mu (IV) q4h |
| CrCl 10–50 mL/min | 1–2 mu (IV) q4h |
| CrCl < 10 mL/min | 1 mu (IV) q8h |
| Post–HD dose | 2 mu (IV) |
| Post–PD dose | 0.5 mu (IV) |
| CVVH/CVVHD/CVVHDF dose | 2 mu (IV) q6h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Probenecid (↑ penicillin G levels).
**Adverse Effects:** Drug fever/rash, E. multiforme/Stevens–Johnson Syndrome; anaphylactic reactions (hypotension, laryngospasm, bronchospasm), hives, serum sickness.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Incompatible in solutions containing erythromycin, aminoglycosides, calcium bicarbonate, or heparin.
Penicillin G (potassium): $K^+$ content = 1.7 mEq/g; $Na^+$ content = 0.3 mEq/g.
Penicillin G (sodium): $Na^+$ content = 2 mEq/g. **1°, 2°, early latent syphilis dose:** PCN benzathine 2.4 mu (IM) × 1 dose. **Late latent syphilis dose:** PCN benzathine 2.4 mu (IM) q8h once weekly × 3. **Neurosyphilis dose:** PCN G 4 mu (IV) q4h × 2 weeks.

Meningeal dose = 4 mu (IV) q4h.
**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges ≤ 1%
Inflamed meninges = 5%
**Bile Penetration:** 500%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**
Falco V, Almirante B, Jordano Q, et al. Influence of penicillin resistance of outcome in adult patients with invasive pneumococcal pneumonia. Is penicillin useful against intermediately resistant strains? J Antimicrob Chemother 54:481–8, 2004.
Giachetto G, Pirez MC, Nanni L, et al. Ampicillin and penicillin concentration in serum and pleural fluid of hospitalized children with community-acquired pneumonia. Pediatr Infect Dis J 7:625–9, 2004.
Sandoe JA, Patel PA, Baig MW, et al. What is the effect of penicillin dosing interval on outcomes in streptococcal infective endocarditis? J antimicrob Chemo 68:2660-2663, 2013.
Wendel Jr GD, Sheffield JS, Hollier LM, et al. Treatment of syphilis in pregnancy and prevention of congenital syphilis. Clin Infect Dis 35(Suppl2):S200–9, 2002.
Wright AJ. The penicillins. Mayo Clin Proc 74:290–307, 1999.
Website: www.pdr.net

## Penicillin V (various)

**Drug Class:** Natural penicillin.
**Usual Dose:** 500 mg (PO) q6h.
(Take without food).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 5 mcg/ml*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Bioavailability: 60%*
*Excreted unchanged (urine): 80%*
*Serum half-life (normal/ESRD): 0.5/8 hrs*
*Plasma protein binding: 70%*
*Volume of distribution ($V_d$): 0.5 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | 250–500 mg (PO) q6h |
| Post–HD dose | 250 mg (PO) |
| Post–PD dose | 250 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (PO) q6h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Probenecid (↑ penicillin V levels).
**Adverse Effects:** Drug fever/rash, E. multiforme/ Stevens-Johnson Syndrome, anaphylactic reactions (hypotension, laryngospasm, bronchospasm), hives, serum sickness C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Jarisch–Herxheimer reactions when treating spirochetal infections, e.g., Lyme disease, syphilis, yaws.

**Cerebrospinal Fluid Penetration:** < 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 508).

**REFERENCES:**

Bisno AL, Gerber MA, Swaltney JM, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. Clin Infect Dis 35:113–25, 2002.
Chiou CC, Does penicillin remain the drug of choice for pneumococcal pneumonia in view of emerging in vitro resistance? Clin Infect Dis 42:234–7, 2006.
Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 490–500, 1993.
Klugman KP, Yu VL. No Impact of Penicillin Resistance on Mortality. Clin Infect Dis 43:261, 2006.
Peterson LR. Penicillin for treatment of pneumococcal pneumonia: does in vitro resistance really matter? Clin Infect Dis 42:224–33, 2006.
Portier H, Filipecki J, Weber P, et al. Five day clarithromycin modified release versus 10 day penicillin V for group A streptococcal pharyngitis: a multi-centre, open-label, randomized study. J Antimicrob Chemother 49:337–44, 2002.
Wright AJ. The penicillins. Mayo Clin Proc 74:290, 1999.
Website: www.pdr.net

## Pentamidine (Pentam 300, NebuPent)

**Drug Class:** Antiparasitic.
**Usual Dose:** 4 mg/kg (IV) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 0.6–1.5 mcg/mL*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 50%*
*Serum half-life (normal/ESRD): 6.4/90 hrs*
*Plasma protein binding: 69%*
*Volume of distribution ($V_d$): 5 L/kg*
**Primary Mode of Elimination:** Metabolized
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate—severe hepatic insufficiency | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Alcohol, valproic acid, didanosine, (↑ risk of pancreatitis); foscarnet (severe hypocalcemia reported; do not combine); amphotericin B, aminoglycosides, capreomycin, cis-platinum, colistin, methoxyflurane, polymyxin B, vancomycin, other nephrotoxic drugs (↑ nephrotoxicity).

**Adverse Effects:** Severe hypotension, hypocalcermia, hypoglycemia, increase in creatinine, pancreatitis, severe leukopenia, anemia and thrombocytopenia. May increase the QT interval with IV administration and cause ventricular tachycardia. Severe hypoglycemic episodes may result in later diabetes mellitus. IV extravasation may cause severe skin necrosis and IM injections can be severely painful and should be avoided if possible. The following tests should be carried out at regular intervals; Daily blood urea nitrogen and serum creatinine, blood glucose, complete blood count and platelet count as well as every other day bilirubin, alkaline phosphatase, AST (SGOT, and ALT (SGPT). An electrocardiogram should be done at regular intervals to calculate the $QT_c$ interval. If creatinine starts to rise the dose should be cut back to 3 or 2 mg/kg. The medication should be held if hypoglycemia occurs and or if the $QT_c$ interval increases.

**Allergic Potential:** High

**Safety in Pregnancy:** C

**Comments: Well absorbed IM, but painful**. Administer IV slowly in $D_5W$ over 1 hour, not saline/may be used at a dose of 300 mg aerosol q month to prevent aerosol pentamidine. Caution should be used with inhalent pentamidine especially around pregnant employees as it can induce spontaneous abortion. Special attention should be made to the proper aerosolization of medication so that it is distributed evenly through the lung. Adverse effects with aerosolized pentamidine include chest pain, arrhythmias, dizziness, wheezing, coughing, dyspnea, headache, anorexia, nausea, diarrhea, rash, pharyngitis. **If PCP patient also has pulmonary TB, aerosolized pentamidine treatments may expose medical personnel to TB via droplet inhalation**. Nebulizer dose: Inhaled pentamidine isethionate (NebuPent) 300 mg monthly via Respirgard II nebulizer can be used for PCP prophylaxis. **Nebulized pentamidine less effective than IV/IM pentamidine and is not effective against extrapulmonary PCP**. Use with caution in renal disease. Subtle creatinine changes may be associated with severe toxicity.

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

Goa KL, Campoli-Richards DM. Pentamidine isethionate: A review of its antiprotozoal activity, pharmacokinetic properties and therapeutic use in Pneumocystis carinii pneumonia. Drugs 33:242–58, 1987.

Guerin PJ, Alar P, Sundar S, et al. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. Lancet Infect Dis 2:494–501, 2002.

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Monk JP, Benfield P. Inhaled pentamidine: An overview of its pharmacological properties and a review of its therapeutic use in Pneumocystis carinii pneumonia. Drugs 39:741–56, 1990.

Rodriquez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev 17:770–82, 2004.

Sattler FR, Cowam R. Nielsen DM, et al. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. Ann Intern Med 109:280–7, 1988.

Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Peramivir (Rapivab)

**Drug Class:** Neuroaminidase inhibitor.
**Usual Dose:** 600 mg (IV) over 30 minutes × 1 dose.
**Pharmacokinetic Parameters:**
*Peak serum level: 17–44 mcg/mL/13 mcg/mL*
*Bioavailability: not applicable*
*Excreted unchanged: no data*
*Serum half-life (normal/ESRD): 7–20 hrs/no data*
*Plasma protein binding: no data*
*Volume of distribution ($V_d$): no data*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***
**Drug Interactions:** No data.
**Adverse Effects:** Diarrhea, nausea, vomiting, hallucinations, delerium, abnormal behavior, drug rash E. multiforme, anaphylaxis.
**Allergic Potential:** Low (do not use if severely allergic to other neuroaminidase inhibitors)
**Safety in Pregnancy:** C
**Comments:** For treatment of admitted adult and pediatric patients with confirmed influenza A.
**The patients not responding to either oral or inhaled antiviral therapy or when drug delivery not possible or suboptimal by another route.** For optimal activity give within 2 days of influenza onset.
***Highly active against influenza A***.
**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

Arya V, Carter WW, Robertson SM. The role of clinical pharmacology in supporting the emergency use authorization of an unapproved anti-influenza drug, peramivir. Clin Pharmacol Ther 88:587–589, 2010.
Bazan JA, Bauer KA, Hollister AS, et al. Peramivir pharmacokinetics in two critically ill adults with 2009 H1N1 influenza A concurrently receiving continuous renal replacement therapy. Pharacotherapy 30:1016–1020, 2010.
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Hernandez JE, Adiga R, Armstrong R, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an emergency IND program in the United States. Clin Infect Dis 52:695–706, 2011.
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Moss RB, Davey RT, Steigbigel RT, et al. Targeting pandemic influenza: a primer on influenza antivirals and drug resistance. J Antimicrob Chemother 65:1086–1093, 2010.
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Nguyen HTm, Sheu TG, Mishin VP, et al. Assessment of pandemic and seasonal influenza A (H1N1) virus suspectibility to neuraminidase inhibitors in three enzyme activity inhibition assays. Antimicrob Agents Chemother 54:3671–3677, 2010.
Thomas B, Hollister AS, Muczynski KA. Peramivir clearance in continuous renal replacement therapy. Hemodial Int 14:339–340, 2010.
Website: www.cdc.gov
Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Piperacillin (Pipracil)

**Drug Class:** Anti-pseudomonal penicillin.
**Usual Dose:** 3 gm (IV) q4-6h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
Pharmacokinetic Parameters:
*Peak serum level: 412 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 50–70%*
*Serum half-life (normal/ESRD): 1/3 hrs*
*Plasma protein binding: 16%*
*Volume of distribution ($V_d$): 0.24 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 4 gm q8h)

| | |
|---|---|
| CrCl 20–50 mL/min | 3 gm (IV) q8h |
| CrCl < 20 mL/min | 3 gm (IV) q12h |
| Post–HD dose | 1 gm (IV) |
| Post–PD dose | 2 gm (IV) |
| CVVH/CVVHD/CVVHDF dose | 3 gm (IV) q8h |
| Moderate or severe hepatic insufficiency | No change |

**Drug Interactions:** Aminoglycosides (inactivation of piperacillin in renal failure); warfarin (↑ INR); oral contraceptives (↓ oral contraceptive effect); cefoxitin (↓ piperacillin effect).
**Adverse Effects:** Drug fever/rash, anaphylactic reactions (hypotension, laryngospasm, broncho-spasm), hives, serum sickness, leukopenia, hemolytic anemia, C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: 75% absorbed when given IM.** Do not mix/administer with aminoglycosides. **Most active antipseudomonal penicillin against P. aeruginosa. Nosocomial pneumonia/P. aeruginosa dose:** 3 gm (IV) q4h.

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 30%
**Bile Penetration:** 1000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**

Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
Kim MK, Capitano B, Mattoes HM, et al. Pharmacokinetic and pharmacodynamic evaluation of two dosing regimens for piperacillin-susceptible organisms. Pharmacotherapy 22:569–77, 2002.
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Tan JS, File TM, Jr. Antipseudomonal penicillins. Med Clin North Am 79:679–93, 1995.
Website: www.pdr.net

## Piperacillin/Tazobactam (Zosyn, Tazocin)

**Drug Class:** Anti-pseudomonal penicillin/β-lactamase inhibitor.
**Usual Dose:** 3.375 gm (IV) q6h **(PI dose)** or 4.5 gm (IV) q8h **(PK dose)** (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 298/34 mcg/ml*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Bioavailability: Not applicable*
*Excreted unchanged (urine): 60/80%*
*Serum half-life (normal/ESRD): [1.5/8] / [1/7] hrs*
*Plasma protein binding: 30/30%*
*Volume of distribution ($V_d$): 0.3/0.21 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (also see comments)

| | |
|---|---|
| CrCl 20–40 mL/min | 2.25 gm (IV) q6h<br>3.375 (IV) q6h for NP |
| CrCl < 20 mL/min | 2.25 gm (IV) q8h 2.25 (IV) q6h for NP |
| CrCl < 10 mL/min | 2.25 gm (IV) q8h |
| Post–HD dose | 0.75 gm (IV) |
| Post–PD dose | None |
| CVVH/CVVHD/<br>CVVHDF dose | 3.375 gm (IV) q6h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Aminoglycosides (↓ aminoglycoside levels); vecuronium (↑ vecuronium effect); probenecid (↑ piperacillin/tazobactam levels); methotrexate (↑ methotrexate levels).
**Adverse Effects:** Drug fever/rash, eosinophilia, ↓/↑ platelets, leukopenia (with prolonged use > 21 days), ↑ PT/PTT, mild transient ↑ SGOT/SGPT, insomnia, nausea, headache, constipation, hypertension, hemolytic anemia, C. difficile diarrhea/colitis. May cause false + BG.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: For P. aeruginosa/nosocomial pneumonia (normal CrCl) use 4.5 g (IV) q6h *plus* amikacin 1 g (IV) q24h. P. aeruginosa/nosocomial pneumonia dosing with ↓ CrCl:**
CrCl > 40 mL/min: 4.5 gm (IV) q6h.
CrCl 20–40 mL/min: 3.375 gm (IV) q6h.
CrCl < 20 mL/min: 2.25 gm (IV) q6h.
**Hemodialysis (HD) doses:** 2.25 gm (IV) q8h; give 0.75 gm (IV) Post–HD on HD days.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 30%
**Bile Penetration:** 6000%
(also see ***Antibiotic Pearls & Pitfalls*** pp. 509, 512).

**REFERENCES:**

Bauer SR, Salem C, Connor MJ Jr, et al. Pharmacokinetics and pharmacodynamics of piperacillin-tazobactam in 42 patients treated with concomitant CRRT. Clin J Am Soc Nephrol 7:452–457, 2012.

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Lau WK, Mercer D, Itani KM, et al. Randomized, open-label, comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. Antimicrob Agents and Chemother 50:3556–61, 2006.

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Mattoes HM, Capitano B, Kim MK, et al. Comparative pharmacokinetic and pharmacodynamic profile of piperacillin/tazobactam 3.375 G Q4H and 4.5 G Q6H. Chemotherapy 458:59–63, 2002.
Minnaganti VR, Cunha BA. Piperacillin/tazobactam. Antibiotics for Clinicians 3:101–8, 1999.
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Yamagishi Y, Terada M, Ohki E, et al. Investigation of the clinical breakpoints of piperacillin-tazobactam against infections caused by Pseudomonas aeruginosa. J Infect Chemother 18:127–129, 2012.
Website: www.pdr.net

## Polymyxin B

**Drug Class:** Cell membrane altering antibiotic.
**Usual Dose:** 1–1.25 mg/kg (IV) q12h (1 mg = 10,000 units) (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Pharmacokinetic Parameters:**
*Peak serum level: 8 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 60%*
*Serum half-life (normal/ESRD): 6/48 hrs*
*Plasma protein binding: < 10%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 20–50 mL/min | 1 mg/kg (IV) q12h |
| CrCl 5–20 mL/min | 0.5 mg/kg (IV) q12h |
| CrCl < 5 mL/min | 0.2 mg/kg (IV) q12h |
| Post–HD/PD dose | No information |
| CVVH/CVVHD/ CVVHDF dose | 0.5 mg/kg (IV) q12h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Amphotericin B, amikacin, gentamicin, tobramycin, vancomycin (↑ nephrotoxicity).
**Adverse Effects:** Renal failure. Neurotoxicity associated with very prolonged/high serum levels; neuromuscular blockade potential with renal failure/neuromuscular disorders.
**Resistance Potential:** Low
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Inhibits endotoxin release from gram-negative bacilli. Avoid intraperitoneal infusion due to risk of neuromuscular blockade. Increased risk of reversible non-oliguric renal failure (ATN) when used with other nephrotoxic drugs. No ototoxic potential. May be given IM with procaine, but painful. **Nebulizer dose for multidrug resistant P. aeruginosa in cystic fibrosis/bronchiectasis:** 80 mg in saline via aerosol/nebulizer q8h (for recurrent infection use 160 mg). **Intrathecal (IT) polymyxin B dose:** 5 mg (50,000 u) q24h × 3 days, then q48h × 2 weeks. Dissolve 50 mg (500,000 u) into 10 ml for IT administration.

**Cerebrospinal Fluid Penetration**: < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 520).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Singh M, Vilsaint M, Quale J. Dose-related clinical efficacy of polymyxin B in a critically ill patient. Infect Dis in Clin Prac 21:131-132, 2013.
Website: www.pdr.net

## Posaconazole (Noxafil)

**Drug Class:** Triazole antifungal.
**Usual Dose:** Prophylaxis of invasive Aspergillus and Candida infections in high-risk patients:† 200 mg (PO) q8h; oropharyngeal candidiasis; 100 mg (PO) q12h × 1 day, then 100 mg (PO) q24h × 13 days; for fluconazole- and/or itraconazole-resistant strains, use 400 mg (PO) q12h with duration of therapy based on underlying condition and clinical response.
**Pharmacokinetic Parameters:**
*Peak serum level: 3 mcg/mL*
*Bioavailability: Absorption is ↑ 2–6-fold by food*
*Excreted unchanged (urine): < 1%*
*Excreted unchanged (feces): 66%*
*Serum half-life (normal/ESRD): 35/35 hrs*
*Plasma protein binding: 98.2%*
*Volume of distribution ($V_d$): 1774 L*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 50 mL/min | No change |
| Post–HD dose | Use IV with caution (PO levels variable) |
| Post–PD dose | Use IV with caution (PO levels variable) |
| CVVH/CVVHD/ CVVHDF dose | Use IV with caution (PO levels variable) |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Posaconazole is metabolized by hepatic glucuronidation. Inducers (e.g., rifampin, phenytoin) may alter disposition. Amiodarone, rifabutin, phenytoin, cimetidine (↓ posaconazole levels 50%). Posaconazole inhibits hepatic CYP3A4 and can increase levels of drugs metabolized by this enzyme. QT prolonging drugs terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine (↑ interacting drug levels, ↑ risk of cardiac arrhythmias); ergot (↑ ergot levels); statins (↑ statin levels and risk of rhabdomyolysis); vinca alkaloids (↑ vinca alkaloid levels and risk of neurotoxicity); cyclosporine, tacrolimus, sirolimus, midazolam and other benzodiazapines metabolized by CYP3A4, calcium channel blockers metabolized by CYP3A4 (diltiazem, verapamil, nifedipine, nisoldipine); digoxin, sulfonylureas, ritonavir, indinavir (↑ interacting drug levels); rifampin, omperazole (↓ posaconazole levels).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.
† (graft-vs-host disease, prolonged neutropenia from chemotherapy) ≥ 13 years of age.

**Adverse Effects:** Nausea, vomiting, diarrhea, headache, ↑ SGOT/SGPT; ↑ QTc. Avoid oral solution or capsules with PMH of CHF or CHF.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Do not crush/chew tablets. Available as a 40 mg/mL oral suspension. Take with a meal or 240 mL of a nutritional supplement. Blood levels not increased with higher dosages. ***Highly active against Candida albicans, most non-albicans Candida, Aspergillus, Crypotococcus, Histoplasmosis, Blastomycocis, Sporotrichosis, Paracoccidiomycosis. Some activity against Coccidiomycosis, Fusarium, C. glabrata, and Mucor. No activity against Pseudoallescheria/Scedosporium.***

**Cerebrospinal Fluid Penetration:** > 10%
**Bile Penetration:** 76%

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Primaquine

**Drug Class:** Antimalarial/Anti-PCP.
**Usual Dose: Antimalarial dose:** 15 mg (base 26.3 mg) (PO) q24h. **PCP dose:** 15–30 mg (PO) q24h plus clindamycin 600 mg (IV) or 300 mg (PO) q6h.

**Pharmacokinetic Parameters:**
*Peak serum level: 30–100 mcg/ml*
*Bioavailability: 90%*
*Excreted unchanged (urine): 3.6%*
*Serum half-life (normal/ESRD): 3.7–9.6/3.7–9.6 hrs*
*Plasma protein binding: 75%*
*Volume of distribution ($V_d$): No data*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 80 mL/min | No change |
| Post–HD/Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Hepatic insufficiency | No change |

**Drug Interactions:** Avoid in patients receiving bone marrow suppressive drugs (↑ risk of agranulocytosis), alcohol (↑ GI side effects), quinacrine (↑ primaquine levels/toxicity).
**Adverse Effects:** Nausea/vomiting, headache, abdominal pain, leukopenia (dose dependent), agranulocytosis, pruritus. Hemolytic anemia in G6PD deficiency; methemoglobinemia in NADH reductase deficiency.
Allergic Potential: Low
Safety in Pregnancy: D
**Comments:** Take with food to ↓ GI side effects. Use with caution in G6PD deficiency. Use with caution in NADH reductase deficiency.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**
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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Pyrazinamide (PZA)

**Drug Class:** TB drug.
**Usual Dose:** 25 mg/kg (PO) q24h (max. 2 gm) (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 30–50 mcg/ml*
*Bioavailability: 90%*
*Excreted unchanged (urine): 10%*
*Serum half-life (normal/ESRD): 9/26 hrs*
*Plasma protein binding: 10%*
*Volume of distribution ($V_d$): 0.9 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 25 mg/kg (PO) 3×/ week |
| Post–HD dose | 25 mg/kg (PO) or 1 gm (PO) |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 25 mg/kg (PO) 3×/ week |
| Moderate hepatic insufficiency | Use with caution |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** INH, rifabutin, rifampin (may ↑ risk of hepatoxicity).
**Adverse Effects:** Drug fever/rash, malaise, nausea, vomiting, anorexia, ↑ SGOT/SGPT, ↑ uric acid, sideroblastic anemia.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Avoid in patients with gout (may precipitate acute attacks). **TB D.O.T. dose:** 4 gm (PO) 2x/week or 3 gm (PO) 3x/week.

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:** 100%

**REFERENCES:**

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Pyrimethamine (Daraprim)

**Drug Class:** Antiparasitic.
**Usual Dose:** 75 mg (PO) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 0.4 mcg/ml*
*Bioavailability: 90%*
*Excreted unchanged (urine): 25%*
*Serum half-life (normal/ESRD): 96/96 hrs*
*Plasma protein binding: 87%*
*Volume of distribution ($V_d$): 2.5 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | Use with caution |
| Post–HD dose | None |
| Post–PD dose | 25 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Folic acid (↓ pyrimethamine effect); lorazepam (↑ risk of hepatotoxicity); sulfamethoxazole, trimethoprim, TMP–SMX (↑ risk of thrombocytopenia, anemia, leukopenia).
**Adverse Effects:** Megaloblastic anemia, leukopenia, thrombocytopenia, ataxia, tremors, seizures.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Antacids decrease absorption.
**Toxoplasmosis dose:** 200 mg (PO) × 1 dose, then 50–75 mg/kg (PO) q24h (with folinic acid 20 mg PO q24h plus either sulfadiazine or clindamycin).

**Cerebrospinal Fluid Penetration:** 10–25%

**REFERENCES:**
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Website: www.pdr.net

## Quinine sulfate

**Drug Class:** Antimalarial.
**Usual Dose:** 650 mg (PO) q8h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 3.8 mcg/ml*
*Bioavailability: 80%*
*Excreted unchanged (urine): 5%*
*Serum half-life (normal/ESRD): 7/14 hrs*
*Plasma protein binding: 95%*
*Volume of distribution ($V_d$): 3 L/kg*
**Primary Mode of Elimination:** Renal/hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 650 mg (PO) q12h |
| CrCl < 10 mL/min | 650 mg (PO) q24h |
| Post–HD dose | None |
| Post–PD dose | 650 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 650 mg (PO) q24h |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 325 mg (PO) q12h; use caution |

**Drug Interactions:** Amiodarone, aluminum-based antacids (↓ quinidine absorption); astemizole, cisapride, terfenadine (↑ interacting drug levels, torsade de pointes; avoid); cimetidine, ritonavir (↑ quinidine toxicity: headache, deafness, blindness, tachycardia); cyclosporine (↓ cyclosporine levels); digoxin (↑ digoxin levels); dofetilide, flecainide (arrhythmias); mefloquine (seizures, may ↑ QT interval, torsade de pointes, cardiac arrest, ↓ mefloquine efficacy); metformin (↑ risk of lactic acidosis); pancuronium, succinylcholine, tubocurarine (neuromuscular blockade); warfarin (↑ INR).
**Adverse Effects:** Drug fever/rash, ↑ $QT_c$ interval, arrhythmias, drug-induced SLE, lightheadedness, diarrhea, abdominal discomfort, nausea, vomiting, cinchonism with chronic use. Avoid in patients with G6PD deficiency.
**Allergic Potential:** High
**Safety in Pregnancy**: C
**Comments: PO malaria dose:** 650 mg (PO) q8h (*plus doxycycline* 100 mg PO q12h) × 3–7 days). **IV malaria dose:** quinine hydrochloride 600 mg (IV) q8h × 3–7 days, or quinidine gluconate 10 mg/kg (IV) × 1 dose (infuse over 1–2 hours) then 0.02 mg/kg/min (IV) × 72 hours or until parasitemia < 1%.

**Cerebrospinal Fluid Penetration:** 2–5%

**REFERENCES:**

Corpelet C, Vacher P, Coudor F, et al. Role of quinine in life-threatening Babesia divergens infection successfully treated with clindamycin. Eur J Clin Microbiol Infect Dis 24:74–75, 2005.
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Website: www.pdr.net

## Quinupristin/dalfopristin (Synercid)

**Drug Class:** Streptogramin.
**Usual Dose:** 7.5 mg/kg (IV) q8h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 3.2/8 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged: 20% (urine); 80% (feces) Serum half-life (normal/ESRD): [3.1/1]/[3.1/1] hrs*
*Plasma protein binding: 55/15%*
*Volume of distribution ($V_d$): 0.45/0.24 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Amiodarone, amlodipine (↑ amlodipine toxicity); astemizole, cisapride (may ↑ QT interval, torsades de pointes); carbamazepine (↑ carbamazepine toxicity: ataxia, nystagmus, diplopia, headache, seizures); cyclosporine, delavirdine, indinavir, nevirapine (↑ interacting drug levels); diazepam, midazolam (↑ interacting drug effect); diltiazem, felodipine, isradipine (↑ interacting drug toxicity: dizziness, hypotension, headache, flushing); disopyramide (↑ disopyramide toxicity: arrhythmias, hypotension, syncope); docetaxel (↑ interacting drug toxicity: neutropenia, anemia, neuropathy); lidocaine (↑ lidocaine toxicity: neurotoxicity, arrhythmias, seizures); methylprednisolone (↑ methylprednisolone toxicity: myopathy, diabetes mellitus, cushing's syndrome); nicardipine, nifedipine, nimodipine (↑ interacting drug toxicity: dizziness, hypotension, flushing, headache); statins (↑ risk of rhabdomyolysis).

**Adverse Effects:** Pain, inflammation, and swelling at infusion site (dose related), severe/prolonged myalgias, hyperbilirubinemia. Hepatic insufficiency increases concentration (AUC) of metabolites by 180%/50%.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Administer in $D_5W$ or sterile water, not in saline. Requires central IV line for administration. ***Not effective against E. faecalis (VSE). May be useful for daptomycin resistant MSSA/MRSA infections.***

**Cerebrospinal Fluid Penetration:** < 10% (also see ***Antibiotic Pearls & Pitfalls*** p. 518).

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Website: www.pdr.net

## Raltegravir (Isentress) RAL

**Drug Class:** HIV integrase inhibitor.

**Usual Dose:** 400 mg (PO) q12h.

**Pharmacokinetic Parameters:**

*Peak serum level: 6.5 μM*

*Bioavailability: ~ 32% (20–43%)*

*Excreted unchanged: 51% (feces); 9% (urine)*

*Serum half-life (normal/ESRD): 9–12 hrs/no data*

*Plasma protein binding: 83%*

*Volume of distribution ($V_d$): not studied*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Primary Mode of Elimination:** Fecal/renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild/moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Atazanavir | No change |
| Atazanavir/ritonavir | No change |
| Efavirenz | No change |
| Rifampin | raltegravir 800 mg q12h |
| Ritonavir | No change |
| Tenofovir | No change |
| Tipranavir/ritonavir | No change |

**Drug Interactions:** Rifampin (↓ raltegravir levels, use with caution). In-vitro, raltegravir does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A and does not induce CYP3A4. In addition, raltegravir does not inhibit P-glycoprotein-mediated transport. Raltegravir is therefore not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, methadone, opioid analgesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives, anti-erectile dysfunction agents).

**Adverse Effects:** Nausea, headache, diarrhea, pyrexia, rash, stevens-Johnson Syndrome, TEN.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** May be taken with or without food. CPK elevations, myopathy and rhabdomyolysis have been reported—use with caution in patients at increased risk for myopathy or rhabdomyolysis, such as those receiving concomitant medications e.g., statins. Raltegravir is indicated for treatment-naive/ experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Slight increase in cancer in severly immunocompromised hosts.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ribavirin (Rebetol) (Copegus)

**Drug Class:** RSV, HCV Antiviral; (see comments).
**Usual Dose:** 600 mg (PO) q12h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 0.07–0.28 mcg/ml*
*Bioavailability: 64%*
*Excreted unchanged (urine): 40%*
*Serum half-life (normal/ESRD): 120 hrs/no data*
*Plasma protein binding: 0%*
*Volume of distribution ($V_d$): 10 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl < 50 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Pegylated interferon (Pegasys) in HIV patients (↓ $CD_4$ counts).
**Adverse Effects:** Hemolytic anemia. The *anemia* associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and non-fatal myocardial infarctions. Patients with a history of significant cardiac disease should not be treated with ribavirin. If hemoglobin level falls < 10 g/dL reduce ribavirin dose to 600 mg daily. If hemoglobin falls < 8.5 g/dL discontinue ribavirin. When combined with interferon adverse effects includes severe depression and suicidal ideation, bone marrow suppression, autoimmune/infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Drug fever/rash, nausea, vomiting, GI upset, leukopenia, hyperbilirubinemia, hemolytic anemia, ↑ uric acid.
**Allergic Potential:** Low
**Safety in Pregnancy:** X (avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and male partners of taking ribavirin)
**Comments: Nebulizer dose for RSV:** 20 mg/ml aerosolized over 12 hours administered once daily × 3–7 days. Also as activity against Lassa fever and HPS. **Transplant Dose:** ***Loading Dose:*** 30 mg/kg (IV) (not to exceed 2g), then 16 mg/kg (IV) q6h × 4 days (not to exceed 1g); ***Maintenance Dose:*** 8 mg/kg (IV) (not to exceed 500 mg) x 3–6 days. ***Highly active against HCV and RSV. Some activity against, HEV, adenoviruses and arboviral hemorragic fever viruses. No activity against EBV, CMV, HBV, HDV.*** For Crimean-Congo hemorrhagic fever give ribavirin initial ***Loading Dose*** 30 mg/kg (PO) × 1 then ***Maintenance Dose:*** 15 mg/kg (PO) q6h × 4 days, then give 7.5 mg/kg (PO) q8h × 6 days.

**Cerebrospinal Fluid Penetration:** 70%

**REFERENCES:**

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Rifabutin (Mycobutin)

**Drug Class:** MAI drug.
**Usual Dose:** 5 mg/kg or 300 mg (PO) q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 0.38 mcg/ml*
*Bioavailability: 20–50%*
*Excreted unchanged (urine): 10%*
*Serum half-life (normal/ESRD): 45/45 hrs*
*Plasma protein binding: 85%*
*Volume of distribution ($V_d$): 9.3 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 150 mcg (PO) q24h |
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | None |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Atovaquone, amprenavir, indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, telithromycin, fluconazole, itraconazole, ketoconazole (↓ interactg drug levels, ↑ rifabutin levels); beta-blockers, clofibrate, cyclosporine, enalapril, oral contraceptives, quinidine, sulfonylureas, tocainide, warfarin (↓ interacting drug effect); corticosteroids (↑ corticosteroid requirement); delavirdine (↓ delavirdine levels, ↑ rifabutin levels; avoid); digoxin, phenytoin, propafenone, theophylline, zidovudine (↓ interacting drug levels); methadone (↓ methadone levels, withdrawal); mexiletine (↑ mexiletine clearance); protease inhibitors (↓ protease inhibitor levels, ↑ rifabutin levels; caution).
**Adverse Effects:** Headache, nausea, vomiting. ↑ SGOT/SGPT, leukopenia, anemia, thrombocytopenia, drug fever/rash. Brown/orange discoloration of body fluids.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Avoid in leukopenic patients with WBC ≤ 1000 cells/mm$^3$. Always use as part of a multi-drug regimen, never as monotherapy.
**Rifabutin doses when co-administered with antiretrovirals:** 450 mg (PO) q24h with EFV; 150 mg (PO) q24h with AVP, IDV, NFV, FPN; 150 mg (PO) q48h with RTV/LPV combination

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:** 50–70%

**REFERENCES:**

Benson CA, Williams PL, Cohn DL, and the ACTG 196/CPCRA 009 Study Team. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of Mycobacterium avium complex disease in patients with AIDS: A randomized, double-blinded, placebo-controlled trial. J Infect Dis 181:1289–97, 2000.

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Rifampin (Rifadin, Rimactane)

**Drug Class:** Antibiotic/TB drug.
**Usual Dose:** 600 mg (PO) q24h (TB dose); 300 mg (PO) q12h (antibiotic dose)
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** High (aerobic GNBs with non-TB monotherapy)
Pharmacokinetic Parameters:
*Peak serum level: 7 mcg/ml*
*Bioavailability: 95%*
*Excreted unchanged (urine): 15%*
*Serum half-life (normal/ESRD): 3.5/11 hrs*
*Plasma protein binding: 80%*
*Volume of distribution ($V_d$): 0.93 L/kg*
**Primary Mode of Elimination:** Hepatic

**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change; use caution |
| Severe hepatic insufficiency | Avoid |

**Drug Interactions:** Amprenavir, indinavir, nelfinavir (↑ rifampin levels); beta-blockers, clofibrate, cyclosporine, oral contraceptives, quinidine, sulfonylureas, tocainamide, warfarin (↓ interacting drug effect); caspofungin (↓ caspofungin levels, may ↓ caspofungin effect); clarithromycin, ketoconazole (↑ rifampin levels, ↓ interacting drug levels); corticosteroids (↑ corticosteroid requirement); delavirdine (↑ rifampin levels, ↓ delavirdine levels; avoid); disopyramide, itraconazole, phenytoin, propafenone, theophylline, methadone, nelfinavir, ritonavir, tacrolimus, drugs whose metabolism is induced by rifampin, e.g., ACE inhibitors, dapsone, diazepam, digoxin, diltiazem, doxycycline, fluconazole, fluvastatin, haloperidol, nifedipine, progestins, triazolam, tricyclics, zidovudine (↓ interacting drug levels); fluconazole, rifampin (↓ posaconazole levels) TMP–SMX (↑ rifampin levels); INH (INH converted into toxic hydrazine); mexiletine (↑ mexiletine clearance); nevirapine (↓ nevirapine levels; avoid).
**Adverse Effects:** Dizziness, Flu–like symptoms, ↑ SGOT/SGPT (rarely severe hepatitis), drug fever/rash, thrombocytopenia. Red/orange discoloration of body secretions.
**Allergic Potential:** Moderate

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Safety in Pregnancy:** C

**Comments:** Potent CYP 3A4 inducer. Contraindicated in HIV. For anti–TB prophylaxis/therapy, monitor potential hepatotoxicity with serial SGOT/SGPTs weekly × 3, then monthly × 3. Take 1 hour before or 2 hours after meals. **TB D.O.T. dose:** 10 mg/kg or 600 mg (PO) 2–3x/week. **Do not use as monotherapy for S. aureus. Of no proven clinical advantage when combined with another anti–MSSA/MRSA antibiotic. With another anti-staphylococcal drug dose:** 300 mg (PO) q12h. 300 mg (PO) q8h may be used for S. aureus PVE or Brucella SBE.

**Nasal carriage dose:** 600 mg (PO) q5h × 72 hours.

Meningeal dose = usual dose.

**Cerebrospinal Fluid Penetration:**

Non-Inflamed meninges = 50%

Inflamed meninges = 50%

**Bile Penetration:** 7000%

**REFERENCES:**


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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Rilpivirine (Edurant) RPV

**Drug class:** HIV NNRTI.
**Usual dose:** 25 mg (PO) q24h (with meal).
**Pharmacokinetic Parameters:**
*Peak serum level: 1 mcg/L*
*Bioavailability: unknown*
*Excreted unchanged: 1%*
*Serum half-life (normal/ESRD): 50/50 hrs*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): unknown*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl <10 mL/min | No change |
| Post-HD dose | None |
| Post-PD dose | None |
| CVVH/CVVHD/CVVHDF dose | No change |
| Mild to moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Clarithromycin (↓ clarithromycin levels). Any drug that induces or inhibits CYP3A may ↑/↓ rilpivirine levels.
**Contraindications:** carbamazepine, oxycarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, proton pump inhibitors, dexamethasone (*except* single dose), St. John's Wort.
**Adverse Effects:** Nausea, vomiting, abdominal pain, fatigue, headache, dizziness, depressive disorders, insomnia, abnormal dreams, rash, ↑ QTc.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Antacid and H2 blockers should be separated. **Do not administer with other NNRTI's.**

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Schrijvers R, Desimmie BA, Debyser Z. Rilipivirine: A step forward in tailored HIV treatment. Lancet ID 16:201–203, 2011.
Website: www.pdr.net

## Rimantadine (Flumadine)

**Drug Class:** Antiviral (influenza)
**Usual Dose:** 100 mg (PO) q12h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 0.7 mcg/ml*
*Bioavailability: 90%*
*Excreted unchanged (urine): 25%*
*Serum half-life (normal/ESRD): 25/38 hrs*
*Plasma protein binding: 40%*
*Volume of distribution ($V_d$): 4.5 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | No change |
| CrCl < 10 mL/min | 100 mg (PO) q24h |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | 100 mg (PO) q24h |

**Drug Interactions:** Alcohol (↑ CNS effects); benztropine, trihexyphenidyl, scopolamine (↑ interacting drug effect: dry mouth, ataxia, blurred vision, slurred speech, toxic psychosis); cimetidine (↓ rimantadine clearance); CNS stimulants (additive stimulation); digoxin (↑ digoxin levels); trimethoprim (↑ rimantadine and trimethoprim levels).
**Adverse Effects:** Dizziness, headache, insomnia, anticholinergic effects (blurry vision, dry mouth, orthostatic hypotension, urinary retention, constipation).
Allergic **Potential:** Low
Safety in Pregnancy: C
**Comments:** Less anticholinergic side effects than amantadine. Patients ≥ 60 years old or with a history of seizures should receive 100 mg (PO) q24h. **Influenza dose (prophylaxis):** 100 mg (PO) q12h for duration of exposure/outbreak. **Influenza dose (therapy):** 100 mg (PO) q12h × 7 days. **May improve peripheral airway function/oxygenation in severe influenza pneumonia. *Highly active against influenza A. No activity against other viruses*.**

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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Wintermeyer SM, Nahata MC. Rimantadine: A clinical perspective. Ann Pharmacotherapy 29:299–310, 1995.
Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ritonavir (Norvir) RTV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** 100–400 mg (PO) q12h–q24h (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 11 mcg/ml*
*Bioavailability: No data*
*Excreted unchanged (urine): 3.5%*
*Serum half-life (normal/ESRD): 4 hrs/no data*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): 0.41 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | None |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Atazanavir | Ritonavir 100 mg q24h + atazanavir 300 mg q24h (with food) |
| Delavirdine | Delavirdine: no change; ritonavir: No data |
| Efavirenz | Ritonavir 600 mg q12h (500 mg q12h for intolerance) |
| Fosamprenavir | Fosamprenavir 1400 mg + ritonavir 200 mg q24h |
| Indinavir | Ritonavir 100–200 mg q12h + indinavir 800 mg q12h, or 400 mg q12h of each drug |
| Nelfinavir | Ritonavir 400 mg q12h + nelfinavir 500–750 mg q12h |
| Nevirapine | No change |
| Saquinavir | Ritonavir 400 mg q12h + saquinavir 400 mg q12h |
| Ketoconazole | Caution; do not exceed ketoconazole 200 mg q24h |
| Rifampin | Avoid |
| Rifabutin | Rifabutin 150 mg q48h or 3x/week |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); saquinavir (↑ QTc/torsades de pointes, ↑ PR intervals) alprazolam, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem, meperidine, propoxyphene, piroxicam, quinidine, amiodarone, encainide, flecainide, propafenone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, pimozide, St. John's wort, terfenadine (avoid); alfentanil, fentanyl, hydrocodone, tramadol, disopyramide, lidocaine, mexiletine, erythromycin, clarithromycin, warfarin, dronabinol, ondansetron, metoprolol, pindolol, propranolol, timolol, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, verapamil, etoposide, paclitaxel, tamoxifen, vinblastine, vincristine, loratadine, tricyclic antidepressants, paroxetine, nefazodone, sertraline, trazodone, fluoxetine, venlafaxine, fluvoxamine, cyclosporine, tacrolimus, chlorpromazine, haloperidol, perphenazine, risperidone, thioridazine, clozapine,

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

pimozide, methamphetamine (↑ interacting drug levels); voriconazole (↓ voriconazole levels); telithromycin (↑ ritonavir levels); codeine, hydromorphone, methadone, morphine, ketoprofen, ketorolac, naproxen, diphenoxylate, oral contraceptives, theophylline (↓ interacting drug levels); carbamazepine, phenytoin, phenobarbital, clonazepam, dexamethasone, prednisone (↓ ritonavir levels, ↑ interacting drug levels; monitor anticonvulsant levels); metronidazole (disulfiram-like reaction); tenofovir, tobacco (↓ ritonavir levels); sildenafil (do not exceed 25 mg in 48 hrs); tadalafil (max. 10 mg/72 hrs); vardenafil (max. 2.5 mg/72 hrs).

**Adverse Effects:** Anorexia, anemia, leukopenia, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ cholesterol/ triglycerides (evaluate risk for coronary disease/ pancreatitis), fat redistribution, ↑ CPK, nausea, vomiting, diarrhea, abdominal pain, circumoral/ extremity paresthesias, ↑ SGOT/SGPT, pancreatitis, taste perversion, possible increased bleeding in hemophilia, ↑ incideuce of renal stones with ritonavir boosted atazanavir.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Usually used at low dose (100–400 mg/day) as pharmacokinetic "booster" of other PI's. GI intolerance decreases over time. Take with food if possible (serum levels increase 15%, fewer GI side effects). Separate dosing from ddI by 2 hours.

**Cerebrospinal Fluid Penetration:** < 1%

**REFERENCES:**

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DeJeus E, Rockstroh JK, Henry K, et al. Co-Formulated elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-infection: a randomized, double-blind, phase 3, non-inferiority trial. Lancet 379–2429–38, 2012.

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Saquinavir (Invirase) SQV

**Drug Class:** HIV protease inhibitor.

**Usual Dose:** 1000 mg (PO) q12h (see comments) with ritonavir 100 mg (PO) q12h.

**Pharmacokinetic Parameters:**

*Peak serum level: 0.07 mcg/mL*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Bioavailability: hard-gel (4%)*
*Excreted unchanged (urine): 13%*
*Serum half-life (normal/ESRD): 13 hrs/no data*
*Plasma protein binding: 98%*
*Volume of distribution ($V_d$): 10 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Moderate hepatic insufficiency | Use with caution |
| Severe hepatic insufficiency | Avoid |

**Antiretroviral Dosage Adjustments**

| | |
|---|---|
| Darunavir | Avoid |
| Delavirdine | No data |
| Efavirenz | Avoid use as sole PI |
| Indinavir | No data |
| Lopinavir/ritonavir 2 capsules q12h | Saquinavir 1 gm q12h |
| Nelfinavir | Saquinavir 1 gm q12h or 1200 mg q12h |
| Nevirapine | No data |
| Ritonavir | Ritonavir 100 mg q12h + saquinavir 1 gm q12h |
| Rifampin | Avoid |
| Rifabutin | Avoid |

**Drug Interactions:** Antiretrovirals, rifabutin, rifampin (see dose adjustment grid, above); astemizole, terfenadine, benzodiazepines, cisapride, ergotamine, statins, St. John's wort (avoid if possible); carbamazepine, phenytoin, phenobarbital, dexamethasone, prednisone (↓ saquinavir levels, ↑ interacting drug levels; monitor anticonvulsant levels); clarithromycin, erythromycin, telithromycin (↑ saquinavir and macrolide levels); grapefruit juice, itraconazole, voriconazole, ketoconazole (↑ saquinavir levels); sildenafil (do not give > 25 mg/48 hrs); tadalafil (max. 10 mg/72 hrs), vardenafil (max. 2.5 mg/72 hrs), ritonavir (↑ QTc, ↑ PR intervals), PPIs(↑ saquinavir leves). Atovaquone/proguanil (↑ saquinavir levels).

**Contraindications:** Rifapentine, trazadone.

**Adverse Effects:** Anorexia, headache, anemia, leukopenia, hyperglycemia (including worsening diabetes, new-onset diabetes, DKA), ↑ cholesterol/ triglycerides (evaluate risk for coronary disease/ pancreatitis), ↑ SGOT/SGPT, hyperuricemia, fat redistribution, night sweats, possible increased bleeding in hemophilia.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** Take with food. Avoid garlic supplements, which ↓ saquinavir levels ~ 50%. Boosted dose: 1 gm saquinavir/100 mg ritonavir (PO) q12h. Preferred formulation is 500 mg hard-gel capsule (Invirase 500). Soft-gel capsules (Fortovase) no longer available.

**Cerebrospinal Fluid Penetration:** < 1%

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Spectinomycin (Spectam, Trobicin)

**Drug Class:** Aminocyclitol.
**Usual Dose:** 2 gm (IM) × 1 dose.
**Pharmacokinetic Parameters:**
*Peak serum level: 100 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 80%*
*Serum half-life (normal/ESRD): 1.6/16 hrs*
*Plasma protein binding: 20%*
*Volume of distribution ($V_d$): 0.25 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | None |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** None.
**Adverse Effects:** Local pain at injection site.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments: Ineffective in pharyngeal GC** (poor penetration into secretions).

**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

Fiumara NJ. The treatment of gonococcal proctitis: An evaluation of 173 patients treated with 4 gm of spectinomycin. JAMA 239:735–7, 1978.
Holloway WJ. Spectinomycin. Med Clin North Am 66:169–173, 1995.
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Tapsall J. Current concepts in the management of gonorrhoea. Expert Opin Pharmacother 3:147–57, 2002.
Website: www.pdr.net

## Stavudine (Zerit) d4T

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor).
**Usual Dose:** ≥ 60 kg: 40 mg (PO) q12h; < 60 kg: 30 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 4.2 mcg/mL*
*Bioavailability: 86%*
*Excreted unchanged (urine): 40%*
*Serum half-life (normal/ESRD): 1.0/5.1 hrs*
*Plasma protein binding: 0%*
*Volume of distribution ($V_d$): 0.5 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** ≥ 60 kg/[≤ 60 kg]

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl 50–80 mL/min | 40 mg (PO) q12h [30 mg (PO) q12h] |
| CrCl 25–50 mL/min | 20 mg (PO) q12h [15 mg (PO) q12h] |
| CrCl ~ 10–25 mL/min | 20 mg (PO) q24h [15 mg (PO) q24h] |
| Post–HD dose | 20 mg (PO) [15 mg (PO)] |
| Post–PD dose | No data |
| CVVH/CVVHD/ CVVHDF dose | 20 mg (PO) q24h [15 mg (PO) q24h] |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Ribavirin (↓ stavudine efficacy, ↑ risk of lactic acidosis); dapsone, INH, other neurotoxic agents (↑ risk of neuropathy), didanosine (↑ risk of neuropathy, lactic acidosis). Avoid combining zidovudine with stavudine.

**Adverse Effects:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who reveived the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine sould be used with great caution during pregnancy and only when necessary. Drug fever/rash, nausea, vomiting, GI upset, diarrhea, headache, insomnia, dose dependent peripheral neuropathy, myalgias, pancreatitis, ↑ SGOT/SGPT, ↑ cholesterol, facial fat pad wasting, lipodystrophy, thrombocytopenia, leukopenia, lactic acidosis with hepatic steatosis. There is an increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. Immune reconstitution syndrome can occur.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Pancreatitis may be severe/fatal. Avoid coadministration with AZT or ddC. Decrease dose in patients with peripheral neuropathy to 20 mg (PO) q12h. Pregnant women may be at increased risk for lactic acidosis/liver damage when stavudine is used with didanosine (ddI). WHO recommends 30 mg q12h regardless of body weight.

**Cerebrospinal Fluid Penetration:** 30%

**REFERENCES:**

Berasconi E, Boubaker K, Junghans C, et al. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: The Swiss HIV Cohort Study. J Acquir Immune Defic Syndr 31:50–5, 2002.

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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.

Website: www.pdr.net

## Streptomycin

**Drug Class:** Aminoglycoside.

**Usual Dose:** 15 mg/kg (IM) q24h or 1 gm (IM) q24h (see comments).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Pharmacokinetic Parameters:**
*Peak serum level: 25–50 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 2.5/100 hrs*
*Plasma protein binding: 35%*
*Volume of distribution ($V_d$): 0.26 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 15 mg/kg (IM) q72h or 1 gm (IM) q72h |
| CrCl < 10 mL/min | 15 mg/kg (IM) q72h or 1 gm (IM) q96h |
| Post–HD dose | 15 mg/kg (IM) or 1 gm (IM) 2–3 x/week |
| Post–PD dose | 15 mg/kg (IM) or 1 gm (IM) or 20–40 mg/ml in dialysate q24h |
| CVVH/CVVHD/ CVVHDF dose | 15 mg/kg (IM) or 1 gm (IM) q96h |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Amphotericin B, cephalothin, cyclosporine, enflurane, methoxyflurane, NSAIDs, polymyxin B, radiographic contrast, vancomycin (↑ nephrotoxicity); cis-platinum (↑ nephrotoxicity, ↑ ototoxicity); loop diuretics (↑ ototoxicity); neuromuscular blocking agents (↑ apnea, prolonged paralysis); non-polarizing muscle relaxants (↑ apnea).

**Adverse Effects:** Most ototoxic aminoglycoside (usually vestibular ototoxicity); least nephrotoxic aminoglycoside.
**Allergic Potential:** Low
**Safety in Pregnancy:** D
**Comments:** May be given IV slowly over 1 hour.
**TB D.O.T. dose:** 20–30 mg/kg (IM) 2–3x/week.
**Tularemia dose:** 1 gm (IV/IM) q12h. **Plague dose:** 2 gm (IV/IM) q12h.

**Cerebrospinal Fluid Penetration:** 20%

**REFERENCES:**

Akaho E, Maekawa T, Uchinashi M. A study of streptomycin blood level information of patients undergoing hemodialysis. Biopharm Drug Dispos 23:47–52, 2002.
Davidson PT, Le HQ. Drug treatment of tuberculosis 1992. Drugs 43:651–73, 1992.
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Ormerod P. The clinical management of the drug-resistant patient. Ann NY Acad Sci 953:185–91, 2001.
Website: www.pdr.net

## Tedizolid (Sivextro)

**Drug Class:** Oxazolidinone
**Usual Dose:** 200 mg (IV) q24h × 6 days; 200 mg (PO) q24h × 6 days
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198-202)

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 2.2–3 mcg/ml*
*Bioavailability: 91%*
*Excreted unchanged: < 3%*
*Serum half-life (normal/ESRD): 11 h/11 h*
*Plasma protein binding: 70–90%*
*Volume of distribution ($V_d$): 1–1.14 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | No change |
| Post-HD dose | No change |
| Post-PD dose | No change |
| CVVH dose | No change |
| Hepatic insufficiency | No change |

**Drug Interactions:** None
**Adverse Effects:** Headache, dizziness, nausea, vomiting, diarrhea, C. difficile, anemia, thrombocytopenia, pancytopenia
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Useful for treatment of linezolid resistant staphylococci. ↓ incidence of thrombocytopenia compared to linezolid (2.3% vs. 4.9%). Only compatible wilh 0.9% NaCl; infuse over 1 hour. PO dose may be taken with or without food. Other anti-staphylococcal antibiotics are preferred, in the setting of febrile neutropenia.

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

Das D, Tulkens PM, Mehra P, et al. Tedizolid phosphate for the management of acute bacterial skin and skin structure infections: safety summary. Clin Infect Dis. 58;Suppl1:S51-57, 2014

Flanagan S, Fang E, Munoz KA, et al. Single- and multiple-dose pharmacokinetics and absolute bioavailability of tedizolid. Pharmacotherapy. 34:891-900, 2014.

Flanagan S, Minassian SL, Morris D, et al. Pharmacokinetics of tedizolid in subjects with renal or hepatic impairment. Antimicrob Agents Chemother. 58:6471-6476, 2014.

Housman ST, Pope JS, Russomanno J, et al. Pulmonary disposition of tedizolid following administration of once-daily oral 200-milligram tedizolid phosphate in healthy adult volunteers. Antimicrob Agents Chemother. 56:2627-2634, 2012.

Kisgen JJ, Mansour H, Unger NR, et al. Tedizolid: a new oxazolidinone antimicrobial. Am J Health Syst Pharm. 71:621-633, 2014.

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Molina-Torres CA, Barba-Marines A, Valles-Guerra O, et al. Intracellular activity of tedizolid phosphate and ACH-702 versus Mycobacterium tuberculosis infected macrophages. Ann Clin Microbiol Antimicrob. 13:13, 2014..

Moran GJ, Fang E, Corey GR, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 14:696-705, 2014.

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Prokocimer P, De Anda C, Fang E, et al. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA. 309:559-569, 2013.

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Urbina O, Ferrandez O, Espona M, Salas E, Ferrandez I, Grau S. Potential role of tedizolid phosphate in the treatment of acute bacterial skin infections. Drug Des Devel Ther. 7:243-265, 2013.

Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Telavancin (Vibativ)

**Drug class:** Lipoglycopeptide.
**Usual dose:** 10 mg/kg (IV) q24h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 93–108 mcg/mL*
*Bioavailability: not applicable*
*Excreted unchanged: 76%*
*Serum half-life (normal/ESRD): 6–9 hrs/no data*
*Plasma protein binding: 93%*
*Volume of distribution ($V_d$): 0.133-0.145 mL/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl > 50 mL/min | No change |
| CrCl 30–50 mL/min | 7.5 mg/kg (IV) q24h |
| CrCl 10–29 mL/min | 10 mg/kg (IV) q48h |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 7.5 mg/kg (IV) q24h |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Drugs that prolong $QT_c$ (additive effect); PT, INR, PTT (↑ levels); other interactions unlikely because is not metabolized through CYP450 system.
**Adverse Effects:** Headache, taste disturbance, nausea, vomiting, diarrhea, ↑ nephrotoxicity, with CrCl < 50 ml/min "red man syndrome."
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Infuse over at least 60 minutes to minimize infusion-related reactions. Effective for MSSA/MRSA cSSSIs. Efficacy may be decreased with CrCl < 50 ml/min.
**Cerebrospinal Fluid Penetration:**
Inflamed meninges: 2%
Non-inflamed meninges: 1%
(also see ***Antibiotic Pearls & Pitfalls*** p. 519).

**REFERENCES:**


Damodaran SE, Madhan S. Telavancin: A novel lipoglycopeptide antibiotic. J Pharmacother 2: 135–137, 2011.

Joson J, Grover C, Downer C, et al. Successful treatment of methicillin-resistant Staphylococcus aureus mitral valve endocarditis with sequential linezolid and telavancin monotherapy following daptomycin failure. J Antimicrob Chemother 66:2186–2188, 2011.

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 46:1683–1693, 2008.
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Wilson SE, O'Rierdan W, Hopkins A, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections associated with surgical procedures. Am J Surg 197:791–796, 2009.
Website: www.pdr.net

## Telithromycin (Ketek)

**Drug Class:** Ketolide.
**Usual Dose:** Acute sinusitis/AECB: 800 mg (PO) q24h × 5 days. Community-acquired pneumonia: 800 mg (PO) q24h × 7–10 days. 800 mg (PO) dose taken as two 400-mg tablets (PO) at once.
**Spectrum:** (see ***Susceptibility Profiles*** pp.186–190).
**Resistance Potential:** Low.
**Pharmacokinetic Parameters:**
*Peak serum level: 2.27 mcg/ml*
*Bioavailability: 57%*
*Excreted unchanged (urine): 13%*
*Serum half-life (normal/ESRD): 9.8/11 hrs*
*Plasma protein binding: 65%*
*Volume of distribution ($V_d$): 2.9 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 30 mL/min | 600 mg (PO) q24h |
| CrCl < 30 mL/min + hepatic impairment | 400 mg (PO) q24h |
| Post–HD/Post–PD dose | 400 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 400 mg (PO) q24h |

**Drug Interactions:** Digoxin (↑ interacting drug levels); ergot derivatives (acute ergot toxicity); itraconazole, ketoconazole (↑ telithromycin level); midazolam, triazolam (↑ interacting drug levels, sedation); oral anticoagulants (may ↑ anticoagulant effects; monitor PT/INR); simvastatin (↑ risk of rhabdomyolysis; giving simvastatin 12h after telithromycin decreases the ↑ in simvastatin levels ~ 50%); theophylline (additive nausea). CYP 3A4 inhibitor/substate. Telithromycin is contraindicated with cisapride and pimozide.
**Adverse Effects:** Nausea, diarrhea, dizziness, syncope, eye accomodation difficulties.
***Contraindicated in patients with history of hepatitis/jaundice*** (rarely fatal acute/fulminant hepatitis or acute liver failure in those with pre-existing liver disease) **or myasthenia gravis (↑ risk of respiratory failure).**
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** May take with or without food.

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Zervos MJ, Heyder AM, Leroy B. Oral telithromycin 800 mg once daily for 5 days versus cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis. J Int Med Res 31:157–69, 2003.
Website: www.pdr.net

## Tenofovir disoproxil fumarate (Viread) TDF

**Drug Class:** HIV nucleotide analogue.
**Usual Dose:** 300 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 0.29 mcg/mL*
*Bioavailability: 25%/39% (fasting/high fat meal)*
*Excreted unchanged (urine): 32%*
*Serum half-life (normal/ESRD): 17 hrs/no data*
*Plasma protein binding: 0.7–7.2%*
*Volume of distribution ($V_d$): 1.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–49 mL/min | 300 mg (PO) q48h |
| CrCl 10–29 mL/min | 300 mg (PO) 2x/week |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | 300 mg q7 days |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| Post–PD dose | No data |
| CVVH/CVVHD/ CVVHDF dose | 300 mg (PO) 2x/week |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Not a substrate/inhibitor of cytochrome P-450 enzymes. Didanosine (if possible, avoid concomitant didanosine due to impaired $CD_4$ response and increased risk of virologic failure); valganciclovir (↑ tenofovir levels); atazanavir, lopinavir/ritonavir (↑ tenofovir levels)(↓ atazanavir levels; use atazanavir 300 mg/ritonavir 100 mg with tenofovir); telaprevir (↑ tenofovir levels).

**Adverse Effects:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, with nucleoside analogs. Severe acute exacerbations of hepatitis in HBV who have discontinued HBV therapy, including teonfovir. Mild nausea, vomiting, GI upset, asthenia, headache, diarrhea renal tubular acidosis, decrease bone density occur. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir. Fanconi-like Syndrome routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. Immune constitution syndrome can occur.

**Allergic Potential:** Low

**Safety in Pregnancy:** B

**Comments:** ***Active against HBV.*** Eliminated by glomerular filtration/tubular secretion. May be taken with or without food. If possible, avoid concomitant didanosine (see drug interactions).

**Cerebrospinal Fluid Penetration:** No data

**REFERENCES:**

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. J Infect Dis 204:1191–201, 2011.
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Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society — USA panel. JAMA 308:387–402, 2012.
Website: www.pdr.net

## Terbinafine (Lamisil, Daskil)

**Drug Class:** Antifungal.
**Usual Dose:** 250 mg (PO) q24h.
**Pharmacokinetic Parameters:**
*Peak serum level: 1 mcg/ml*
*Bioavailability: 70%*
*Excreted unchanged (urine): < 1%*
*Serum half-life (normal/ESRD): 24 hrs/no data*
*Plasma protein binding: 99%*
*Volume of distribution ($V_d$): 13.5 L/kg*
**Primary Mode of Elimination:** Renal/Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl ~ 50–60 mL/min | No change |
| CrCl < 50 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Avoid |
| CVVH/CVVHD/CVVHDF dose | Avoid |
| Moderate—severe hepatic insufficiency | Avoid |

**Drug Interactions:** Cimetidine (↓ terbinafine clearance, ↑ terbinafine levels); phenobarbital, rifampin (↑ terbinafine clearance, ↓ terbinafine levels).
**Adverse Effects:** Drug fever/rash, lymphopenia, leukopenia, ↑ SGOT/SGPT, visual disturbances, nausea, vomiting, GI upset.
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** May cause green vision and changes in the lens/retina.
**Cerebrospinal Fluid Penetration:** < 10%

**REFERENCES:**

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Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Tetracycline (various)

**Drug Class:** Tetracycline.
**Usual Dose:** 500 mg (PO) q6h
(Take without food).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** High (S. pneumoniae, MSSA)
**Pharmacokinetic Parameters:**
*Peak serum level: 1.5 mcg/ml*
*Bioavailability: 60%*
*Excreted unchanged (urine): 60%*
*Serum half-life (normal/ESRD): 8/108 hrs*
*Plasma protein binding: 5%*
*Volume of distribution ($V_d$): 0.7 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 500 mg (PO) q12h |
| CrCl 10–50 mL/min | 500 mg (PO) q24h |
| Post–HD/Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | ≤ 1 gm (PO) q24h |

**Drug Interactions:** Antacids, $Al^{++}$, $Ca^{++}$, $Fe^{++}$, $Mg^{++}$, $Zn^{++}$, multivitamins, sucralfate (↓ absorption of tetracycline); barbiturates, carbamazepine, phenytoin (↓ half-life of tetracycline); bicarbonate (↓ absorption and ↑ clearance of tetracycline); digoxin (↑ digoxin levels); insulin (↑ insulin effect); methoxyflurane (↑ nephrotoxicity).

**Adverse Effects:** Nausea, vomiting, GI upset, diarrhea, hepatotoxicity, vaginal candidiasis, photosensitizing reactions, benign intracranial hypertension (pseudotumor cerebri).
**Allergic Potential:** Low
**Safety in Pregnancy:** D
**Comments:** Take without food. *Hepatotoxicity dose dependent (≥ 2 gm/day), especially in pregnancy/renal failure. Avoid prolonged sun exposure. Doxycycline or minocycline preferred for all tetracycline indications.*

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 5%
Inflamed meninges = 5%
**Bile Penetration:** 1000%
(also see ***Antibiotic Pearls & Pitfalls*** p. 512).

**REFERENCES:**

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Pugliese A, Cunha BA. Tetracyclines. Int J Urogyn 5:221–7, 1994.
Smilack JD, Wilson WE, Cocerill Fr 3rd. Tetracycline, chloramphenicol, erythromycin, clindamycin, and metronidazole. Mayo Clin Proc 66:1270–80, 1991.
Website: www.pdr.net

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

## Ticarcillin (Ticar)

**Drug Class:** Anti-pseudomonal penicillin.
**Usual Dose:** 3 gm (IV) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 118–300 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 95%*
*Serum half-life (normal/ESRD): 1/5 hrs*
*Plasma protein binding: 45%*
*Volume of distribution ($V_d$): 0.2 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | 2 gm (IV) q8h |
| CrCl < 10 mL/min | 2 gm (IV) q12h |
| Post–HD dose | 2 gm (IV) |
| Post–PD dose | 3 gm (IV) |
| CVVH/CVVHD/ CVVHDF dose | 2 gm (IV) q8h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Aminoglycosides (inactivation of ticarcillin in renal failure); warfarin (↑ INR); oral contraceptives (↓ oral contraceptive effect); cefoxitin (↓ ticarcillin effect).
**Adverse Effects:** Drug fever/rash; E. multiforme/ Stevens-Johnson Syndrome, anaphylactic reactions (hypotension, laryngospasm, bronchospasm), hives, serum sickness. Dose-dependent inhibition of platelet aggregation is minimal/absent (usual dose is less than carbenicillin). C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments:** Administer 1 hour before or after aminoglycoside. $Na^+$ content = 5.2 mEq/g

Meningeal dose = usual dose.
**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = 1%
Inflamed meninges = 30%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**

Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
Tan JS, File TM, Jr. Antipseudomonal penicillins. Med Clin North Am 79:679–93, 1995.
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Website: www.pdr.net

## Ticarcillin/Clavulanate (Timentin)

**Drug Class:** Anti-pseudomonal penicillin.
**Usual Dose:** 3.1 gm (IV) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** Low
**Pharmacokinetic Parameters:**
*Peak serum level: 330 mcg/ml*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 95/45%*
*Serum half-life (normal/ESRD): [1/13]/[1/2] hrs*
*Plasma protein binding: 45/25%*

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

*Volume of distribution ($V_d$): 0.2/0.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 30–60 mL/min | 3.1 gm (IV) q8h |
| CrCl 10–30 mL/min | 3.1 gm (IV) q12h |
| CrCl < 10 mL/min | 2 gm (IV) q12h |
| Post–HD dose | 3.1 gm (IV) |
| Post–PD dose | 3.1 gm (IV) |
| CVVH/CVVHD/ CVVHDF dose | 3.1 gm (IV) q8h |
| Moderate hepatic insufficiency | If CrCl < 10 mL/min: 2 gm (IV) q24h |
| Severe hepatic insufficiency | If CrCl < 10 mL/min: 2 gm (IV) q24h |

**Drug Interactions:** Aminoglycosides (↓ aminoglycoside levels); methotrexate (↑ methotrexate levels); vecuronium (↑ vecuronium effect).
**Adverse Effects:** Drug fever/rash, E. multiforme/ Stevens-Johnson Syndrome, anaphylactic reactions (hypotension, laryngospasm, bronchospasm), hives, serum sickness. C. difficile diarrhea/colitis.
**Allergic Potential:** High
**Safety in Pregnancy:** B
**Comments: 20% of clavulanate removed by dialysis**. $Na^+$ content = 4.75 mEq/g. $K^+$ content = 0.15 mEq/g.
**Cerebrospinal Fluid Penetration:** < 10%
**Bile Penetration:**
Without obstruction = 100%
With obstruction = 10%
(also see ***Antibiotic Pearls & Pitfalls*** p. 509).

**REFERENCES:**
Donowitz GR, Mandell GL. Beta-lactam antibiotics. N Engl J Med 318:419–26 and 318:490–500, 1993.
Graham DR, Talan DA, Nichols RL, et al. Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. Clin Infect Dis 35:381–9, 2002.
Itokazu GS, Danziger LH. Ampicillin-sulbactam and ticarcillin-clavulanic acid: A comparison of their in vitro activity and review of their clinical efficacy. Pharmacotherapy 11:382–414, 1991.
Winston LG, Charlebois ED, Pang S, et al. Impact of a formulary switch from ticarcillin-clavulanate to piperacillin-tazobactam on colonization with vancomycin-resistant enterococci. Am J Infect Control 32:462–9, 2004.
Website: www.pdr.net

## Tigecycline (Tygacil)

**Drug Class:** Glycylcycline.
**Usual Dose:** ***Loading Dose:*** 100 mg (IV) × 1 dose, (PI dose) **or 200 mg (IV) × 1 dose, (PK dose)** then ***Maintenance Dose:*** 50 mg (IV) q12h (PI dosing) **or 100 mg (IV) q24h (PK dosing) (see comments†)**.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low (Acinetobacter baumanii–dose related)
**Pharmacokinetic Parameters:**
*Peak serum level: 1.45 mcg/ml (100 mg dose); 0.87 mcg/ml (50 mg dose)*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 22%*
*Serum half-life (normal/ESRD): 42/42 hrs*
*Plasma protein binding: 89%*
*Volume of distribution ($V_d$): 8 L/kg*
**Primary Mode of Elimination:** Biliary
**Dosage Adjustments***

PI = Package insert
PK = Pharmacokinetic

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | None |
| Post–PD dose | None |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency (Child Pugh C) | 100 mg (IV) × 1 dose, then 25 mg (IV) q12h |

**Drug Interactions:** Warfarin (↑ INR). Does not inhibit and is not metabolized by CYP450.
**Adverse Effects:** N/V, dyspepsia, diarrhea, dizziness, asthenia, thrombocytosis, ↑ alkaline phosphatase, pancreatitis, (↑ amylase/lipase), ↑ LDH, ↑ BUN, ↓ total protein.
**Allergic Potential:** Low
**Safety in Pregnancy:** D
**Comments:** Tetracycline or doxycycline susceptibilities not predictive of tigecycline susceptibilities. If any question re: tetracycline/doxycycline susceptibility, request tigecycline Etest susceptibilities.
***Higher loading (LD)/Maintenance doses (MD) suggested for serious systemic infections or infection due to MDR Klebsiella pneumoniae, CRE, or MDR Acinetobacter baumanii.*§† Following the initial Loading Dose*** (based on PK parameters), ***tigecycline may also be given as a single daily (q24h) Maintenance Dose (since $t_{½}$ = 42 hrs). Misses only P. aeruginosa and most Proteus sp., but effective against all other GNBs, MSSA/MRSA, VSE/VRE, and B. fragilis.*** *Tigacycline rarely causes N/V if sufficiently diluted and slowly infused.* If N/V occurs, ↑ infusion volume and infusion time as shown

| Tigecycline Dose† | Volume | Infusion Time |
|---|---|---|
| 100 mg | 100 ml | 30 min |
| 200 mg* | 250 ml | 60 min |
| 400 mg§ | 500 ml | 120 min |

* For systemic infections.
§ For serious systemic infections or UTIs due to susceptible MDR GNBs.
† Maintence dose → half of the loading dose.

**Cerebrospinal Fluid Penetration:** 8%
**Bile Penetration:** 3800%
(also see ***Antibiotic Pearls & Pitfalls*** p. 518).

**REFERENCES:**

Babinchak T, Ellis-Grosse E, Dartois N, et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis 41(Suppl 5:S3):54–67, 2005.
Baines SD, Saxton K, Freeman K, et al. Tigecycline does not induce proliferation or cytotoxin production by epidemic Clostridium difficile strains in a human gut model. J Antimicrob Chemother 58:1062–1065, 2006.
Balandin MB, Fernandez SI, Pintado GV, et al. Tigecycline therapy for infections due to carbapenemase-producing Klebsiella pneumonia in critically ill patients. Scand J Infect Dis. 46:175-180, 2014.
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Website: www.pdr.net

## Tipranavir (Aptivus) TPV

**Drug Class:** HIV protease inhibitor.
**Usual Dose:** 500 mg (PO) q12h with ritonavir 200 mg (PO) q12h.
**Pharmacokinetic Parameters:**
*Peak serum level: 77–94 mcg/mL*
*Bioavailability: No data*
*Excreted unchanged (urine): 44%*
*Serum half-life (normal/ESRD): 5.5–6/5.5–6 hrs*
*Plasma protein binding: 99.9%*
*Volume of distribution ($V_d$): 7–10 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 10 mL/min | No change |
| Post–HD dose | No change |
| Post–PD dose | No change |
| CVVH/CVVHD/ CVVHDF dose | No change |
| Mild hepatic insufficiency | No change |
| Moderate—severe hepatic insufficiency | Avoid |

**Drug Interactions:** Metabolized via CYP3A4 rifabutin (↑ levels), clarithromycin (↑ levels), loperamide (↓ levels), statins (↑ risk of myopathy); abacavir, saquinavir, tenofovir, zidovudine, amprenavir/RTV, lopinavir/RTV (↓ levels). Aluminum/magnesium antacids (↓ absorption 25–30%). Ritonavir (↑ risk of hepatitis). St. John's Wort (↓ tipranavir levels). Fluconazole (↑ tipranavir levels).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Contraindications:** simavastatin, atorvastatin, lovastatin, rifapentine
**Adverse Effects:** Contraindicated in moderate/severe hepatic insufficiency. ↑ risk of hepatotoxicity in HIV patients co-infected with HBV/HCV. Intracerebral hemorrhage–use with caution in patients with coagulopathies.
**Allergic Potential:** High. Tipranavir is a sulfonamide; use with caution in patients with sulfonamide allergies
**Safety in Pregnancy:** C
**Comments:** Should be taken with food. Keep refrigerated 2–8°C.
**simvastatin, atorvastatin, lovastatin, rifapentine** Increased bioavailability when taken with meals. Must be co-administered with 200 mg ritonavir. Tipranavir contains a sulfa moiety (as do darunavir and fosamprenavir).

**Cerebrospinal Fluid Penetration:** No data

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Website: www.pdr.net

## Tobramycin (Nebcin)

**Drug Class:** Aminoglycoside.
**Usual Dose:** 240 mg or 5 mg/kg (IV) q24h (preferred over q8h dosing) (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** High (P. aeruginosa, aerobic GNBs)
Pharmacokinetic Parameters:
*Peak serum levels: 4–8 mcg/ml (q8h dosing); 16–24 mcg/ml (q24h dosing)*
*Bioavailability: Not applicable*
*Excreted unchanged (urine): 95%*
*Serum half-life (normal/ESRD): 2.5/56 hrs*
*Plasma protein binding: 10%*
*Volume of distribution ($V_d$): 0.24 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 120 mg (IV) q24h<br>or 2.5 mg/kg (IV) q24h |
| CrCl 10–50 mL/min | 120 mg (IV) q48h<br>or 2.5 mg/kg (IV) q48h |
| CrCl < 10 mL/min | 60 mg (IV) q48h<br>or 1.25 mg/kg (IV) q48h |
| Post–HD dose | 80 mg (IV)<br>or 1 mg/kg (IV) |
| Post–HFHD dose | 120 mg (IV)<br>or 2.5 mg/kg (IV) |
| Post–PD dose | 40 mg (IV) or 0.5 mg/kg (IV) or 2–4 mg/L in dialysate q24h |
| CVVH/CVVHD/CVVHDF dose | 120 mg (IV) q48h<br>or 2.5 mg/kg (IV) |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Drug Interactions:** Amphotericin B, cyclosporine, enflurane, methoxyflurane, NSAIDs, polymyxin B, radiographic contrast, vancomycin (↑ nephrotoxicity); cis-platinum (↑ nephrotoxicity, ↑ ototoxicity); loop diuretics (↑ ototoxicity); neuromuscular blocking agents (↑ apnea, prolonged paralysis); non-polarizing muscle relaxants (↑ apnea).

**Adverse Effects:** Neuromuscular blockade with rapid infusion/absorption. Nephrotoxicity only with prolonged/extremely high serum trough levels; may cause reversible non-oliguric renal failure (ATN). Ototoxicity associated with prolonged/extremely high peak serum levels (usually irreversible): Cochlear toxicity (1/3 of ototoxicity) manifests as decreased high frequency hearing, but deafness is unusual. Vestibular toxicity (2/3 of ototoxicity) develops before ototoxicity, and typically manifests as tinnitus.

**Allergic Potential:** Low

**Safety in Pregnancy:** D

**Comments: Single daily dosing greatly reduces nephrotoxic/ototoxic potential.** Incompatible with solutions containing β–lactams, erythromycin, chloramphenicol, furosemide, sodium bicarbonate. IV infusion should be given slowly over 1 hour. May be given IM. ***Avoid intraperitoneal infusion due to risk of neuromuscular blockade. Avoid intratracheal/aerosolized intrapulmonary instillation, which predisposes to antibiotic resistance***. $V_d$ increases with edema/ascites, trauma, burns, cystic fibrosis; may require ↑ dose. $V_d$ decreases with dehydration, obesity; may require ↓ dose. **Renal cast counts are the best indicator of aminoglycoside nephrotoxicity, not serum creatinines**. Dialysis removes ~ 1/3 of tobramycin from serum. Tobramycin nebulizer dose: 300 mg via nebulizer q12h ***(not recommended due to ↑ risk of resistance)***.

**CAPD dose:** 2–4 mg/L in dialysate (I.P.) with each exchange.

**Therapeutic Serum Concentrations**
(for therapeutic efficacy, *not toxicity*):
Peak (q24h/q8h dosing) = 16–24/8–10 mcg/ ml
Trough (q24h/q8h dosing) = 0/1–2 mcg/ml

**Synergy dose:** 120 mg (IV) q24h or 2.5 mg/kg (IV) q24h

**Intrathecal (IT) dose:** 5 mg (IT) q24h

**Cerebrospinal Fluid Penetration:**
Non-inflamed meninges = 0%
Inflamed meninges = 20%

**Bile Penetration:** 30%

(also see ***Antibiotic Pearls & Pitfalls*** p. 514).

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Website: www.pdr.net

## Trimethoprim (Proloprim, Trimpex) TMP

**Drug Class:** Folate antagonist.
**Usual Dose:** 100 mg (PO) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).
**Resistance Potential:** High (S. pneumoniae, E. coli)
**Pharmacokinetic Parameters:**
*Peak serum level: 2–8 mcg/ml*
*Bioavailability: 98%*
*Excreted unchanged (urine): 67%*
*Serum half-life (normal/ESRD): 8/24 hrs*
*Plasma protein binding: 44%*
*Volume of distribution ($V_d$): 1.8 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–30 mL/min | 50 mg (PO) q12h |
| CrCl < 10 mL/min | Avoid (except for PCP, see TMP–SMX) |
| Post–HD dose | Avoid (except for PCP, see TMP–SMX) |
| Post–PD dose | 100 mg (PO) |
| CVVH/CVVHD/ CVVHDF dose | 50 mg (PO) q12h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** Azathioprine (leukopenia); amantadine, dapsone, digoxin, methotrexate, phenytoin, rifampin, zidovudine (↑ interacting drug levels, nystagmus with phenytoin); diuretics (↑ serum $K^+$ with $K^+$-sparing diuretics, ↓ serum $Na^+$ with thiazide diuretics); warfarin (↑ INR, bleeding).
**Adverse Effects:** Folate deficiency, hyperkalemia.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments: Useful in sulfa-allergic patients unable to take TMP–SMX. PCP dose:** 5 mg/kg (PO) q8h plus dapsone 100 mg (PO) q24h.

**Meningeal Dose:** 300 mg or 5 mg/kg (PO) q6h.
**Cerebrospinal Fluid Penetration:** 40%
**Bile Penetration:** 100%
(also see ***Antibiotic Pearls & Pitfalls*** p. 515).

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Website: www.pdr.net

## Trimethoprim–Sulfamethoxazole (Bactrim, Septra) TMP–SMX

**Drug Class:** Folate antagonist/sulfonamide.
**Usual Dose:** 2.5–5 mg/kg (IV/PO) q6h.
**Spectrum:** (see ***Susceptibility Profiles*** pp. 186–190).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Resistance Potential:** High (S. pneumoniae, E. coli)

**Pharmacokinetic Parameters:**

*Peak serum level: 2–8/40–80 mcg/ml*
*Bioavailability: 98%*
*Excreted unchanged (urine): 67/85%*
*Serum half-life (normal/ESRD): (10/8)/40–80 hrs*
*Plasma protein binding: 44–70%*
*Volume of distribution ($V_d$): 1.8/0.3 L/kg*

**Primary Mode of Elimination:** Renal

**Dosage Adjustments***

| | |
|---|---|
| CrCl 15–30 mL/min | 1.25–2.5 mg/kg (IV/PO) q6h |
| CrCl < 15 mL/min | Avoid (except for PCP use 1.25–2.5 mg/kg [IV/PO] q8h) |
| Post–HD dose | 2.5 mg/kg (IV/PO) |
| Post–PD dose | 0.16 mg/kg (IV/PO) |
| CVVH/CVVHD/CVVHDF dose | 2.5 mg/kg (IV/PO) q6h |
| Moderate—severe hepatic insufficiency | No change |

**Drug Interactions:** *TMP component:* Azathioprine (leukopenia); amantadine, dapsone, digoxin, methotrexate, phenytoin, rifampin, zidovudine (↑ interacting drug levels, nystagmus with phenytoin); diuretics (↑ serum $K^+$ with $K^+$-sparing diuretics, ↓ serum $Na^+$ with thiazide diuretics); warfarin (↑ INR, bleeding). *SMX component*: Cyclosporine (↓ cyclosporine levels); phenytoin (↑ phenytoin levels, nystagmus, ataxia); methotrexate (↑ antifolate activity); sulfonylureas, thiopental (↑ interacting drug effect); warfarin (↑ INR, bleeding).

**Adverse Effects:** Common cause of drug induced aseptic meningitis.

**TMP:** Folate deficiency, hyperkalemia.

**SMX:** Leukopenia, thrombocytopenia, hemolytic anemia ± G6PD deficiency, aplastic anemia, ↑ SGOT/SGPT, severe hypersensitivity reactions (E. multiforme/Stevens–Johnson Syndrome), ↑ risk of hypoglycemia in chronic renal failure.

**Allergic Potential:** Very high (SMX); none (TMP)

**Safety in Pregnancy:** C

**Comments:** Drug fever/rash

Excellent bioavailability (IV = PO).

**TMP–SMX IV and PO Equivalence:**

**TMP-SMX** (TMP component) **10 mg/kg (IV) q24h** (70 kg patient)

**= 2 SS† tablets (PO) q6h**

***or***

**= 1 DS†† tablet (PO) q6h**

**TMP-SMX** (TMP component) **20 mg/kg (IV) q24h** (70 kg patient)

**= 4 SS tablets (PO) q6h**

***or***

**= 2 DS tablets (PO) q6h**

† 1 SS tablet = TMP 80 mg + SMX 400 mg.

†† 1 DS tablet = TMP 160 mg + SMX 800 mg.

**In sulfa allergic patients, use TMP (SMX is the allergic component) which is equally effective as TMP–SMX.**

Meningeal dose = 5 mg/kg (IV/PO) q6h.

**Cerebrospinal Fluid Penetration:**

Non-Inflamed meninges = 40%

Inflamed meninges = 40%

**Bile Penetration:** 100%

(also see ***Antibiotic Pearls & Pitfalls*** p. 515).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Valacyclovir (Valtrex)

**Drug Class:** HSV, VZV antiviral (see comments).
**Usual Dose:**
**HSV-1/2:** Herpes labialis: 2 gm (PO) q12h × 1 day. Genital herpes: *Initial therapy:* 1 gm (PO) q12h × 3 days. *Recurrent/intermittent therapy* (< 6 episodes/year): normal host: 500 mg (PO) q24h × 5 days; HIV-positive: 1 gm (PO) q12h × 7–10 days. *Chronic suppressive therapy* (> 6 episodes/year): normal host: 1 gm (PO) q24h × 1 year;
HIV-positive: 500 mg (PO) q12h × 1 year.
HSV-1 late onset VAP: 1 gm (PO) q8h × 10 days. Meningitis/encephalitis: **1 gm (PO) q8h** × 10 days.*
**VZV:** Chickenpox: 1 gm (PO) q8h × 5 days.
VZV pneumonia: 1–2 gm (PO) q8h × 10 days.
Herpes zoster (shingles) (dermatomal/disseminated): 1 gm (PO) q8h × 7–10 days.
VZV meningitis/encephalitis: **2 gm (PO) q6h** × 10 days.*
**Pharmacokinetic Parameters:**
*Peak serum level: 3.7–5 mcg/ml*
*Bioavailability: 55%*
*Excreted unchanged (urine): 1%*
*Serum half-life (normal/ESRD): 3/14 hrs*
*Plasma protein binding: 15%*
*Volume of distribution ($V_d$): 0.7 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments*** (based on 1 gm q8h)

* Severe HSV encephalitis may require 14–21 days of therapy

| | |
|---|---|
| CrCl 30–50 mL/min | 1 gm (PO) q12h |
| CrCl 10–30 mL/min | 1 gm (PO) q24h |
| CrCl < 10 mL/min | 500 mg (PO) q24h |
| Post–HD dose | 1 gm (PO) |
| Post–PD dose | 500 mg |
| CVVH/CVVHD/ CVVHDF dose | 500 mg (PO) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Cimetidine, probenecid (↑ acyclovir levels).
**Adverse Effects:** Headache, nausea, diarrhea, abdominal pain, weakness. Rarely, HUS/TTP (only in HIV).
**Allergic Potential:** Low
**Safety in Pregnancy:** B
**Comments:** Converted to acyclovir in liver. ***Highly active against HSV > VZV. Some activity against CMV. No activity against EBV, RSV or adenoviruses.***
VZV $IC_{90}$ (mean) ~ 2 × HSV.
Meningitis/Encephalitis dose = HSV: 1 gm (PO) q8h
VZV: 2 gm (PO) q6h
**Cerebrospinal Fluid Penetration:** 54%

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Website: www.pdr.net

## Valganciclovir (Valcyte)

**Drug Class:** CMV, HSV, HHV-6 antiviral (see comments).
**Usual Dose:** ***Induction Dose:*** 900 mg (PO) q12h × 21 days, then ***Maintanance Dose:*** 900 mg (PO) q24h (Normal hosts: until cured; Compromised hosts: chronic suppressive therapy). 900 mg dose taken as two 450-mg tablets once daily.
**Pharmacokinetic Parameters:**
*Peak serum level: 5.6 mcg/ml*
*Bioavailability: 59.4%*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 4.1/67.5 hrs*
*Plasma protein binding: 1%*
*Volume of distribution ($V_d$): 15.3 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl 40–60 mL/min | 450 mg (PO) q12h (induction), then 450 mg (PO) q24h (maintenance) |
| CrCl 25–40 mL/min | 450 mg (PO) q24h (induction), then 450 mg (PO) q48h (maintenance) |
| CrCl 10–25 mL/min | 450 mg (PO) q48h (induction), then 450 mg (PO) 2x/week (maintenance) |
| CrCl < 10 mL/min | Avoid |
| Post–HD dose | Avoid |
| Post–PD dose | Use same dose as CrCl 25–40 mL/min |
| CVVH/CVVHD/ CVVHDF dose | Use same dose as CrCl 25–50 mL/min |
| Mild-moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Cytotoxic drugs (may produce additive toxicity: stomatitis, bone marrow depression, alopecia); imipenem (↑ risk of seizures); probenecid (↑ valganciclovir levels); zidovudine (↓ valganciclovir levels, ↑ zidovudine levels, possible neutropenia); didanosine (↑ didanosine); cyclosporine amphotericin, (↑ nephrotoxicity); mycophenolate mofetil (↑ mycophenolate mofetil and gangcyclovir levels in renal insufficiency); tenofovir (↑ tenofovir, gangcyclovir levels).

**Adverse Effects:** Drug fever/rash, diarrhea, nausea, vomiting, leukopenia, anemia, thrombocytopenia, paresthesias/peripheral neuropathy, retinal detachment, potential BM suppression.

**Allergic Potential:** Low

**Safety in Pregnancy:** C

**Comments:** Valganciclovir exposures (AUC) larger than for IV ganciclovir. Tablets should be taken with food. Valganciclovir is rapidly hydrolyzed to ganciclovir. Not interchangeable on a tablet-to-tablet basis with oral ganciclovir. Much higher bioavailability than ganciclovir capsules; serum concentration equivalent to IV ganciclovir. Indicated for induction/maintenance therapy of CMV infection. ***Highly active against CMV, HHV-6, and HSV. Some activity against VZV, EBV and adenoviruses. No activity against RSV.***

Meningeal dose = usual dose.

**Cerebrospinal Fluid Penetration:** 70%

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Vancomycin (Vancocin)

**Drug Class:** Glycopeptide.
**Usual Dose:** 1 gm (IV) q12h (see comments).
**Spectrum:** (see ***Susceptibility Profiles*** pp. 198–202).
**Resistance Potential:** Low (MSSA, MRSA VSE; ↑ prevalence of VRE)
**Pharmacokinetic Parameters:**
*Peak serum level: 63 mcg/ml*
*Bioavailability: IV (not applicable)/PO (0%)*
*Excreted unchanged (urine): 90%*
*Serum half-life (normal/ESRD): 6/180 hrs*
*Plasma protein binding: 55%*
*Volume of distribution ($V_d$): 0.7 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 50–80 mL/min | 1 gm (IV) q12h |
| CrCl 10–50 mL/min | 1 gm (IV) q24h |
| CrCl < 10 mL/min | 1 gm (IV) q week |
| Post–HD dose | None |
| Post--HFHD dose | 500 mg (IV) |
| Post–PD dose | None |
| CVVH/CVVHD/CVVHDF dose | 1 gm (IV) q24h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Aminoglycosides, amphotericin B, polymyxin B (↑ nephrotoxicity).
**Adverse Effects:** "Red man/neck syndrome" with rapid IV infusion (histamine mediated), leukopenia, thrombocytopenia, cardiac arrest, hypotension.
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Not nephrotoxic. "Red man/neck syndrome" can be prevented/minimized by infusing IV vancomycin slowly over 1–2 hours. Intraperitoneal absorption = 40%. **IV vancomycin increases VRE prevalence. C. difficile diarrhea dose:** oral vancomycin 250 mg (PO) q6h. *If no response in 72 hours ↑ dose to 500 mg (PO) q6h to complete therapy.* **C. difficile diarrhea relapse dose:** 500 mg (PO) q6h × 1 month and reevaluate. **Do *not* taper dose.** Should C. difficle recur, treat × 2 or 3 months with 500 mg (PO) q6h.
**C. difficile colitis: *Oral vancomycin ineffective for C. difficile colitis***. Vancomycin doesn't penetrate well into the CSF with non-inflamed

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

meninges. For therapeutic CSF concentrations, use IV vancomycin *plus* IT vancomycin.

**Therapeutic Serum Concentrations**
(for therapeutic efficacy, *not toxicity*):
Peak = 25–40 mcg/ml
Trough = 5–12 mcg/ml

There are **no convincing data that vancomycin is ototoxic or nephrotoxic. CrCl, not serum levels, should be used to adjust vancomycin dosing**. Prolonged/high dose vancomycin (60 mg/kg/day or 2 gm [IV] q12h) has been useful in treating S. aureus osteomyelitis, S. aureus infections with high MICs (VISA), and infections in difficult-to-penetrate tissues without toxicity. In bone or CSF, vancomycin tissue concentrations are ~ 15% of serum levels.

**Intrathecal (IT) dose:** 20 mg (IT) in preservative free NaCl.

**Cerebrospinal Fluid Penetration:**
Non-Inflamed meninges = <1%
Inflamed meninges = 15%

**Bile Penetration:** 50%

(also see ***Antibiotic Pearls & Pitfalls*** p. 517).

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Voriconazole (Vfend)

**Drug Class:** Triazole antifungal.
**Usual Dose:** IV dosing: **Loading dose:** 6 mg/kg (IV) q12h × 1 day, then **Maintenance dose:** 4 mg/kg (IV) q12h. Can switch to weight-based PO maintenance dosing anytime while on maintenance IV dose (see comments).
PO dosing: *Weight ≥ 40 kg*: Loading dose of 400 mg (PO) q12h × 1 day, then maintenance dose of 200 mg (PO) q12h. If response is inadequate, the dose may be increased to 300 mg (PO) q12h. *Weight* < 40 kg: Loading dose of 200 mg (PO) × 1 day, then maintenance dose of 100 mg (PO) q12h. If response is inadequate, the dose may be increased to 150 mg (PO) q12h. For chronic/non-life-threatening infections, loading dose may be given PO (see comments).
**Pharmacokinetic Parameters:**
*Peak serum level: 2.3–4.7 mcg/ml*
*Bioavailability: 96%*
*Excreted unchanged (urine): 2%*
*Serum half-life (normal/ESRD): 6/6 hrs*
*Plasma protein binding: 58%*
*Volume of distribution ($V_d$): 4.6 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

| | |
|---|---|
| CrCl 50–80 mL/min | No change |
| CrCl 10–50 mL/min | No change PO; avoid IV |
| CrCl < 10 mL/min | No change PO; avoid IV |
| Post–HD dose | Usual dose PO; avoid IV |
| Post–PD dose | No data |
| CVVH/CVVHD/ CVVHDF dose | 4 mg/kg (PO) q12h; avoid (IV) |
| Moderate hepatic insufficiency | 6 mg/kg (IV) q12h × 1 day or 200 mg (PO) q12h × 1 day, then 2 mg/kg (IV) q12h or 100 mg (PO) q12h (> 40 kg) |
| Severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Benzodiazepines, vinca alkaloids (↑ interacting drug levels); carbamazepine, ergot alkaloids, rifampin, rifabutin, sirolimus, long-acting barbiturates (contraindicated with voriconazole); cyclosporine, ↓ (cyclosporine by 1/2 and monitor); efavirenz (↑ maintence dose of voriconazole to 400 mg (PO) q12h and decrease efavirenz dose to 300mg (PO) q12h while on voriconazole); omeprazole (↑ interacting drug levels, ↓ interacting drug dose by 50%); tacrolimus (↑ tacrolimus levels, ↓ tacrolimus dose by 66%); phenytoin (↓ voriconazole levels); ↑ voriconazole dose from 4 mg/kg [IV] to 5 mg/kg [IV] and from 200 mg [PO] to 400 mg [PO]; warfarin (↑ INR); statins (↑ risk of rhabdomyolysis); dihydropyridine calcium channel blockers (hypotension); tacrolimus (reduce tacrolimus dose by 1/3 and monitor while on voriconazole); sulfonylureas (hypoglycemia). Voriconozole has not been studied with protease inhibitors or NNRTIs, but ↑ voriconazole levels are predicted (↑ hepatotoxicity/adverse effects).

**Adverse Effects:** ↑ SGOT/SGPT; visual events (blurring vision, ↑ brightness, pain; occurs soon after ingestion and usually resolves quickly (~ ½ hour), hallucinations, hypoglycemia, dose-dependent arrhythmias, ↑ $QT_c$ interval; rash, including Stevens-Johnson Syndrome; photosensitivity reactions (avoid direct sunlight); melanoma (↑ risk of with chronic therapy).

**Allergic Potential:** High

Safety in Pregnancy: D

**Comments:** If intolerance to therapy develops, the IV maintenance dose may be reduced to 3 mg/kg and the PO maintenance dose may be reduced in steps of 50 mg/d to a minimum of 200 mg/d q12h (weight ≥ 40 kg) or 100 mg q12h (weight < 40 kg). Non-linear kinetics (doubling of oral dose = 2.8-fold increase in serum levels). 10–15% of patients have serum levels > 6 mcg/ml. Food decreases bioavailability; take 1 hour before or after meals. Do not use IV voriconazole if CrCl < 50 mL/min to prevent accumulation of voriconazole IV vehicle, sulphobutyl ether cyclodextrin (SBECD); instead use oral formulation, which has no SBECD. Loading dose may be given PO for chronic/non-life-threatening infections. Because of visual effects, do not drive or operate machinery. Monitor LFTs before and during therapy. Take without food; suspension contains sucrose.

***Highly active against C. albicans, non-albicans Candida, Aspergillus, Cryptococcus, Hansenula and Pseudoallescheria/ Scedosporium. Some activity against Fusaria, Fluconazole/Itraconazole resistant C. albicans,***

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

***Coccidiomycosis, and Penicillium marneffei. No activity against Rhizopus or Mucor.***

Meningeal dose = usual dose.

**Cerebrospinal Fluid Penetration:** 90%

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"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

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Website: www.pdr.net

## Zalcitabine (HIVID) ddC

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 0.75 mg (PO) q8h.
**Pharmacokinetic Parameters:**
*Peak serum level: 0.08 mcg/ml*
*Bioavailability: 80%*
*Excreted unchanged (urine): 75%*
*Serum half-life (normal/ESRD): 2/8.5 hrs*
*Plasma protein binding: 0%*
*Volume of distribution ($V_d$): 0.54 L/kg*
**Primary Mode of Elimination:** Renal
**Dosage Adjustments***

| | |
|---|---|
| CrCl 10–50 mL/min | 0.75 mg (PO) q12h |
| CrCl < 10 mL/min | 0.75 mg (PO) q24h |
| Post–HD dose | No data |
| Post–PD dose | No data |
| CVVH/CVVHD/ CVVHDF dose | 0.75 mg (PO) q12h |
| Moderate hepatic insufficiency | No change |
| Severe hepatic insufficiency | No change |

**Drug Interactions:** Cimetidine, probenecid, TMP–SMX (↑ zalcitabine levels); dapsone, didanosine, stavudine, INH, phenytoin, metronidazole, other neurotoxic agents or history of neuropathy (↑ risk of peripheral neuropathy); magnesium/aluminum containing antacids, metoclopramide (↓ bioavailability of zalcitabine); pentamidine IV, valproic acid, alcohol, other agents known to cause pancreatitis (↑ risk of pancreatitis).
**Adverse Effects:** Drug fever/rash, leukopenia, anemia, thrombocytopenia, hepatomegaly, hepatotoxicity/hepatic necrosis, peripheral neuropathy, pancreatitis, stomatitis, oral/genital ulcers, dysphagia, arthritis, hyperglycemia, lipotrodystrophy, wasting, night sweats, lactic acidosis with hepatic steatosis (rare, but potentially life-threatening toxicity with use of NRTIs).

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

**Allergic Potential:** High
**Safety in Pregnancy:** C
**Comments:** Foscarnet may increase toxicity. Do not use with stavudine, didanosine, or lamivudine to avoid additive toxicities. Food decreases absorption by 39%. Effective antiretroviral therapy consists of at least 3 antiretrovirals (same/different classes).

**Cerebrospinal Fluid Penetration:** 25%

**REFERENCES:**
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Website: www.pdr.net

## Zidovudine (Retrovir) ZDV Azidothymidine AZT

**Drug Class:** HIV NRTI (nucleoside reverse transcriptase inhibitor).
**Usual Dose:** 300 mg (PO) q12h or 200 mg (PO) q8h (see comments). IV solution 10 mg/mL (dose 1 mg/kg 5–6 x/day).
**Pharmacokinetic Parameters:**
*Peak serum level: 1.2 mcg/mL*
*Bioavailability: 64%*
*Excreted unchanged (urine): 16%*
*Serum half-life (normal/ESRD): 1.1/1.4 hrs*
*Plasma protein binding: < 38%*
*Volume of distribution ($V_d$): 1.6 L/kg*
**Primary Mode of Elimination:** Hepatic
**Dosage Adjustments***

| | |
|---|---|
| CrCl < 15 mL/min | 100 mg (PO) q8h or 300 mg (PO) q24h |
| Post–HD/PD dose | 100 mg or 300 mg |
| CVVH/CVVHD/CVVHDF dose | 300 mg (PO) q24h |
| Moderate—severe hepatic insufficiency | Use with caution |

**Drug Interactions:** Acetaminophen, atovaquone, fluconazole, methadone, probenecid, valproic acid (↑ zidovudine levels); clarithromycin, nelfinavir, rifampin, rifabutin (↓ zidovudine levels); dapsone, flucytosine, ganciclovir, interferon alpha, bone marrow suppressive/cytotoxic agents (↑ risk of hematologic toxicity); indomethacin (↑ levels of zidovudine toxic metabolite); phenytoin (↑ zidovudine levels, ↑ or ↓ phenytoin levels); ribavirin (↓ zidovudine effect; avoid).
**Adverse Effects:** Zidovudine, has been associated with hematologic toxicity including neutropenia and severe anemia. Prolonged use of zidovudine has been associated with symptomatic myopathy as well as lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. May cause nausea, vomiting, GI upset, diarrhea, malaise, anorexia, macrocytosis, headachese, insomnia, blue/black nail discoloration and asthenia. Nausea, vomiting, GI upset, diarrhea, malaise, anorexia, leukopenia, severe anemia, macrocytosis, thrombocytopenia, headaches, ↑ SGOT/SGPT, hepatotoxicity, myalgias, myositis, symptomatic myopathy, insomnia, blue/black nail discoloration, asthenia, lactic acidosis with hepatic steatosis (rare, but potentially life-threatening toxicity with use of NRTI's).
**Allergic Potential:** Low
**Safety in Pregnancy:** C
**Comments:** Antagonized by ganciclovir or ribavirin. Also a component of Combivir and Trizivir. Patients on IV therapy should be switched

"Usual dose" assumes normal renal/hepatic function. * For renal insufficiency, give usual dose × 1 followed by maintenance dose per CrCl. For dialysis patients, dose the same as for CrCl < 10 mL/min and give supplemental (post-HD/PD dose) immediately after dialysis. CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD/PD = hemodialysis/peritoneal dialysis.

to PO as soon as able to take oral medication. For IV administration, dilute in D5W to a concentration no greater than 4 mg/mL and infuse over 1 hour.

**Cerebrospinal Fluid Penetration:** 60%

**REFERENCES:**

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# APPENDIX

## Malaria in Adults (United States)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Adult Drug Doses |
|---|---|---|
| **Severe malaria[1,2,3,4]** | **All regions** | **Quinidine gluconate[2] *plus* either: Doxycycline or Clindamycin**<br>**Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) (IV over 1–2 hrs) then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours q8h, starting 8 hours after the loading dose. Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America.<br>**Doxycycline:** Treatment as above, give 100 mg (IV/PO) q12h × 7 days.<br>**Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg (IV) then 5 mg base/kg (IV/PO) q8h × 7 days. |
| **Uncomplicated malaria/ *P. falciparum*** or Species not identified (If "species not identified" is subsequently diagnosed as *P. vivax* or *P. ovale*: see *P. vivax* and *P. ovale* treat with primaquine) | **Chloroquine-resistant or unknown resistance[5]** (Middle Eastern countries with chloroquine-resistant *P. falciparum* include Iran, Oman, Saudi Arabia, and Yemen. Malaria acquired in the newly independent states of the former Soviet Union and Korea to date have been uniformly caused by *P. vivax* and should therefore be treated as chloroquine-sensitive infections.) | **A. Atovaquone-proguanil (Malarone)[6]**<br>*Adult tab = 250 mg atovaquone/100 mg proguanil*<br>4 adult tabs (PO) q24h × 3 days<br>**or** |

## Malaria in Adults (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Adult Drug Doses |
|---|---|---|
| **Uncomplicated malaria/ *P. falciparum*** (cont'd) | **Chloroquine-resistant or unknown resistance** (cont'd) | **B. Artemether-lumefantrine (Coartem)[6]**<br>*1 tablet = 20 mg artemether/120 mg lumefantrine*<br>A 3-day treatment schedule with a total of 6 oral doses is recommended based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose (PO) q12h × 2 days.<br>≥35 kg: 4 tablets per dose<br>**or**<br>**C. Quinine sulfate *plus* either: Doxycycline[9] or Clindamycin**<br>**Quinine sulfate[8]:** 542 mg base (=650 mg salt)[7] (PO) q8h × 3 or 7 days<br>**Doxycycline:** 100 mg (PO) q12h × 7 days<br>**Clindamycin:** 20 mg base/kg/day (PO) divided q8h × 7 days<br>**or**<br>**D. Mefloquine (Lariam)[10]**<br>684 mg base (=750 mg salt) (PO) as initial dose, followed by 456 mg base (=500 mg salt) (PO) given 6–12 hours after initial dose<br>Total dose = 1,250 mg salt |
| **Uncomplicated malaria/ *P. falciparum*** or *Species not identified* | **Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East) | **Chloroquine phosphate (Aralen)** 600 mg base (=1,000 mg salt) (PO) immediately, followed by 300 mg base (=500 mg salt) (PO) at 6, 24, and 48 hours Total dose: 1,500 mg base (=2,500 mg salt)<br>**or**<br>**Hydroxychloroquine (Plaquenil)**<br>620 mg base (=800 mg salt) (PO) immediately, followed by 310 mg base (=400 mg salt) (PO) at 6, 24, and 48 hours<br>Total dose: 1,550 mg base (=2,000 mg salt) |

## Malaria in Adults (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Adult Drug Doses |
|---|---|---|
| **Uncomplicated malaria/ *P. malariae*** or ***P. knowlesi*** | **All regions** | **Chloroquine phosphate:** Treatment as above<br>**or**<br>**Hydroxychloroquine:** Treatment as above |
| **Uncomplicated malaria/ *P. vivax*** or ***P. ovale*** | **All regions** (for suspected chloroquine-resistant *P. vivax*, see below) | **Chloroquine phosphate *plus* Primaquine phosphate[11]**<br>**Chloroquine phosphate:** Treatment as above<br>**Primaquine phosphate:** 30 mg base (PO) q24h × 14 days<br>**or**<br>**Hydroxychloroquine *plus* Primaquine phosphate[11]**<br>**Hydroxychloroquine:** Treatment as above<br>**Primaquine phosphate:** 30 mg base (PO) q24h × 14 days |
| **Uncomplicated malaria/ *P. vivax*** | **Chloroquine-resistant[12]** (Papua New Guinea and Indonesia) | **A. Quinine sulfate *plus* either: Doxycycline *plus* Primaquine phosphate[11]**<br>**Quinine sulfate:** Treatment as above<br>**Doxycycline:** Treatment as above<br>**Primaquine phosphate:** Treatment as above<br>**or**<br>**B. Atovaquone-proguanil *plus* Primaquine phosphate**<br>**Atovaquone-proguanil:** Treatment as above<br>**Primaquine phosphate:** Treatment as above<br>**or**<br>**C. Mefloquine[10] *plus* Primaquine phosphate[11]**<br>**Mefloquine:** Treatment as above<br>**Primaquine phosphate:** Treatment as above |

## Malaria in Adults (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Adult Drug Doses |
|---|---|---|
| **Uncomplicated malaria: alternatives for pregnant women**[13,14,15,16] | **Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region) | **Chloroquine phosphate:** Treatment as above<br>**or**<br>**Hydroxychloroquine:** Treatment as above |
| **Uncomplicated malaria: alternatives for pregnant women** (cont'd) | **Chloroquine resistant *P. falciparum*[1]** (see sections above for regions with chloroquine resistant ***P. falciparum***) | **Quinine sulfate *plus* Clindamycin**<br>**Quinine sulfate:** Treatment as above<br>**Clindamycin:** Treatment as above |
| | **Chloroquine-resistant *P. vivax*** (see uncomplicated malaria sections above for regions with chloroquine-resistant *P. vivax*) | **Quinine sulfate**<br>**Quinine sulfate[7]:** 650 mg salt (PO) q8h × 7 days |

1. Persons with a positive blood smear or history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*.
2. Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.
3. Consider exchange transfusion if the parasite density (i.e. parasitemia) is >10% OR if the patient has altered mental status, non-volume overload pulmonary edema, or renal complications. The parasite density can be estimated by examining a monolayer of red blood cells (RBCs) on the thin smear under oil immersion magnification. The slide should be examined where the RBCs are more or less touching (approximately 400 RBCs per field). The parasite density can then be estimated from the percentage of infected RBCs and should be monitored every 12 hours. Exchange transfusion should be continued until the parasite density is <1% (usually requires 8–10 units). IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout the exchange transfusion.
4. Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.
5. There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, option D (mefloquine) not recommend unless the other options cannot

be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline, these treatment combinations preferred to quinine with clindamycin.

6. Take with with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.
7. US manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.
8. For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.
9. Doxycycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.
10. Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.
11. Primaquine is used to eradicate any hypnozoites in the liver, to prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.
12. There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed below). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.
13. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline is generally not indicated. However, doxycycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.
14. Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.
15. Because of a possible association with mefloquine treatment during pregnancy and an increase in stillbirths, mefloquine is generally not recommended for treatment in pregnant women. However, mefloquine may be used if it is the only treatment option available and if the potential benefit is judged to outweigh the potential risks.
16. For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

**Based on CDC Recommendations for Malaria in the US**
**CDC Malaria Hotline: weekdays 8 am – 4:30 pm EST: (770) 488-7788**
**after hours, weekends and holidays: (770) 488-7100**

## Malaria in Children (United States)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Drugs and Pediatric Dose (*pediatric dose should not exceed adult dose*) |
|---|---|---|
| **Severe malaria**[1,2,3] | **All regions** | **Quinidine gluconate**[2] ***plus*** **either: Doxycycline**[8] **or Clindamycin**<br>**Quinidine gluconate:** Same mg/kg dosing and recommendations as for adults.<br>**Doxycycline:** Treatment as above. For children <45 kg, give 2.2 mg/kg (IV) q12h and then switch to (PO) doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. Treatment × 7 days.<br>**Clindamycin:** Treatment as above. 10 mg base/kg loading dose (IV) followed by 5 mg base/kg (IV/PO) q8h. Treatment × 7 days. |
| **Uncomplicated malaria/ *P. falciparum*** or Species not identified[4] | **Chloroquine-resistant or unknown resistance**[11] (Middle Eastern countries with chloroquine-resistant *P. falciparum* include Iran, Oman, Saudi Arabia, and Yemen. Of note, infections acquired in the | **A. Atovaquone-proguanil (Malarone)**[5]<br>*Adult tab = 250 mg atovaquone/ 100 mg proguanil*<br>*Peds tab = 62.5 mg atovaquone/ 25 mg proguanil*<br>5–8 kg: 2 peds tabs (PO) q24h × 3d<br>9–10 kg: 3 peds tabs (PO) q24h × 3d<br>11–20 kg: 1 adult tab (PO) q24h × 3d<br>21–30 kg: 2 adult tabs (PO) q24h × 3d<br>31–40 kg: 3 adult tabs (PO) q24h × 3d<br>>40 kg: 4 adult tabs (PO) q24h × 3d<br>**or** |

## Malaria in Children (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Drugs and Pediatric Dose (*pediatric dose should not exceed adult dose*) |
|---|---|---|
| If "species not identified" is subsequently diagnosed as *P. vivax* or *P. ovale*: see *P. vivax* and *P. ovale* (below) re. treatment with primaquine | Newly Independent States of the former Soviet Union and Korea to date have been uniformly caused by *P. vivax* and should therefore be treated as chloroquine-sensitive infections). | **B. Artemether-lumefantrine (Coartem)[5]**<br>*1 tablet = 20 mg artemether/120 mg lumefantrine*<br>A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose (PO) q12h × 2 days.<br>5–<15 kg: 1 tablet per dose<br>15–<25 kg: 2 tablets per dose<br>25–<35 kg: 3 tablets per dose<br>≥35 kg: 4 tablets per dose<br>**or**<br>**C. Quinine sulfate[3] *plus* either: Doxycycline[8] or Clindamycin**<br>**Quinine sulfate[6,7]:** 8.3 mg base/kg (=10 mg salt/kg) (PO) tid × 3 or 7 days<br>**Doxycycline:** 2.2 mg/kg (PO) q12h × 7 days<br>**Clindamycin:** 20 mg base/kg/day (PO) divided q8h × 7 days<br>**or**<br>**D. Mefloquine (Lariam)[9]**<br>13.7 mg base/kg (=15 mg salt/kg) (PO) as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) (PO) given 6–12 hours after initial dose. Total dose = 25 mg salt/kg |

## Malaria in Children (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Drugs and Pediatric Dose (*pediatric dose should not exceed adult dose*) |
|---|---|---|
| **Uncomplicated malaria/*P. falciparum*** or *Species not identified* | **Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East) | **Chloroquine phosphate (Aralen)** 10 mg base/kg (PO) immediately, followed by 5 mg base/kg (PO) at 6, 24, and 48 hours<br>Total dose: 25 mg base/kg<br>**or**<br>**Hydroxychloroquine (Plaquenil and generics)** 10 mg base/kg (PO) immediately, followed by 5 mg base/kg (PO) at 6, 24, and 48 hours<br>Total dose: 25 mg base/kg |
| **Uncomplicated malaria/ *P. malariae*** or ***P. knowlesi*** | **All regions** | **Chloroquine phosphate:** Treatment as above<br>**or**<br>**Hydroxychloroquine:** Treatment as above |
| **Uncomplicated malaria/ *P. vivax*** or ***P. ovale*** | **All regions**<br>For suspected chloroquine-resistant *P. vivax*, see below | **Chloroquine phosphate *plus* Primaquine phosphate[10]**<br>**Chloroquine phosphate:** Treatment as above<br>**Primaquine:** 0.5 mg base/kg (PO) qd × 14 days<br>**or**<br>**Hydroxychloroquine *plus* Primaquine phosphate[10]**<br>**Hydroxychloroquine:** Treatment as above<br>**Primaquine phosphate:** 0.5 mg base/kg (PO) qd × 14 days |

## Malaria in Children (United States) (cont'd)

| Clinical Diagnosis/ *Plasmodium* species | Region Acquired | Recommended Drugs and Pediatric Dose (*pediatric dose should not exceed adult dose*) |
|---|---|---|
| **Uncomplicated malaria/ *P. vivax*** | **Chloroquine-resistant**[11] (Papua New Guinea and Indonesia) | **A. Quinine sulfate *plus* either Doxycycline**[8] ***plus*** **Primaquine phosphate**[10]<br>**Quinine sulfate:** Treatment as above<br>**Doxycycline** Treatment as above<br>**Primaquine phosphate:** Treatment as above<br>**or**<br>**B. Atovaquone-proguanil *plus* Primaquine phosphate**<br>**Atovaquone-proguanil:** Treatment as above<br>**Primaquine phosphate:** Treatment as above<br>**or**<br>**C. Mefloquine *plus* Primaquine phosphate**[10]<br>**Mefloquine:** Treatment as above<br>**Primaquine phosphate:** Treatment as above |

1. Persons with a positive blood smear or history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*.
2. Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.
3. Consider exchange transfusion if the parasite density (i.e. parasitemia) is >10% OR if the patient has altered mental status, non-volume overload pulmonary edema, or renal complications. The parasite density can be estimated by examining a monolayer of red blood cells (RBCs) on the thin smear under oil immersion magnification. The slide should be examined where the RBCs are more or less touching (approximately 400 RBCs per field). The parasite density can then be estimated from the percentage of infected RBCs and

should be monitored every 12 hours. Exchange transfusion should be continued until the parasite density is <1% (usually requires 8–10 units). IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout the exchange transfusion.

4. There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.
5. Take with with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.
6. US manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.
7. For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.
8. Doxycycline is not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.
9. Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.
10. Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.
11. There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rares due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

**Based on CDC Recommendations for Malaria in the US**
**CDC Malaria Hotline: weekdays 8 am – 4:30 pm EST: (770) 488-7788**
**after hours, weekends and holidays: (770) 488-7100**

## INDEX

Note: Tables are noted with a *t*.

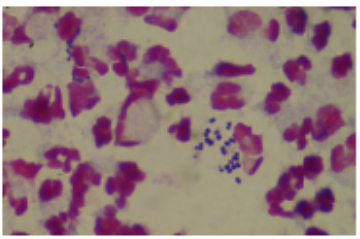
## **Q**-fever

# COLOR ATLAS

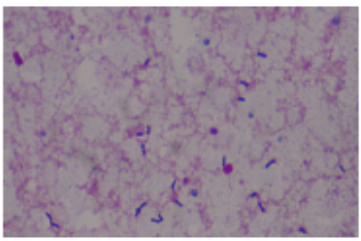
## *CSF, Sputum, and Urine Gram Stains*

Paul E. Schoch, PhD
Edward J. Bottone, PhD
Daniel Caplivski, MD

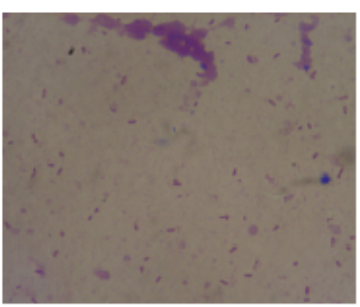
## CSF GRAM STAINS



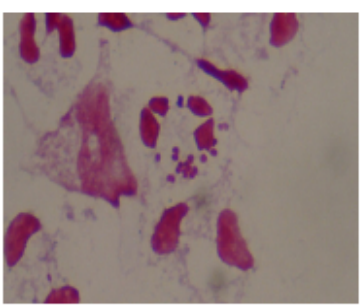
Staphylococcus aureus



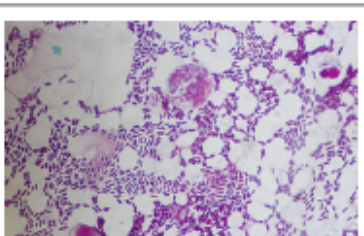
Listeria monocytogenes



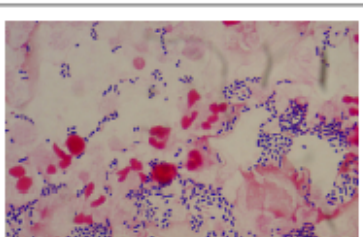
H. influenzae



Neisseria meningitidis

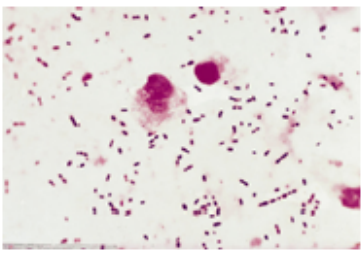


Klebsiella pneumoniae

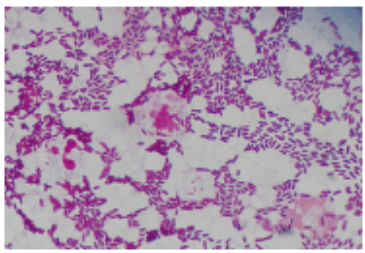


Streptococcus pneumoniae

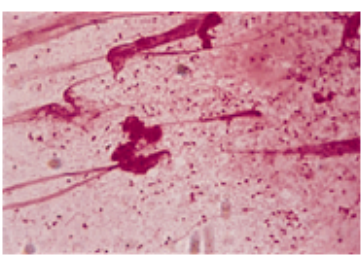
## SPUTUM GRAM STAINS



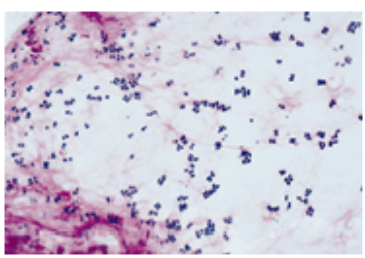
Streptococcus pneumoniae



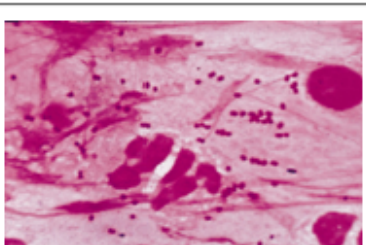
Klebsiella pneumoniae



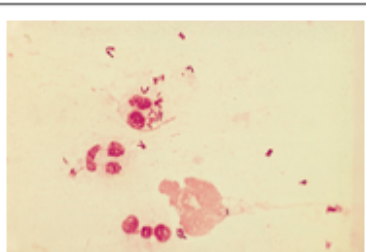
Haemophilus influenzae



Staphylococcus aureus

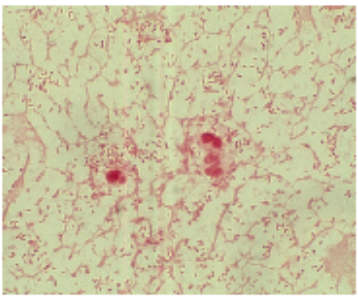


Moraxella catarrhalis

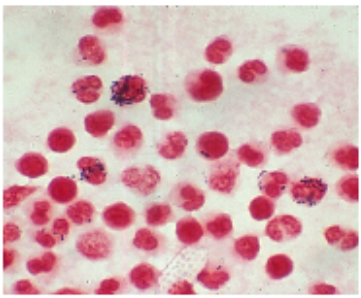


Pseudomonas aeruginosa

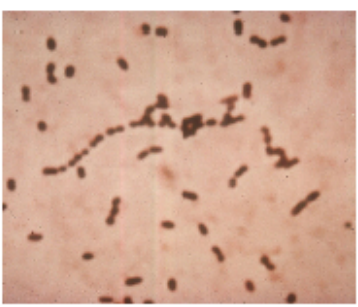
## URINE GRAM STAINS



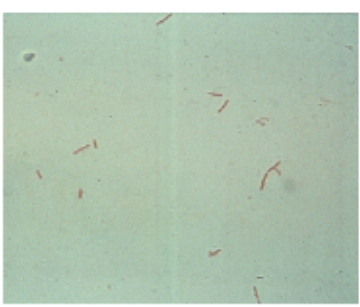
E. coli



Group B streptococci



Enterococci



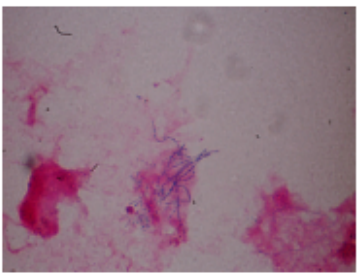
Pseudomonas aeruginosa

# COLOR ATLAS

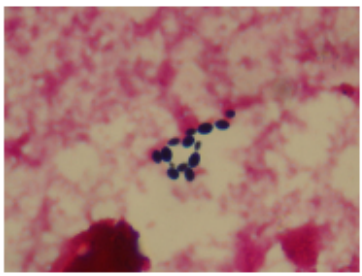
## *Fungal Stains*

Daniel Caplivski, MD
Edward J. Bottone, PhD

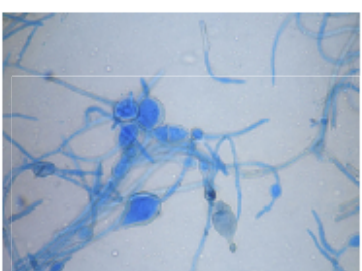
## FUNGAL STAINS



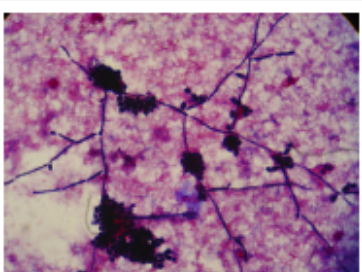
Actinomyces (lung biopsy)



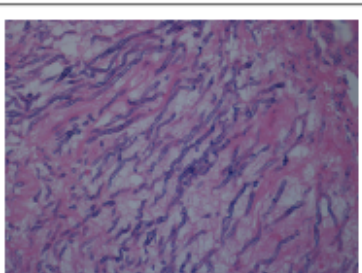
Candida albicans (blood)



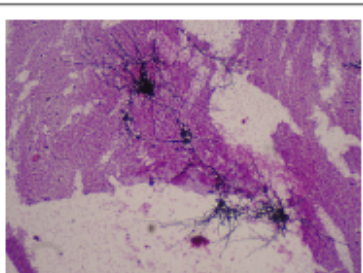
Alternaria (skin biopsy)



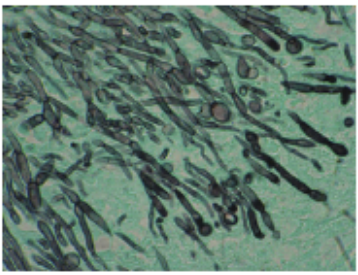
Candida albicans with pseudohyphae (blood)



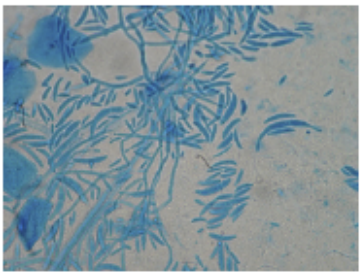
Aspergillus (lung biopsy)



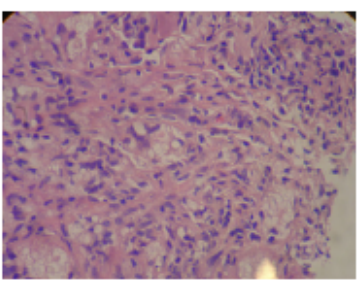
Candida as fungal ball (lung biopsy)



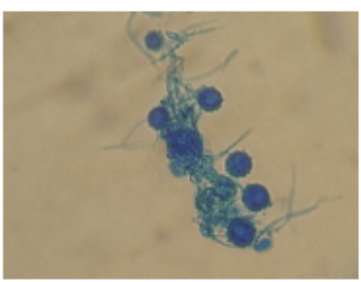
Candida (liver biopsy)



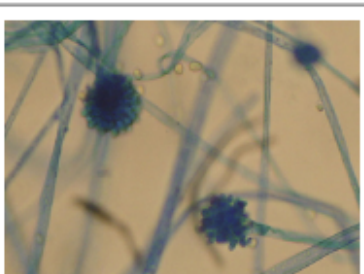
Fusarium (skin biopsy)



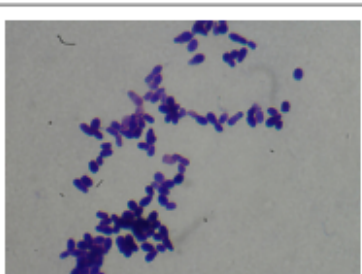
Cryptococcus (lung biopsy)



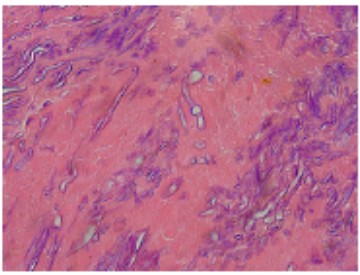
Histoplasma capsulatum (lung biopsy)



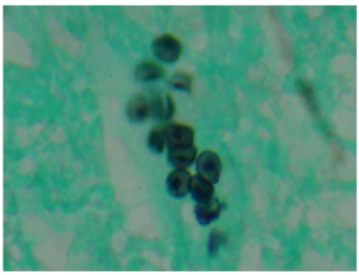
Cunninghamella (lung biopsy)



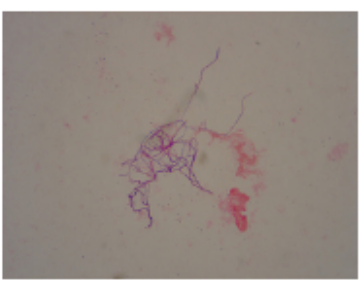
Malassezia (blood)



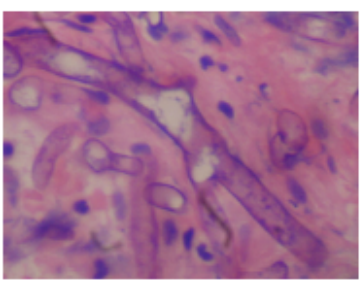
Mucormycosis (bone marrow)



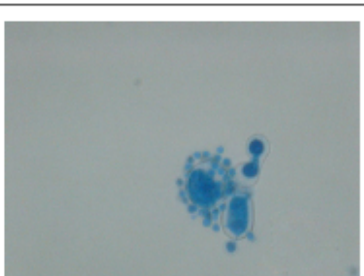
Pneumocystis (lung biopsy)



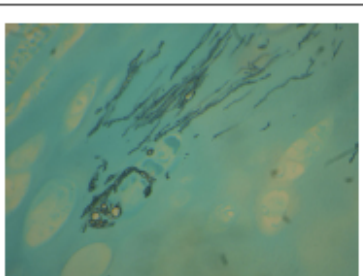
Nocardia (lung biopsy)



Rhizomucor (sinus biopsy)



Paracoccidioidomycosis (bone biopsy)



Scedosporium (lung biopsy)