Mayo Clinic Antimicrobial Therapy

QUICK GUIDE

John W. Wilson, MD

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MAYO CLINIC SCIENTIFIC PRESS

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MAYO CLINIC SCIENTIFIC PRESS
and INFORMA HEALTHCARE USA, INC.

ISBN-13: 978-1-4200-8518-1

For order inquiries, contact: Informa Healthcare, Kentucky Distribution Center, 7625 Empire Drive, Florence, KY 41042 USA.
E-mail: orders@taylorandfrancis.com;
Web site: www.informahealthcare.com

Library of Congress Cataloging-in-Publication Data

Mayo Clinic antimicrobial therapy : quick guide/edited by John W. Wilson, Lynn L. Estes.
p. ; cm.
Includes bibliographical references.
ISBN-13: 978-1-4200-8518-1 (pb : alk. paper)
ISBN-10: 1-4200-8518-2 (pb : alk. paper) 1. Anti-infective agents--Handbooks, manuals, etc. 2. Communicable diseases--Chemotherapy--Handbooks, manuals, etc. I. Wilson, John W., 1967- II. Estes, Lynn L. III. Mayo Clinic. IV. Title: Antimicrobial therapy.
[DNLM: 1. Anti-Infective Agents--therapeutic use--Handbooks. 2. Communicable Diseases--drug therapy--Handbooks. QV 39 M473 2007]
RM262.M377 2007
615'.1--dc22
2007027808

Dedication

We dedicate this book to the patients under our care and to our families, who continue to support us in our work.

About the Cover

The image on the cover illustrates the dichotomous impact of human intervention on infectious diseases and antimicrobial therapy worldwide. Landmark achievements of mankind against infectious diseases include vaccine and antimicrobial drug development, along with a growing international cooperative in disease awareness, surveillance, and containment. In contrast to such accomplishments, however, are human-driven problems of inappropriate antimicrobial prescribing with secondary development of drug-resistant microbes and the proliferation of the human immunodeficiency virus, tuberculosis, and sexually transmitted diseases through socioeconomic and educational inequalities and maladaptive behaviors. Finally, in the age of jet aviation and global tourism, infectious diseases that were once remote and geographically localized are emerging in new locations. In the 21st century, health care providers and scientists worldwide have the opportunity and the growing responsibility through antimicrobial stewardship to collectively work toward effective and responsible management of infectious diseases.

Preface

The medical management of infectious diseases and antimicrobial therapy can be a daunting task for health care professionals. Although expansive textbooks and online resources are available, we believe that a more simplified, quick reference guide is needed for the day-to-day office and hospital clinical practice. This book is designed to provide information about infectious diseases and antimicrobial therapy in a format that is readily accessible and easily applicable to the clinical environment.

Highlights of this book include simplified and thorough drug dosing recommendations for renal function and renal replacement therapies, drugs of choice for specific organisms (including bacteria, fungi, and viruses), and simplified antimicrobial and management recommendations for specific infectious syndromes.

We hope that this book will assist health care providers in the management of infectious diseases and in the selection of appropriate antimicrobial therapy in a time-efficient manner. This book is not meant to serve as a comprehensive review of all infectious diseases topics. Instead, readers are encouraged to seek supplemental information from additional published resources and from the prescribing information provided by pharmaceutical manufacturers.

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[a] Tables are listed only for Sections I and II.

admin, administration
AFB, acid-fast bacilli
ALT, alanine aminotransferase
anti-HBs, antibody to hepatitis B surface antigen
antistaph, antistaphylococcal
AUC, area under the curve
BCG, bacille Calmette-Guérin
bid, 2 times a day
BMT, bone marrow transplant
BP, blood pressure
BV, bacterial vaginosis
CA-MRSA, community-acquired *Staphylococcus aureus*
cap, capsule
CAP, community-acquired pneumonia
CAPD, continuous ambulatory peritoneal dialysis
CBC, complete blood cell count
CDC, Centers for Disease Control and Prevention
CF, cystic fibrosis
CFU, colony-forming units
CHF, congestive heart failure
CI, clinically insignificant
CK, creatine kinase
Cl_{Cr}, creatinine clearance
CMV, cytomegalovirus
CNS, central nervous system
CRRT, continuous renal replacement therapy
CSF, cerebrospinal fluid
cSSSI, complicated skin and skin structure infections
CYP, cytochrome P-450
D/C, discontinue
DIC, disseminated intravascular coagulation
DOT, directly observed therapy
DS, double strength
DT, diphtheria and tetanus toxoids vaccine
DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP, diphtheria and tetanus toxoids and inactivated pertussis vaccines
DW, dosing weight
EC, enteric coated

ECG, electrocardiogram
ECM, erythema chronicum migrans
EIA, enzyme immunoassay
EIEC, enteroinvasive *Escherichia coli*
ELISA, enzyme-linked immunosorbent assay
ERCP, endoscopic retrograde cholangiopancreatography
ESLD, end-stage liver disease
ETEC, enterotoxigenic *Escherichia coli*
ESBL, extended-spectrum β-lactamase
gen, generation
GI, gastrointestinal
GU, genitourinary
h, hour
HA, headache
HAART, highly active antiretroviral therapy
HACEK, *Haemophilus parainfluenzae, H aphrophilus, H paraphrolus, H influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*
HAV, hepatitis A virus
HBeAg, hepatitis B e antigen
HBIG, hepatitis B immunoglobulin
HBsAg, hepatitis B surface antigen
HBV, hepatitis B virus
HCP, health care professional
HCV, hepatitis C virus
HD, hemodialysis
HDV, hepatitis D virus
HGE, human granulocytic ehrlichiosis
Hib, *Haemophilus influenzae* type b
HIDA, hepatobiliary iminodiacetic acid
HIV, human immunodeficiency virus
HME, human monocytic ehrlichiosis
HPF, high-power field
HPV, human papillomavirus
HSV, herpes simplex virus
IBW, ideal body weight
ICU, intensive care unit
IE, infective endocarditis
IFA, indirect fluorescent antibody
IFN, interferon

IgE, immunoglobulin E
IGRA, interferon-γ release assay
IM, intramuscular
Inh, inhalation
INR, international normalized ratio
IPV, inactivated poliovirus
IV, intravenous
K, age-specific constant of proportionality
KOH, potassium hydroxide
L, length
LFTs, liver function tests
LGV, lymphogranuloma venereum
MAC, *Mycobacterium avium* complex
MALT, mucosa-associated lymphoid tissue
max, maximum
MCV4, meningococcal conjugate vaccine
MDR, multidrug-resistant
MIC, minimal inhibitory concentration
min, minute
misc, miscellaneous
MMR, measles, mumps, and rubella vaccine
MPSV4, meningococcal polysaccharide vaccine
MRSA, methicillin-resistant *Staphylococcus aureus*
MRSE, methicillin-resistant *S epidermidis*
MSSA, methicillin-sensitive *S aureus*
MSSE, methicillin-sensitive *S epidermidis*
MTT, methyltetrazolethiol
NAA, nucleic acid amplification
NGU, nongonococcal urethritis
NNRTI, non-nucleoside reverse transcriptase inhibitor
NRTI, nucleoside reverse transcriptase inhibitor
NSAIDs, nonsteroidal anti-inflammatory drugs
NTM, nontuberculosis mycobacteria
ODA, once-daily aminoglycosides
PAIR, puncture, aspiration, injection, reaspiration
PCP, *Pneumocystis jiroveci* pneumonia; previously known as *Pneumocystis carinii* pneumonia
PCR, polymerase chain reaction
PCV, pneumococcal conjugate vaccine
pen, penicillin

PEP, postexposure prophylaxis

PI, protease inhibitor

PID, pelvic inflammatory disease

PPD, purified protein derivative (tuberculin)

PPV, pneumococcal polysaccharide vaccine

PRP-OMP, *Haemophilus influenzae* type b capsular polysaccharide (polyribosylribitol phosphate [PRP]) that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures

PSA, prostate-specific antigen

q, every

qid, 4 times a day

RIG, rabies immunoglobulin

Rota, rotavirus

RTI, respiratory tract infection

S&S, swish and swallow

SCr, serum creatinine

SDD, susceptible dose-dependent

SLED, sustained low-efficiency dialysis

smx, sulfamethoxazole

SQ, subcutaneous

SS, single strength

SSTI, skin and skin structure infections

STD, sexually transmitted disease

supplement, supplemental dose

syn, synergistic activity; synergy

tab, tablet; tablets

TB, tuberculosis

Td, tetanus and diphtheria toxoids vaccine

Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis adsorbed

TEE, transesophageal echocardiography

tid, 3 times a day

tmp, trimethoprim

tmp/smx, trimethoprim-sulfamethoxazole

TSH, thyroid-stimulating hormone

TST, tuberculosis skin test; tuberculin skin test

TTE, transthoracic echocardiography

U/A, urinalysis

USDHHS, US Department of Health and Human Services

USSR, Union of Soviet Socialist Republics

UTI, urinary tract infection
VAERS, Vaccine Adverse Event Reporting System
Vd, volume of distribution
VL, viral load
VRE, vancomycin-resistant *Enterococcus*
VZV, varicella-zoster virus
WBC, white blood cell count
wk, week
XL, extended release
XR, extended release

Spectrum of Activity

Table 1A. Aerobic Gram-Negative Bacteria: Aminoglycosides, Carbapenems, Cephalosporins, Aztreonam, and Fluoroquinolones

Aerobes	Aminoglycosides			Carbapenems		Cephalosporins[a]						Monobactams	Fluoroquinolones		
						1st Gen	2nd Gen		3rd Gen		4th Gen				
	amikacin	gentamicin	tobramycin	ertapenem	imipenem, meropenem	cefazolin, cephalexin	cefotetan, cefoxitin	cefuroxime	cefotaxime, ceftriaxone	ceftazidime	cefepime	aztreonam	ciprofloxacin	levofloxacin	moxifloxacin, gemifloxacin
Acinetobacter sp	2(!)	1-2(!)	2(!)	0-1	2(!)	0	0-1	0	1	1-2	1-2	1	1-2[b]	1-2[b]	1-2[b]
Aeromonas hydrophila	2	2	2	2	2	0		1	1	1	1	1	2	2	2
Escherichia coli (non-ESBL)	2	2	2	2	2	1-2(!)	1-2(!)	1-2	2	2	2	2	2[c]	2[c]	2[c]
ESBL (*E coli*, *Klebsiella* sp)	1-2[d]	1[d]	1[d]	1-2[c]	2[c]	0	0-1	0	0	0	0	0	1[d]	1[d]	1[d]
Enterobacter, *Citrobacter*, *Serratia* spp	2	2	2	1-2	2	0	0	1	1[e]	1[e]	1-2	1-2	2	2	2
Haemophilus influenzae	2	2	2	2	2	1	1-2	1-2	2	2	2	2	2	2	2
Klebsiella sp (non-ESBL)	2	2	2	2	2	1	1	1-2	2	2	2	2	2	2	2
Legionella sp	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2
Moraxella catarrhalis	2	2	2	2	2	0	1	1-2	2	2	2	2	2	2	2

Aerobes	Aminoglycosides			Carbapenems		Cephalosporins[a]						Monobactams	Fluoroquinolones		
						1st Gen	2nd Gen		3rd Gen		4th Gen				
	amikacin	gentamicin	tobramycin	ertapenem	imipenem, meropenem	cefazolin, cephalexin	cefotetan, cefoxitin	cefuroxime	cefotaxime, ceftriaxone	ceftazidime	cefepime	aztreonam	ciprofloxacin	levofloxacin	moxifloxacin, gemifloxacin
Neisseria gonorrhoeae	0	0	0	2	2	1	1	1	2	1	1-2	1-2	2[f(!)]	2[f(!)]	2[f(!)]
N meningitidis	0	0	0	2	2	0	1	1	2	1	2	2	2	2	2
Proteus mirabilis	2	2	2	2	2	1	1	1-2	2	2	2	2	2	2	2
Proteus vulgaris, Providencia spp	2	1-2	1-2	2	2	0	1	0	2	2	2	2	2	2	2
Pseudomonas aeruginosa	2	1-2	2	0	2	0	0	0	0	2	2	2	1-2	1-2	0
Salmonella sp				2	2	0		1	2	2	2	2	2[c]	2[c]	2[c]
Shigella sp	1	1	1	1	1			1	1	1	1	1	2	2	2
Stenotrophomonas maltophilia	0	0	0	0	0	0	0	0	0	0-1	0-1	0	1	1-2	1-2

[a] Representative agents; not all inclusive.
[b] Some treatment centers or geographic regions have high rates of fluoroquinolone resistance in *Acinetobacter* sp.
[c] Increased resistance may be observed in some local areas.
[d] Coresistance may be found in ESBL-producing organisms.
[e] Use of third-generation cephalosporins for *Enterobacter* or *Citrobacter* sp is generally not advised, because they can induce resistance during therapy.
[f] Higher fluoroquinolone resistance rates for *N gonorrhoeae* are now being widely reported. As of 2007, the Centers for Disease Control and Prevention no longer recommend routine treatment of gonorrhea with fluoroquinolone.
0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.
[(!)] High or increasing rates of resistance reported. Do not use empirically without susceptibility data.

Table 1B. Aerobic Gram-Negative Bacteria: Penicillins, Macrolides, Tetracyclines, Tigecycline, and Miscellaneous Medication Classes

Aerobes	Penicillins						Macrolides		Tetracyclines		Glycylcycline	Misc	
	Natural penicillins	Antistaph penicillins[a]	Aminopenicillins		Antipseudomonal penicillins								
	penicillin	nafcillin, dicloxacillin	ampicillin, amoxicillin	amoxicillin/ clavulanate, ampicillin/ sulbactam	ticarcillin/ clavulanate	piperacillin/ tazobactam	erythromycin	clarithromycin, azithromycin	tetracycline, doxycycline	minocycline	tigecycline	colistin	cotrimoxazole (tmp/smx)
Acinetobacter sp	0	0	0	0-2[b]	1-2	1-2	0	0	0	0	1-2[(f)]	1-2	1-2
Aeromonas hydrophila	0	0	0	0-1	0-1	1-2	0	0	2		2[c]		2
Escherichia coli (non-ESBL)	0	0	1	1-2	2	2	0	0	1		2	2	1
ESBL (*E coli, Klebsiella* sp)	0	0	0	0	0	1	0	0	0	1	1-2	1	0
Enterobacter, Citrobacter, Serratia spp	0	0	0	0	1-2	1-2	0	0	0	0	1-2	0-2[d]	1-2
Haemophilus influenzae	0-1	0	1	2	2	2	1	1-2	1-2	1-2	2	2	1-2
Klebsiella sp (non-ESBL)	0	0	0	2	2	2	0	0	1		2	2	2
Legionella sp	0	0	0	0	0	0	1-2	2	1	1	1-2[c]		1

Aerobes	Penicillins						Macrolides		Tetracyclines		Glycylcycline	Misc	
	Natural penicillins	Antistaph penicillins[a]	Aminopenicillins		Antipseudomonal penicillins								
	penicillin	nafcillin, dicloxacillin	ampicillin, amoxicillin	amoxicillin/ clavulanate, ampicillin/ sulbactam	ticarcillin/ clavulanate	piperacillin/ tazobactam	erythromycin	clarithromycin, azithromycin	tetracycline, doxycycline	minocycline	tigecycline	colistin	cotrimoxazole (tmp/smx)
Moraxella catarrhalis	0	0	0	1-2	2	2	0	2	0	0	2	2	
Neisseria gonorrhoeae	1(!)	0	1(!)	1	2	2	0	1	1(!)	1(!)	1	0	0
N meningitidis	2	0	2	2	2	2	*	*	*	*	*		1
Proteus mirabilis	0	0	1	2	2	2	0	0	1	1	0-1	2	2
Proteus vulgaris, Providencia spp	0	0	0	1	2	2	0	0	0	0	0-1	0	1
Pseudomonas aeruginosa	0	0	0	0	1	1-2	0	0	0	0	0	2	0
Salmonella sp	0	0	0-1	2	2	2	0	1	0-1	0-1	1		1
Shigella sp	0	0	0-1	1	1	1		1	0-1	0-1	1		1-2
Stenotrophomonas maltophilia	0	0	0	0	1-2	1	0	0		1-2	1-2	0	1-2

[a] Representative agents; not all inclusive.

[b] For *Acinetobacter* sp, ampicillin/sulbactam (Unasyn) has activity, whereas amoxicillin/clavulanate (Augmentin) does not.

[c] In vitro or animal models; limited clinical experience.

[d] Colistin is not active against *Serratia* sp.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.
(!) High or increasing rates of resistance reported. Do not use empirically without susceptibility data.
* Concern exists about antimicrobial tissue penetration related to the most common infectious syndrome caused by the organism.

Table 2A. Aerobic Gram-Positive Bacteria: Aminoglycosides, Carbapenems, Cephalosporins, and Penicillins

Aerobes	Aminoglycosides	Carbapenems		Cephalosporins[a]						Penicillins[a]					
				1st Gen	2nd Gen		3rd Gen		4th Gen	Natural penicillins	Antistaph penicillins	Amino-penicillins		Anti-pseudomonal penicillins	
	gentamicin, streptomycin	ertapenem	imipenem, meropenem	cefazolin, cephalexin	cefotetan, cefoxitin	cefuroxime	cefotaxime, ceftriaxone	ceftazidime	cefepime	penicillin	nafcillin, dicloxacillin	ampicillin, amoxicillin	amoxicillin/ clavulanate, ampicillin/ sulbactam	ticarcillin/ clavulanate	piperacillin/ tazobactam
Corynebaterium jeikeium	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Enterococcus															
E faecalis	syn[b]	0	1	0	0	0	0	0	0	2[c]	0	2[c]	2[c]	0	1-2[c]
E faecium	syn[b]	0	1	0	0	0	0	0	0	1[c]	0	1[c]	1[c]	0	1[c]
VRE	syn[b]	0	0	0	0	0	0	0	0	1[c]	0	1[c]	1[c]	0	0
Listeria monocytogenes	syn[b]		1-2	0	0	0	0	0	0	1-2	0	2	2		1
Nocardia sp	syn[b]	1	1	0	0	0	1	1	1	0	0	0	1		
Staphylococcus															
MSSA, MSSE	syn[b]	1-2	1-2	2	0-1	1	1	0	1	0-2[d(!)]	2	0-2[d(!)]	1-2	1-2	1-2
MRSA, MRSE	syn[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Aerobes	Aminoglycosides	Carbapenems		Cephalosporins[a]						Penicillins[a]					
				1st Gen	2nd Gen		3rd Gen		4th Gen	Natural penicillins	Antistaph penicillins	Amino-penicillins		Anti-pseudomonal penicillins	
	gentamicin, streptomycin	ertapenem	imipenem, meropenem	cefazolin, cephalexin	cefotetan, cefoxitin	cefuroxime	cefotaxime, ceftriaxone	ceftazidime	cefepime	penicillin	nafcillin, dicloxacillin	ampicillin, amoxicillin	amoxicillin/ clavulanate, ampicillin/ sulbactam	ticarcillin/ clavulanate	piperacillin/ tazobactam
Streptococcus															
Group A, B, C	0-syn[b]	2	2	2	1	1	2	1	2	2	2	2	2	2	2
S pneumoniae (pen sensitive)	0	2	2	1	0-1	1	2	1	2	2		2	2	2	2
S pneumoniae (pen intermediate)	0	2	2	0	0	1	1-2	0	2	1		1	1	1	1
S pneumoniae (pen resistant)	0	2	2	0	0	0	1	0	1	0-1	0	0-1	0-1	0-1	0-1
Viridans group	0	2	2	1	0-1	0-1	2	1	2	2	1	2	2	2	2

[a] Representative agents; not all inclusive.

[b] Synergistic activity when combined with appropriate agent; do not use as monotherapy.

[c] Activity for susceptible isolates.

[d] More than 80% of staphylococci are resistant to penicillin or ampicillin.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.

(!) High or increasing rates of resistance reported. Do not use empirically without susceptibility data.

Table 2B. Aerobic Gram-Positive Bacteria: Macrolides, Fluoroquinolones, Tetracyclines, Tigecycline, and Antibacterial Classes

	Macrolides		Fluoroquinolones			Tetracyclines		Glycylcycline	Misc					
Aerobes	erythromycin	clarithromycin, azithromycin	ciprofloxacin	levofloxacin	moxifloxacin, gemifloxacin	tetracycline, doxycycline	minocycline	tigecycline	clindamycin	tmp/smx	daptomycin	linezolid	metronidazole	vancomycin
Corynebaterium jeikeium	0	0	0	0	0	0	0		0	0	1-2[a]	2[a]	0	2
Enterococcus														
E faecalis	0	0	0-1	1[b]	1[b]	0	0-1	1-2[c]	0	0	1-2[c]	2	0	2
E faecium (non-VRE)	0	0	0-1	1[b]	1[b]	0	1	1-2[c]	0	0	1-2[c]	2	0	2
VRE	0	0	0	0	0	0	1	1-2[c]	0	0	1-2[c]	1-2	0	0
Listeria monocytogenes	*	*				*	*	*	*	1-2	*	1-2	0	1
Nocardia sp	0-1	0-1	0-1	1	1	1	1	1	0	2		1-2	0	0
Staphylococcus														
MSSA, MSSE	1	1	0-1	1	1	1	1-2	2	1-2	1-2	2	2	0	2
MRSA, MRSE	1[d]	1[d]	0-1	1[d]	1[d]	1	1	2	1[d]	1[d]	2	2	0	2
Streptococcus														
Group A, B, C	1	1	0-1	1	1-2	1	1	2	1	0-1	2	2	0	2

Aerobes	Macrolides		Fluoroquinolones			Tetracyclines		Glycylcycline	Misc					
	erythromycin	clarithromycin, azithromycin	ciprofloxacin	levofloxacin	moxifloxacin, gemifloxacin	tetracycline, doxycycline	minocycline	tigecycline	clindamycin	tmp/smx	daptomycin	linezolid	metronidazole	vancomycin
S pneumoniae (pen sensitive)	1	1	0	1-2	2	1	1	2	1	1	*	2	0	2
S pneumoniae (pen intermediate)	1	1	0	1-2	2	1	1	2		1	*	2	0	2
S pneumoniae (pen resistant)	0-1	0-1	0	1-2	2	0-1	0-1	2[a]	0	0	*	2[a]	0	2
Viridans group	1	1		1-2	1-2	1	1	1-2	1	0-1	2[a]	2[a]	0	2

[a] In vitro or animal models; limited clinical experience.

[b] More active agents are available for systemic infections.

[c] For severe enterococcal infections, tigecycline and daptomycin have not been studied extensively.

[d] May be more active against community-acquired methicillin-resistant *S aureus*.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.

* Concern exists about antimicrobial tissue penetration related to the most common infectious syndrome caused by the organism.

Table 3A. Anaerobic Bacteria: Aminoglycosides, Carbapenems, Cephalosporins, and Penicillins

Anaerobes	Aminoglycosides	Carbapenems		Cephalosporins[a]						Penicillins[a]					
				1st Gen	2nd Gen		3rd Gen		4th Gen	Natural penicillins	Antistaph penicillins	Amino-penicillins		Anti-pseudomonal penicillins	
	gentamicin, streptomycin	ertapenem	imipenem, meropenem	cefazolin, cephalexin	cefotetan, cefoxitin	cefuroxime	cefotaxime, ceftriaxone	ceftazidime	cefepime	penicillin	nafcillin, dicloxacillin	ampicillin, amoxicillin	amoxicillin/ clavulanate, ampicillin/ sulbactam	ticarcillin/ clavulanate	piperacillin/ tazobactam
Actinomyces sp	0	2	2				1-2[b]		1-2[b]	2	0	2	2[b]	2[b]	2[b]
Bacteroides sp	0	2	2	0	1		1	0		0-1	0	0-1	1-2	2	2
Clostridium difficile (enteric)															
C perfringens	0	2	2		1	1	1		1	2	0	1	2	2	2
Fusobacterium sp	0	2	2		1		1		1	1-2		1	2	2	2
Peptostreptococcus sp	0	2	2	2	2	2	2	1	2	2	0	1-2	2	2	2
Prevotella, Porphyromonas spp	0	2	2	0	1	1	1			1	0	1	2	2	2

[a] Representative agents; not all inclusive.
[b] In vitro or animal models; limited clinical experience
0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.

Table 3B. Anaerobic Bacteria: Macrolides, Fluoroquinolones, Tetracyclines, Tigecycline, and Other Medication Classes

Anaerobes	Macrolides		Fluoroquinolones			Tetracyclines		Glycylcyline	Misc						
	erythromycin	clarithromycin, azithromycin	ciprofloxacin	levofloxacin	moxifloxacin, gemifloxacin	tetracycline, doxycycline	minocycline	tigecycline	clindamycin	tmp/smx	daptomycin	linezolid	metronidazole	dalfopristin/ quinupristin	vancomycin
Actinomyces sp	1-2	1-2	1[a]	1[a]	1[a]	1-2	1-2	1-2	1-2		1[a]	1-2[a]	0	1[a]	1-2[a]
Bacteroides sp	0	0	0	0	1-2	0-1	0-1	1-2	1[(!)]	0	0	1[a]	2	0	0
Clostridium difficile (enteric)													2		2[b]
C perfringens	1	1			1	1	1	2	2		2[a]	2[a]	2	2[a]	1
Fusobacterium sp					1-2	1	1	1-2[a]	2	0	0		2		0
Peptostreptococcus sp	1	1		1	1-2	1	1	2	2	0	2[a]	1-2[a]	2	2[a]	2
Prevotella, Porphyromonas spp					1-2			2	2			2[a]	2		

[a] In vitro or animal models; limited clinical experience.

[b] Use oral vancomycin for *C difficile*.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.

[(!)] High or increasing rates of resistance reported. Do not use empirically without susceptibility data.

Table 4. Select Fungal Organisms

Medication	*Aspergillus sp*	*Blastomyces dermatitidis*	*Candida albicans, C tropicalis, C parapsilosis*	*C glabrata*	*C krusei*	*C lusitaniae, C guilliermondii*	*Coccidioides sp*	*Cryptococcus sp*	*Fusarium sp*	*Histoplasma sp*	*Pseudallescheria boydii (Scedosporium apiospermum)*	*Zygomycetes*
amphotericin products	2[a]	2	2	1-2	1-2	(!)	2	2	1	2	1	2
caspofungin, micafungin, anidulafungin	1-2[a]	0-1[b]	2[c]	2	2	1-2	0	0	0	1[b]	0	0
fluconazole	0	1	2	1[d]	0	1-2	1-2	2	0	1		0
flucytosine	0	0	2[e]	2[e]	0	1[e]	1[e]	1-2[e]	0	0	0	0
itraconazole	1-2	1-2	2	1[d]	0	1	1-2	1	0	1-2	1	0-1
posaconazole	2[b]	1-2[b]	2	1-2[f]	2	1-2	1-2[b]	1-2[b]	1[b]	1-2[b]	1-2[b]	1-2[b]
voriconazole	2[a]	1[b]	2	1-2[f]	2	1-2	1-2[b]	1-2[b]	1	1[b]	1-2	0

[a] Combination therapy with an echinocandin plus voriconazole or an amphotericin product is sometimes used for severe infections (no randomized controlled trials but retrospective cohort studies suggest improved outcomes). *Aspergillus terreus* is less susceptible to amphotericin.

[b] Limited clinical data.

[c] Higher minimum inhibitory concentrations noted against *C parapsilosis* and some failures reported. Clinical significance not entirely clear.

[d] Susceptibilities often in the susceptible, dose-dependent range (requires more aggressive dosing).

[e] Not typically used alone. Flucytosine should be used in combination therapy to treat candidal infections and in combination induction therapy to treat cryptococcal meningitis.

[f] Some azole cross-resistance observed. Not preferred in patients with recent azole therapy without susceptibility testing.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity; blank box=inadequate data to rank.

(!) High or increasing rates of resistance reported. Do not use empirically without susceptibility data.

Table 5. Select Viral Organisms (Excluding Human Immunodeficiency Virus)

Medication	HSV	VZV	CMV	HBV	HCV	Influenza	
						A	B
acyclovir	2	2	0	0	0	0	0
adefovir	1	0	0	1	0	0	0
amantadine	0	0	0	0	0	1[a]	0
cidofovir	2[b]	2[c]	2	0	0	0	0
entecavir	0	0	0	2	0	0	0
famciclovir (penciclovir)	2	2	0	0-1	0	0	0
foscarnet	2[b]	2[c]	2[d]	0	0	0	0
ganciclovir	2[c]	2[c]	2	0	0	0	0
interferon alpha	0	0	0	2	2[e]	0	0
lamivudine	0	0	0	1	0	0	0
oseltamivir	0	0	0	0	0	2	2
ribavirin	0	0	0	0	2[e]	0	0
rimantadine	0	0	0	0	0	1[a]	0
tenofovir	0	0	0	1-2	0	0	0
valacyclovir	2	2	0	0	0	0	0
valganciclovir	2[c]	2[c]	2	0	0	0	0

Medication	HSV	VZV	CMV	HBV	HCV	Influenza	
						A	B
zanamivir	0	0	0	0	0	2	2

[a] High rates of resistance were reported in 2005 and 2006 for amantadine or rimantadine in patients with influenza A, so neither is currently recommended by the Centers for Disease Control and Prevention for treatment or prophylaxis.

[b] Active against many acyclovir-resistant strains of herpes simplex virus; not used as a first-line treatment for sensitive strains due to enhanced toxicity compared with that of alternate drugs.

[c] Not used as a first-line treatment due to enhanced toxicity compared with that of alternate drugs.

[d] Foscarnet is active against many ganciclovir-resistant strains.

[e] Interferon (pegylated) is used in combination with ribavirin.

0=Little or no activity; 1=moderate activity, with some resistance noted; 2=good activity.

Pharmacokinetics of Antimicrobial Agents

Table 6. Pharmacokinetic Highlights of Antimicrobial Agents (Normal Organ Function)

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
ANTIBACTERIALS						
AMINOGLYCOSIDES						
amikacin	IV	Renal	1.5-4	Poor	Good	Yes
gentamicin	IV	Renal	1.5-4	Poor	Good	Yes
tobramycin	IV, Inh	Renal	1.5-4	Poor	Good	Yes
β-LACTAMS						
Carbapenems						
ertapenem	IV	Renal	4	Fair	Good	Yes
imipenem/ cilastatin	IV	Renal	1	Fair	Good	Yes
meropenem	IV	Renal	1	Fair	Good	Yes
Cephalosporins						
cefadroxil	Oral	Renal	1.2-1.7	Poor	Good	Yes
cefazolin	IV	Renal	1.9	Poor	Good	Yes
cefepime	IV	Renal	2	Fair	Good	Yes
cefotaxime	IV	Hepatic (renal)	1.2	Fair	Good	Yes

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
cefotetan	IV	Renal	4	Poor	Good	Yes
cefoxitin	IV	Renal	0.8-1	Poor	Good	Yes
cefpodoxime proxetil	Oral	Renal	2.1-2.8	Poor	Fair	Yes
cefprozil	Oral	Renal	1.3	Poor	Good	Yes
ceftazidime	IV	Renal	1.9	Fair	Good	Yes
ceftriaxone	IV	Biliary, renal	5.8-8.7	Fair	Good	CI
cefuroxime	IV, oral	Renal	1.2-1.9		Good	Yes
cephalexin	Oral	Renal	1	Poor	Good	Yes
Monobactams						
aztreonam	IV	Renal	1.7	Fair	Good	Yes
Penicillins						
ampicillin	IV, oral	Renal	0.7-1.4	Fair	Good	Yes
ampicillin/ sulbactam	IV	Renal	1	Fair	Good	Yes
amoxicillin	Oral	Renal	1	Poor	Good	Yes
amoxicillin/ clavulanate	Oral	Renal	1-1.4	Poor	Good	Yes
dicloxacillin	Oral	Renal	0.7	Poor	Good	CI

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
nafcillin	IV	Hepatic	0.5-1	Fair	Fair	CI
oxacillin	IV	Hepatic	0.3-0.8	Poor	Fair	CI
penicillin G	IV	Renal	0.3-0.8	Fair	Good	Yes
penicillin V	Oral	Renal	0.5	Poor	Good	Yes
piperacillin	IV	Renal	0.6-1.2	Fair	Good	Yes
piperacillin/ tazobactam	IV	Renal	0.7-1.2	Fair	Good	Yes
ticarcillin/ clavulanate	IV	Renal	1.1	Fair	Good	Yes
FLUOROQUINOLONES						
ciprofloxacin	IV, oral	Renal (hepatic)	4	Fair	Good	CI
gemifloxacin	Oral	Fecal, biliary (renal)	7		Fair	CI
levofloxacin	IV, oral	Renal	6-8	Fair	Good	CI
moxifloxacin	IV, oral	Hepatic	8-16	Fair	Poor	CI
MACROLIDES, CLINDAMYCIN, AND KETOLIDES						
azithromycin	IV, oral	Biliary	68	Poor	Poor	CI
clarithromycin	Oral	Hepatic	3-7	Poor	Fair	CI
clindamycin	IV, oral	Hepatic	2.4	Poor	Fair	CI
erythromycin	IV, oral	Hepatic	1.4	Poor	Poor	CI

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
telithromycin	Oral	Hepatic	10	Poor	Poor	CI
TETRACYCLINES AND GLYCYLCYCLINE						
doxycycline	IV, oral	Hepatic	18-22	Fair to good	Fair	CI
minocycline	IV, oral	Hepatic	15.5	Fair to good	Fair	CI
tetracycline	IV, oral	Renal	6-12	Poor	Good	CI
tigecycline	IV	Biliary, fecal	42		Fair	CI
MISC. ANTIBIOTICS						
atovaquone	Oral	Fecal	67-78	Poor	Poor	CI
colistin	IV, Inh	Renal	2-3	Poor	Good	CI
dalfopristin/ quinupristin	IV	Fecal, Biliary	0.7/0.85		Fair	CI
dapsone	Oral	Renal (hepatic)	28			Yes
daptomycin	IV	Renal	8-9		Good	CI
linezolid	IV, oral	Hepatic	4-5	Good	Good	Yes
metronidazole	IV, oral	Hepatic (renal)	6-14	Good	Good	Yes
nitrofurantoin	Oral	Renal	0.5	Poor	Good	Yes
trimethoprim/ sulfamethoxazole	IV, oral	Renal	8-10	Good	Good	Yes
trimethoprim	IV, oral	Renal	8-10	Good	Good	Yes

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
vancomycin[d]	IV	Renal	4-6	Poor to fair	Good	CI[e]
ANTIFUNGALS						
amphotericin B	IV	Biliary, fecal	15 days	Poor	Poor	CI
lipid complex	IV		173	Poor	Poor	CI
liposomal	IV		153	Poor	Poor	CI
anidulafungin	IV	Chemical degradation	40-50	Poor	Poor	CI
caspofungin	IV	Hepatic	9-11	Poor	Poor	CI
fluconazole	IV, oral	Renal	30	Good	Good	Yes
flucytosine	Oral	Renal	2.4-4.8	Good	Good	Yes
itraconazole	IV, oral	Hepatic	64	Poor	Poor	CI
micafungin	IV	Hepatic	14-17	Poor	Poor	CI
posaconazole	Oral	Hepatic	16-36	Poor	Poor	CI
voriconazole	IV, oral	Hepatic	6	Good	Poor	CI
SELECT ANTIMYCOBACTERIALS						
ethambutol	Oral	Renal	2.4-4	Fair	Good	CI
isoniazid	IV, oral	Hepatic	1-4	Good	Fair	CI
pyrazinamide	Oral	Hepatic (renal)	9-10	Good	Good	Yes
rifabutin	Oral	Hepatic (renal)	45	Fair	Poor	CI

Medication	Usual admin. route	Major elimination route (minor component)	Usual half-life, h	CSF penetration (poor, fair, good)[a]	Urinary concentration (poor, fair, good)	Removal by conventional HD[b,c,*]
rifampin	IV, oral	Hepatic	1.5-5	Fair	Fair	CI
ANTIVIRALS (NON-HIV)						
acyclovir	IV, oral	Renal	2.5-3.3	Good	Good	Yes
cidofovir	IV	Renal	2.5	Poor	Good	Contraindicated
entecavir	Oral	Renal	128-149		Good	CI
famciclovir	Oral	Hepatic (renal)	2-3		Good	Yes
foscarnet	IV	Renal	2-4	Fair	Good	Yes
ganciclovir	IV, oral	Renal	3	Good	Good	Yes
oseltamivir	Oral	Hepatic (renal)	6-10			Yes
ribavirin	Oral, Inh	Renal	Oral=298; Inh=9.5			CI
valacyclovir	Oral	Renal	3	Fair	Good	Yes
valganciclovir	Oral	Renal	4	Good	Good	Yes
zanamivir	Inh	Renal	2.5-5.1	Poor	Poor	CI

[a] Poor=low penetration into central spinal fluid; fair=moderate penetration or good penetration in presence of meningeal inflammation; good=good penetration, regardless of presence of meningeal inflammation.

[b] Yes=removal of ≥30% of dose.

[c] CI=clinically insignificant (<30% of dose removed).

[d] Oral vancomycin formulation available (not absorbed); listed pharmacokinetic data refer to IV form.

[e] Not removed significantly by conventional hemodialysis, but can have significant removal with high-flux or high-permeability dialysis membranes.

* Data from Johnson CA. 2007 Dialysis of drugs. Nephrology Pharmacy Associates, Inc; c2007 [cited 2007 Jul 7]. Available from: http://www.nephrologypharmacy.com.

Antimicrobial Assays/Drug Levels

Table 7. Select Antimicrobial Assays: Infusion Times and Timing of Levels

Medication	Route	Infusion time or rate	Timing of levels[a]	Desired levels, mcg/mL
amikacin	IV or IM	IV: 30-60 min	Peak: 30 min after IV dose; draw 1 h after IM dose Trough: Just before dose	Peak for conventional dosing: 20-35 mcg/mL (diagnosis dependent) Trough for conventional dosing: <8 mcg/mL
chloramphenicol	IV or oral	IV: 15 min	Peak: 1-1.5 h after IV chloramphenicol (requires hydrolysis to active form); 2-4 h after oral dose Trough: Just before dose	Peak: 15-25 mcg/mL Trough: 5-10 mcg/mL
fluconazole	IV or oral	IV: 200 mg/h	Levels not routinely performed; long half-life makes timing not important; consider a steady-state trough (usually in 5-7 days) or random level	No clearly defined therapeutic range
flucytosine	Oral	NA	Peak: 2 h after dose Trough: Just before dose	Therapeutic level: 50-100 mcg/mL; increased toxicity with >100 mcg/mL
fluoroquinolones	IV or oral	IV: 60 min	Levels not routinely performed Peak: 1.5-2 h after oral dose; 30 min after IV dose	levofloxacin: Normal steady-state peak level after 500-mg dosing is 5.5-6.5 mcg/mL and after 750-mg dosing is 9-12 mcg/mL ciprofloxacin: Normal steady-state peak level after 400-mg IV q8h or q12h is about 4.5 mcg/mL; after 500-mg oral q12h is about 3 mcg/mL; after 750-mg oral q12h is about 3.6 mcg/mL

Medication	Route	Infusion time or rate	Timing of levels[a]	Desired levels, mcg/mL
gentamicin	IV or IM	IV: 30-60 min	Peak for conventional dosing: 30 min after IV dose; 60 min after IM dose Trough for conventional dosing: Just before dose Pulse dosing: 6- to 14-h level: Apply to Hartford nomogram; consider periodic trough monitoring (goal undetectable) Individualized pulse dosing: 2 h and 8-12 h after first dose	Peak for conventional dosing: 3-10 mcg/mL for most patients (diagnosis dependent) Trough for conventional dosing: <1.3 mcg/mL Pulse dosing: Apply 6- to 14-h level to Hartford nomogram; if trough level is measured, it should typically be undetectable
itraconazole	Oral or IV	IV: >1 h	Because of long half-life, timing is not important; consider steady-state trough or random level (after absorption phase); steady state usually occurs in about 7 days	No clearly defined therapeutic range but detectable level is needed; for serious infections (eg, *Aspergillus* sp, cryptococcal meningitis), consider target range for itraconazole plus hydroxyitraconazole ≥2.5 mcg/mL
sulfamethoxazole level (for tmp/smx)	IV or oral	IV: 1 h	Levels usually not indicated except for long-term therapy, serious infection, or substantial risk of toxicity; may check when treating *Pneumocystis jiroveci* pneumonia (PCP) or *Nocardia* sp and in patients with renal dysfunction Peak: 1 h after IV dose or 2-3 h after oral dose	100-150 mcg/mL (for PCP or *Nocardia* sp); for other indications, lower levels should be adequate
vancomycin	IV	≤1 g: 60 min 1.1-1.5 g: 90 min 1.6-2 g: 2 h >2 g: 1 g/h	Peak: 1 h after dose (longer in renal dysfunction); trough-only monitoring is appropriate in most patients Trough: Just before dose	Peak: 20-45 mcg/mL Trough: 5-15 mcg/mL (15-20 mcg/mL for select serious infections; see vancomycin-dosing nomogram for discussion)

Medication	Route	Infusion time or rate	Timing of levels[a]	Desired levels, mcg/mL
voriconazole	IV or oral	Over 1-2 h (max rate of 3 mg/kg/h)	Peak: 2 h after oral dose; about 30 min after IV dose Trough: Just before dose	Limited information Peak: <6-8 mcg/mL (higher levels may increase toxicity risk) Trough: >1-2 mcg/mL (lower levels may be associated with failure)

[a]Do not draw blood for peak levels through the same line where the medication was infused.

Laboratory and Clinical Toxicity Monitoring

Table 8. Laboratory and Clinical Toxicity Monitoring for Antimicrobials[a]

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
		ANTIBACTERIALS	
aminoglycoside class (eg, gentamicin, tobramycin, amikacin, streptomycin)	Nephrotoxicity, auditory toxicity, vestibular toxicity, neuromuscular blockade	SCr at least 2x/wk (for dose-adjustment and nephrotoxicity assessments), serum levels if therapy to continue >72 hours	Baseline and periodic hearing and vestibular function questioning (audiologic testing with prolonged therapy)
aztreonam	GI effects, hypersensitivity	SCr weekly (for dose-adjustment assessment)	Hypersensitivity, diarrhea
carbapenem class (eg, ertapenem, imipenem, meropenem)	Hypersensitivity, GI effects, *Clostridium difficile*, seizures (especially with high dose or doses not adjusted for renal function)	SCr weekly (for dose-adjustment assessment)	Hypersensitivity, GI effects, seizures (rare but often seen with renal dysfunction without dose adjustment or with underlying seizure disorder)

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
cephalosporin class	GI effects, hypersensitivity reactions, *C difficile*	For IV cephalosporins: SCr weekly (for dose-adjustment assessment) except for ceftriaxone, which does not require dose adjustment for renal function	Hypersensitivity, diarrhea, other GI effects
With MTT side chain (eg, cefotetan, cefmetazole, moxalactam, cefoperazone, cefamandole)	As for cephalosporin class plus hypoprothrombinemia and disulfiram-like reactions with alcohol	As for IV cephalosporins plus INR for prolonged use	As for cephalosporins plus avoid alcohol; bleeding with long-term use; diarrhea
ceftriaxone	As for cephalosporin class plus biliary sludging (especially in young children), gallstones	As for IV cephalosporins plus consider LFTs in pediatric patients with prolonged use	As for cephalosporins plus signs of biliary sludge or gallstones
clindamycin	Diarrhea, *C difficile* colitis, nausea, vomiting	Not routinely indicated	Hypersensitivity, GI effects, photosensitivity
dalfopristin/quinupristin	Pain or inflammation at infusion site, arthralgia or myalgia, hyperbilirubinemia	LFTs weekly	Phlebitis, arthralgias, myalgias
daptomycin	GI effects, hypersensitivity, headache, elevated CK, myalgias; rarely rhabdomyolysis	CK weekly; SCr weekly (dose-adjustment assessment)	Hypersensitivity, GI effects, myalgias, rhabdomyolysis

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
fluoroquinolone class (eg, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin)	GI effects, arthropathy (especially in pediatric patients), tendon rupture, prolongation of QT interval, hypersensitivity (especially gemifloxacin), CNS effects (especially with ciprofloxacin)	Consider periodic SCr and LFTs with prolonged use	Hypersensitivity, GI effects, drug-to-drug interactions, prolongation of QT interval with risk factors (avoid use with other QT-prolonging agents), CNS effects, photosensitivity
ketolides (eg, telithromycin)	Nausea, diarrhea, dizziness, headache, prolongation of QT interval, visual effects, rash, hepatotoxicity	LFTs at baseline (do not use with significant hepatic impairment) and weekly for prolonged use	Symptoms associated with liver dysfunction, hypersensitivity, diarrhea, other GI effects, visual disturbances, QT prolongation with risk factors (avoid use with other QT-prolonging agents), photosensitivity, drug-to-drug interactions
linezolid	Myelosuppression, diarrhea, nausea, rash, optic neuritis, peripheral neuropathy	CBC baseline and weekly; consider periodic LFTs with prolonged use	Hypersensitivity, GI effects, optic or peripheral neuropathy (with prolonged use), drug-to-drug interactions (eg, with serotonergic or adrenergic drugs)

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
macrolide class (eg, erythromycin, clarithromycin, azithromycin)	GI effects (less with clarithromycin and azithromycin), cholestatic jaundice, transient hearing loss (at high doses), prolongation of QT interval or torsades de pointes (primarily with erythromycin and clarithromycin), allergic reaction	Consider periodic LFTs with prolonged use; baseline SCr for clarithromycin (dose-adjustment assessment)	Hypersensitivity, GI effects, drug-to-drug interactions, QT prolongation with risk factors (avoid use with other QT-prolonging agents), hearing (especially with high-dose IV erythromycin)
metronidazole	Nausea, diarrhea, disulfiram-like reactions with alcohol, metallic taste, reversible neutropenia	Consider baseline LFTs (dose-adjustment assessment)	GI effects (avoid alcohol)

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
penicillin class	Hypersensitivity reactions, GI effects (nausea, vomiting, diarrhea, *C difficile*)	For IV penicillins: SCr weekly (dose-adjustment assessment except penicillinase-resistant penicillins)	Hypersensitivity, diarrhea, other GI effects
natural penicillins	IV form: As for penicillin class plus: Seizures (with high dose), phlebitis, pain during infusion, sodium or potassium excess (depending on salt form)	As for IV penicillins and sodium or potassium (depending on salt form)	As for penicillin class plus phlebitis
aminopenicillins (eg, ampicillin, amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam)	As for penicillin class: amoxicillin/clavulanate results in greater incidence of diarrhea and hepatitis	As for IV penicillins plus periodic LFTs with prolonged use	As for penicillin class plus higher incidence of diarrhea
penicillinase-resistant penicillins (eg, nafcillin, oxacillin)	As for penicillin class plus thrombophlebitis, hepatitis, neutropenia (with prolonged use), interstitial nephritis	As for IV penicillins plus weekly WBC and weekly LFTs	As for penicillin class plus phlebitis
carboxypenicillins (eg, ticarcillin, ticarcillin/clavulanate)	As for penicillin class plus hypokalemia, hypernatremia, platelet dysfunction, neutropenia	As for IV penicillins plus weekly CBC, weekly potassium, weekly sodium	As for penicillin class plus bleeding
ureidopenicillins (eg, piperacillin, piperacillin/tazobactam)	As for penicillin class plus neutropenia or thrombocytopenia (with prolonged use)	As for IV penicillins plus weekly CBC with prolonged use	As for penicillin class

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
tetracycline class (eg, tetracycline, doxycycline, minocycline)	Photosensitivity, permanent staining of developing teeth (avoid in pregnant women and children <8 y), GI effects, rash, vestibular toxicity (minocycline)	Consider periodic LFTs with prolonged use	Hypersensitivity, diarrhea, other GI effects, drug-to-drug interactions (chelators with oral tetracyclines), vestibular toxicity (minocycline), photosensitivity
tigecycline	Nausea and vomiting (higher incidence than comparators), permanent staining of developing teeth (avoid in pregnancy and in children <8 y)	LFTs weekly	GI effects
tmp/smx	Nausea, vomiting, hypersensitivity reactions, bone marrow suppression, hyperkalemia	With high dose: Consider baseline and periodic measurement of SCr (dose-adjustment and nephrotoxicity assessments), CBC, potassium, and LFTs	Hypersensitivity, GI effects
vancomycin	Ototoxicity, red man syndrome, nephrotoxicity (usually in combination with other nephrotoxins), phlebitis, reversible neutropenia	SCr baseline and weekly (for potential dose-adjustment and nephrotoxicity assessments); CBC weekly; serum levels as appropriate	Phlebitis, consider audiologic testing for long-term use, hypersensitivity, GI effects
ANTITUBERCULAR AGENTS (ALSO SEE FLUOROQUINOLONES AND LINEZOLID)			
isoniazid	Hepatitis, hypersensitivity reactions, lupus-like reactions, peripheral neuropathy	LFTs monthly in patients with underlying liver dysfunction	Hypersensitivity, neuropathy, drug-to-drug interactions

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
rifamycins (eg, rifampin, rifabutin, rifapentine)	Orange discoloration of body fluids, thrombocytopenia, hepatitis, uveitis (with rifabutin)	LFTs monthly in patients with underlying liver dysfunction	Uveitis (with rifabutin), numerous drug-to-drug interactions, hypersensitivity
pyrazinamide	Hepatitis, hyperuricemia, nausea, anorexia, polyarthralgia	LFTs monthly in patients with underlying liver dysfunction; uric acid as indicated	GI effects, hypersensitivity
ethambutol	Retrobulbar neuritis, optic neuritis, hyperuricemia	Not routinely indicated	Baseline vision or color discrimination testing and monthly questioning (repeat testing with prolonged use or with doses >25 mg/kg per day); consider monthly vision or color discrimination testing; GI effects
ethionamide	High incidence of GI effects, drowsiness, asthenia, psychiatric effects, hepatitis, hypothyroidism	LFTs in patients with underlying liver dysfunction; TSH baseline and monthly	GI effects, CNS effects
para-aminosalicylic acid	Rash, GI effects, hypersensitivity, hypothyroidism	LFTs and TSH at baseline; TSH every 3 months for prolonged use	Hypersensitivity, GI effects
cycloserine	CNS toxic effects (somnolence, headache, tremor, psychosis, seizures)	Serum levels may help establish optimum dose	Monthly assessment of neuropsychiatric effects
streptomycin, amikacin, kanamycin, capreomycin	Nephrotoxicity, auditory toxicity, vestibular toxicity, neuromuscular blockade	SCr baseline and weekly; serum levels when available	Baseline hearing, vestibular, or Romberg testing; monthly questioning of symptoms; repeat testing as indicated

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
		ANTIFUNGAL AGENTS	
amphotericin B deoxycholate	Infusion-related reactions (fever, chills, rigors, nausea, hypertension, hypotension), nephrotoxicity, hypokalemia, hypomagnesemia, reversible anemia	Twice-weekly SCr, twice-weekly potassium, and twice-weekly magnesium; weekly LFTs and weekly CBC	Infusion-related effects, BP check as indicated
lipid amphotericin product	Lower incidence of nephrotoxicity than amphotericin B dexoycholate; lower incidence of infusion-related effects with liposomal amphotericin	Twice-weekly SCr, twice-weekly potassium, and twice-weekly magnesium; weekly LFTs and weekly CBC	Infusion-related effects
flucytosine	Bone marrow suppression, GI effects, hepatitis	Twice-weekly SCr (dose-adjustment assessment) and twice-weekly CBC; weekly LFTs; periodic serum levels as indicated	Nausea and vomiting (often associated with elevated serum levels)

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
triazole antifungal class (eg, fluconazole, itraconazole, voriconazole, posaconazole)	GI effects, hepatitis, prolongation of QT interval, hypersensitivity	Baseline and periodic LFTs and SCr (dose-adjustment assessment with fluconazole; cyclodextrin vehicle accumulation with IV voriconazole or itraconazole)	GI effects, prolongation of QT interval with risk factors (avoid if possible with other QT-prolonging agents), hypersensitivity, photosensitivity, many drug-to-drug interactions
itraconazole	As above and congestive heart failure, cyclodextrin vehicle accumulation with IV formulation in patients with renal dysfunction (clinical significance of risk vs benefit unknown), high doses can sometimes produce endocrine effects similar to those of ketoconazole	As above for triazole class and periodic SCr with IV or oral solution (cyclodextrin vehicle accumulation with renal dysfunction, so avoid or consider risk vs benefit); consider periodic potassium and sodium; consider serum levels as indicated	As above and edema, signs of CHF (uncommon)
voriconazole	Transient visual disturbances, cyclodextrin vehicle accumulation with IV formulation in patients with renal dysfunction (clinical significance of risk vs benefit unknown)	As above for triazole class and periodic SCr with IV (cyclodextrin vehicle accumulation with renal dysfunction, so avoid or consider risk vs benefit); consider serum levels as indicated	As above and visual side effects, hallucinations
echinocandin class (eg, caspofungin, micafungin, anidulafungin)	Facial flushing or swelling (histamine mediated but rare), hypersensitivity, hepatitis	LFTs weekly	Hypersensitivity, a few drug-to-drug interactions with caspofungin

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
ANTIVIRAL AGENTS			
CYTOMEGALOVIRUS AGENTS			
cidofovir	Renal impairment, neutropenia, ocular hypotonia, headache, asthenia, alopecia, rash, GI effects	SCr (also give saline load and probenecid), WBC, and U/A, all 2x/wk and before each dose	GI effects, hypersensitivity (especially with probenecid)
foscarnet	Renal impairment, electrolyte disturbances, seizures, GI effects	SCr 2x/wk (dose-adjustment and nephrotoxicity assessments); electrolytes weekly	GI effects, hypersensitivity
ganciclovir or valganciclovir	Myelosuppression, GI effects	CBC 1-2x/wk; SCr weekly (dose-adjustment assessment)	GI effects
INFLUENZA AGENTS			
oseltamivir	GI effects (usually well tolerated)	SCr at baseline (dose-adjustment assessment)	GI effects
zanamivir	Bronchospasm in patients with underlying lung disease	NA	Bronchospasm (avoid in patients with lung injury or asthma)
HERPES VIRUS AGENTS			
acyclovir or valacyclovir	Malaise, nausea, vomiting, diarrhea; phlebitis (with IV acyclovir); nephrotoxicity and CNS effects more common with high-dose IV therapy	SCr weekly with IV acyclovir (dose-adjustment and nephrotoxicity assessments)	Phlebitis, CNS effects (IV), GI effects

Medication	Select toxicities	Minimum laboratory monitoring[b]	Clinical monitoring
famciclovir	Headache, dizziness, nausea, diarrhea, fatigue	SCr at baseline (dose-adjustment assessment)	GI effects

[a] Also monitor for signs or symptoms of infection improvement or worsening.

[b] Monitor more frequently if tests are abnormal or changing and in critically ill patients.

Data from Tice et al. Clin Infect Dis. 2004 Jun 15;38:1651-72. Epub 2004 May 26.

Notes:

Adult Antimicrobial Dosing

Table 9. Dosing Information for Antimicrobials in Adult Patients

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
abacavir	300 mg bid	Unchanged	Unchanged	Unchanged	No information; probably not affected by conventional HD
abacavir/lamivudine (600 mg abacavir plus 300 mg lamivudine)	1 tab q24h	Unchanged	Use agents individually; see dosing instructions for individual drugs		
abacavir/ lamivudine/ zidovudine (300 mg abacavir plus 150 mg lamivudine plus 300 mg zidovudine)	1 tab bid	Unchanged	Use agents individually; see dosing instructions for individual drugs		
acyclovir IV					
Mucocutaneous disease	5 mg/kg q8h	Unchanged	Cl_{Cr} 25-49: 5 mg/kg q12h Cl_{Cr} 10-24: 5 mg/kg q24h	2.5 mg/kg q24h	2.5 mg/kg q24h; on dialysis days, give after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
HSV encephalitis	10 mg/kg q8h	Unchanged	Cl_{Cr} 25-49: 10 mg/kg q12h Cl_{Cr} 10-24: 10 mg/kg q24h	5 mg/kg q24h	5 mg/kg q24h; on dialysis days, give after HD
Varicella-zoster virus (immuno-compromised patients)	10-12 mg/kg q8h	Unchanged	Cl_{Cr} 25-49: 10 mg/kg q12h Cl_{Cr} 10-24: 10 mg/kg q24h	5 mg/kg q24h	5 mg/kg q24h; on dialysis days, give after HD
acyclovir oral					
Genital herpes	400 mg tid or 800 mg bid or 200 mg 5x/day	Unchanged	Cl_{Cr} 25-49: Unchanged Cl_{Cr} 10-24: 200 mg tid	200 mg bid	200 mg bid; on dialysis days, schedule 1 dose after HD
Varicella-zoster virus	600-800 mg 5x/day for 7 days or 1,000 mg q6h for 5 days	Unchanged	Cl_{Cr} 25-49: Unchanged Cl_{Cr} 10-24: 800 mg tid	800 mg bid	800 mg bid; on dialysis days, schedule 1 dose after HD
Chronic suppression for recurrent infection	400 mg bid (or 400-800 mg bid or tid for HIV)	Unchanged	Unchanged	200 mg bid	200 mg bid; on dialysis days, schedule 1 dose after HD
albendazole	400 mg daily or bid	Unchanged	Unchanged	Unchanged	No data; probably not affected by HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
amikacin	15-20 mg/kg q24h (7.5 mg/kg q12h)	See Aminoglycoside Adult Dosing and Monitoring (page 79)			Up to 66% removed; dose based on serum levels
amoxicillin	250-500 mg tid or 875 mg bid (for UTI 500 mg bid)	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 250-500 mg bid Do **not** use 875-mg tab with Cl_{Cr} <30	250-500 mg q24h	250-500 mg q24h; on dialysis days, give dose after HD or give 250-mg supplement after HD
amoxicillin/ clavulanate	250-500 mg tid or 875 mg bid; if XR give 2,000 mg q12h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 250-500 mg bid Do **not** use 875-mg tab or XR formulation with Cl_{Cr} <30	250-500 mg q24h Do **not** use XR formulation	250-500 mg q24h; on dialysis days, give dose after HD or give 250-mg supplement after HD
amphotericin B deoxycholate	0.5-1.5 mg/kg q24h; dose based on indication Yeasts: 0.5-1 mg/kg q24h *Aspergillus* and other filamentous fungi: 1-1.5 mg/kg q24h	Not eliminated renally but may need to reduce dose or dose every other day to reduce risk of further nephrotoxicity			Not dialyzed

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
amphotericin B lipid complex	5 mg/kg q24h; higher or lower doses based on indication	Not significantly cleared renally so dose adjustment not needed for renal dysfunction			Not dialyzed
amphotericin B liposomal	Empiric therapy: 3 mg/kg q24h Known systemic infections: 3-5 mg/kg q24h Cryptococcal meninigitis in HIV: 6 mg/kg q24h; higher doses based on indication	Not significantly cleared renally so dose adjustment not needed for renal dysfunction			Unknown but probably not dialyzed
ampicillin IV	1-2 g q4-6h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 1-2 g q8-12h	1-2 g q12-24h	1-2 g q12-24h; on dialysis days, schedule dose or give 1-2 g supplement after HD
ampicillin/sulbactam	1.5-3 g q6-8h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 15-29: 1.5-3 g q12h Cl_{Cr} 10-14: 1.5-3 g q24h	1.5-3 g q24h	1.5-3 g q24h; on dialysis days, schedule dose after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
anidulafungin	Candidemia or candidiasis: 200 mg x1 then 100 mg q24h Esophageal candidiasis: 100 mg x1 then 50 mg q24h	Unchanged	Unchanged	Unchanged	Unchanged
atazanavir	400 mg q24h	Unchanged	Unchanged	Unchanged	No data; probably not significantly affected by HD
atazanavir plus ritonavir	300 mg atazanavir plus 100 mg ritonavir q24h	Unchanged	Unchanged	Unchanged	No data; probably not significantly affected by HD
atovaquone oral suspension	750 mg bid or 1,500 mg q24h	Unchanged	Unchanged	Probably unchanged	No data; probably not affected by HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
atovaquone/ proguanil	Malaria prophylaxis: 250 mg/100 mg (1 tab) q24h; start 1-2 days before travel to endemic area and continue for 7 days after return Malaria treatment: 1 g/400 mg q24h (4 tab) for 3 days Take with high-fat meals	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} <30: Not recommended	Cl_{Cr} <10: Not recommended	
azithromycin IV	RTI or PID: 500 mg q24h; may switch to oral after 1-2 days	Unchanged	Unchanged	Unchanged	No supplement needed

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
azithromycin oral	RTI: Follow-up to IV azithromycin: 500 mg q24h Mild RTI: 500 mg on day 1 then 250 mg on days 2 to 5 (Zmax formulation: 2 g x1) PID: Follow-up to IV 250 mg q24h MAC prophylaxis: 1,200 mg per week *Chlamydia trachomatis*, chancroid, or NGU: 1 g x1	Unchanged	Unchanged	Unchanged	Unchanged
aztreonam	0.5-2 g q6h, q8h, or q12h depending on organism and severity	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 2 g x1 then 50% of usual maintenance dose q6h, q8h, or q12h	1-2 g x1 then 25% of dose q8h (125-500 mg q8h); dose depends on severity of infection	0.5-2 g x1 then 125-500 mg q8h; on dialysis days, schedule 1 dose after HD; dose depends on severity of infection

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
caspofungin	70 mg x1 followed by 50 mg q24h (use 70 mg q24h with concomitant enzyme inducers and in nonresponders)	Unchanged	Unchanged	Unchanged	Not affected by HD
cefadroxil	500 mg to 1 g bid	Unchanged	Cl_{Cr} 25-49: 500 mg bid Cl_{Cr} 10-24: 500 mg q24h	500 mg q24h or every other day	500 mg q24h or every other day; on dialysis days, schedule dose after HD
cefazolin	1-2 g q8h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 1-2 g q12h	1 g q24h	1 g q24h; on dialysis days, give after HD; alternately give 1-2 g after HD on dialysis days only
cefdinir	300 mg bid (can use 600 mg q24h for pharyngitis or sinusitis)	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} <30: 300 mg q24h	300 mg q24h	300 mg every other day; on dialysis days, schedule dose after HD
cefditoren	200-400 mg bid	Unchanged	Cl_{Cr} 30-49: 200 mg bid Cl_{Cr} 10-29: 200 mg q24h	Unknown; consider 200 mg q24h	Unknown; consider 200 mg q24h; on dialysis days, give after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
cefepime	1-2 g q12h for most infections Consider 2 g q8h for life-threatening infections, systemic pseudomonal infections, and neutropenic fever	Cl_{Cr} ≥60: Usual dose Cl_{Cr} 50-59: 1-2 g q24h Cl_{Cr} ≥60: Usual dose Cl_{Cr} 50-59: 2 g q12h	Cl_{Cr} 30-49: 1-2 g q24h Cl_{Cr} 10-29: 500 mg to 1g q24h Cl_{Cr} 30-49: 2 g q12h Cl_{Cr} 10-29: 2 g q24h	250-500 mg q24h 1 g q24h	250 mg to 1 g q24h; on dialysis days, give dose after HD; alternately, give 2 g after HD on dialysis days only
cefixime	400 mg q24h or 200 mg bid	Unchanged	Cl_{Cr} 20-49: 300 mg q24h Cl_{Cr} <20: 200 mg q24h	200 mg q24h	300 mg q24h; on dialysis days, give after HD
cefotaxime	1-2 g q4-12h; usually 1-2 g q8h	Unchanged	Cl_{Cr} 10-49: 1-2 g q8-12h	1-2 g q24h	1-2 g q24h; on dialysis days, give after HD
cefotetan	1-2 g q12h	Unchanged	Cl_{Cr} 10-49: 50% of usual dose q12h or usual dose q24h	1-2 g q48h	Give 50% of usual dose q24h; on dialysis days, schedule after HD
cefoxitin	1-2 g q6-8h	Unchanged	Cl_{Cr} 30-49: 1-2 g q8-12h Cl_{Cr} 10-29: 1-2 g q12-24h	1-2 g q24-48h	1-2 g q24-48h; on dialysis days, schedule after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
cefpodoxime proxetil	100-400 mg bid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 100-400 mg q24h	100-400 mg q24h	100-400 mg 3x/wk after HD
cefprozil	250-500 mg bid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 125-250 mg bid	250 mg q24h	250 mg q24h; on dialysis days, schedule after HD or give supplement
ceftazidime	1-2 g q8h	Unchanged	Cl_{Cr} 30-49: 1-2 g q12h Cl_{Cr} 10-29: 1-2 g q24h	500 mg to 1 g q24-48h	1-2 g load then 1 g after each HD session
ceftibuten	400 mg q24h	Unchanged	Cl_{Cr} 30-49: 200 mg q24h Cl_{Cr} 10-29: 100 mg q24h	100 mg q24h	Consider 400 mg after HD on dialysis days only
ceftriaxone	1-2 g q24h (2 g q12h for CNS infection)	Unchanged	Unchanged	Unchanged	1-2 g q24h or 2 g q12h for CNS infection; on dialysis days, give after HD
cefuroxime oral	125-500 mg bid	Unchanged	Unchanged	250-500 mg q24h	250-500 mg q24h; on dialysis days, schedule after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
cefuroxime IV	750 mg or 1.5 g q8h (1.5 g q6h for serious infections)	Unchanged	Cl_{Cr} 20-49: Unchanged Cl_{Cr} 10-19: 750 mg q12h	750 mg q24h	750 mg q24h; on dialysis days, schedule after HD
cephalexin	250 mg to 1 g qid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: Usual dose bid or tid	250-500 mg bid or daily	250-500 mg q24h; on dialysis days, schedule after HD
chloramphenicol	50-100 mg/kg/24h divided q6h (4 g q24h max)	Unchanged; monitor levels	Unchanged; monitor levels	Unchanged; monitor levels	Slightly hemodialyzed; schedule 1 dose after HD; monitor levels
chloroquine	Malaria treatment: 1.5 g (base) over 3 days Malaria prophylaxis: 300 mg/wk (base)	Unchanged	Unchanged	50% decrease in dose	Not appreciably dialyzed; give 50% of dose
cidofovir (must administer with probenicid and fluid)	Induction: 5 mg/kg/wk x2 Maintenance: 5 mg/kg q2wk	Reduce dose to 3 mg/kg if SCr increases 0.3-0.4 mg/dL above baseline; D/C if SCr increases ≥0.5 mg/dL above baseline or with ≥3+ proteinuria; contraindicated if Cl_{Cr} ≤55, SCr ≥1.5 mg/dL, or urine protein ≥100 mg/dL (2+)			

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
ciprofloxacin IV[e]	200-400 mg q12h; 400 mg q8h for severe infection (eg, nosocomial pneumonia)	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 200-400 mg q18-24h	200-400 mg q18-24h	200-400 mg q24h; on dialysis days, give after HD
ciprofloxacin oral[e]	250-750 mg bid (or 500-1,000 mg q24h XR)	Unchanged	250-500 mg bid (or 500 mg q24h XR)	250-500 mg q18-24h (or 500 mg q24h XR)	250-500 mg q24h (or 500 mg q24h XR); on dialysis days, give after HD
clarithromycin	250-500 mg bid (XL; 1,000 mg q24h)	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 500-mg load then give 50% of dose or double the interval	250 mg q24h	250 mg q24h; on dialysis days, give after HD
clindamycin oral	150-450 mg qid	Unchanged	Unchanged	Unchanged	Usual regimen
clindamycin IV	300-900 mg q6-8h	Unchanged	Unchanged	Unchanged	Usual regimen
clotrimazole lozenges	10 mg 5x/day	Unchanged	Unchanged	Unchanged	Usual regimen
colistin IM or IV (as colistimethate)	5-8 mg/kg/24h in 2-3 divided doses	2.5-3.8 mg/kg/24h in 2 divided doses	2.5 mg/kg q24h	1.5-2.5 mg/kg q48h	Not affected by HD; give 1.5-2.5 mg/kg q48h
colistin Inh (as colistimethate)	75 mg bid; use after bronchodilator	Unchanged	Unchanged	Unchanged	Unchanged

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
cotrimoxazole[e]: See trimethoprim-sulfamethoxazole					
dalfopristin/ quinupristin	7.5 mg/kg actual body weight q8-12h	Unchanged	Unchanged	Unchanged	Not likely to be removed by conventional HD
dapsone	50-100 mg q24h	Unchanged	Unchanged	Insufficient information	Insufficient information; not likely to be removed by HD
daptomycin	4 mg/kg q24h for cSSSI; or 6 mg/kg q24h for bacteremia or endocarditis and consider for bone or joint infections	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: Usual dose q48h	Usual dose q48h	Usual dose q48h; on dialysis days, give after HD
delavirdine	400 mg tid	Unchanged	Unchanged	Unchanged	Unknown; probably not affected
dicloxacillin	125-500 mg qid	Unchanged	Unchanged	Unchanged	Usual regimen

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
didanosine EC	>60 kg: 400 mg q24h ≤60 kg: 250 mg q24h	Cl_{Cr} ≥60: Unchanged Cl_{Cr} 50-59: If >60 kg: 200 mg q24h If ≤60 kg: 125 mg q24h	If >60 kg: Cl_{Cr} 30-49: 200 mg q24h Cl_{Cr} 10-29: 125 mg q24h If ≤60 kg: Cl_{Cr} 30-49: 125 mg q24h Cl_{Cr} 10-29: 100 mg q24h	If >60 kg: 125 mg q24h If ≤60 kg: 75 mg q24h	If >60 kg: 125 mg q24h If ≤60 kg: 75 mg q24h
diethylcarbamazine	Varies by indication (see Micromedex)	Unchanged	Dose reduction needed but specific recommendations lacking		
dirithromycin	500 mg q24h	Unchanged	Unchanged	Unchanged	Usual regimen
doxycycline[e] IV or oral	200 mg then 100 mg bid	Unchanged	Unchanged	Unchanged	Usual regimen
efavirenz	600 mg q24h	Unchanged	Unchanged	Unchanged	Unknown but probably not affected by HD
emtricitabine	200 mg q24h	200 mg q24h	Cl_{Cr} 30-49: 200 mg q48h Cl_{Cr} 15-29: 200 mg q72h Cl_{Cr} 10-14: 200 mg q96h	200 mg q96h	200 mg q96h; give after HD if giving on dialysis day

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
emtricitabine plus tenofovir	1 tab q24h	Unchanged	Cl_{Cr} 30-49: 1 tab q48h Cl_{Cr} 10-29: Use individual agents separately	Use individual agents separately	Use individual agents separately
enfuvirtide	90 mg SQ bid	Unchanged	Cl_{Cr} 35-49: Usual dose Cl_{Cr} 15-34: No data	No data	No data
ertapenem	1 g q24h	Unchanged	Cl_{Cr} 30-49: 1 g q24h Cl_{Cr} 10-29: 500 mg q24h	500 mg q24h	500 mg q24h; on dialysis days, give after HD
erythromycin IV	500 mg to 1 g q6h	Unchanged	Unchanged	50-75% of usual dose at normal intervals	Not dialyzed; give 50-75% of usual dose at normal intervals
erythromycin oral (base)	250-500 mg qid	Unchanged	Unchanged	50-75% of usual dose at normal intervals	Not dialyzed; give 50-75% of usual dose at normal intervals
ethambutol	15-25 mg/kg q24h (max 2.5 g q24h) or DOT 50 mg/kg oral 2x/wk or DOT 25-30 mg/kg oral 3x/wk	Unchanged	15 mg/kg q24-36h	15 mg/kg q48h	15-25 mg/kg after each HD on dialysis days only

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
famciclovir					
Herpes zoster	500 mg tid	Unchanged	Cl_{Cr} 40-49: 500 mg bid Cl_{Cr} 20-39: 500 mg q24h Cl_{Cr} <20: 250 mg q24h	250 mg q24h	250 mg after each HD on dialysis days only
Recurrent orolabial or genital herpes in HIV-infected patients	500 mg bid	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 500 mg q24h Cl_{Cr} <20: 250 mg q24h	250 mg q24h	250 mg after each HD on dialysis days only
Recurrent genital herpes non-HIV	125 mg bid	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 125 mg q24h Cl_{Cr} <20: 125 mg q24h	125 mg q24h	125 mg after each HD on dialysis days only
Suppression of recurrent genital herpes	250 mg bid	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 125 mg bid Cl_{Cr} <20: 125 mg q24h	125 mg q24h	125 mg after each HD on dialysis days only

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
fluconazole[e] IV or oral	200-800 mg q24h (consider load of 2x maintenance dose) Mucocutaneous or urinary infection: 100-200 mg q24h Candidemia or systemic candidiasis: 200-800 mg q24h; use higher end for SDD isolates (eg, *Candida glabrata*)	Unchanged	Load then 50% of dose q24h	Load then 25% of dose q24h	Give usual dose after HD on dialysis days only
flucytosine	12.5-37.5 mg/kg q6h	Unchanged; monitor levels	12.5-37.5 mg/kg q12-24h; monitor levels	12.5-37.5 mg/kg q24-48h; monitor levels	Maintenance dose after HD on dialysis days only; adjust based on levels
fosamprenavir	1,400 mg bid (naïve patients only)	Unchanged	Unchanged	Unchanged	Unchanged

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
fosamprenavir plus ritonavir	1,400 mg fosamprenavir plus 200 mg q24h ritonavir (naïve patients only) 700 mg fosamprenavir plus 100 mg ritonavir bid (experienced patients only)	Unchanged	Unchanged	Unchanged	Unchanged
foscarnet induction	60 mg/kg q8h or 90 mg/kg q12h x2-3 weeks	See product labeling	See product labeling	Not recommended	No specific data; could start with 45-60 mg/kg after each HD
foscarnet maintenance	90-120 mg/kg q24h	See product labeling	See product labeling	Not recommended	No specific data; could start with 45-60 mg/kg after each HD
ganciclovir IV induction	5 mg/kg q12h	Cl_{Cr} 70-80: Unchanged Cl_{Cr} 50-69: 2.5 mg/kg q12h	Cl_{Cr} 25-49: 2.5 mg/kg q24h Cl_{Cr} 10-24: 1.25 mg/kg q24h	1.25 mg/kg 3x/wk	1.25 mg/kg 3x/wk; on dialysis days, give after HD
ganciclovir IV maintenance	5 mg/kg q24h	Cl_{Cr} 70-80: Unchanged Cl_{Cr} 50-69: 2.5 mg/kg q24h	Cl_{Cr} 25-49: 1.25 mg/kg q24h Cl_{Cr} 10-24: 0.625 mg/kg q24h	0.625 mg/kg 3x/wk	0.625 mg/kg 3x/wk; on dialysis days, give after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
ganciclovir oral	1 g tid	Cl_{Cr} 70-80: Unchanged Cl_{Cr} 50-69: 1,500 mg q24h or 500 mg tid	Cl_{Cr} 25-49: 1 g q24h or 500 mg bid Cl_{Cr} 10-24: 500 mg q24h	500 mg 3x/wk	500 mg 3x/wk; on dialysis days, give after HD
gentamicin	3-7 mg/kg/24h in divided doses or daily as pulse dosing; monitor levels	See Aminoglycoside Adult Dosing and Monitoring (page 79); monitor levels			About 60% removed; dose based on serum levels
imipenem/cilastatin	500 mg q6h (usual) or up to 3-4 g q24h in serious infections with moderately susceptible organisms	500 mg q6-8h	500 mg q8-12h	250-500 mg q12h	250-500 mg q12h; on dialysis days, schedule 1 dose after HD or give supplement after HD
indinavir	800 mg q8h or 600-800 mg bid with ritonavir 100-200 mg bid	Unchanged	Unchanged	Unchanged	No data; probably not affected
iodoquinol	630-650 mg tid	Unchanged	Unchanged	No data	No data; probably not affected

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
isoniazid	5 mg/kg q24h (max 300 mg q24h) or DOT 15 mg/kg 2-3x/wk (max 900 mg q24h)	Unchanged	Unchanged	Unchanged; can use 50% in slow acetylators	Usual regimen; give 50% in slow acetylators; on dialysis days, give after HD
itraconazole cap or oral liquid	200 mg q24h or 200 mg bid; higher doses may be used based on levels	Unchanged	Unchanged	Unchanged	Usual regimen
itraconazole IV	200 mg q12h x4, then 200 mg q24h; higher doses may be used based on levels	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: Unchanged but excipient accumulation occurs; significance unknown; avoid unless benefit justifies risk	Unchanged but excipient accumulation occurs; significance unknown; avoid unless benefit justifies risk	Unchanged but excipient accumulation occurs; significance unknown; avoid unless benefit justifies risk
ivermectin	50-200 mcg/kg x1	Unchanged	Unchanged	No data; probably unchanged	No data; probably not affected
ketoconazole	200-400 mg q24h	Unchanged	Unchanged	Unchanged	Usual regimen

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
lamivudine					
HBV	100 mg q24h	Unchanged	Cl_{Cr} 30-49: 100-mg load then 50 mg q24h Cl_{Cr} 15-29: 100-mg load then 25 mg q24h Cl_{Cr} 10-14: 35-mg load then 15 mg q24h	Cl_{Cr} 5-9: 35-mg load then 15 mg q24h Cl_{Cr} <5: 35-mg load then 10 mg q24h	35-mg load then 10 mg q24h
HIV	150 mg bid (2 mg/kg if <50 kg) or 300 mg q24h	Unchanged	Cl_{Cr} 30-49: 150 mg q24h Cl_{Cr} 15-29: 150-mg load then 100 mg q24h Cl_{Cr} 10-14: 150-mg load then 50 mg q24h	Cl_{Cr} 5-9: 150-mg load then 50 mg q24h Cl_{Cr} <5: 50-mg load then 25 mg q24h	50-mg load then 25 mg q24h
lamivudine/ zidovudine (150 mg lamivudine plus 300 mg zidovudine)	1 tab bid	Unchanged	Use agents individually; see dosing instructions for individual drugs		

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
levofloxacin[e] IV and oral	250-750 mg q24h (750 mg for nosocomial pneumonia, complicated SSTI, or 5-day therapy for CAP)	Unchanged	Cl_{Cr} 20-49: 500-mg load then 250 mg daily or 750-mg q48h Cl_{Cr} 10-19: 500-750 mg load then 250-500 mg q48h	500-750 mg load then 250-500 mg q48h	Not affected by HD; 500-750 mg load then 250-500 mg q48h
linezolid[e] IV or oral	600 mg q12h	Unchanged	Unchanged	Unchanged	Unchanged; schedule 1 dose after HD or give a 200-mg supplement after HD
lopinavir/ritonavir	400 mg/100 mg (2 tab) bid or 800 mg/200 mg (4 tab) once daily (naïve patients only)	Unchanged	Unchanged	Unchanged	No data; probably not affected

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
mebendazole	Pinworms: 100 mg x1; may repeat in 3 weeks Whipworms, roundworms, and hookworms: 100 mg bid for 3 days; may repeat in 3-4 weeks Capillariasis: 200 mg bid for 20 days	Unchanged	Unchanged	Unchanged	Not significantly affected
mefloquine	Mild or moderate malaria: 1,250 mg x1 Multidrug-resistant falciparum malaria: 15 mg/kg x1 followed by 10 mg/kg q8-24h later Malaria prophylaxis: 250 mg/wk	Unchanged	Unchanged	No data	No data; probably not affected
meropenem	1 g q8h (usual) (or 0.5 g q8h for complicated SSTI)	Unchanged	Cl_{Cr} 26-49: 0.5-1 g q12h Cl_{Cr} 10-25: 250-500 mg q12h	250-500 mg q24h	250-500 mg q24h; on dialysis days, give dose or supplement after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
metronidazole[e] IV or oral	15 mg/kg x1 then 7.5 mg/kg (500 mg) q6-12h	Unchanged	Unchanged	Consider 500 mg q12h or decrease dose by 50% at normal intervals	Consider 500 mg q12h or decrease dose by 50% at normal intervals; on dialysis days, schedule at least 1 dose after HD
micafungin	Esophageal candidiasis: 150 mg q24h BMT prophylaxis: 50 mg q24h Systemic infection: 100 mg q24h (studied dose)	Unchanged	Unchanged	Unchanged	Usual regimen
minocycline[e] IV or oral	200 mg x1 then 100 mg bid	Unchanged	Unchanged	Unchanged or consider 200 mg then 100 mg q24h	Not affected by HD; unchanged or consider 200 mg then 100 mg q24h
moxifloxacin[e] IV or oral	400 mg q24h	Unchanged	Unchanged	Unchanged	Not affected; use usual dose
nafcillin	1-2 g q4-6h	Unchanged	Unchanged	Unchanged	Usual regimen
nelfinavir	750 mg tid or 1,250 mg bid	Unchanged	Unchanged	No data; probably unchanged	No data; probably not affected

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
nevirapine	Initiate with 200 mg q24h for 14 days then increase to 200 mg bid	Unchanged	Unchanged	Unchanged	No data; probably not affected by HD
nitazoxanide	500 mg bid	Unchanged	Unchanged	No data	No data
nitrofurantoin	50-100 mg qid	Unchanged	Avoid if Cl_{Cr} <50 mL/min	Avoid	Avoid
nitrofurantoin monohydrate macrocrystals	100 mg bid	Unchanged	Avoid if Cl_{Cr} <50 mL/min	Avoid	Avoid
nystatin oral lozenges	200,000-400,000 units 5x/day	Unchanged	Unchanged	Unchanged	Usual regimen
nystatin S&S	0.4-1 million units 3-5x/day	Unchanged	Unchanged	Unchanged	Usual regimen
oseltamivir	Treatment: 75 mg bid Prophylaxis: 75 mg q24h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 75 mg q24h for treatment or 75 mg q48h for prophylaxis	No data	No data
oxacillin IV	500 mg to 2 g q4-6h	Unchanged	Unchanged	Unchanged	Usual regimen

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
paromomycin	Intestinal amebiasis: 25-35 mg/kg/24h in 3 divided doses *Cryptosporidium* sp: 1.5-2.5 g/24h in 3-6 divided doses Tapeworm: 1 g q15min x4 doses	Unchanged	Unchanged	No data; avoid if possible	No data
penicillin G IV	5-24 million units per day divided q4h or as a continuous infusion (give load for serious infections)	Unchanged	Normal load then 75% of normal dose q4-6h (or 75% of normal daily dose as continuous infusion)	Normal load then 25-50% of normal dose q4-6h or 25-50% of normal daily dose as continuous infusion	Normal load then 25-50% of normal dose q4-6h; or 25-50% of normal daily dose as continuous infusion; on dialysis days, schedule at least 1 dose after HD
penicillin V oral	250-500 mg tid or qid	Unchanged	Unchanged	250 mg tid or qid	250 mg tid or qid; on dialysis days, schedule at least 1 dose after HD or give 250-mg supplement after HD
pentamidine Inh	300 mg/mo	Unchanged	Unchanged	Unchanged	Unchanged
pentamidine IV	4 mg/kg q24h	Unchanged	Unchanged	Probably unchanged	Probably unchanged

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
piperacillin	3-4 g q4-6h	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 3-4 g q8h Cl_{Cr} 10-19: 3-4 g q12h	3-4 g q12h	2 g q8h; on dialysis days, schedule at least 1 dose after HD or give 1-g supplement after HD
piperacillin/ tazobactam	3.375 g q6h	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 2.25 g q6h Cl_{Cr} 10-19: 2.25 g q8h	2.25 g q8h	2.25 g q8h; on dialysis days, schedule at least 1 dose after HD or give 0.75-g supplement after HD
	For nosocomial pneumonia: 4.5 g q6h	Unchanged	Cl_{Cr} 40-49: Unchanged Cl_{Cr} 20-39: 3.375 g q6h Cl_{Cr} 10-19: 2.25 g q6h	2.25 g q6h	2.25 g q8h; on dialysis days, schedule at least 1 dose after HD or give 0.75-g supplement after HD
posaconazole	Prophylaxis: 200 mg tid Oropharyngeal candidiasis: 100 mg bid on day 1 then 100 mg q24h *Zygomycetes* sp and other filamentous fungi: 200 mg qid or 400 mg bid has been studied	Unchanged	Unchanged	Unchanged but variability in AUC noted; monitor for efficacy	Not expected to be affected

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
praziquantel	Varies by indication (see Micromedex)	Unchanged	Unchanged	No data	No data; probably not affected
primaquine	15 mg q24h base (for malaria) or 45 mg/wk base	Unchanged	Unchanged	No data	No data
pyrazinamide	15-30 mg/kg q24h (max 2 g per dose) or DOT 50-70 mg/kg (max 4 g per dose) 2x/wk; or DOT 50-70 mg/kg (max 3 g per dose) 3x/wk	Unchanged	Unchanged	12-20 mg/kg q24h	25-35 mg/kg after each HD
pyrimethamine	25-100 mg q24h based on indication	Unchanged	Unchanged	Unchanged	Not affected by HD; usual dose

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
quinidine gluconate IV (for malaria)	10 mg/kg load then 0.02 mg/kg/min x72 hours; or 24 mg/kg over 4-hour load then 12 mg/kg over 4 hours q8h x7 days (modify based on ECG, BP, and serum levels, as appropriate)	Unchanged	Unchanged	Consider 75-100% of dose (modify based on clinical response, ECG, BP, and serum levels)	5-20% excreted by HD; dose for Cl_{Cr} <10
quinine (for malaria)	648 mg tid	Unchanged	Not well defined; consider 648 mg bid or tid	648-mg load then 324 mg bid	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
rifabutin	300 mg q24h or 150 mg bid or 300-450 mg DOT 2x/wk	Unchanged	Unchanged	No data	No data

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
rifampin	Mycobacterial infection: 600 mg q24h; or 600 mg DOT 2-3x/wk Staphylococcal infection: 600-1,200 mg q24h in 2-3 divided doses (not used as monotherapy)	Unchanged	Unchanged	Give 50-100% of usual dose	Not affected; give 50-100% of usual dose
rifaximin	200 mg tid (for traveler's diarrhea due to *E coli*)	Unchanged	Unchanged	No data; probably no change	Probably not affected by HD
ritonavir	600 mg bid (boosting doses of 100-200 mg q24h have been given with other protease inhibitors)	Unchanged	No data; probably no change	No data; probably no change	No data; probably no change
saquinavir	1,200 mg tid	Unchanged	No information; dose change probably not needed		No information available; probably no change
saquinavir plus ritonavir	1,000 mg saquinavir plus ritonavir 100 mg bid	Unchanged	No information; dose change probably not needed		No information available; probably no change

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
stavudine					
<60 kg	30 mg bid; or 75 mg q24h (for XR formulation)	30 mg bid; or 75 mg q24h (for XR formulation)	Cl_{Cr} 26-49: 15 mg bid immediate release Cl_{Cr} 10-25: 15 mg q24h immediate release	15 mg q24h immediate release	15 mg q24h immediate release; on dialysis days, give after HD
≥60 kg	40 mg bid; or 100 mg q24h (for XR formulation)	40 mg bid; or 100 mg q24h (for XR formulation)	Cl_{Cr} 26-49: 20 mg bid immediate release Cl_{Cr} 10-25: 20 mg q24h immediate release	20 mg q24h immediate release	20 mg q24h immediate release; on dialysis days, give after HD
streptomycin	7.5 mg/kg q12h	7.5 mg/kg q24h; dose based on serum levels	7.5 mg/kg q24-72h; dose based on serum levels	7.5 mg/kg q72-96h; dose based on serum levels	50-75% removed by HD; dose based on serum levels
tenofovir	300 mg q24h	Unchanged	Cl_{Cr} 30-49: 300 mg q48h Cl_{Cr} 10-29: 300 mg 2x/wk	300 mg 1x/wk	300 mg 1x/wk; on dialysis days, give after HD
tetracycline	250-500 mg qid	250-500 mg q8-12h	doxycycline preferred; or use tetracycline 250-500 mg q12-24h	doxycycline preferred; or use tetracycline 250-500 mg q24h	doxycycline

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
ticarcillin/ clavulanate	3.1 g q4-6h	Unchanged	3.1-g load then: Cl_{Cr} 30-49: 2 g q4h Cl_{Cr} 10-29: 2 g q8h	3.1-g load then 2 g q12h	Dose as for Cl_{Cr} <10; on dialysis days, schedule dose after HD or give 3.1-g supplement after HD
tigecycline	100-mg load then 50 mg q12h	Unchanged	Unchanged	Unchanged	Unchanged
tipranavir	500 mg (2 cap) plus ritonavir 200 mg (2 cap) bid	Unchanged	Unchanged	Unchanged	No data; probably unchanged
tobramycin Inh formulation	CF: 300 mg bid for 28-day cycle Non-CF: Usually 300 mg bid or 60-80 mg tid	Unchanged	Unchanged	Unchanged	Unchanged
tobramycin IV	3-7 mg/kg/24h in divided doses or daily as pulse dosing; monitor serum levels	See Aminoglycoside Adult Dosing and Monitoring (page 79); monitor serum levels			About 60% removed; dose based on serum levels
trimethoprim	100 mg bid or 200 mg q24h	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 15-29: 100 mg q24h or 50 mg bid	Avoid or consider further reducing dose	Avoid

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
trimethoprim-sulfamethoxazole[e] (cotrimoxazole)					
Non-PCP (IV)	8-10 mg/kg/24h tmp component in 2-4 divided doses	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 15-29: Consider normal dose for 1-2 days then 4-6 mg/kg/24h divided q12-24h Cl_{Cr} 10-14: 8-12 mg/kg q48h or 4-6 mg/kg/24h divided q12-24h	Avoid; or 4-6 mg/kg/24h divided q12h	Dose as per Cl_{Cr} <10; on dialysis days, schedule dose after HD; adjust based on serum levels
PCP or *Nocardia* sp (IV)	15-20 mg/kg/24h tmp component in 3-4 divided doses	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 15-29: Normal dose q48h then 7-10 mg/kg/24h in 2 divided doses	7-10 mg/kg/24h divided q12h	Dose as per Cl_{Cr} <10; on dialysis days, schedule dose after HD; adjust based on serum levels
PCP prophylaxis (oral)	1 DS daily or 3x/wk or 1 SS daily	Unchanged	1 DS 3x/wk	1 DS 3x/wk	1 DS tab on dialysis days after HD
Most other indications (oral)	1 DS bid	Unchanged	DS q24h or SS bid	Avoid or 1 DS q48h	Dose as per Cl_{Cr} <10; on dialysis days, schedule dose after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
valacyclovir					
Herpes zoster	1 g tid	Unchanged	Cl_{Cr} 30-49: 1 g bid Cl_{Cr} 10-29: 1 g q24h	500 mg q24h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
First episode genital herpes	1 g bid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 1 g q24h	500 mg q24h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
Recurrent genital herpes	500 mg bid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 500 mg q24h	500 mg q24h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
Suppression of genital herpes (non-HIV patients)	Less frequent recurrences: 500 mg q24h	Unchanged	Cl_{Cr} 30-49: 500 mg q24h Cl_{Cr} 10-29: 500 mg q48h	500 mg q48h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
	Frequent recurrences: 1 g q24h	Unchanged	Cl_{Cr} 30-49: 1 g q24h Cl_{Cr} 10-29: 500 mg q24h	500 mg q24h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD
Suppression of genital herpes (HIV patients)	500 mg bid	Unchanged	Cl_{Cr} 30-49: Unchanged Cl_{Cr} 10-29: 500 mg q24h	500 mg q24h	Dose as for Cl_{Cr} <10; on dialysis days, schedule after HD

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
valganciclovir induction therapy	900 mg bid	Cl_{Cr} ≥60: Unchanged Cl_{Cr} 50-59: 450 mg bid	Cl_{Cr} 40-49: 450 mg bid Cl_{Cr} 25-39: 450 mg q24h Cl_{Cr} 10-24: 450 mg q48h	Not recommended	Not recommended
valganciclovir maintenance therapy	900 mg q24h	Cl_{Cr} ≥60: Unchanged Cl_{Cr} 50-59: 450 mg q24h	Cl_{Cr} 40-49: 450 mg q24h Cl_{Cr} 25-39: 450 mg q48h Cl_{Cr} 10-24: 450 mg 2x/wk	Not recommended	Not recommended
vancomycin IV	15-20 mg/kg q12h; consider load; monitor serum levels	See Vancomycin Dosing and Monitoring (page 74); monitor serum levels			20-25 mg/kg; monitor levels; 25-40% removed by high-flux HD (not appreciably dialyzed by traditional HD)
vancomycin oral (for *Clostridium difficile*; not systemically absorbed)	125 g to 500 mg qid	Unchanged	Unchanged	Unchanged	Usual regimen

Medication	Usual dose[a]	Dose adjustment for renal impairment[b,c]			
	Cl_{Cr} >80 mL/min	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min (or anuric)	Intermittent HD dosing[d] (see also CRRT dosing information on page 71)
voriconazole IV	6 mg/kg q12h x2 doses; then 3-4 mg/kg q12h (reduce to 3 mg/kg if not tolerated)	Unchanged	Cl_{Cr} <50: Avoid IV unless benefit justifies risk because of accumulation of IV vehicle sulfobutyl ether β-cyclodextrin sodium (consequences of accumulation in humans not known)		
voriconazole oral	≥40 kg: 200 mg q12h (increase to 300 mg q12h if inadequate response) <40 kg: 100 mg q12h (increase to 150 mg q12h if inadequate response)	Unchanged	Unchanged	Unchanged	Unchanged
zanamivir	10 mg (2 Inh) bid	Unchanged	Unchanged	Unchanged	Unchanged
zidovudine	200 mg tid or 300 mg bid	Unchanged	Cl_{Cr} 25-49: Unchanged Cl_{Cr} <25: 100 mg tid	100 mg tid	Not significantly affected; 100 mg tid

[a] Usual doses are for most common indications. Doses may differ for meningitis, atypical or serious infections, or atypical organisms. Doses may need to be modified for patients with hepatic dysfunction.

[b] Loading doses should generally not be modified in patients with renal dysfunction. Subsequent (maintenance) doses or dosing intervals should be adjusted.

[c] Serum creatinine levels may be deceptively low in elderly, malnourished, or debilitated patients because of reduced muscle mass, which can artificially increase the calculated creatinine clearance.

[d] For conventional (not high-flux) hemodialysis. Dosing does not apply for continuous renal replacement therapy.

[e] Serum levels are similar with oral and intravenous therapy. Use oral route when possible.

Adult Dosing for Continuous Renal Replacement Therapy (CRRT)

Table 10. Adult Dosing for Continuous Renal Replacement Therapy (CRRT)

Medication[a]	CRRT empiric dosing[b,c,d]
anidulafungin	Unlikely to be affected by CRRT due to high protein binding and fairly large Vd Use usual dose[e]
caspofungin	Unlikely to be affected by CRRT due to high protein binding Use usual dose but adjust for hepatic dysfunction if pertinent[e]
cefazolin	1-2 g q12h[e]
cefepime	Consider 2 g q12h for life-threatening infections or intermediately susceptible organisms 1 g q12h should be adequate for susceptible organisms
ceftazidime	1-2 g q12h
ceftriaxone	Use usual dose 1-2 g q24h for non-CNS infections or 2 g q12h for CNS infections
ciprofloxacin	400 mg q12-24h
dalfopristin/quinupristin	Use usual dose; adjust for hepatic dysfunction if pertinent 7.5 mg/kg q8-12h
daptomycin	Unlikely to be affected by CRRT Use usual dose for renal failure (4-6 mg/kg q48h) with close monitoring[e]
fluconazole	Use about double the daily dose with CRRT compared with usual dose in patients with normal renal function for the specific infection type

Medication[a]	CRRT empiric dosing[b,c,d]
ganciclovir	Maintenance: 2.5 mg/kg q24h Induction: 2.5 mg/kg q12h (also consider 5 mg/kg q24h)[e]
gentamicin	Use conventional dosing (1-2.5 mg/kg), depending on type of infection, with initial dosing interval of about q24h Monitor serum levels and adjust dose accordingly No data for pulse dosing
itraconazole	Use usual IV dose Not affected significantly by CRRT, which appears to remove vehicle
levofloxacin	500-mg load, then 250 mg q24h Consider 500 mg q24h for severe or nosocomial infections when targeting levels similar to 750 mg q24h in healthy patients[e]
linezolid	Use usual dose of 600 mg q12h Studied with lower flow rates of 1.5-3 L/h; consider increase to 800 mg q12h or 600 mg q8h with higher flow rates or more resistant organisms
meropenem	1 g q8-12h
metronidazole	500 mg q6-8h[e] Adjust dose for hepatic dysfunction if pertinent
micafungin	Unlikely to be affected by CRRT due to high protein binding Use usual dose[e]
moxifloxacin	Use usual dose of 400 mg q24h[e]
penicillin	Consider about 6 million units per day (comparable to 20 million units when renal function is normal)[e]
piperacillin/tazobactam	2.25-3.375 g q6h[e] or 4.5 g q8h[e]

Medication[a]	CRRT empiric dosing[b,c,d]
posaconazole	Unlikely to be affected due to large Vd, high protein binding, and low serum levels[e] Use usual dose
tigecycline	Unlikely to be affected[e] Use usual doses of 100-mg load, then 50 mg q12h, with close monitoring
trimethoprim-sulfamethoxazole (tmp/smx)	Consider 5 mg/kg tmp q12h (comparable to about 15 mg/kg q24h tmp when renal function is normal)[e] Monitor serum levels and adjust dose accordingly
vancomycin	15-20 mg/kg q24-48h is reasonable empiric therapy Monitor serum levels and adjust dose accordingly
voriconazole	Use usual dose but adjust for hepatic dysfunction if pertinent[e] CRRT appears to remove vehicle

[a] For drugs not included, even in the absence of good studies, equations can be used to make predictions about how they might be affected by CRRT.

[b] CRRT flow rates affect the clearance of drugs removed by this modality. If lower flow rates are used, doses of drugs that are removed may need to be decreased. For considerably higher flow rates, doses may need to be increased.

[c] Dosing recommendations apply to total CRRT flow rates of 3-4 L/h. Other forms of continuous replacement therapy (eg, SLED) or use of higher or lower flow rates may have different dosing needs.

[d] Assuming minimal residual renal function, normal liver function, and total flow rates of 3-4 L/h.

[e] Support in the medical literature is unavailable or limited; check levels when possible to confirm dose.

Vancomycin Adult Dosing and Monitoring

(Several vancomycin-dosing or monitoring protocols exist; this is the one used at Mayo Clinic.)

Usual Dose

- **Loading dose:** 20-25 mg/kg; consider 25 mg/kg load for serious infections (eg, meningitis) and for health care–associated pneumonia, endocarditis, and critically ill or hemodialysis (HD) patients.
- **Maintenance dose:** 15-20 mg/kg based on actual body weight for most patients (an adjusted weight may be reasonable for very obese patients). See also HD and continuous renal replacement therapy (CRRT) sections below.

Dosing Interval

Dosing frequency depends on renal function (Table 11). If a measured creatinine clearance (Cl_{Cr}) is not available, the estimated Cl_{Cr} can be calculated with the equation below. The measured or estimated Cl_{Cr} is used to select the appropriate dosing interval.

Cl_{Cr} estimation:

Males: $$\frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

Females: $$0.85 \times \frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

Table 11. Dosing Interval Based on Creatinine Clearance Estimation

Cl_{Cr}, mL/min	Vancomycin dosing interval[a]
≥65	q12h (in younger patients with good renal function, q8h may be needed)
35-64	q24h (for severe infections, consider q12h initial dose for Cl_{Cr}>50[a] and adjust based on levels)
21-34	About q48h (for severe infections, consider q24h initial dose[a] and adjust based on levels)
≤20	Redose based on serum levels
HD	Give 25 mg/kg and monitor serum levels for when to redose (see section on "Patients Receiving Intermittent Hemodialysis")

[a] For severe infections, including meningitis, a shorter dosing interval or a larger dose may be considered when initiating therapy. Serum levels can be measured to determine necessary dosage modifications, as the drug will likely accumulate over time.

Infusion Rate

Infusion-related side effects may occur with rapid administration. The infusion rate can be further extended if poorly tolerated (Table 12).

Table 12. Vancomycin Infusion Rate

Dose	Minimum infusion time[a]
≤1 g	60 min
1.1-1.5 g	90 min
1.6-2 g	120 min
>2 g	About 1 g/h

[a] It may be appropriate in some instances (eg, outpatient therapy) to infuse more rapidly if tolerated.

Monitoring

Renal Function

- Serum creatinine (SCr) should be measured and Cl_{Cr} should be measured or calculated at the start of therapy (baseline).
- In stable hospitalized patients, SCr should be monitored a minimum of every 3-5 days.
- In patients with critical illness, changing renal function, or concomitant nephrotoxic agents, SCr monitoring should occur more often (ie, every 1-3 days).

Serum Levels

- Serum levels do **not** need to be checked if initial dosing is chosen using the nomogram above, if renal function is stable, and if the expected duration of therapy is <5 days.
- Trough levels correlate better with efficacy than peak levels. Trough level–only monitoring can be done in most patients.
- Peak levels do not correlate well with efficacy so do not need to be checked in most patients. Checking peak levels may be reasonable in special patient populations.
- For patients with severe renal dysfunction, drawing 2 levels after the same dose at least 1 half-life apart allows for calculation of Ke, half-life, and time needed for level to drop to desired value. This information is useful when determining the appropriate time to redose without requiring daily random levels. A pharmacist can assist with these calculations.

Trough Level–Only Monitoring

(See also the following sections on peak and trough monitoring, first-dose levels, HD, and CRRT.)

- **Timing:** Draw trough level at steady state (after 4-5 half-lives) immediately before dose.
  - Half-life can be estimated with the following equation:

    $Ke = 0.0044 + (0.00083 \times Cl_{Cr})$; half-life = 0.693/Ke; steady state occurs after 4-5 half-lives
- **Goal trough levels**
  - 7-15 mcg/mL for most patients
  - Consider 10-15 mcg/mL for endocarditis and osteomyelitis
  - Consider 15-20 mcg/mL for nosocomial pneumonia or meningitis

- **Level frequency:** Draw trough level at steady state and at least once per week thereafter. More frequent monitoring is needed for serious infections, with concurrent nephrotoxic agents, or with changing renal function.

Peak and Trough Monitoring or First-Dose Levels in Special Patient Populations

Vancomycin displays time-dependent (peak-independent) antimicrobial activity. Thus peak levels do not correlate well with efficacy. Toxicity also is typically not seen until peak levels are >80 mcg/mL. Since peak levels are unlikely to be in the toxic range if trough levels are appropriate, trough level monitoring can be used in most patients. In some patients, initial peak and trough levels may be appropriate to ensure penetration or to allow for pharmacokinetic analysis and individualization of the dosing regimen. Then most patients can often be followed with trough-only monitoring.

Special Patient Populations for Whom Peak and Trough Monitoring May Be Reasonable

- Patients with serious infections (eg, meningitis or hospital- or ventilator-acquired pneumonia) for which higher doses and trough targets are used
- Obese patients in whom doses >4 g/24h are used
- Very cachectic patients in whom it may be difficult to estimate renal function
- Patients who are critically ill or expected to have a large volume of distribution
- Patients with slow or unresponsive gram-positive infections
- Patients with considerable renal dysfunction, rapidly changing renal function, or renal function that is difficult to estimate
- Patients whose levels were previously uninterpretable or considerably out of the desired range

Peak and Trough Monitoring in Special Populations

- **Timing:** Levels should generally be performed at steady state (after 4-5 half-lives). If the dosing interval chart (Table 11) is used and renal function is relatively stable, steady state typically occurs on the 3rd to 4th dose. A pharmacist can assist with a determination of time to steady state.
  - Half-life can be estimated with the following equation:

    $Ke = 0.0044 + (0.00083 \times Cl_{Cr})$; half-life = 0.693/Ke; steady state occurs after 4-5 half-lives
- **Peak levels:** If used, they should be drawn at least 1 hour after infusion, and up to 2-3 hours after infusion in patients with renal dysfunction, to ensure that complete distribution has taken place.
- **Trough levels:** Draw immediately before the dose.

Usual Goal Levels

- **Trough levels**
  - 7-15 mcg/mL for most patients
  - Consider 10-15 mcg/mL for endocarditis and

osteomyelitis and for organisms with higher minimum inhibitory concentrations (MICs)
    - Consider 15-20 mcg/mL for serious infections (eg, meningitis or hospital- or ventilator-associated pneumonia) where penetration is limited
- **Peak levels:** Usually 25-50 mcg/mL (higher peaks may be acceptable for more serious infections)
- **Level frequency:** After dosing is optimized using initial peak and trough levels, most patients should be followed with trough-only monitoring every 5-7 days or when renal function changes

First-Dose Levels

In select patients, 2-3 levels after the first dose may be reasonable to allow for rapid dose individualization based on pharmacokinetic parameters. Levels drawn after the first dose can be used to determine pharmacokinetic parameters, estimated steady-state levels, and dosing needs. This approach allows for rapid dose adjustment rather than waiting for steady state.

First-dose levels may be reasonable in patients with meningitis or other serious infections; in patients with unpredictable renal function, critical illness, or morbid obesity; or in patients on HD or CRRT. Levels should be scheduled over about 1.5 half-lives. A pharmacist can assist with appropriate scheduling and interpretation of levels.

Patients Receiving Intermittent Hemodialysis

- **Loading dose:** Because of the higher than usual volume of distribution (Vd) in end-stage renal failure patients, a load of 25 mg/kg should be used initially (to target a peak level of about 28 mcg/mL, assuming a Vd of about 0.9 L/kg). Doses and intervals can be modified on the basis of serum levels.
- **Removal by HD:** The newer high-flux HD filters used at many treatment centers remove 25-40% of vancomycin (removal by filters at other hospitals may differ). Thus dosing intervals should be more frequent than the previous interval of every 5-7 days that is used with conventional, lower-efficiency HD filters. For institutions **not** using high-flux HD filters, vancomycin removal by HD is insignificant.
- **Empiric options:** One empiric option for patients getting high-flux HD every 2-3 days is a 25-mg/kg load followed by 7-10 mg/kg after each dialysis. Another empiric option is 25 mg/kg after every 2-3 HD sessions. (A couple of small studies support a load of 1 g followed by 500 mg at the end of high-flux HD.) Levels should be done to confirm attainment of appropriate target levels.
- **Serum levels:** Consider an initial serum level 6 hours after the first dose, a predialysis level, and a 6-hour post-HD level to individualize dosing, determine kinetic variables, and determine percentage of drug removed by HD. Occasional predialysis random levels can be used to monitor ongoing therapy; redosing can typically occur when the level is (or is anticipated to be) 8-15 mcg/mL, depending on type of infection. A pharmacist can provide assistance.

Patients Receiving CRRT

- **Loading dose:** An initial dose of 25 mg/kg of actual body weight can be used.
- **Empiric options:** Requirements in patients on CRRT will vary by flow rates. Empiric dosing of about 15-25 mg/kg q24-48h is reasonable initially, and serum levels can be used to make adjustments.
- **Serum levels:** Draw levels after first dose, if feasible, to allow for individualization of dosing interval. Check initial level 2 hours after dose and check random level about 24 hours after dose. Consult with pharmacist for assistance in calculating doses based on pharmacokinetic analysis (eg, half-life, Vd).

Aminoglycoside Adult Dosing and Monitoring

Empiric Conventional Aminoglycoside Dosing and Monitoring Guidelines in Adults

Several protocols exist, but this is the one used at Mayo Clinic. (See also guidelines that follow for pulse [extended-interval or once-daily] dosing.)

Creatinine clearance (Cl_{Cr}) calculation:

Males: $$\frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

Females: $$0.85 \times \frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

For obese patients (>20% of ideal body weight [IBW]), use dosing weight (DW) rather than actual body weight for calculating mg/kg dosing per table below.

Dosing weight = IBW + 0.4 (actual body weight – IBW):

IBW calculation:

Males: 50 kg + 2.3 kg/inch >60 inches

Females: 45.5 kg + 2.3 kg/inch >60 inches*

Table 13. Conventional Maintenance Dosing[a,b,c]

Indication	Desired gentamicin and tobramycin concentration, mcg/mL	Dose for gentamicin and tobramycin, mg/kg (see Table 14 for frequency)	Desired amikacin concentration, mcg/mL	Dose for amikacin, mg/kg (see Table 14 for frequency)
Cystic fibrosis	Peak: 10-12 mcg/mL or higher Trough: 0.6-1.2 mcg/mL	2-3 mg/kg	Peak: 25-35 mcg/mL Trough: 2.5-8 mcg/mL	7-8 mg/kg
Pneumonia, septic shock, life-threatening infection	Peak: 7-10 mcg/mL Trough: 0.6-1.2 mcg/mL	1.7-2.5 mg/kg (may need higher dose for patients with high estimated Vd)	Peak: 25-35 mcg/mL Trough: 2.5-8 mcg/mL	7-8 mg/kg
Bacteremia, skin soft-tissue pyelonephritis	Peak: 6-8 mcg/mL Trough: 0.6-1.2 mcg/mL	1.5-1.7 mg/kg	Peak: 20-30 mcg/mL Trough: 2.5-4 mcg/mL	6 mg/kg
UTI	Peak: 4-5 mcg/mL Trough: 0.6-1.2 mcg/mL	1-1.3 mg/kg	Peak: 15-20 mcg/mL Trough: 2.5-4 mcg/mL	5-6 mg/kg
Gram-positive syn	Peak: 3-4 mcg/mL Trough: 0.6-1.2 mcg/mL	1 mg/kg (gentamicin only)	NA	NA

[a] Loading dose can be given regardless of renal function to achieve therapeutic levels quickly. Loading doses for gentamicin-tobramycin are typically 2-3 mg/kg for gram-negative infections.

[b] The appropriate dose and resulting serum concentrations depend on the seriousness and the site of infection.

[c] Fluid status may also affect the required dosing regimen to achieve goal serum levels. Patients with considerably higher than normal fluid status have higher volumes of distribution (Vd) and may require higher doses to achieve desired serum concentrations. Subsequent doses may need adjustment with diuresis.

Table 14. Empiric Dosing Interval Selection: Based on Estimated Creatinine Clearance

Cl_{Cr}	Dosing interval
>80 mL/min	q8h
50-80 mL/min	q12h
30-49 mL/min	q12-24h
15-29 mL/min	q24-36h
<15 mL/min	Base on serum level

Serum Level and Toxicity Monitoring for Conventional Aminoglycoside Therapy

Renal Function and Ototoxicity Monitoring

- Check serum creatinine (SCr) (or Cl_{Cr} or both) at baseline.
- Check SCr (or measured Cl_{Cr}) at least every 4 days in hospitalized patients and more often in patients with changing renal function or critical illness or who are receiving another nephrotoxic medication.
- Monitor signs and symptoms consistent with ototoxicity (eg, tinnitus, feeling of ear-fullness, hearing loss). Instruct patients to alert their physician if these symptoms occur. Consider audiology or vestibular testing at baseline and periodically for longer-term use.

Aminoglycoside Levels

- If therapy is expected to continue for >72 hours, measure peak and trough levels at steady state, which occurs after 4-5 half-lives (usually 3rd or 4th dose), and adjust doses accordingly.
- Estimate the half-life with the following equation:

  $Ke = 0.01 + (0.0024 \times Cl_{Cr})$; half-life = 0.693/Ke; steady state occurs after 4-5 half-lives
- Draw peak levels 30 minutes after infusion; draw trough levels immediately before dose.
- In severely ill patients or patients expected to have unusual pharmacokinetics, first-dose or non–steady-state levels can help determine pharmacokinetic parameters and dosage requirements more quickly. A pharmacist can assist with scheduling levels and interpretation.
- In patients receiving intermittent hemodialysis (HD), 3 levels can be drawn after the first dose as follows: A 2-hour postdose level, a predialysis level, and a level 2 hours after completion of dialysis. A pharmacist can assist with interpretation of levels, pharmacokinetic analysis, and dosage calculations.
- Monitor fluid status, because fluid shifts can affect dosing requirements and serum levels.

Pulse Dosing Aminoglycoside Therapy Guidelines

Rationale for Pulse Dosing of Aminoglycosides

- Aminoglycosides display concentration- or peak-dependent killing. Goal peak levels are about 10 times the minimum inhibitory concentration (MIC) of the organism.
- Aminoglycosides have postantibiotic and sub-MIC effects that allow for continued activity even after the concentration has fallen below the MIC.
- Pulse dosing may minimize development of adaptive resistance.
- Nephrotoxicity may be decreased or delayed.
- Pulse dosing may reduce costs associated with drug administration and monitoring.

Patients (or Conditions) That May NOT Be Good Candidates for Pulse Dosing (Limited Data)

- **Enterococcal endocarditis:** Evidence suggests that traditional (multiple daily dose) dosing is more effective than pulse dosing for treatment of enterococcal endocarditis. However, data support pulse dosing of aminoglycosides in combination with a β-lactam for treatment of penicillin-susceptible viridans group streptococci.
- **Immunosuppression or neutropenia:** Some studies have shown efficacy in this patient group, but data are limited. The duration of the postantibiotic effect may be shorter in neutropenic patients. If pulse dosing is used, the aminoglycoside should be combined with a broad-spectrum β-lactam or other agent active against suspected or known pathogens.
- **Pediatric patients:** Several studies have shown efficacy with pulse dosing, but pediatric patients may need more frequent dosing because of altered pharmacokinetics. With pulse dosing, it may be advisable to administer aminoglycosides with another active agent and to monitor serum levels to determine whether the dose or interval needs to be modified (q12h dosing may be required).
- **Cystic fibrosis (CF):** These patients generally have an increased volume of distribution and more rapid clearance than other patients. Higher daily doses or q12h dosing may be necessary.
- **Pregnancy or postpartum:** Pharmacokinetic alterations exist in pregnant or postpartum patients. Until more studies are available, caution should be used with pulse dosing in this patient group.
- **Renal insufficiency:** Because of insufficient data about the optimal dosing method and the possibility of increased nephrotoxicity due to prolonged drug exposure in patients with renal dysfunction, we suggest using traditional dosing in patients with an estimated Cl_{Cr} <40 mL/min.
- **Neuromuscular diseases:** Consideration should be given to other antimicrobial choices in patients with neuromuscular diseases (eg, myasthenia gravis) or in patients taking a neuromuscular blocker. These patients may be at higher risk for neuromuscular blockade when

given large doses of aminoglycosides.

- **Other:** Caution should be exercised in patients with serious liver disease or ascites, and in patients with burns covering >20% of their body surface area. The volume of distribution can be altered in these subpopulations as well as in critically ill patients.

Patient Selection for Pulse Dosing of Aminoglycosides

- Most studies have been performed in patients with low failure rates (eg, those with urinary tract infections, abdominal infections, or pelvic infections). These patient groups may be good candidates for pulse dosing.
- It may be advisable, especially in critically ill patients, to use pulse dosing of aminoglycosides **in combination with** a β-lactam or other agent with gram-negative coverage. This will ensure adequate serum concentrations of an appropriate antibiotic in the event that the postantibiotic or sub-MIC effects of the aminoglycoside are exceeded.

Dosing

Pulse (Extended-Interval) Aminoglycoside Therapy

Cl_{Cr} calculation:

Males: $$\frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

Females: $$0.85 \times \frac{(140 - \text{age [y]}) \times (\text{weight [kg]})}{\text{SCr [mg/dL]} \times 72}$$

For obese patients (>20% IBW), use DW rather than actual body weight for calculating mg/kg dosing per Table 15.

Dosing weight = IBW + 0.4 (actual body weight – IBW):

IBW calculation:

Males: 50 kg + 2.3 kg/inch >60 inches

Females: 45.5 kg + 2.3 kg/inch >60 inches

Table 15. Pulse Dosing: Empiric Dosage Selection for Gram-Negative Organisms

Estimated Cl_{Cr}	Dose for gentamicin or tobramycin,[a,b] mg/kg	Dose for amikacin,[a,b,c] mg/kg	Dosing interval, h	Level (mcg/mL) 6-14 h
≥60 mL/min	5-7 mg/kg	15-20 mg/kg	q24h	See nomogram[c]
40-59 mL/min	5-7 mg/kg	15-20 mg/kg	q36h	See nomogram
<40 mL/min	Conventional dosing[d]	NA	Conventional dosing[d]	NA

[a] For obese patients, use DW for dosage determination: DW = IBW + 0.4 (actual body weight – IBW).

[b] Consider higher dose of 7 mg/kg for gentamicin and tobramycin and 20 mg/kg for amikacin in patients with normal renal function who are septic or critically ill, volume overloaded or with ascites, or who have hospital-acquired or ventilator-associated pneumonia, or who are suspected to be infected with more resistant organisms (eg, *Pseudomonas aeruginosa*).

[c] For amikacin use in mycobacterial infections, peak levels of 35-45 for a 15 mg/kg dose and 65-80 for a 25 mg/kg dose are recommended by National Jewish Medical and Research Center.

[d] At Mayo Clinic, we do not recommend pulse dosing in patients with a Cl_{Cr} <40 mL/min due to the potential for a long duration of relatively high serum levels that may lead to toxicity.

Administration

To minimize the possibility of neuromuscular blockade, give pulse doses of aminoglycoside over 60 minutes.

Renal Function and Ototoxicity Monitoring

- Check SCr (or measured Cl_{Cr}) at baseline.
- Check SCr (or measured Cl_{Cr}) at least twice weekly in hospitalized patients or more often in patients with changing renal function or who are receiving another nephrotoxic medication.
- Monitor for signs and symptoms consistent with ototoxicity (eg, tinnitus, feeling of ear-fullness, hearing loss). Instruct patients to alert their physician when these symptoms occur. Consider audiology or vestibular testing at baseline and periodically for longer-term use.

Aminoglycoside Levels

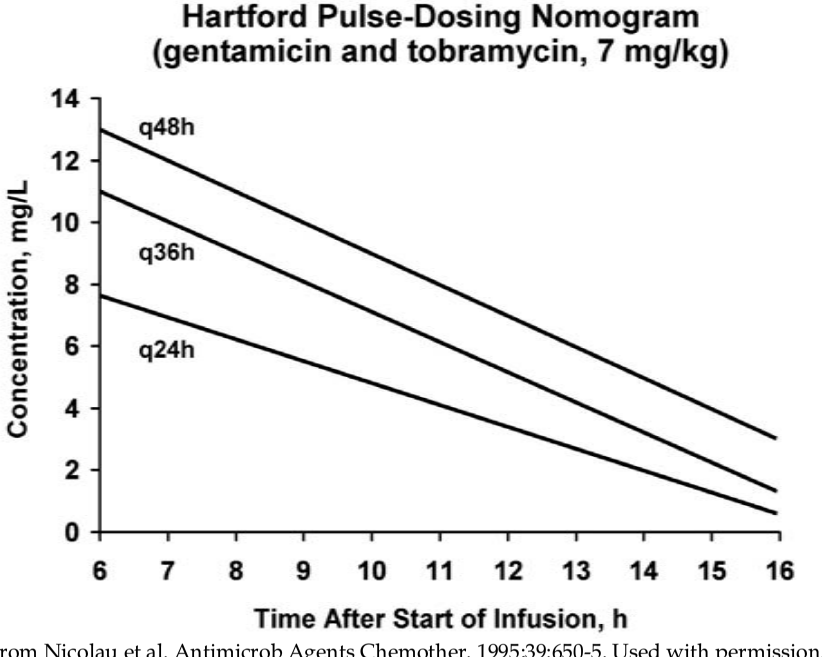
- **Stable patients not expected to have abnormal pharmacokinetics:** If anticipated duration of therapy is <4 doses, consider no levels unless patient is severely ill or receiving concomitant nephrotoxins.
- **Hartford or Urban and Craig nomogram:** For most other patients (see "individualized dosing" below for critically ill or volume-overloaded patients), draw a level 6-14 hours after the start of the first infusion and apply the nomogram (see below).
- Other clinicians have suggested just a periodic trough level to ensure that the drug is not accumulating (goal would be an undetectable trough) in stable patients.
- **Individualized dosing:** In critically ill, septic, or volume-overloaded patients, it may be desirable to individualize dosing at least once. It may be prudent to measure levels at 2 hours and then at 8-12 hours after the end of the first dose. These levels can be used to calculate individual patient pharmacokinetic parameters (eg, extrapolated peak, trough, half-life) and to optimize the dose. Anticipated extrapolated peaks for gentamicin and tobramycin are typically 20-24 mcg/mL, and peaks for amikacin are about 40-70 mcg/mL. Extrapolated troughs should be undetectable. A pharmacist can assist with pharmacokinetic and dosing calculations.

Interpretation of 6- to 14-Hour Level (After Start of Infusion) According to Hartford Nomogram or Urban and Craig Nomogram

If the serum interval level is within the area marked as q24h or q36h, the dosing interval should be every 24 hours and every 36 hours, respectively. At Mayo Clinic, we suggest discontinuing pulse dosing and changing to conventional dosing if the level is above the q36h dosing interval area.

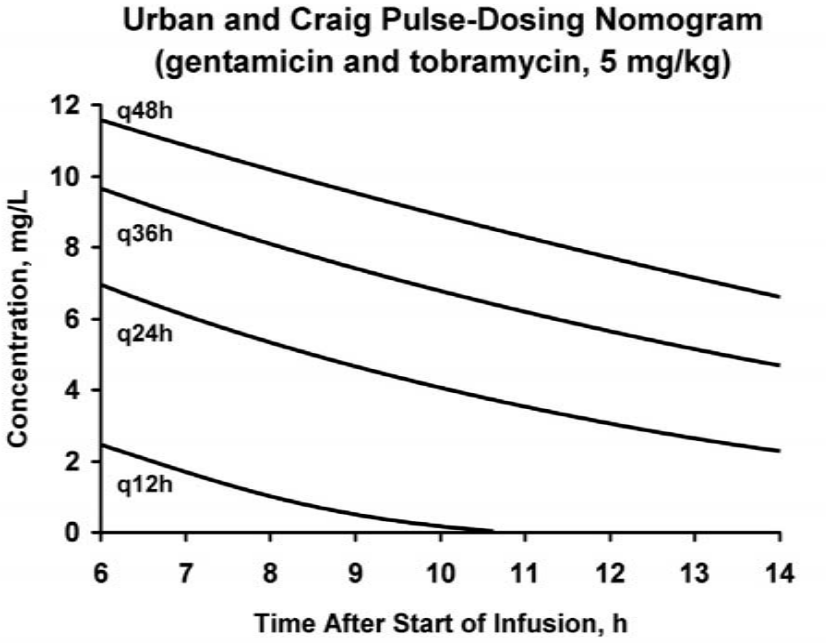
With amikacin, there is not much literature to support the use of the Hartford nomogram. Consider multiplying the serum concentration scale for gentamicin and tobramycin by a factor of 3 or use individualized dosing.

Figure 1.



From Nicolau et al. Antimicrob Agents Chemother. 1995;39:650-5. Used with permission.

Figure 2.



From Urban et al. Curr Clin Top Infect Dis. 1997;17:236-55. Used with permission.

Pediatric Antimicrobial Dosing

Definitions of Age Categories

- Neonate=full-term newborn 0-4 weeks postnatal age
- Infant=1 month to 1 year of age
- Child=1-12 years of age
- Adolescent=13-18 years of age
- Adult=>18 years of age

Table 16. Creatinine Clearance-Estimating Method[a] in Pediatric Patients With Stable Renal Function

Age	*K*
Low birth weight (≤1 y)	0.33
Full term (≤1 y)	0.45
2-12 y	0.55
13- to 21-year-old female	0.55
13- to 21-year-old male	0.70

[a] Cl_{Cr}=*K* x L/SCr; Cl_{Cr}=creatinine clearance in mL/min/1.73 m^2; *K*=age-specific constant of proportionality; L=length in cm; SCr=serum creatinine concentration in mg/dL.

Pediatric Antimicrobial Dosing Guidelines

The following tables do **not** apply to the dosing of antimicrobials in neonates. When calculating a pediatric antimicrobial dose, keep the patient's clinical condition in mind and be sure to compare the results with those of the usual adult dose so as not to exceed usual adult-dosing guidelines.

For antiparasitic or antimalarial agents, see Red book,* or consult a pediatric infectious diseases specialist.

* Red book: Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2003. p. 744-70 (Table 4.13 and 4.14).

Table 17. Pediatric Antibacterial Dosing Guidelines[a]

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
amikacin	15-22.5 mg/kg/24h divided q8h Monitor serum levels (see recommendations in Table 21 and Table 22)	See aminoglycoside-dosing protocol (Table 21 and Table 22)		
amoxicillin	Infants ≤3 mo: 20-30 mg/kg/24h divided q12h	2-3 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 10 mg/kg/dose q12h	10 mg/kg/dose q24h
	Infants >3 mo and children: 25-50 mg/kg/24h divided q8-12h		Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 12.5-20 mg/kg/dose q12h	20 mg/kg/dose q24h
	Acute otitis media, sinusitis, pneumonia: 80-90 mg/kg/24h divided q12h		Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 20 mg/kg/dose q12h	20 mg/kg/dose q24h
	Bone or joint infection: 100 mg/kg/24h divided q6h		Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} ≤30: 20 mg/kg/dose q12h; do **not** use 875-mg tab	20 mg/kg/dose q24h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
amoxicillin/clavulanate	4:1 formulation: 40 mg/kg/24h amoxicillin divided q8h 7:1 formulation: 25-45 mg/kg/24h amoxicillin divided q12h 7:1 formulation: Otitis media, sinusitis, pneumonia: 80-90 mg/kg/24h amoxicillin divided q8-12h	500 mg q8h 875 mg q12h 2,000 mg q12h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 10 mg/kg/dose amoxicillin q12h Cl_{Cr} <30: Do **not** use 875-mg tab or XR tab Cl_{Cr} 10-30: 20 mg/kg/dose amoxicillin q12h	10 mg/kg/dose amoxicillin q24h 20 mg/kg/dose amoxicillin q24h
ampicillin	IV: 100-200 mg/kg/24h divided q6h IV: Meningitis: 200-400 mg/kg/24h divided q6h Oral: 50-100 mg/kg/24h divided q6h	12 g/24h 2-3 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 50 mg/kg/dose q8-12h 12.5-25 mg/kg/dose q6-12h	50 mg/kg/dose q12h 25 mg/kg/dose q12h
ampicillin/sulbactam	Dose based on ampicillin content: Infants: 100-150 mg/kg/24h divided q6h Meningitis (infants): 200-300 mg/kg/24h divided q6h Children: 100-200 mg/kg/24h divided q6h Meningitis (children): 200-400 mg/kg/24h divided q6h	ampicillin 8 g/24h	Cl_{Cr} 30-49: Use usual daily dose Cl_{Cr} 10-29: 50 mg/kg/dose ampicillin q12h	50 mg/kg/dose ampicillin q24h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
azithromycin	Otitis or pneumonia: 10 mg/kg on day 1, then 5 mg/kg on days 2-5; or for otitis 30 mg/kg as single dose or 10 mg/kg q24h for 3 days Group A streptococcal pharyngitis: 12 mg/kg q24h for 5 days	Day 1: 500 mg Days 2-5: 250 mg 500 mg	Unchanged	No information
aztreonam	90-120 mg/kg/24h divided q6-8h CF: 200 mg/kg/24h divided q6h	8 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 15-20 mg/kg/dose q8h CF: Cl_{Cr} 10-30: 25 mg/kg/dose q6h	7.5-10 mg/kg/dose q8h CF: 12.5 mg/kg/dose q6h
cefadroxil	30 mg/kg/24h divided q12-24h Osteomyelitis: 50 mg/kg/24h divided q12h	2 g/24h 4 g/24h	Cl_{Cr} 26-49: Use usual daily dose Cl_{Cr} 10-25: 15 mg/kg/dose q24h Cl_{Cr} 26-49: Use usual daily dose Cl_{Cr} 10-25: 25 mg/kg/dose q24h	15 mg/kg/dose q36h 25 mg/kg/dose q36h
cefazolin	50-100 mg/kg/24h divided q8h	Children: 6 g/24h Adults: 12 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 25 mg/kg/dose q12h	25 mg/kg/dose q24h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
cefdinir	14 mg/kg/24h divided q12h	600 mg/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} ≤30: 7 mg/kg/dose q24h	7 mg/kg/dose q24h
cefditoren	9-18 mg/kg/24h divided q8h	800 mg/24h	Cl_{Cr} 30-49: 3-6 mg/kg/dose q12h Cl_{Cr} <30: 3-6 mg/kg/dose q24h	Data NA
cefepime	100 mg/kg/24h divided q12h Meningitis or life-threatening infection: 150 mg/kg/24h divided q8h	2-6 g/24h	Cl_{Cr} 30-49: 50 mg/kg/dose q24h Cl_{Cr} 11-29: 50 mg/kg/dose q24h	50 mg/kg/dose q48h
cefixime	8 mg/kg/24h divided q12-24h Cl_{Cr} 50-60: 6 mg/kg/dose q24h Acute UTI: 16 mg/kg/24h divided q12h on day 1, then 8 mg/kg q24h	400 mg/24h	Cl_{Cr} 21-49: 6 mg/kg/dose q24h Cl_{Cr} ≤20: 4 mg/kg/dose q24h	4 mg/kg/dose q24h
cefotaxime	100-200 mg/kg/24h divided q6-8h Meningitis: 200-300 mg/kg/24h divided q6h	12 g/24h	Cl_{Cr} 20-49: Use usual daily dose Cl_{Cr} <20: 50 mg/kg/dose q12h or 70 mg/kg/dose q12h for meningitis	50 mg/kg/dose q24h or 70 mg/kg/dose q24h for meningitis

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
cefotetan	40-80 mg/kg/24h divided q12h	6 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 20-40 mg/kg/dose q24h	20-40 mg/kg/dose q48h
cefoxitin	80-160 mg/kg/24h divided q6-8h	12 g/24h	Cl_{Cr} 30-49: 20-53 mg/kg/dose q8-12h Cl_{Cr} 10-29: 20-53 mg/kg/dose q12h	20-53 mg/kg/dose q24h
cefpodoxime	10 mg/kg/24h divided q12h	800 mg/24h	Cl_{Cr} 30-49: Use usual daily dose Cl_{Cr} <30: 5 mg/kg/dose q24h	5 mg/kg/dose q24h
cefprozil	Pharyngitis: 15 mg/kg/24h divided q12h Otitis media: 30 mg/kg/24h divided q12h SSTI: 20 mg/kg q24h	1,000 mg/24h	Cl_{Cr} 30-49: Use usual daily dose Cl_{Cr} <30: 3.75-7.5 mg/kg/dose q12h	3.75-7.5 mg/kg/dose q12h
ceftazidime	100-150 mg/kg/24h divided q8h Meningitis: 150 mg/kg/24h divided q8h	6 g/24h	Cl_{Cr} 30-49: 33-50 mg/kg/dose q12h Cl_{Cr} 10-29: 33-50 mg/kg/dose q24h	33-50 mg/kg/dose q48h
ceftibuten	9 mg/kg/24h divided q24h	400 mg/24h	Cl_{Cr} 30-49: 4.5 mg/kg/dose q24h Cl_{Cr} 10-29: 2.25 mg/kg/dose q24h	2.25 mg/kg/dose q24h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
ceftizoxime	150-200 mg/kg/24h divided q6-8h Cl_{Cr} 50-80: 50 mg/kg/dose q8-12h	12 g/24h	Cl_{Cr} 10-29: 50 mg/kg/dose q12h Cl_{Cr} 30-49: 50 mg/kg/dose q8h	50 mg/kg/dose q24h
ceftriaxone	50-75 mg/kg/24h divided q12-24h Meningitis: 100 mg/kg/24h divided q12-24h	4 g/24h	Unchanged for ≤2 g/24h	Unchanged for ≤2 g/24h
cefuroxime	IV: 75-150 mg/kg/24h divided q8h Oral: Pharyngitis: 20 mg/kg/24h divided q12h Otitis media, sinusitis, impetigo: 30 mg/kg/24h divided q12h	6 g/24h 1,000 mg/24h	Cl_{Cr} 30-49: Use usual daily dose Cl_{Cr} 10-29: 25-50 mg/kg/dose q12h Cl_{Cr} 30-49: Use usual daily dose Cl_{Cr} 10-29: 10-15 mg/kg/dose q12h	25-50 mg/kg/dose q24h 15 mg/kg/dose q24h
cephalexin	25-50 mg/kg/24h divided q6-8h Bone or joint infection: 100-150 mg/kg/24h divided q6h	4 g/24h	Cl_{Cr} 41-49: Use usual daily dose Cl_{Cr} 10-40: 6.25-12.5 mg/kg/dose q8-12h Cl_{Cr} 41-49: Use usual daily dose Cl_{Cr} 10-40: 25-37.5 mg/kg/dose q8-12h	6.25-12.5 mg/kg/dose q24h 25-37.5 mg/kg/dose q24h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
cephradine	25-50 mg/kg/24h divided q6-12h Otitis media: 75-100 mg/kg/24h divided q6-12h	4 g/24h	3-6.25 mg/kg/dose q6h 9-12.5 mg/kg/dose q6h	12.5-50 mg/kg/dose q36h 12.5-50 mg/kg/dose q36h
chloramphenicol	50-75 mg/kg/24h divided q6h Meningitis: 75-100 mg/kg/dose divided q6h	4 g/24h	Base dose reduction on serum levels	Base dose reduction on serum levels
ciprofloxacin	IV: 20-30 mg/kg/24h divided q12h Oral: 20-40 mg/kg/24h divided q12h CF: IV: 30 mg/kg/24h divided q8-12h CF: Oral: 40 mg/kg/24h divided q12h	IV: 800 mg/24h Oral: 1,500 mg/24h CF: IV: 1,200 mg/24h CF: Oral: 2,000 mg/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 10-15 mg/kg/dose IV or oral q18-24h CF: IV: 15 mg/kg/dose q18-24h CF: Oral: 20 mg/kg/dose q18-24h	10-15 mg/kg/dose IV or oral q24h 15 mg/kg/dose q24h 20 mg/kg/dose q24h
clarithromycin	15 mg/kg/24h divided q12h	1 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 3.75 mg/kg/dose q12h	3.75 mg/kg/dose q12h
clindamycin	IV: 25-40 mg/kg/24h divided q6-8h Oral: 10-30 mg/kg/24h divided q6-8h Oral (bone or joint infection): 40 mg/kg/24h divided q6h	4.8 g/24h 1.8 g/24h	Unchanged	Reduce dose with severe renal impairment

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
colistimethate (colistin)	Dosage expressed in terms of colistin and based on estimated IBW: IV: 2.5-5 mg/kg/24h divided q6-12h			
	CF: IV: 5-8 mg/kg/24h divided q8h (max 160 mg) CF: Inh: 75 mg nebulized q12h	480 mg/24h	SCr 1.3-1.5: 1.25-1.9 mg/kg/dose q12h SCr 1.6-2.5: 1.25 mg/kg/dose q12h SCr 2.6-4: 1.5 mg/kg/dose q36h Unchanged	SCr 1.3-1.5: 1.25-1.9 mg/kg/dose q12h SCr 1.6-2.5: 1.25 mg/kg/dose q12h SCr 2.6-4: 1.5 mg/kg/dose q36h Unchanged
dalfopristin/quinupristin	VRE infection: 22.5 mg/kg/24h divided q8h CSSI: 15 mg/kg/24h divided q12h		Unchanged	Unchanged
dapsone	Leprosy: 1-2 mg/kg q24h PCP prophylaxis: 2 mg/kg q24h or 4 mg/kg/dose 1 x/wk	100 mg/24h 200 mg/dose	Unchanged	Necessary, but insufficient information available to make recommendation
daptomycin	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			
dicloxacillin	25-50 mg/kg/24h divided q6h Bone or joint infection: 100 mg/kg/24h divided q6h	2 g/24h	Unchanged	Unchanged
doxycycline	IV or oral (children >7 y): 2-4 mg/kg/24h divided q12-24h	200 mg/24h	Unchanged	1 mg/kg/dose q12h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
ertapenem	30 mg/kg/24h divided q12h	1 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} ≤30: 7.5 mg/kg/dose q12h	7.5 mg/kg/dose q12h
erythromycin lactobionate IV	15-50 mg/kg/24h divided q6h	4 g/24h	Unchanged	10-17 mg/kg/dose q8h
erythromycin base	Oral: 30-50 mg/kg/24h divided q6-8h	2 g/24h	Unchanged	10-17 mg/kg/dose q8h
erythromycin/ sulfisoxazole	Children ≥2 mo: 40-50 mg/kg/24h erythromycin divided q6-8h	2 g/24h erythromycin	10 mg/kg/dose erythromycin q8-12h	10 mg/kg/dose erythromycin q12-24h
gemifloxacin	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			
gentamicin	5-7.5 mg/kg/24h divided q8h CF: 7.5-10 mg/kg/24h divided q8h Single daily dosing may be considered in some children; monitor serum levels (see Table 21 and Table 22)	See aminoglycoside-dosing protocol (Table 21 and Table 22)		

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
imipenem-cilastatin	Infants >4 wk and <3 mo: 100 mg/kg/24h divided q6h Infants ≥3 mo: 60-100 mg/kg/24h divided q6h Cl_{Cr} 50-70: 7.5-12.5 mg/kg/dose q6h	4 g/24h	Cl_{Cr} 30-49: 7.5-12.5 mg/kg/dose q8h Cl_{Cr} 10-29: 7.5-12.5 mg/kg/dose q12h	7.5-12.5 mg/kg/dose q24h Cl_{Cr} <5: Do **not** give unless patient is on HD
levofloxacin	IV or oral: 10-15 mg/kg q24h	500 mg/24h	Cl_{Cr} 20-49: Give initial full dose, then 5-7.5 mg/kg/dose (max 250 mg) q24h Cl_{Cr} 10-19: Give initial full dose, then 5-7.5 mg/kg/dose (max 250 mg) q48h	
linezolid	30 mg/kg/24h divided q8h	1,200 mg/24h	No adjustment necessary	Consider dosage adjustment
lomefloxacin	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			
loracarbef	Otitis media: 30 mg/kg/24h divided q12h Pharyngitis: 15 mg/kg/24h divided q12h	800 mg/24h	3.75-7.5 mg/kg/dose q12h	7.5-15 mg/kg/dose every 3-5 days
meropenem	60 mg/kg/24h divided q8h Meningitis: 120 mg/kg/24h divided q8h	6 g/24h	Cl_{Cr} 26-49: 20-40 mg/kg/dose q12h Cl_{Cr} 10-25: 10-20 mg/kg/dose q12h	10-20 mg/kg/dose q24h
metronidazole oral or IV	Anaerobic infections: 30 mg/kg/24h divided q6h	4 g/24h	Unchanged	4 mg/kg/dose q6h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
moxifloxacin	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			
nafcillin	Mild to moderate infection: 50-100 mg/kg/24h divided q6h Severe infection: 100-200 mg/kg/24h divided q6h	12 g/24h	Unchanged	12.5 mg/kg/dose q6h 25 mg/kg/dose q6h
nitrofurantoin	Infants >1 mo and children: 5-7 mg/kg/24h divided q6h Cl_{Cr} <50: Avoid UTI prophylaxis: 1-2 mg/kg q24h	400 mg/24h	100 mg/24h	Avoid
ofloxacin	15 mg/kg/24h divided q12h; consult a pediatric infectious diseases specialist	800 mg/24h	Cl_{Cr} 20-49: 7.5 mg/kg/dose q24h Cl_{Cr} <20: 3.75 mg/kg/dose q24h	3.75 mg/kg/dose q24h
oxacillin	IV: Mild to moderate infection: 100-150 mg/kg/24h divided q6h Severe infection: 150-200 mg/kg/24h divided q6h	12 g/24h	Unchanged	25 mg/kg/dose q6h 37.5 mg/kg/dose q6h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
penicillin G	IV: 100,000-250,000 units/kg/24h divided q4-6h Severe infection: 250,000-400,000 units/kg/24h divided q4-6h	24 million units per day	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 17,000-62,500 units/kg/dose q8-12h Cl_{Cr} 10-30: 42,000-100,000 units/kg/dose q8-12h	17,000-62,500 units/kg/dose q12-18h 42,000-100,000 units/kg/dose q12-18h
penicillin V	Oral: 25-50 mg/kg/24h divided q6-8h Oral (for bone or joint infection): 125 mg/kg/24h divided q6h	3 g/24h	Unchanged	10 mg/kg/dose q8h 31 mg/kg/dose q8h
piperacillin	200-300 mg/kg/24h divided q6h CF: 350-500 mg/kg/24h divided q4h	24 g/24h	Cl_{Cr} 41-49: Use usual daily dose Cl_{Cr} 20-40: 50-75 mg/kg/dose q8h CF: Cl_{Cr} 41-49: Use usual daily dose CF: Cl_{Cr} 20-40: 60-125 mg/kg/dose q8h	Cl_{Cr} <20: 50-75 mg/kg/dose q12h CF: Cl_{Cr} <20: 60-125 mg/kg/dose q12h

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
piperacillin/tazobactam	Infants <6 mo: 150-300 mg/kg/24h piperacillin divided q6-8h Children ≥6 mo: 240-300 mg/kg/24h piperacillin divided q8h CF: 300-400 mg/kg/24h piperacillin divided q6h	18 g/24h piperacillin	Cl_{Cr} 41-49: Use usual daily dose Cl_{Cr} 20-40: 25-50 mg/kg/dose q6h Cl_{Cr} <20: 25-50 mg/kg/dose q8h CF: Cl_{Cr} 20-40: 50-70 mg/kg/dose q6h CF: Cl_{Cr} <20: 50-70 mg/kg/dose q8h	25-50 mg/kg/dose q8h 50-70 mg/kg/dose q8h
rifampin	*H influenzae* prophylaxis: Infants <1 mo: 10 mg/kg q24h for 4 days Infants and children ≥1 mo: 20 mg/kg q24h for 4 days Meningococcal prophylaxis: Infants <1 mo: 10 mg/kg/24h divided q12h for 2 days Infants and children ≥1 mo: 20 mg/kg/24h divided q12h for 2 days Staphylococcal endocarditis (with standard treatments): 10-20 mg/kg q24h	600 mg/24h	Unchanged	2.5-10 mg/kg/dose q12-24h (give 50% of usual daily dose)
telithromycin	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
tetracycline	Oral: >8 y: 25-50 mg/kg/24h divided q6h Cl_{Cr} 50-80: 6-12 mg/kg/dose q8-12h	3 g/24h	Cl_{Cr} 10-49: 6-12 mg/kg/dose q12-24h	6-12 mg/kg/dose q24h or avoid
ticarcillin	Oral: 200-300 mg/kg/24h divided q4-6h Oral: CF: 400 mg/kg/24h divided q4-6h	24 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 50-75 mg/kg/dose q8h CF: Cl_{Cr} 31-49: Use usual daily dose CF: Cl_{Cr} 10-30: 100 mg/kg/dose q8h	50-75 mg/kg/dose q12h CF: 100 mg/kg/dose q12h
ticarcillin/clavulanate	200-300 mg/kg/24h ticarcillin divided q6h	18-24 g/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: 50-75 mg/kg/dose q8h	50-75 mg/kg/dose q12h
tobramycin	5-7.5 mg/kg/24h divided q8h CF: 7.5-10 mg/kg/24h divided q8h; single daily dosing may be considered in some children; monitor serum levels (see Table 21 and Table 22) Nebulization: ≥6 y: 300 mg nebulized q12h	See aminoglycoside-dosing protocol (Table 21 and Table 22)		

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
trimethoprim	Oral: Infants ≥2 mo and children: Acute otitis media: 10 mg/kg/24h divided q12h UTI: 4-6 mg/kg/24h divided q12h	200 mg/24h	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 15-30: 2.5 mg/kg/dose q12h Cl_{Cr} 15-30: 1-1.5 mg/kg/dose q12h Cl_{Cr} <15: Avoid	Avoid
trimethoprim/sufamethoxazole	Children >2 mo: 6-12 mg/kg/24h trimethoprim divided q12h PCP treatment: 15-20 mg/kg/24h trimethoprim divided q6-8h PCP prophylaxis: 5 mg/kg/24h (or 150 mg/m^2/24h trimethoprim) divided q12h for 3 consecutive days per week UTI prophylaxis: 2 mg/kg trimethoprim q24h or 5 mg/kg/dose trimethoprim 2 x/wk	20 mg/kg/24h trimethoprim (PCP dosing) 320 mg/24h trimethoprim	Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 15-30: Reduce total daily dose 50% and maintain interval as for usual dose; monitor sulfa levels Cl_{Cr} <15: Avoid	Avoid

Antimicrobial	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
vancomycin	IV: 40 mg/kg/24h divided q6h CNS infection: 60 mg/kg/24h divided q6h; monitor serum levels (see Table 23 and Table 24)	See vancomycin-dosing protocol (Table 23 and Table 24)		
	Oral: *C difficile*–associated diarrhea (metronidazole is drug of first choice): 40 mg/kg/24h divided q6h	2,000 mg/24h	Unchanged	Unchanged

Table 18. Pediatric Antifungal Dosing Guidelines

Antifungal	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
amphotericin B	0.25-1 mg/kg q24h; may increase short-term dose to 1.5 mg/kg q24h; consider test dose of 0.1 mg/kg/dose (max 1 mg) at start of therapy		May need to reduce dose due to nephrotoxicity	
amphotericin B lipid complex	2.5-5 mg/kg q24h		May need to reduce dose due to nephrotoxicity	
amphotericin B liposomal	3-5 mg/kg q24h; higher doses may be used for CNS or severe or life-threatening infection		May need to reduce dose due to nephrotoxicity	
anidulafungin	2-11 y: 0.75 mg/kg q24h 12-17 y: 1.5 mg/kg q24h Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			
caspofungin	2-11 y: 70 mg/m^2 on day 1, then 50 mg/m^2 q24h >11 y: 70 mg on day 1, then 50 mg q24h	Day 1: 70 mg max, then 50 mg/24h max	Unchanged	Unchanged
clotrimazole	10 mg tab 5x/24h (dissolve slowly in mouth)			

Antifungal	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
fluconazole	IV or oral: 6-12 mg/kg/dose load, then 3-6 mg/kg q24h	800 mg/24h	Cl_{Cr} 21-49: 3-6 mg/kg/dose load, then 1.5-3 mg/kg/dose q24h Cl_{Cr} ≤20: 1.5-3 mg/kg/dose load, then 0.75-1.5 mg/kg/dose q24h	1.5-3 mg/kg load, then 0.75-1.5 mg/kg/dose q24h
flucytosine	100-150 mg/kg/24h divided q6h; monitor serum levels		Cl_{Cr} 41-49: Use usual daily dose Cl_{Cr} 20-40: 25-37.5 mg/kg/dose q12h Cl_{Cr} 10-19: 25-37.5 mg/kg/dose q24h Monitor serum levels	12.5-37.5 mg/kg/dose q24-48h; monitor serum levels
griseofulvin	Microsize: 10-20 mg/kg/24h divided q12-24h Ultramicrosize: 5-10 mg/kg/24h divided q12-24h	Microsize: 1,000 mg/24h Ultramicrosize: 750 mg/24h		
itraconazole	3-10 mg/kg q24h or divided bid Starting dose: 5 mg/kg q24h Monitor serum levels	600 mg/24h; monitor serum levels	Unchanged Cl_{Cr} <30: Do **not** use injectable dose form	Unchanged; do **not** use injectable dose form

Antifungal	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
micafungin	Infants <120 days: 10 mg/kg q24h under investigation Infants ≥120 days and children <8 y: Esophageal candidiasis: 3 mg/kg q24h Prophylaxis of *Candida* infections: 1-2 mg/kg q24h with 50-mg max dose Invasive aspergillosis: 3-4 mg/kg q24h under investigation Limited information about dosing in children; consult pediatric infectious diseases specialist	150 mg/24h	Unchanged	Unchanged
nystatin	Infants: 200,000 units qid Children: 200,000-600,000 units qid		Unchanged	Unchanged

Antifungal	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
posaconazole oral	Patients ≥13 y: Disseminated candidiasis or severely immunocompromised: Prophylaxis: 200 mg tid (with full meal) Infection due to *Aspergillus* sp or severely immunocompromised: Prophylaxis: 200 mg tid (with full meal)	No information available	Patients ≥13 y: Disseminated candidiasis or severely immunocompromised: Prophylaxis: 200 mg tid (with full meal) Infection due to *Aspergillus* sp or severely immunocompromised: Prophylaxis: 200 mg tid (with full meal)	

Antifungal	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
voriconazole IV	Children 2-11 y: Load: 12 mg/kg/24h divided q12h for day 1 Maintenance: 8 mg/kg/24h divided q12h Children ≥12 y with inadequate response: Increase dose to 300 mg q12h Esophageal candidiasis: 200 mg q12h If on concurrent phenytoin therapy: <40 kg: Increase maintenance dose from 100 mg q12h to 200 mg q12h ≥40 kg: Increase maintenance dose from 200 mg q12h to 400 mg q12h		Cl_{Cr} <50: Change to oral voriconazole, as parenteral formulation contains an excipient that accumulates in renal impairment	

Table 19. Pediatric Antimycobacterial Dosing Guidelines

Antimycobacterial agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
ethambutol	15-25 mg/kg q24h or 50 mg/kg/dose 2 x/wk	2.5-g dose	15-25 mg/kg/dose q24-36h	15-25 mg/kg/dose q48h or 7.5-12.5 mg/kg/dose q24h
isoniazid	10-15 mg/kg/24h divided q12-24h or 20-30 mg/kg/dose 2 x/wk	300 mg/24h or 900-mg dose 2 x/wk	Unchanged	5-7.5 mg/kg/dose q24h in slow acetylators
pyrazinamide	20-40 mg/kg/24h divided q12-24h	2 g/24h	Cl_{Cr} <50: Avoid or reduce to 12-20 mg/kg/dose q24h	Avoid or reduce to 12-20 mg/kg/dose q24h
rifampin	10-20 mg/kg q24h	600 mg/24h	Unchanged	2.5-10 mg/kg/dose q12-24h (50% of usual daily dose)
streptomycin	Children with TB 20-40 mg/kg q24h 20-40 mg/kg q24h 2 x/wk Cl_{Cr} 50-80: 7.5 mg/kg/dose q24h Dose based on serum levels	 1 g/24h or 1.5 g 2 x/wk Dose based on serum levels	7.5 mg/kg/dose q24-72h Dose based on serum levels	7.5 mg/kg/dose q72-96h Dose based on serum levels

Antimycobacterial agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
Agents used for drug-resistant TB (capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin, para-aminosalicylic acid)	See Red book: Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2003. p. 642-60 (Table 3.71), or consult a pediatric infectious diseases specialist.			
Agents used for non-TB mycobacterial infections	See Red book: Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2003. p. 661-6 (Table 3.74), or consult a pediatric infectious diseases specialist.			

Table 20. Pediatric Antiviral Dosing Guidelines[a]

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
acyclovir IV	Base dosage for obese patients on IBW Oral, cutaneous, or genital HSV: 15 mg/kg/24h (or 750 mg/m^2/24h if ≥1 y) divided q8h		Cl_{Cr} 25-49: 5 mg/kg/dose (or 250 mg/m^2/dose) q12h Cl_{Cr} 10-24: 5 mg/kg/dose (or 250 mg/m^2/dose) q24h	2.5 mg/kg/dose (or 125 mg/m^2/dose) q24h
	Immunocompromised: Consult pediatric infectious diseases specialist; 15-30 mg/kg/24h (or 750-1,500 mg/m^2/24h if ≥1 y) divided q8h		Cl_{Cr} 25-49: 10 mg/kg/dose (or 500 mg/m^2/dose) q12h Cl_{Cr} 10-24: 10 mg/kg/dose (or 500 mg/m^2/dose) q24h	5 mg/kg/dose (or 250 mg/m^2/dose) q24h
	HSV prophylaxis in immunocompromised: 15 mg/kg/24h (or 750 mg/m^2/24h if ≥1 y) divided q8h		Cl_{Cr} 25-49: 5 mg/kg/dose (or 250 mg/m^2/dose) q12h Cl_{Cr} 10-24: 5 mg/kg/dose (or 250 mg/m^2/dose) q24h	2.5 mg/kg/dose (or 125 mg/m^2/dose) q24h

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
acyclovir IV (continued)	HSV encephalitis (nonneonatal): Consult pediatric infectious diseases specialist; 30 mg/kg/24h (or 1,500 mg/m^2/24h if ≥1 y) divided q8h (larger dose may be indicated in some cases)		Cl_{Cr} 25-49: 10 mg/kg/dose (or 500 mg/m^2/dose) q12h Cl_{Cr} 10-24: 10 mg/kg/dose (or 500 mg/m^2/dose) q24h	5 mg/kg/dose (or 250 mg/m^2/dose) q24h
	HSV encephalitis (neonatal): Consult pediatric infectious diseases specialist; 60 mg/kg/24h divided q8h		Cl_{Cr} 25-49: 20 mg/kg/dose q12h Cl_{Cr} 10-24: 20 mg/kg/dose q24h	10 mg/kg/dose q24h
	VZV: 30 mg/kg/24h (or 1,500 mg/m^2/24h if ≥1 y) divided q8h		Cl_{Cr} 25-49: 10 mg/kg/dose (or 500 mg/m^2/dose) q12h Cl_{Cr} 10-24: 10 mg/kg/dose (or 500 mg/m^2/dose) q24h	5 mg/kg/dose (or 250 mg/m^2/dose) q24h
adefovir	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist			

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
cidofovir	Accompany with concomitant oral probenecid and IV usual saline (0.9 normal saline) hydration Adenovirus: 1 mg/kg/dose 3 x/wk CMV Induction: 5 mg/kg/dose once Maintenance: 3 mg/kg/dose 1 x/wk		If SCr increases by 0.3-0.4 mg/dL above baseline, reduce cidofovir dose by 40%; discontinue therapy for SCr increases ≥0.5 mg/dL above baseline or development of ≥3+ proteinuria	Contraindicated for preexisting renal impairment of SCr >1.5, Cl_{Cr} ≤55, or urine protein ≥2+
famciclovir	Little or no information exists on dosing in children Adolescents: Genital herpes: 250 mg oral tid Episodic recurrent genital herpes: 125 mg oral bid Daily suppressive therapy: 125-250 mg oral bid for 1 year, then reassess for recurrence	1,500 mg/24h	See product labeling	See product labeling
foscarnet	Induction: 180 mg/kg/24h divided q8h Maintenance: 90-120 mg/kg q24h		See product labeling	Contraindicated

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
ganciclovir	Induction (IV): 10 mg/kg/24h divided q12h Cl_{Cr} 50-69: 2.5 mg/kg/dose q12h		Cl_{Cr} 25-49: 2.5 mg/kg/dose q24h Cl_{Cr} 10-24: 1.25 mg/kg/dose q24h	1.25 mg/kg/dose 3 x/wk after HD
	Maintenance or prophylaxis (IV): 5 mg/kg q24h Cl_{Cr} 50-69: 2.5 mg/kg/dose q24h		Cl_{Cr} 25-49: 1.25 mg/kg/dose q24h Cl_{Cr} 10-24: 0.625 mg/kg/dose q24h	0.625 mg/kg/dose 3 x/wk after HD
	Maintenance or prophylaxis (oral): 90 mg/kg/24h divided q8h Cl_{Cr} 50-69: 15 mg/kg/dose q8h	1,000 mg q8h	Cl_{Cr} 25-49: 15 mg/kg/dose q12h Cl_{Cr} 10-24: 7.5 mg/kg/dose q24h	7.5 mg/kg/dose 3 x/wk after HD

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
oseltamivir	Oral: Influenza type A and B: Children >1-12 y: ≤15 kg: 30 mg bid for 5 days 16-23 kg: 45 mg bid for 5 days 24-40 kg: 60 mg bid for 5 days >40 kg: 75 mg bid for 5 days For prophylaxis, give the corresponding treatment dose, but only once daily for 10 days For example, if patient is >1 y and ≤15 kg, give 30 mg q24h for 10 days		Cl_{Cr} 31-49: Use usual daily dose Cl_{Cr} 10-30: Give dose once daily instead of twice daily Prophylaxis: Give dose every other day instead of daily	No information available
ribavirin	See product labeling			
valacyclovir	Little or no information exists on dosing in children (adolescents only): Genital HSV: 1,000 mg q12h (7-10 days) Recurrent genital HSV: 500 mg q12h Suppression of genital HSV: 500-1,000 mg q24h	2 g/24h	Cl_{Cr} 30-49: 20 mg/kg/dose q12h Cl_{Cr} 10-29: 20 mg/kg/dose q24h	10 mg/kg/dose q24h

Antiviral agents	Usual daily dose	Max daily dose	Dose adjustment for renal impairment	
	Cl_{Cr} ≥50 mL/min	Cl_{Cr} ≥50 mL/min	Cl_{Cr} 10-49 mL/min	Cl_{Cr} <10 mL/min or anuric
valganciclovir	Little or no information exists on dosing in children; consult a pediatric infectious diseases specialist Adolescents or adults: CMV retinitis (induction): 900 mg bid for 21 days CMV maintenance: 900 mg q24h CMV infection (prophylaxis): 900 mg q24h	1,800 mg/24h	Induction Cl_{Cr} 40-49: 450 mg bid Cl_{Cr} 25-39: 450 mg q24h Cl_{Cr} 10-24: 450 mg q48h Maintenance Cl_{Cr} 40-49: 450 mg q24h Cl_{Cr} 25-39: 450 mg q48h Cl_{Cr} 10-24: 450 mg 2 x/wk	
zanamivir	Children ≥7 y: 10 mg (2 inh) bid (for 5 days)			

[a] For antiretroviral agents, see AIDSinfo* or consult a pediatric infectious diseases specialist.

* Guidelines for the use of antiretroviral agents in pediatric HIV infection. Rockville (MD): AIDSinfo; [cited: 2007 Jul 20]. Available from: http://www.aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf.

Conventional Empiric Pediatric Aminoglycoside Dosing

The following tables do not apply to the dosing of antimicrobials in neonates.

Table 21. Interval Determination[a]

Cl_{Cr}	Interval
≥60 mL/min	q8h
40-59 mL/min	q12h
20-39 mL/min	q24h

[a] Single daily dosing may be considered for some children.

Table 22. Maintenance Dosing for Aminoglycosides[a]

Disease state	gentamicin or tobramycin NF (mg/kg/dose)	Desired peak and trough (mcg/mL)[b]	amikacin (mg/kg/dose)	Desired peak and trough (mcg/mL)[b]
CF[c]	2.5-3 mg/kg/dose	Peak: 8-10 mcg/mL Trough: 1-1.5 mcg/mL	7.5 mg/kg/dose	Peak: 25-30 mcg/mL Trough: 5-10 mcg/mL
Life-threatening illness, fever, neutropenia	2.5 mg/kg/dose	Peak: 7-10 mcg/mL Trough: 1-1.5 mcg/mL	7.5 mg/kg/dose	Peak: 25-30 mcg/mL Trough: 5-10 mcg/mL
Bacteremia, soft-tissue infection, pyelonephritis	2-2.5 mg/kg/dose	Peak: 6-8 mcg/mL Trough: 0.5-1.5 mcg/mL	6-7.5 mg/kg/dose	Peak: 20-25 mcg/mL Trough: 5-8 mcg/mL
UTI	1.5-2 mg/kg/dose	Peak: 4-6 mcg/mL Trough: 0.5-1 mcg/mL	5 mg/kg/dose	Peak: 20 mcg/mL Trough: 5-8 mcg/mL
Synergy (endocarditis)	1.5 mg/kg/dose	Peak: 3-4 mcg/mL Trough: <1 mcg/mL		

[a] Individualization of dosing and dosing interval is critical due to narrow therapeutic index. Renal function should be assessed before initiation of therapy and periodically thereafter.

[b] Recommendations for measurement of aminoglycoside serum levels (peak and trough) include duration of therapy of at least 5 days, unstable or changing renal function, and administration of other nephrotoxic drugs.

[c] May require q6h dosing interval.

Conventional Empiric Pediatric Vancomycin Dosing

Information in the following tables does not apply to the dosing of antimicrobials in neonates.

Table 23. Maintenance Dosing for Vancomycin

Cl_{Cr}	Dose[a]
>90 mL/min	10 mg/kg/dose q6h[b] (40 mg/kg/24h; max dose 3 g/24h)
70-89 mL/min	10 mg/kg/dose q8h
46-69 mL/min	10 mg/kg/dose q12h
30-45 mL/min	10 mg/kg/dose q18h
15-29 mL/min	10 mg/kg/dose q24h
<15 mL/min	Dose intermittently by serum levels

[a] The same total daily dose may be administered using intervals of q8h or q12h for older children and adolescents with normal renal function.

[b] 60 mg/kg/24h divided q6h for central nervous system infections.

Recommendations for Measurement of Vancomycin Serum Levels

- Measure vancomycin serum levels (trough) in cases of
  1) Unstable or changing renal function
  2) Administration of other nephrotoxic drugs
  3) Positive blood cultures or other cultures
- Measure vancomycin serum levels (peak and trough) in cases of
  1) Meningitis infection (to document penetration)
  2) Osteomyelitis infection (to document penetration)

Table 24. Infusion Rates for Vancomycin

Dose	Rate
<1 g	Infuse over 60 min (some patients may require longer)
1-1.5 g	Infuse over 90 min (some patients may require longer)

Bacteria: Preferred and Alternate Treatment Options

Bacterial Organisms

Table 25. Specific Treatment of Bacterial Organisms

Organisms	First-line treatment[a]	Alternate treatment[a]
Acinetobacter sp	meropenem, imipenem (not ertapenem)	tigecycline, piperacillin/tazobactam, ampicillin/sulbactam, ceftazidime, cefepime, fluoroquinolone, aminoglycoside, colistin, minocycline, doxycycline, tmp/smx, sulbactam
Actinomyces sp	penicillin	ampicillin, amoxicillin, doxycycline, cephalosporin, clindamycin, erythromycin
Aeromonas sp	tmp/smx, fluoroquinolone	carbapenem,[b] aminoglycoside, 3rd-gen cephalosporin
Bacillus sp	vancomycin	clindamycin, carbapenem,[b] fluoroquinolone
B anthracis (anthrax)	ciprofloxacin, doxycycline	amoxicillin, penicillin, levofloxacin, imipenem
Bacteroides fragilis	metronidazole	carbapenem,[b] β-lactam/β-lactamase inhibitor,[c] clindamycin, moxifloxicin, cefotetan, cefoxitin, tigecycline
Bartonella sp		
B henselae	macrolide,[d] doxycycline	fluoroquinolone
B quintana	macrolide,[d] doxycycline	
Bordetella pertussis	macrolide[d]	tmp/smx
Borrelia burgdorferi (Lyme disease)	doxycycline, amoxicillin	penicillin, cefuroxime, cefotaxime, ceftriaxone, azithromycin, clarithromycin

Treatment

Organisms	First-line treatment[a]	Alternate treatment[a]
Brucella sp	doxycycline plus gentamicin or doxycycline plus streptomycin or doxycycline plus rifampin	tmp/smx, ciprofloxacin, chloramphenicol; each with or without either gentamicin or streptomycin or rifampin
Burkholderia cepacia	Often a colonizer not requiring treatment; tmp/smx	ceftazidime, cefepime, carbapenem,[b] fluoroquinolone, minocycline, tigecycline
Campylobacter jejuni	erythromycin, azithromycin	doxycycline, fluoroquinolone, gentamicin, furazolidone
Capnocytophaga sp	clindamycin, amoxicillin/clavulanate	erythromycin, fluoroquinolone, carbapenem,[b] doxycycline, β-lactam/β-lactamase inhibitor[c]
Chlamydophila pneumoniae	doxycycline, macrolide[d]	fluoroquinolone, a different tetracycline, tigecycline
Citrobacter freundii	carbapenem[b]	fluoroquinolone, aminoglycoside, tmp/smx, cefepime, piperacillin/tazobactam, tigecycline, aztreonam
Clostridium sp		
C difficile	metronidazole, vancomycin (oral)	
C perfringens	penicillin	metronidazole, clindamycin, β-lactam/β-lactamase inhibitor,[c] carbapenem[b]
C tetani	metronidazole plus tetanus immune globulin and tetanus toxoid	doxycycline, penicillin

Organisms	First-line treatment[a]	Alternate treatment[a]
Corynebacterium sp		
C diphtheriae	erythromycin plus antitoxin	clindamycin, penicillin
Group JK	vancomycin	Base treatment on susceptibility results; consider linezolid, daptomycin, dalfopristin/quinupristin
Coxiella burnetii (Q fever)	Acute: doxycycline Chronic (eg, endocarditis): doxycycline plus hydroxychloroquine; or doxycycline plus fluoroquinolone	Acute: fluoroquinolone, macrolide[d] Chronic: doxycycline plus fluoroquinolone; or doxycycline plus rifampin
Ehrlichia sp	doxycycline	
Eikenella corrodens	ampicillin, amoxicillin, 3rd-gen cephalosporin	doxycycline, β-lactam/β-lactamase inhibitor,[c] fluoroquinolone
Enterobacter sp	carbapenem[b]	fluoroquinolone, tmp/smx, cefepime, piperacillin/tazobactam, aminoglycoside, tigecycline, aztreonam
Enterococcus sp[f]		
ampicillin-sensitive	ampicillin, amoxicillin, penicillin	vancomycin, linezolid, β-lactam/β-lactamase inhibitor,[c] dalfopristin/quinupristin (active for *E faecium* only), daptomycin, tigecycline
ampicillin-resistant, vancomycin-sensitive	vancomycin	linezolid, daptomycin,[f] dalfopristin/quinupristin (*E faecium* only), tigecycline

Organisms	First-line treatment[a]	Alternate treatment[a]
VRE	linezolid[c]	daptomycin,[f] dalfopristin/quinupristin (*E faecium* only), tigecycline
Erysipelothrix rhusiopathiae	penicillin	cephalosporin, fluoroquinolone, clindamycin, carbapenem[b]
Escherichia coli	ceftriaxone, cefotaxime, cefepime ESBL-producing strains: carbapenem[b]	fluoroquinolone, aminoglycoside, another cephalosporin, β-lactam/β-lactamase inhibitor,[c] ampicillin, tmp/smx, tigecycline, aztreonam
Francisella tularensis (tularemia)	streptomycin, gentamicin CNS infections: doxycycline plus either gentamicin or streptomycin	doxycycline, fluoroquinolone, chloramphenicol
Fusobacterium sp	penicillin	metronidazole, clindamycin, β-lactam/β-lactamase inhibitor,[c] carbapenem[b]
Gardnerella vaginalis (bacterial vaginosis)	metronidazole	metronidazole (vaginal) or clindamycin (vaginal or oral)
Haemophilus influenzae	ceftriaxone, cefotaxime	fluoroquinolone, tmp/smx, azithromycin, clarithromycin, β-lactam/β-lactamase inhibitor,[c] doxycycline, 2nd-, 3rd-, or 4th-gen cephalosporin
Klebsiella pneumoniae	ceftriaxone, cefotaxime, cefepime ESBL-producing strains: carbapenem[b]	fluoroquinolone, aminoglycoside, tmp/smx, β-lactam/β-lactamase inhibitor,[c] carbapenem,[b] tigecycline

Organisms	First-line treatment[a]	Alternate treatment[a]
Legionella sp	Newer fluoroquinolone,[g] azithromycin with or without rifampin	Another macrolide,[d] doxycycline, tmp/smx, any of these 3 drugs with or without rifampin
Leuconostoc sp	ampicillin, amoxicillin, penicillin	clindamycin, doxycycline, macrolide[d]
Listeria monocytogenes	ampicillin or penicillin with or without gentamicin	tmp/smx
Moraxella catarrhalis	2nd- or 3rd-gen cephalosporin	fluoroquinolone, azithromycin, clarithromycin, tmp/smx, cefepime,[b] tetracycline, tigecycline, β-lactam/β-lactamase inhibitor[c]
Morganella morganii	cefepime, fluoroquinolone	carbapenem,[b] piperacillin/tazobactam, aminoglycoside, tmp/smx, aztreonam
Mycobacterium sp	See treatment sections for tuberculosis and nontuberculosis mycobacterial infections (pp. 225, 230)	
Mycoplasma pneumoniae	macrolide[d]	doxycycline, fluoroquinolone, tigecycline
Neisseria sp		
N gonorrhoeae	ceftriaxone, cefixime	cefotaxime, fluoroquinolone (variable resistance)
N meningitidis	penicillin, ceftriaxone, cefotaxime	ampicillin, fluoroquinolone, tmp/smx
Nocardia asteroides	tmp/smx	minocycline, imipenem with or without amikacin, another sulfonamide, ceftriaxone with or without amikacin, amoxicillin/clavulanate, linezolid

Treatment

Organisms	First-line treatment[a]	Alternate treatment[a]
Pasteurella multocida	penicillin, ampicillin, amoxicillin	doxycycline, 2nd- or 3rd-gen cephalosporin, tmp/smx, β-lactam/β-lactamase inhibitor,[c] carbapenem[b]
Peptostreptococcus sp	penicillin, ampicillin, amoxicillin	clindamycin, cephalosporin, newer fluoroquinolone,[g] carbapenem,[b] vancomycin, β-lactam/β-lactamase inhibitor[c]
Propionibacterium acnes (systemic infection)	(Common blood culture contaminant not requiring treatment) penicillin	clindamycin, doxycycline, carbapenem[b]
Proteus sp		
P mirabilis	ampicillin, amoxicillin	cephalosporin, fluoroquinolone, aminoglycoside, tmp/smx, β-lactam/β-lactamase inhibitor,[c] carbapenem[b]
P vulgaris	carbapenem[b]	fluoroquinolone, aminoglycoside, tmp/smx, β-lactam/β-lactamase inhibitor,[c] 3rd- or 4th-gen cephalosporin, aztreonam
Providencia sp	carbapenem[b]	fluoroquinolone, aminoglycoside, tmp/smx, β-lactam/β-lactamase inhibitor,[c] 3rd- or 4th-gen cephalosporin, aztreonam
Pseudomonas aeruginosa	cefepime, ceftazidime, meropenem or imipenem (not ertapenem); consider addition of aminoglycoside or ciprofloxacin for severe infection or until susceptibilities are known	ciprofloxacin, levofloxacin, piperacillin/tazobactam, colistin, aztreonam

Organisms	First-line treatment[a]	Alternate treatment[a]
Rickettsia sp	doxycycline	fluoroquinolone, chloramphenicol
Salmonella sp	Treatment not indicated for uncomplicated disease; fluoroquinolone, ceftriaxone	amoxicillin, ampicillin, chloramphenicol, tmp/smx, another 3rd- or 4th-gen cephalosporin, furazolidone
Serratia sp	carbapenem[b]	fluoroquinolone, aminoglycoside, cefepime, tmp/smx, piperacillin/tazobactam, aztreonam
Shigella sp	fluoroquinolone	tmp/smx, azithromycin, furazolidone, 3rd- or 4th-gen cephalosporin
Staphylococcus sp[h]		
penicillin-sensitive (rare)	penicillin	Any of the agents listed under first-line or alternate treatment is active below
oxacillin/ methicillin-sensitive	nafcillin, oxacillin, 1st-gen cephalosporin, dicloxacillin	clindamycin (if double-disk diffusion test is negative), tmp/smx, minocycline Broad-spectrum agents with activity against oxacillin-sensitive staphylococci include cefepime, ceftriaxone, β-lactam/β-lactamase inhibitor,[c] carbapenem,[b] newer fluoroquinolone[g]
oxacillin-resistant (MRSA, MRSE)	vancomycin, linezolid, daptomycin[f]	tigecycline; or, depending on susceptibility for mild to moderate infections or step-down therapy: tmp/smx, minocycline, newer fluoroquinolone,[g] dalfopristin/quinupristin

Organisms	Treatment	
	First-line treatment[a]	Alternate treatment[a]
vancomycin-intermediate or vancomycin-resistant (VISA, VRSA)	Notify infection control immediately; obtain infectious diseases consultation	
Stenotrophomonas maltophilia	tmp/smx (consider adding ticarcillin/clavulanate for severe infection)	ticarcillin/clavulanate, tigecycline, fluoroquinolone, minocycline
Streptococcus sp		
S pneumoniae		
penicillin-susceptible (MIC <0.1)	penicillin, ampicillin	cephalosporin, macrolide,[d] clindamycin, doxycycline, newer fluoroquinolone,[g] or any of the agents listed below under first-line or alternate treatment, tmp/smx
penicillin-intermediate (MIC 0.1 to ≤2)	ceftriaxone, cefotaxime, newer fluoroquinolone[g]; high-dose penicillin, ampicillin, or amoxicillin	cefepime, vancomycin, linezolid, tigecycline, carbapenem[b]; variable resistance may be seen with macrolides,[d] clindamycin, tmp/smx
penicillin high-level resistance (MIC >2)	Meningitis: vancomycin plus either ceftriaxone or cefotaxime with or without rifampin Other infections: Newer fluoroquinolone,[g] vancomycin with or without cefotaxime or ceftriaxone	linezolid, dalfopristin/quinupristin, tigecycline

Organisms	First-line treatment[a]	Alternate treatment[a]
Group A, B, C, or G	penicillin, cephalosporin	Another penicillin class drug, macrolide[d] or clindamycin (variable resistance), vancomycin, linezolid, daptomycin, tigecycline
Viridans group	penicillin, cephalosporin; for endocarditis and infections in immunocompromised patients, base treatment on susceptibility testing	vancomycin, newer fluoroquinolone,[g] β-lactam/β-lactamase inhibitor[c]
Treponema pallidum (syphilis)	penicillin	doxycycline, ceftriaxone
Ureaplasma sp	macrolide,[d] doxycycline	
Vibrio sp		
V cholerae	doxycycline	fluoroquinolone, tmp/smx
V vulnificus	doxycycline	ceftriaxone, cefotaxime, ciprofloxacin
Yersinia sp		
Y enterocolitica	fluoroquinolone, gentamicin, tmp/smx, doxycycline	chloramphenicol, ceftriaxone, cefotaxime
Y pestis (plague)	streptomycin	tmp/smx, gentamicin, doxycycline, chloramphenicol, ciprofloxacin

[a] Depending on susceptibility.

[b] Carbapenems: meropenem, imipenem, ertapenem; ertapenem has minimal activity against *Pseudomonas*, *Acinetobacter*, and *Enterococcus* spp.

[c] β-Lactam/β-lactamase inhibitors: piperacillin/tazobactam, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate.

[d] Macrolides include erythromycin, clarithromycin, and azithromycin.

[e] Add gentamicin or streptomycin when cidal activity is required (eg, for infective endocarditis) and agents are susceptible for synergy.

[f] Insufficient data exist for use of daptomycin for serious enterococcal infections; do **not** use for pneumonia (high failure rates, inactivated by surfactant).

[g] Newer (respiratory) fluoroquinolones include moxifloxacin, levofloxacin, and gemifloxacin.

[h] Consider addition of rifampin for deep-seated staphylococcal infections (eg, infective endocarditis) that do not respond well or are in the presence of prosthetic material. *S coagulase*-negative bacteria is a common contaminant that can also cause serious infection.

Modified from Choice of antibacterial drugs. Treat Guidel Med Lett. 2007;5:33-50. Erratum in: Treat Guidel Med Lett. 2007;5:58.

Bacterial Drug Resistance Issues

Table 26. Select Bacterial Resistance Issues

Pertinent organisms	Resistance issue	Treatment
EXTENDED-SPECTRUM β-LACTAMASE–PRODUCING (ESBL) GRAM-NEGATIVE BACILLI		
Escherichia coli, *Klebsiella* sp Less common: *Proteus mirabilis*, *Enterobacter* spp	Generally resistant to penicillins and cephalosporins[a]; may appear susceptible to piperacillin/tazobactam but with potentially higher failure rate than with a carbapenem	First-line: carbapenem (Note: Some regions have seen considerable carbapenem resistance by a different mechanism in *Klebsiella* sp) Alternates: fluoroquinolone or tigecycline, but there is less clinical experience with these
***ampC*-MEDIATED RESISTANCE IN GRAM-NEGATIVE BACILLI**		
Enterobacter and *Citrobacter* spp (also may be seen in *Morganella morganii*, *Providencia*, *Serratia*, and indole-positive *Proteus* spp)	2nd- and 3rd-gen cephalosporin should generally be avoided even if organism is reported to be susceptible, because of potential for induction or selection of *ampC*-mediated β-lactamase (derepressed β-lactamase production), which can lead to development of resistance during treatment	First-line: carbapenem Alternates (depending on susceptibility testing): fluoroquinolone, tmp/smx, tigecycline, piperacillin/tazobactam, aminoglycoside, cefepime (better activity than 3rd-gen cephalosporins[b]) If *ampC*-mediated resistance occurs, a carbapenem is typically the only active β-lactam
METHICILLIN-RESISTANT *Staphylococcus aureus* (MRSA)		

Pertinent organisms	Resistance issue	Treatment
Staphylococcus aureus	Oxacillin-resistant (methicillin-resistant) staphylococci are resistant to all currently available β-lactam antibiotics; both nosocomial and community-acquired strains are seen CA-MRSA isolates tend to be more susceptible to non–β-lactams (eg, tmp/smx, clindamycin, tetracycline, fluoroquinolone) than nosocomial isolates	First-line: vancomycin, linezolid, daptomycin[c] Alternates (depending on susceptibility testing): doxycycline, minocycline, tmp/smx, clindamycin (test for inducible resistance), dalfopristin/quinupristin, tigecycline, newer fluoroquinolone[d]
VANCOMYCIN INTERMEDIATE- OR VANCOMYCIN-RESISTANT STAPHYLOCOCCI (VISA OR VRSA)		
S aureus with vancomycin MIC ≥4	Organisms with reduced susceptibility or complete resistance to vancomycin have been reported	Contact infection control immediately and obtain infectious diseases consultation
VANCOMYCIN-RESISTANT ENTEROCOCCI (VRE)		
Enterococcus sp	Enterococci with resistance to vancomycin	First-line: linezolid Alternates: daptomycin,[c] dalfopristin/quinupristin (only for *E faecium*), tigecycline; may be susceptible to penicillin and ampicillin

[a] May show in vivo susceptibility to cephamycins (eg, cefotetan, cefoxitin), but failures have been reported and other mechanisms can confer resistance.

[b] Cefepime is less likely than 3rd-generation agents to induce resistance, but resistance has been reported. If inducible β-lactamase production occurs, organisms should be considered resistant to penicillins and cephalosporins.

[c] Daptomycin should not be used for pneumonia because it is inactivated by surfactant. It has in vitro activity against enterococci, but studies are limited for serious enterococcal infections.

[d] Newer fluoroquinolone (eg, moxifloxacin, levofloxacin, gemifloxacin). Staphylococcal resistance to fluoroquinolone has been reported to develop while patients are receiving therapy.

Fungi: Preferred and Alternate Treatment Options

Table 27. Fungal Organism–Specific Treatment

Organism	First-line treatment	Alternate treatment (depending on susceptibility)
Aspergillus sp	voriconazole	amphotericin product[a] (less active for *A flavus* and *A terreus*), itraconazole, echinocandin[b] (often used in combination therapy), posaconazole
Blastomyces sp	amphotericin product[a] (life-threatening or CNS disease) itraconazole (for mild-to-moderate disease)	voriconazole, fluconazole
Systemic candidal infection		
Candida unspeciated[c]	fluconazole (stable patient and no azole preexpsoure), echinocandin[b] (for life-threatening disease or unstable patient or with azole preexposure)	voriconazole, amphotericin product,[a] itraconazole
C albicans, *C parapsilosis*, or *C tropicalis*	fluconazole, echinocandin[b] (for life-threatening disease or unstable patient)	amphotericin product,[a] voriconazole, itraconazole
C glabrata	echinocandin,[b] voriconazole (if no azole preexposure or with documented susceptibility)	amphotericin product,[a,e] itraconazole,[d] higher-dose fluconazole[d] (if no preexposure or with documented susceptibility), posaconazole
C guilliermondii or *C lusitaniae*	voriconazole, fluconazole	echinocandin,[b] amphotericin product,[a,e] posaconazole
C krusei	echinocandin,[b] voriconazole	amphotericin product,[a,e] posaconazole

Treatment

Organism	First-line treatment	Alternate treatment (depending on susceptibility)
Candidal oropharyngeal or thrush	nystatin (topical), clotrimazole, fluconazole	voriconazole, amphotericin (oral liquid), itraconazole, echinocandin,[b] posaconazole
Candidal esophagitis[f]	fluconazole	voriconazole, amphotericin product,[a] itraconazole, echinocandin, posaconazole
Candidal urinary tract infection	fluconazole	amphotericin product[a]
Candidal vulvovaginal infection	azole (intravaginal), oral fluconazole	itraconazole, intravaginal boric acid (refractory cases)
Coccidioides sp	fluconazole, itraconazole, amphotericin product[a] (initial therapy for diffuse or disseminated disease)	voriconazole
Cryptococcus sp	fluconazole, amphotericin product[a] (often with flucytosine for induction therapy for CNS disease)	itraconazole, voriconazole
Fusarium sp	voriconazole, amphotericin product[a]	posaconazole
Histoplasma sp	itraconazole, amphotericin product[a]	voriconazole, fluconazole (after amphotericin induction for CNS disease)
Paracoccidioides	itraconazole	voriconazole, sulfonamide, amphotericin product[a] (with maintenance sulfonamide or azole), ketoconazole, terbinafine

Organism	First-line treatment	Alternate treatment (depending on susceptibility)
Pneumocystis jiroveci	tmp/smx; add corticosteroids for severe disease	pentamidine IV, tmp plus dapsone, atovaquone, clindamycin plus primaquine, trimetrexate
Scedosporium sp (*Pseudallescheria* sp)	voriconazole	posaconazole, itraconazole, terbinafine (in combination with azole)
Sporothrix sp	itraconazole, amphotericin product[a]	
Tinea pedis	terbinafine (topical), azole (topical)	oral fluconazole, griseofulvin, or itraconazole
Zygomycetes (eg, *Mucor* sp, *Rhizopus* sp)	amphotericin product[a,e]	posaconazole

[a] Includes amphotericin B deoxycholate, liposomal amphotericin, and amphotericin B lipid complex.

[b] Echinocandins include caspofungin, micafungin, and anidulafungin. Echinocandins may display higher minimum inhibitory concentrations (MICs) for *C guilliermondii* and *C parapsilosis*, but clinical implication is unclear.

[c] Speciation and susceptibility testing for serious infections is recommended.

[d] Both fluconazole and itraconazole MICs for *C glabrata* are often in the susceptible but dose-dependent category. If either drug is used, higher than usual doses are suggested. If susceptibility results show susceptible isolate (MIC ≤8 for fluconazole or ≤0.125 for itraconazole), use usual doses. When there is no susceptibility information in the setting of azole preexposure, echinocandin or amphotericin product is preferable due to the possibility of azole cross-resistance.

[e] May exhibit higher MICs with amphotericin; consider use of higher than usual doses. Some resistance seen.

[f] Do **not** use topical therapy (eg, nystatin, clotrimazole, or amphotericin oral suspension) for esophageal disease. Systemic therapy is needed.

Viruses: Preferred and Alternate Treatment Options

Table 28. Antiviral Organism–Specific Treatment (Non-HIV Infections)

Organism	First-line treatment	Alternate treatment
CMV	ganciclovir, valganciclovir	foscarnet, cidofovir, ganciclovir ocular implant,[a] fomivirsen[a] intravitreal injection
HSV	acyclovir,[b] famciclovir, valacyclovir	foscarnet (for acyclovir-resistant strains), trifluridine eye drops (for keratoconjunctivitis), ganciclovir,[c] valganciclovir[c]
HBV[d]	pegylated interferon, entecavir, lamivudine,[e] adefovir, telbivudine, tenofovir,[e] emtricitabine[e]	
HCV	pegylated interferon plus ribavirin	
Influenza virus (treatment or prophylaxis)	oseltamivir, zanamivir	
Varicella-zoster virus	acyclovir,[b] famciclovir, valacyclovir	foscarnet (for acyclovir-resistant strains)

[a] Ocular implants and intravitreal injections for cytomegalovirus retinitis should generally be used in combination with systemic therapy to prevent spread to the contralateral eye and other organs.

[b] Intravenous acyclovir should be used for herpes simplex virus CNS disease and for sight-threatening disease or severe varicella-zoster virus in immunocompromised patients.

[c] Active against acyclovir-susceptible strains of HSV, but not the preferred treatment due to its toxicity and cost.

[d] HBV vaccine should be administered as a preventive strategy to persons at risk (including health care workers).

[e] Lamivudine, emtricitabine, and tenofovir also have anti-HIV activity and thus are commonly used in HIV patients with HCV coinfection.

Clinical Approach to Patients With Infection

Four-Step Approach to Successful Management of Infectious Diseases

1) **Define the host:** Identify factors that influence the types of infection, disease progression, and prognosis, which include:
   a) Host factors such as patient age, immune status (eg, immunosuppression; presence or absence of a spleen), other comorbid conditions, and medical problems; and
   b) The environmental setting (community-acquired vs hospital-acquired or nursing home–acquired infection).
2) **Define the infection syndrome:** Determine the anatomical location of infection and the extent of inflammation (the "-itis," eg, meningitis, pyelonephritis, peritonitis, pneumonitis, endocarditis), the rate of progression, and the severity of infection (eg, localized vs multiorgan involvement or hemodynamic instability).
3) **Define the microbiology:** Determine the suspected pathogen(s) on the basis of the host and syndrome information above or identify the confirmed pathogen(s) from available laboratory testing (eg, cultures, stains, serologies, antigens).
4) **Determine the optimal antimicrobial therapy:** Base decisions about antimicrobial therapy on an integration of the information about host, syndrome, and suspected or confirmed microbiology. When appropriate, direct antimicrobial therapy in a targeted fashion against confirmed or suspected pathogens. Ensure that the selected antimicrobial therapy is dosed correctly and can adequately penetrate the anatomical site of infection.

Additional Considerations

- Identify infections that require urgent surgical and medical intervention (eg, fasciitis, myonecrosis, cholangitis due to biliary obstruction)
- Identify syndromes requiring urgent medical intervention (eg, neutropenia with gram-negative bacteremia, bacterial meningitis, empyema, severe sepsis, septic shock)
- Pay particular attention to the results of the Gram stain (rapidly available), to the culture results, and to the drug susceptibility information to further direct therapy
- Review each patient's drug allergies and organ function (eg, renal, hepatic) for optimal selection and dosing of antimicrobial therapy
- Obtain an infectious diseases consultation for all serious and complex infections

Respiratory Tract Infections

Clinical Syndromes and Common Pathogens

Acute Bronchitis

Diagnostic criteria include productive cough, symptoms of upper respiratory infection, and negative findings on chest radiographs. Viral agents are the most common cause; antibiotics are therefore not beneficial.

- **Viral causes:** Influenza, parainfluenza, and other respiratory viruses affect >70% of patients
- **Less common but potentially antibiotic-responsive infectious agents:** *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis*

Community-Acquired Pneumonia

Diagnostic criteria for community-acquired pneumonia (CAP) include acute or subacute onset of fever, cough, dyspnea, or pleuritic chest pain that develops in previously healthy persons.

- **Common bacteria:** *Streptococcus pneumoniae, M pneumoniae, C pneumoniae, Legionella pneumophila, Haemophilus influenzae*, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) (occasional)
- **Viral causes:** Influenza (seasonal), parainfluenza, varicella, respiratory syncytial virus (seasonal in infants and immunocompromised adults)
- **More chronic symptoms in specific epidemiologic conditions:** Tuberculosis, fungi (*Histoplasma* sp, *Coccidioides* sp), zoonoses (Q fever)

Aspiration Pneumonia

Diagnostic criteria include fever, cough, or pulmonary infiltrate in a lower lung field after a single or recurrent aspiration event. Acute aspiration may cause chemical lung injury, which does not require antibiotic therapy. Not all aspiration results in bacterial pneumonia.

- Mixed oral or upper intestinal bacterial flora; may include anaerobes

Hospital-Acquired or Health Care–Associated Pneumonia

Hospitalized patients or those in a nursing home or a skilled care facility for >2 days are at risk of hospital-acquired or health care–associated pneumonia; the diagnosis excludes patients in whom the organism was incubating at admission. This type of infection is most common in patients who are intubated for >2-3 days. Diagnostic criteria include fever, new pulmonary infiltrate, and respiratory distress. Clinical diagnosis is difficult in intubated patients.

- **Early onset:** Within 4 days after admission to a health care facility, with no risk factors for multidrug-resistant (MDR) organisms (see Table 29): *S pneumoniae, H influenzae, S aureus, Escherichia coli, Klebsiella pneumoniae, Proteus* sp, *Serratia marcescens*
- **Late onset:** Onset ≥5 days after admission to a health care facility or risk factors for MDR pathogens (Table 29): Organisms as delineated above, for early onset, plus *Pseudomonas aeruginosa, Enterobacter* sp, *K pneumoniae* (including ESBL), *Acinetobacter* sp, and MRSA

Data from Mandell et al. Clin Infect Dis. 2007;44 Suppl 2:S27-72.

Table 29. Risk Factors for MDR Pathogens Causing Hospital-Acquired Pneumonia, Health Care–Associated Pneumonia, and Ventilator-Associated Pneumonia

Antimicrobial therapy in preceding 90 days
Current hospitalization of ≥5 days
High frequency of antibiotic resistance in community or in specific hospital unit
Presence of risk factors for health care–associated pneumonia Hospitalization for ≥2 days in preceding 90 days Residence in nursing home or extended-care facility Home infusion therapy (including antibiotics) Chronic dialysis in preceding 30 days Home wound care Family member with MDR pathogen
Immunosuppressive disease or therapy

From American Thoracic Society et al. Am J Respir Crit Care Med. 2005;171:388-416. Used with permission.

Pneumonia in Immunocompromised Hosts

Diagnostic criteria include fever, cough, dyspnea, and pleuritic chest pain. Dyspnea may be more pronounced than indicated by findings on chest radiographs. Management often requires invasive procedures (bronchoscopy or open-lung biopsy) for diagnosis of opportunistic infections.

- Cell-Mediated (T-Cell) Immune Dysfunction (HIV, Organ Transplant, Chronic Corticosteroids)
  1) Usual CAP pathogens
  2) *Legionella* sp, *Nocardia* sp, *Pneumocystis jiroveci* (PCP; formerly *P carinii*), *Cryptococcus neoformans*, *Histoplasma capsulatum*, cytomegalovirus, *Toxoplasma gondii*
- Neutropenia
  1) Usual CAP pathogens
  2) *P aeruginosa*, *Aspergillus* sp (eg, *A fumigatus*), Zygomycetes

Novel Characteristics of Respiratory Pathogens

- ***S pneumoniae*:** Acute development of high fever, productive cough, shortness of breath; rapid progression; chest radiographs commonly show air-space consolidation; bacteremia and pleural space infections also common
- ***M pneumoniae*:** Sore throat, dry cough, headache; occasional pleural effusion; chest radiographs and examination findings often discordant with mild symptoms; extrapulmonary findings include erythema multiforme and Stevens-Johnson syndrome, hemolytic anemia, changes in cardiac conduction, myocarditis or pericarditis, aseptic meningitis or encephalitis, Guillain-Barré syndrome, Raynaud phenomenon, glomerulonephritis, bullous myringitis

- ***C pneumoniae*:** Sore throat and prolonged dry cough; biphasic symptoms; variable findings on chest radiographs; less common extrapulmonary findings include endocarditis, meningoradiculitis, encephalitis
- ***L pneumophila* and other species:** Typically high fever; nonproductive or minimally productive cough; variable presentation with sometimes severe symptoms; rapidly progressive and often fatal; findings on chest radiographs include segmental to lobar infiltrate; hyponatremia and diarrhea
- ***H influenzae***
  - Type B more common in children 4 months to 4 years of age (decreased incidence with *H influenzae* type B vaccine); also associated with pediatric meningitis, epiglottis, otitis, and cellulitis
  - Non–type B *H influenzae* pneumonia common in elderly patients and patients with chronic obstructive pulmonary disease; also associated with sinusitis and otitis
- **CA-MRSA:** Infrequent cause of pneumonia but can be rapidly progressive or necrotizing

Data from Mandell et al. Clin Infect Dis. 2007;44 Suppl 2:S27-72.

Table 30. Empiric Therapy[a]

Condition	Treatment options
Acute bronchitis	Supportive measures only; antibiotic therapy not indicated in most cases
Community-acquired pneumonia (CAP)	
Outpatient, no previous antibiotic therapy	azithromycin or clarithromycin (if high-level resistance in region is uncommon[b]), doxycycline, respiratory fluoroquinolone[c] (levofloxacin, moxifloxacin, gemifloxacin)
Outpatient, recent antibiotic therapy, presence of comorbid conditions[d] or other risk factors for drug-resistant *S pneumoniae*	After recent antibiotic therapy, use alternate antimicrobial class: Newer fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin) or a combination of either azithromycin or clarithromycin plus either high-dose amoxicillin or amoxicillin/clavulanate Alternate β-lactams include ceftriaxone, cefuroxime, and cefpodoxime
Hospitalized patient (non-ICU)	fluoroquinolone (levofloxacin or moxifloxacin) or a combination of a select β-lactam (ceftriaxone, cefotaxime, ertapenem, ampicillin) plus a select macrolide (azithromycin or clarithromycin)
ICU admission	Combination therapy with a select β-lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam) plus fluoroquinolone (levofloxacin or moxifloxacin); azithromycin may be substituted for fluoroquinolone If *P aeruginosa* is a concern, use either antipseudomonal β-lactam[e] plus ciprofloxacin or levofloxacin; or antipseudomonal β-lactam plus aminoglycoside and plus azithromycin
Possible CA-MRSA	Add vancomycin or linezolid to a CAP regimen; avoid daptomycin because it is inactive in the lungs

Condition	Treatment options
Aspiration pneumonia	
Outpatient management	amoxicillin/clavulanate or clindamycin
Hospitalized patient	A select β-lactam (ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate) or 3rd- or 4th-gen cephalosporin combined with metronidazole or clindamycin; or fluoroquinolone combined with metronidazole or clindamycin; or carbapenem
Hospital-acquired or health care–associated pneumonia[f]	
Early onset and no risk factors for MDR organism	ceftriaxone, cefotaxime, respiratory fluoroquinolone, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, or ertapenem
Late onset or risk factors for MDR organisms	A select β-lactam (cefepime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin, levofloxacin, or aminoglycoside; if MRSA is suspected, add vancomycin or linezolid

[a] Initiate therapy after cultures are obtained. For pathogen-directed therapy, see section III: Treatment of Specific Organisms.

[b] In regions with high-level (MIC≥16), macrolide-resistant *S pneumoniae* rates >25%, consider alternate treatments.

[c] Levofloxacin 750 mg for 5 days or 500 mg for 10 days. Fluoroquinolones should generally not be used as first-line treatment for outpatient therapy in previously healthy patients with no risk factors for drug-resistant *S pneumoniae* due to concern about possible overuse that can lead to increased resistance.

[d] Comorbid conditions include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the past 3 months (in which case, an alternate drug from a different class should be selected); and other risks for drug-resistant *S pneumoniae* infection.

[e] Antipseudomonal β-lactams include piperacillin/tazobactam, cefepime, ceftazidime, imipenem, and meropenem.

[f] De-escalate antimicrobials on the basis of culture results. For hospital-acquired or health care–associated pneumonia, shorten the traditional duration of therapy to 7-8 days when patients respond and the etiologic agent is not *Pseudomonas* (similar success rates, less super-resistance, fewer adverse effects)

Data from Mandell et al. Clin Infect Dis. 2007;44 Suppl 2:S27-72 and Am J Respir Crit Care Med. 2005;171:388-416.

Other Considerations

- With persistent fever despite apparently appropriate therapy, consider empyema
- With CAP, early transition to oral therapy is not associated with adverse outcomes; it decreases costs and adverse effects, and it may lead to shorter length of stay
- With CAP, administer antibiotics as soon as feasible for hospitalized patients; draw blood cultures (if any) before administration of antibiotics
- Vaccination for *S pneumoniae* and influenza virus decreases incidence and severity of CAP (now a core measure of the Centers for Medicare and Medicaid Services and the Joint Commission on Accreditation of Healthcare Organizations for hospitalized patients)

Infective Endocarditis: Diagnosis and Treatment

Common Infective Endocarditis Pathogens

Native Valves

- Viridans streptococci
- *Staphylococcus aureus*
- Enterococci
- HACEK organisms

Prosthetic Valves

- Same as native valves, plus
  - Coagulase-negative staphylococci
  - Fungi
  - Gram-negative rods (early postoperative period)

Elements of Diagnosis

The diagnosis of infective endocarditis (IE) rests on demonstrated evidence of cardiac involvement and persistent bacteremia due to microorganisms that typically cause endocarditis. Establishing a microbiologic diagnosis is critical to therapeutic decisions. Every effort should be made to identify the causative organism.

Table 31. Definition of Infective Endocarditis by the Modified Duke Criteria

Definite IE
- Pathologic criteria
  - Microorganisms: Demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
  - Pathologic lesions: Vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
- Clinical criteria
  - 2 major criteria; or
  - 1 major criterion and 3 minor criteria; or
  - 5 minor criteria

Possible IE
- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected
- Firm alternate diagnosis explaining evidence of IE; or
- Resolution of IE syndrome with antibiotic therapy for ≤4 days; or
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

Modified from Li et al. Clin Infect Dis 2000;30:633-8. Used with permission.

Table 32. Definition of Terms Used in the Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major criteria

- Blood culture positive for IE
  - Typical microorganisms consistent with IE from 2 separate blood cultures:
    - Viridans streptococci, *Streptococcus bovis*, HACEK group, *S aureus*; or
    - Community-acquired enterococci, in the absence of a primary focus; or
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
    - At least 2 positive cultures of blood samples drawn >12 hours apart; or
    - All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart)
  - Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800
- Evidence of endocardial involvement
- Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or
  - Abscess; or
  - New partial dehiscence of prosthetic valve;
- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

- Predisposition: Predisposing heart condition or injection drug use
- Fever: Temperature ≥38°C
- Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiological evidence: Positive blood culture but does not meet a major criterion as noted above[a] or serologic evidence of active infection with organism consistent with IE

[a] Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

Modified from Li et al. Clin Infect Dis 2000;30:633-8. Used with permission.

Table 33. Use of Echocardiography During Diagnosis and Treatment

Initial echocardiography
- Perform as soon as possible (<12 hours after initial evaluation)
- Use TEE primarily; obtain TTE views of any abnormal findings for later comparison
- Perform TTE if TEE is not immediately available
- Use TTE in small children, as it may be sufficient

Repeat echocardiography
- Perform TEE as soon as possible after positive TTE in patients at high risk of complications for potential impact on prognosis and management
- Repeat TEE 7-10 days after initial TEE if suspicion exists without diagnosis of IE or with worrisome clinical course during early treatment of IE

Modified from Baddour et al. Circulation. 2005;111:e394-434. Erratum in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 34. Echocardiographic Features That Suggest Potential Need for Surgical Intervention

Vegetation
- Persistent vegetation after systemic embolization
- Anterior mitral leaflet vegetation, particularly >10 mm[a]
- Embolic events (≥1) during first 2 weeks of antimicrobial therapy[a]
- Increased vegetation size despite appropriate antimicrobial therapy[a,b]

Valvular dysfunction
- Acute aortic or mitral insufficiency with signs of ventricular failure[b]
- Heart failure unresponsive to medical therapy[b]
- Valve perforation or rupture[b]

Perivalvular extension
- Valvular dehiscence, rupture, or fistula[c]
- New heart block[b,c]
- Large abscess or extension of abscess despite appropriate antimicrobial therapy

[a] Surgery may be required because of risk of embolization.

[b] Surgery may be required because of heart failure or failure of medical therapy.

[c] Echocardiography should not be the primary modality used to detect or monitor heart block.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Erratum in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 35. Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *S bovis* (MIC ≤0.12 mcg/mL)

Regimen	Dosage[a] and route	Duration	Comments
penicillin G	12-18 million units per day IV either continuously or in 4-6 equally divided doses	4 wk	Preferred options in most patients >65 y or with impaired 8th cranial nerve function or impaired renal function
or			
ceftriaxone	2 g IV or IM q24h	4 wk	
penicillin G	12-18 million units per day IV, either continuously or in 6 equally divided doses	2 wk	The 2-week regimen is not intended for patients with known cardiac or extracardiac abscess or for those with Cl_{Cr} <20 mL/min, impaired 8th cranial nerve function, or infection with *Abiotrophia*, *Granulicatella*, or *Gemella* spp
or			
ceftriaxone	2 g IV or IM q24h	2 wk	
(1 of the above 2 agents) plus			
gentamicin[b]	3 mg/kg IV or IM q24h	2 wk	Use nomogram for once-daily dosing of gentamicin

Regimen	Dosage[a] and route	Duration	Comments
vancomycin[c]	30 mg/kg/24h IV in 2 equally divided doses not to exceed 2 g q24h unless serum levels are inappropriately low	4 wk	Use vancomycin for patients unable to tolerate penicillin or ceftriaxone Adjust dosage to obtain peak (1 hour after infusion) serum level of 30-45 mcg/mL and trough level of 10-15 mcg/mL

[a] Recommended dosages are for adult patients with normal renal function.

[b] Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

[c] Vancomycin dosages should be infused over at least 1 hour to reduce the risk of histamine release (red man syndrome).

Modified from Baddour et al. Circulation. 2005;111:e394-434. Erratum in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 36. Therapy of Native Valve Endocarditis Caused by Relatively Penicillin-Resistant Strains of Viridans Group Streptococci and *S bovis* (MIC >0.12 mcg/mL to ≤0.5 mcg/mL)

Regimen	Dosage[a] and route	Duration	Comments
penicillin G **or**	24 million units per day IV either continuously or in 4-6 equally divided doses	4 wk	Use an enterococcal endocarditis regimen for patients with endocarditis caused by penicillin-resistant strains (MIC >0.5 mcg/mL)
ceftriaxone **(1 of the above 2 agents)** **plus**	2 g IV or IM q24h	4 wk	
gentamicin	3 mg/kg IV or IM q24h	2 wk	

Regimen	Dosage[a] and route	Duration	Comments
vancomycin[b]	30 mg/kg/24h IV in 2 equally divided doses not to exceed 2 g q24h unless serum levels are inappropriately low	4 wk	Use vancomycin only for patients unable to tolerate penicillin or ceftriaxone

[a] Recommended dosages are for adult patients with normal renal function.

[b] Adjust vancomycin dosage to obtain a peak (1 hour after infusion) serum level of 30-45 mcg/mL and a trough level of 10-15 mcg/mL.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Errata in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 37. Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *S bovis*

Regimen	Dosage[a] and route	Duration	Comments
PENICILLIN-SUSCEPTIBLE STRAIN (MIC ≤0.12 mcg/mL)			
penicillin G	24 million units per day IV either continuously or in 4-6 equally divided doses	6 wk	Use of either penicillin with gentamicin or ceftriaxone with gentamicin has **not** demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with a highly susceptible strain
or			
ceftriaxone **(1 of the above 2 agents) plus optional addition of**	2 g IV or IM q24h	6 wk	
gentamicin	3 mg/kg IV or IM q24h	2 wk	Do **not** use gentamicin in patients with Cl_{Cr} <30 mL/min

Regimen	Dosage[a] and route	Duration	Comments
vancomycin[b]	30 mg/kg/24h IV in 2 equally divided doses	6 wk	Use vancomycin only for patients unable to tolerate penicillin or ceftriaxone
PENICILLIN-RESISTANT (RELATIVELY OR FULLY) STRAIN (MIC >0.12 mcg/mL)			
penicillin G **or**	24 million units per day IV either continuously or in 4-6 equally divided doses	6 wk	
ceftriaxone **(1 of the above 2 agents)** **plus**	2 g IV or IM q24h	6 wk	
gentamicin	3 mg/kg IV or IM q24h	6 wk	
vancomycin[b]	30 mg/kg/24h IV in 2 equally divided doses	6 wk	Use vancomycin only for patients unable to tolerate penicillin or ceftriaxone

[a] Recommended dosages are for adult patients with normal renal function.

[b] Adjust vancomycin dosage to obtain a peak (1 hour after infusion) serum level of 30-45 mcg/mL and a trough level of 10-15 mcg/mL.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Errata in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 38. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage[a] and route	Duration	Comments
OXACILLIN-SUSCEPTIBLE STRAINS			
nafcillin[b]	12 g/24h IV in 4-6 equally divided doses	6 wk	Use 6 weeks for complicated right-sided IE and for left-sided IE; or use 2 weeks for uncomplicated right-sided IE
or			
oxacillin[b]	12 g/24h IV in 4-6 equally divided doses	6 wk	
(1 of the above 2 agents) plus optional addition of			
gentamicin[c]	3 mg/kg/24h IV or IM in 2-3 equally divided doses	3-5 days	Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (non-anaphylactoid type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and with a questionable history of immediate-type hypersensitivity to penicillin
cefazolin	6 g/24h IV in 3 equally divided doses	6 wk	Avoid cephalosporins in patients with anaphylactoid-type hypersensitivity to β-lactams; use vancomycin[d] instead
plus optional addition of			
gentamicin[b]	3 mg/kg/24h IV or IM in 2-3 equally divided doses	3-5 days	Clinical benefit of aminoglycosides has **not** been established

Regimen	Dosage[a] and route	Duration	Comments
OXACILLIN-RESISTANT STRAINS			
vancomycin[d]	30 mg/kg/24h IV in 2 equally divided doses	6 wk	Adjust vancomycin to achieve 1-hour peak serum level of 30-45 mcg/mL and trough level of 10-15 mcg/mL

[a] Recommended dosages are for adult patients with normal renal function.

[b] Use penicillin G 24 million units per day in place of nafcillin or oxacillin for penicillin-susceptible strain (MIC ≤0.1 mcg/mL).

[c] Administer gentamicin in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.

[d] Adjust vancomycin dosage to obtain a peak (1 hour after infusion) serum level of 30-45 mcg/mL and a trough level of 10-15 mcg/mL.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Errata in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 39. Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage[a] and route	Duration	Comments
OXACILLIN-SUSCEPTIBLE STRAINS			
nafcillin **or** oxacillin **(1 of the above 2 agents)** **plus** rifampin **and plus** gentamicin[b]	12 g/24h IV in 6 equally divided doses 12 g/24h IV in 6 equally divided doses 900 mg/24h IV or oral in 3 equally divided doses 3 mg/kg/24h IV or IM in 2-3 equally divided doses	≥6 wk ≥6 wk ≥6 wk 2 wk	Use penicillin G 24 million units per day instead of nafcillin or oxacillin if strain is penicillin-susceptible (MIC ≤0.1 mcg/mL) and does not produce β-lactamase Use vancomycin in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics Substitute cefazolin for nafcillin or oxacillin in patients with nonimmediate–type hypersensitivity reactions to penicillin
OXACILLIN-RESISTANT STRAINS			
vancomycin **plus** rifampin **and plus** gentamicin	30 mg/kg/24h IV in 2 equally divided doses 900 mg/24h IV or oral in 3 equally divided doses 3 mg/kg/24h IV or IM in 2-3 equally divided doses	≥6 wk ≥6 wk 2 wk	Adjust vancomycin to achieve 1-hour peak serum level of 30-45 mcg/mL and trough level of 10-15 mcg/mL

[a] Recommended dosages are for adult patients with normal renal function.

[b] Adjust gentamicin dosage to achieve a peak serum level of 3-4 mcg/mL and a trough level of <1 mcg/mL.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Errata in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 40. Therapy for Native Valve or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin[a]

Regimen	Dosage[b] and route	Duration	Comments
ampicillin **or**	12 g/24h IV in 6 equally divided doses	4-6 wk	Native valve: Use 4-week therapy for patients with symptoms of illness lasting ≤3 months and 6-week therapy for patients with symptoms lasting >3 months Prosthetic valve or other prosthetic cardiac material: Use 6-week minimum therapy
penicillin G **(1 of the above 2 agents)** **plus**	18-30 million units per day IV either continuously or in 6 equally divided doses	4-6 wk	
gentamicin[c]	3 mg/kg/24h IV or IM in 3 equally divided doses	4-6 wk	
vancomycin[d] **plus**	30 mg/kg/24h IV in 2 equally divided doses	6 wk	Use vancomycin only for patients unable to tolerate penicillin or ampicillin
gentamicin[c]	3 mg/kg/24h IV or IM in 3 equally divided doses	6 wk	Use 6 weeks of vancomycin therapy because of decreased activity against enterococci

[a] For strains resistant to gentamicin and susceptible to streptomycin, substitute streptomycin IV or IM 15 mg/kg/24h in 2 divided doses. See full-text article of Baddour (see below) for management of enterococcal IE strains that are penicillin resistant and management of strains resistant to penicillin, aminoglycosides, and vancomycin.

[b] Recommended dosages are for adult patients with normal renal function.

[c] Adjust gentamicin dosage to achieve a peak serum level of 3-4 mcg/mL and a trough level of <1 mcg/mL. Patients with Cl_{Cr} <50 mL/min should be treated in consultation with an infectious diseases specialist.

[d] Adjust vancomycin dosage to obtain a peak (1 hour after infusion) serum level of 30-45 mcg/mL and a trough level of 10-15 mcg/mL.

Modified from Baddour et al. Circulation. 2005;111:e394-434. Errata in: Circulation. 2005;112:2373. Circulation. 2007;115:e408. Used with permission.

Table 41. Therapy for Both Native Valve and Prosthetic Valve Endocarditis Caused by HACEK[a] Microorganisms

Regimen	Dosage[b] and route	Duration	Comments
ceftriaxone[c] **or**	2 g IV or IM q24h	4 wk	Substitute cefotaxime or another 3rd- or 4th-gen cephalosporin for ceftriaxone
ampicillin-sulbactam **or**	12 g/24h IV in 4 equally divided doses	4 wk	
ciprofloxacin[b,c,d]	1,000 mg/24h oral or 800 mg/24h IV in 2 equally divided doses	4 wk	Use fluoroquinolone therapy only for patients unable to tolerate a cephalosporin and ampicillin; levofloxacin or moxifloxacin may be substituted; fluoroquinolones not generally recommended for patients <18 y

[a] *Haemophilus parainfluenzae, H aphrophilus, H paraphrolus, H influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

[b] Recommended dosages are for adult patients with normal renal function.

[c] Patients should be informed that IM injection of ceftriaxone is painful.

[d] Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal.

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Other Treatment Considerations

Role of Surgery

Obtain prompt surgical evaluation of patients with congestive heart failure, fungal IE, multiresistant organisms, gram-negative IE, or endocarditis of prosthetic valves, and of patients with echocardiographic features suggesting the need for surgical intervention (see preceding Elements of Diagnosis section).

Care During and After Completion of Antimicrobial Treatment

- Initiate before or at completion of antimicrobial therapy:
  1) Transthoracic echocardiogram to establish new baseline
  2) Drug rehabilitation referral for patients who use illicit injection drugs
  3) Patient education about the signs of endocarditis and the need for antibiotic prophylaxis before certain dental, surgical, or invasive procedures
  4) Thorough dental evaluation and treatment, if not performed earlier in the evaluation
  5) Prompt removal of intravenous catheter after administration of antimicrobial therapy
- Short-term follow-up:
  1) Obtain at least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
  2) Conduct a physical examination for evidence of congestive heart failure
  3) Evaluate for toxicity due to current or prior antimicrobial therapy
- Long-term follow-up:
  1) Obtain at least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
  2) Evaluate valvular and ventricular function (eg, echocardiography)
  3) Encourage scrupulous oral hygiene and frequent professional office visits

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Infective Endocarditis Prophylaxis

Prevention of Endocarditis

The guidelines for the prevention of infective endocarditis (IE) issued by the American Heart Association underwent a major revision in 2007. Key changes include the following:

- Dental procedures have been found to be associated with a small number of cases of IE. Prophylaxis, even if 100% effective, would thus prevent only an extremely small number of cases.
- The emphasis has shifted from antibiotic prophylaxis to good oral health and increased access to dental care.
- Prophylactic antibiotics based on a patient's lifetime risk for acquiring IE are no longer recommended. Instead, prophylaxis focuses on patients with the highest risk for adverse outcomes from endocarditis.

Candidates for Prophylaxis

Only those patients with conditions that expose them to the highest risk for adverse outcomes from IE should receive prophylaxis. These high-risk conditions include:

- Prosthetic cardiac valve
- Previous IE
- Congenital heart disease (CHD) **only** for the following specific conditions
  1) Unrepaired cyanotic CHD, including palliative shunts and conduits
  2) Completely repaired congenital heart defect with prosthetic material or a prosthetic device placed either during surgery or by catheter intervention, during the first 6 months after the procedure
  3) CHD repair with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
- Development of cardiac valvulopathy after cardiac transplantation

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Dental Procedures

Prophylaxis is directed against viridans group streptococci.

- Procedures for which dental prophylaxis should be given to appropriate candidates include any procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa.
- Procedures that do **not** require prophylaxis include routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, and placement of orthodontic brackets. Prophylaxis is also not necessary after the shedding of deciduous teeth or for bleeding from trauma to the lips or oral mucosa.

Table 42. Prophylactic Regimens for Infective Endocarditis Before Dental Procedures[a,b]

Clinical situation	Adult prophylaxis (use only one drug per clinical situation)	Pediatric prophylaxis (use only one drug per clinical situation)
Oral regimen	amoxicillin 2 g oral	amoxicillin 50 mg/kg oral
Unable to take oral medication	ampicillin 2 g IM or IV **or** cefazolin 1 g IM or IV **or** ceftriaxone 1 g IM or IV	ampicillin 50 mg/kg IM or IV **or** cefazolin 50 mg/kg IM or IV **or** ceftriaxone 50 mg/kg IM or IV
Allergy to penicillin or ampicillin (oral regimen)	cephalexin[c,d] 2 g oral **or** clindamycin 600 mg oral **or** azithromycin 500 mg oral **or** clarithromycin 500 mg oral	cephalexin[c,d] 50 mg/kg oral **or** clindamycin 20 mg/kg oral **or** azithromycin 15 mg/kg oral **or** clarithromycin 15 mg/kg oral
Allergy to penicillin or ampicillin (unable to take oral medication)	cefazolin[d] 1 g IM or IV **or** ceftriaxone[d] 1 g IM or IV **or** clindamycin 600 mg IM or IV	cefazolin[d] 50 mg/kg IM or IV **or** ceftriaxone[d] 50 mg/kg IM or IV **or** clindamycin 20 mg/kg IM or IV

[a] Give single dose 30-60 minutes before procedure.

[b] If the antibiotic is inadvertently not administered before the procedure, it may be administered up to 2 hours after the procedure.

[c] Or another 1st- or 2nd-generation cephalosporin in equivalent dose.

[d] Do not use cephalosporin in patients with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

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Respiratory Procedures

For candidates for prophylaxis as listed above:

- It may be reasonable to give one of the above prophylactic regimens recommended for dental procedures (Table 42) before an invasive procedure (eg, tonsillectomy, adenoidectomy) involving the respiratory tract that necessitates incision or biopsy of the respiratory mucosa.
- Prophylaxis is not recommended for bronchoscopy unless the procedure involves incision of the respiratory tract mucosa.

Gastrointestinal or Genitourinary Procedures

For candidates for prophylaxis as listed above:

- Prophylaxis solely to prevent IE is no longer recommended.
- For patients scheduled for an elective urinary tract manipulation who also have an enterococcal urinary tract infection or colonization, it may be reasonable to administer antibiotic therapy to eradicate enterococci from the urine before the procedure.
- If the urinary tract procedure is not elective, it may be reasonable to administer an antimicrobial regimen to the patient that contains an agent active against enterococci.
- Amoxicillin or ampicillin is the preferred agent for enterococcal coverage; vancomycin may be administered to patients unable to tolerate ampicillin.

Procedures Involving Infected Skin, Skin Structure, or Musculoskeletal Tissue

For candidates for prophylaxis as listed above:

- It is reasonable that the regimen administered for treatment of the infection contain an agent active against staphylococci and β-hemolytic streptococci.
- An antistaphylococcal penicillin or cephalosporin is preferable; vancomycin or clindamycin may be administered to patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by methicillin-resistant staphylococcus.

Other Prophylactic Considerations

- The presence of fever or other manifestations of systemic infection indicates the possibility of IE. In these cases, it is important to obtain blood cultures and other relevant tests before administration of a prophylactic antibiotic. Failure to do so may result in a delay to diagnosis or treatment of a concomitant case of IE.
- If a patient is already receiving long-term antibiotic therapy with an antibiotic that is also recommended for IE prophylaxis for a dental procedure, an antibiotic from a different class should be used.
- If a patient requires a dental procedure while receiving parenteral antibiotic therapy for treatment of IE, the antibiotic therapy should be continued and the timing adjusted so that a dose is administered 30-60 minutes before the dental procedure.

- Patients who undergo surgery for placement of prosthetic heart valves or prosthetic intravascular or intracardiac material should be given surgical prophylaxis directed primarily against *Staphylococcus* sp.
- Antibiotic prophylaxis for dental procedures is not recommended for patients with coronary artery bypass grafting or coronary artery stents.

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Central Nervous System Infections

Empiric Therapy for Acute Bacterial Meningitis

Elements of Diagnosis and Treatment

- **Clinical:** The diagnosis of meningitis is suggested by the constellation of headache, fever, and neck stiffness. Some patients may also experience changes in mental status.
- **Radiology:** Computed tomograms or magnetic resonance imaging of the brain may be indicated for patients with compromised immune function and for those with papilledema and focal neurologic deficits. However, neuroimaging should not delay initiation of antimicrobial therapy.
- **Laboratory:** Cerebrospinal fluid (CSF) typically shows neutrophilic pleocytosis, high protein, and low glucose. Gram stain may provide rapid initial clues to the causative agent while awaiting results of CSF and blood cultures.
- **Treatment**
  - Acute bacterial meningitis is a medical emergency. Institute empiric antimicrobial therapy promptly and adjust it after isolating the etiologic agent. The duration of pathogen-directed therapy depends on the causative organism (Table 44).
  - Use adjunctive dexamethasone (0.15 mg/kg q6h for 2-4 days) for children or neonates with *Haemophilus influenzae* meningitis and for adults with proven or suspected *Streptococcus pneumoniae* meningitis. Administer the first dose of dexamethasone before or concurrent with the first dose of antimicrobial therapy.
  - Consider adding rifampin for suspected *S pneumoniae*, pending susceptibilities if dexamethasone is used. If *S pneumoniae* is β-lactam susceptible, rifampin can be discontinued.

Table 43. Empiric Therapy

Patient variable	Suspected pathogens	First-line treatment
Age		
<1 mo	*Streptococcus agalactiae* *Escherichia coli* *Listeria monocytogenes* *Klebsiella* sp	ampicillin plus cefotaxime or ampicillin plus aminoglycoside
1-23 mo	*S pneumoniae* *Neisseria meningitidis* *E coli* *S agalactiae* *Haemophilus influenzae*	vancomycin[a] plus either ceftriaxone or cefotaxime
2-50 y	*N meningitidis* *S pneumoniae*	vancomycin[a] plus either ceftriaxone or cefotaxime
>50 y	*S pneumoniae* *N meningitidis* *L monocytogenes* Aerobic gram-negative bacilli	vancomycin[a] plus ampicillin plus either ceftriaxone or cefotaxime
Head trauma		
Basilar skull fracture	*S pneumoniae* *H influenzae* Group A (β-hemolytic) streptococci	vancomycin[a] plus either ceftriaxone or cefotaxime

Patient variable	Suspected pathogens	First-line treatment
Penetrating trauma	*Staphylococcus aureus* Coagulase-negative staphylococci Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*	vancomycin[a] plus cefepime, or plus ceftazidime, or plus meropenem
Postneurosurgery	*S aureus* Coagulase-negative staphylococci Aerobic gram-negative bacilli, including *P aeruginosa*	vancomycin[a] plus cefepime, or plus ceftazidime, or plus meropenem
CSF shunt-related	Coagulase-negative staphylococci *S aureus* Aerobic gram-negative bacilli, including *P aeruginosa* *Propionibacterium acnes*	vancomycin[a] plus cefepime, or plus ceftazidime, or plus meropenem

[a] Monitor serum levels. Maintain vancomycin trough concentration at 15-20 mcg/mL.
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Pathogen-Directed Therapy for Acute Bacterial Meningitis

Elements of Diagnosis and Treatment

- **Clinical:** Adjust antimicrobial therapy based on the results of Gram stain and bacterial cultures.
- **Laboratory:** Use results of antimicrobial susceptibilities to guide the choice of pathogen-directed therapy.
- **Treatment:** Continue adjunctive dexamethasone (0.15 mg/kg q6h) for 2-4 days in children or neonates with *H influenzae* meningitis and in adults with proven or suspected *S pneumoniae* meningitis.

Table 44. Pathogen-Directed Therapy

Pathogens	First-line treatment	Alternate treatment	Duration
Enterococcus sp ampicillin-susceptible ampicillin-resistant ampicillin- and vancomycin-resistant	ampicillin plus gentamicin vancomycin plus gentamicin linezolid	linezolid	[a]
Escherichia coli and other Enterobacteriaceae	3rd- or 4th-gen cephalosporin (eg, ceftriaxone, cefotaxime, ceftazidime, cefepime)	meropenem, aztreonam, tmp/smx, or fluoroquinolone[b]	21 days[a]
Haemophilus influenzae β-Lactamase negative β-Lactamase positive	 ampicillin, or cefotaxime, or ceftriaxone ceftriaxone or cefotaxime	 cefepime or fluoroquinolone[a] cefepime or fluoroquinolone[a]	 7 days[a]
Listeria monocytogenes	ampicillin with or without aminoglycoside or penicillin G with or without aminoglycoside	tmp/smx or meropenem	21 days[a]

Pathogens	First-line treatment	Alternate treatment	Duration
Neisseria meningitidis penicillin MIC <0.1 mcg/mL 0.1-1.0 mcg/mL	 penicillin, or ampicillin, or ceftriaxone, or cefotaxime ceftriaxone or cefotaxime	 meropenem or a fluoroquinolone[b]	7 days[a]
Pseudomonas aeruginosa	cefepime or ceftazidime	meropenem, or ciprofloxacin, or levofloxacin, or aztreonam	[a]
Staphylococcus aureus MSSA MRSA	 nafcillin or oxacillin vancomycin	 vancomycin or meropenem tmp/smx or linezolid	[a]
S epidermidis (MRSE)	vancomycin	linezolid	[a]
Streptococcus agalactiae	penicillin, or ampicillin, or ceftriaxone, or cefotaxime		14-21 days[a]
S pneumoniae penicillin MIC <0.1 mcg/mL 0.1-1.0 mcg/mL ≥2.0 mcg/mL cefotaxime or ceftriaxone MIC ≥1.0 mcg/mL	 penicillin G, or ampicillin, or ceftriaxone, or cefotaxime ceftriaxone or cefotaxime vancomycin plus either cefotaxime or ceftriaxone vancomycin plus either cefotaxime or ceftriaxone	 cefepime or meropenem	10-14 days[a]

[a] Duration of therapy may need to be individualized on the basis of the patient's clinical response.
[b] Cerebrospinal fluid levels vary by agent.
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Table 45. Recommended Doses of Select Antimicrobial Agents for Treatment of Meningitis in Children and Adults With Normal Renal and Hepatic Function

Antimicrobial agents	Children (after neonatal period)		Adults	
	Dose	Total max daily dose	Dose	Total daily dose
ampicillin	300 mg/kg/24h divided q6h	12 g	2 g q4h	12 g
cefepime	150 mg/kg/24h divided q8h	6 g	2 g q8h	6 g
cefotaxime	225-300 mg/kg/24h divided q6h	12 g	2 g q4h (3 g q6h)	12 g
ceftazidime	150 mg/kg/24h divided q8h	6 g	2 g q8h	6 g
ceftriaxone	80-100 mg/kg/24h divided q12h	4 g	2 g q12h	4 g
ciprofloxacin	NA	NA	400 mg q8h (600 mg q12h)	800-1,200 mg
meropenem	120 mg/kg/24h divided q8h	6 g	2 g q8h	6 g
moxifloxacin	NA	NA	400 mg q24h	400 mg
nafcillin	200 mg/kg/24h divided q6h	12 g	2 g q4h	12 g
oxacillin	200 mg/kg/24h divided q6h	12 g	2 g q4h	12 g
penicillin G	300,000 units/kg/24h divided q4-6h	24 million units	20-24 million units per day or 4 million units q4h, as continuous IV infusion (load with 4-5 million units)	20-24 million units

Antimicrobial agents	Children (after neonatal period)		Adults	
	Dose	Total max daily dose	Dose	Total daily dose
rifampin	10-20 mg/kg/24h divided q12-24h	600 mg	600 mg q24h	600 mg
tmp/smx	10-20 mg/kg/24h divided q6-12h		15-20 mg/kg/24h divided q6-12h	15-20 mg/kg
vancomycin[a]	60 mg/kg/24h divided q6h		40-45 mg/kg/24h divided q8-12h[a]	[a]

[a] Monitor serum levels and maintain trough concentration of 15-20 mcg/mL.
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Cryptococcal and Tuberculosis Meningitis

Elements of Diagnosis and Treatment

- **Clinical:** The constellation of headache, fever, and neck stiffness is frequently associated with cryptococcal or tuberculosis meningitis. Changes in mental status may occur in many cases. Certain risk factors (eg, immune-compromised state or exposure history) may be apparent.
- **Radiology:** Neuroimaging may be indicated for immunocompromised patients and for those with papilledema and focal neurologic deficits.
- **Laboratory:** Conduct cerebrospinal fluid (CSF) examination with Gram stain and culture of CSF, along with blood cultures. Cryptococcal antigen may be detected in CSF and blood.
- **Adjunctive treatment:** Administer adjunctive dexamethasone (0.15 mg/kg q6h for 2-4 days) to patients with tuberculosis meninigitis.

Table 46. Therapy for Cryptococcal and Tuberculosis Meningitis

Empiric therapy	First-line treatment	Alternate treatment
Cryptococcus neoformans Immunocompetent patients	amphotericin B 0.7-1.0 mg/kg/24h plus flucytosine 100 mg/kg/24h for 2 weeks or lipid amphotericin product 4-6 mg/kg plus flucytosine 100 mg/kg/24h for 2 weeks; then fluconazole 400 mg/24h for at least 10 weeks or for as long as 6-12 months, depending on clinical status of patient; amphotericin B 0.7-1.0 mg/kg/24h plus flucytosine 100 mg/kg/24h for 6-10 weeks or lipid amphotericin product 4-6 mg/kg/24h plus flucytosine 100 mg/kg/24h for 6-10 weeks	amphotericin B 0.7-1.0 mg/kg/24h or lipid amphotericin product 4-6 mg/kg/24h for 6-10 weeks fluconazole 400-800 mg/24h plus flucytosine 100-150 mg/kg/24h for 6 weeks

Empiric therapy	First-line treatment	Alternate treatment
HIV-infected or transplant patients	Induction or consolidation phase: amphotericin B 0.7-1.0 mg/kg/24h plus flucytosine 100 mg/kg/24h for 2 weeks; or lipid amphotericin product 4-6 mg/kg/24h plus flucytosine 100 mg/kg/24h for 2 weeks; then fluconazole 400 mg/24h for at least 10 weeks amphotericin B 0.7-1.0 mg/kg/24h plus flucytosine 100 mg/kg/24h for 6-10 weeks; or lipid amphotericin product 4-6 mg/kg/24h plus flucytosine 100 mg/kg/24h for 6-10 weeks Maintenance phase[a]: fluconazole 200-400 mg/24h for life[a] or itraconazole 400 mg/24h for life[a]	Induction or consolidation phase: amphotericin B 0.7-1.0 mg/kg/24h or lipid amphotericin product 4-6 mg/kg/24h for 6-10 weeks fluconazole 400-800 mg/24h for 10-12 weeks fluconazole 400-800 mg/24h plus flucytosine 100-150 mg/kg/24h for 6 weeks Maintenance phase[a]: amphotericin B 1 mg/kg IV 1-3x/wk for life[a]
Mycobacterium tuberculosis	isoniazid (300 mg/24h) plus rifampin (600 mg/24h) plus pyrazinamide (15-30 mg/kg/24h) plus ethambutol (15-20 mg/kg/24h) for 2 months; then isoniazid (300 mg/24h) and rifampin (600 mg/24h) for 7-10 months	Management of drug-resistant TB should be guided by susceptibility testing and patients should be referred to a TB management expert

[a] Consider discontinuing cryptococcal maintenance therapy in HIV patients after successful completion of treatment course if patients remain asymptomatic and have a sustained (≥6 months) CD4 cell count of >100-200 cells/mm^3.

Urinary Tract Infections

Elements of Diagnosis

Table 47. Elements of Diagnosis of Urinary Tract Infections

Clinical syndromes	Diagnostic considerations
Asymptomatic bacteriuria	**Clinical diagnosis:** Urine culture >10^5 CFU/mL in absence of symptoms; common in elderly and in patients with chronic catheterization, spinal cord injuries, and neurogenic bladder; typically requires no treatment **except** during pregnancy and in young children
Cystitis in women (uncomplicated)	**Clinical diagnosis:** Cultures typically not needed; urine dipstick esterase-positive urine culture (if done) shows >10^2 CFU/mL; symptoms include dysuria and frequency **Common pathogens:** 75-95% *Escherichia coli* and other gram-negative bacteria; 5-20% *Staphylococcus saprophyticus* and *Enterococcus* sp
Pyelonephritis (community acquired)	**Clinical diagnosis:** Symptoms same as for cystitis (see above) plus low back or flank pain and fever; urinalysis for pyuria and bacteriuria; urine culture recommended **Common pathogens:** *E coli* and other gram-negative bacteria (eg, *Klebsiella* sp, *Enterobacter* sp, *Proteus mirabilis*); most common gram-positive pathogens are *S saprophyticus* and *Enterococcus* sp
UTI in men (community acquired)	**Clinical diagnosis:** Dysuria, urinary frequency; evaluate for anatomical obstructive anomaly (ie, postvoiding urinary tract ultrasound) in noncatheterized men **Common pathogens:** 80% *E coli*; in elderly, *Enterococcus* sp

Bacterial prostatitis	
Acute	**Clinical diagnosis:** Fever, dysuria, urinary frequency, pelvic pain, rectal examination with tender prostate, possibly elevated PSA; urinalysis (pyuria and bacteriuria); culture of expressed prostate secretions for pathogen **Common pathogens:** *E coli*; less frequent pathogens include *Klebsiella* sp, *Enterobacter* sp, *P mirabilis*, *Staphylococcus aureus*
Chronic	**Clinical diagnosis:** Low-grade fever, recurrent bacteriuria, pyuria; possibly elevated PSA; rectal examination with nontender prostate; culture of expressed prostate secretions for pathogen **Common pathogens:** *E coli* (80%), *Klebsiella* sp, *Enterobacter* sp, *P mirabilis*, *Enterococcus* sp, *S aureus*
Catheter-associated UTI	**Clinical diagnosis:** Presence of indwelling urinary catheter, urine culture $>10^2$ CFU/mL; pyuria **Common pathogens:** *E coli* and *Proteus*, *Enterobacter*, *Pseudomonas*, and *Serratia* spp; usually no treatment needed unless symptomatic
Candiduria	**Clinical diagnosis:** Urinalysis with yeast (ie, *Candida* sp); urine culture $>10^3$ CFU/mL with or without pyuria; urine dipstick not contributory May represent colonization, common with urinary catheters and poor collection procedures; depending on presentation, may not require treatment
Ileal conduit or urinary diversion	**Clinical diagnosis:** Nonsterile source for urine collection; urine cultures often polymicrobial and noninterpretable

Empiric Antimicrobial Selection

Table 48. Empiric Therapy for Acute Uncomplicated Cystitis

Host considerations	Empiric antimicrobial selection
Healthy women	3-day regimens • tmp/smx 160/800 mg bid[a] • tmp 100 mg bid[a] • ciprofloxacin 250 mg bid • ciprofloxacin XR 500 mg daily • levofloxacin 250 mg daily 5-7 day regimens • amoxicillin 250 mg tid or 500 mg bid[b] (amoxicillin/clavulanate can be used empirically if amoxicillin resistance suspected) • nitrofurantoin monohydrate macrocrystals 100 mg bid[c] • nitrofurantoin macrocrystals 50-100 mg qid[c] • 1st-, 2nd-, or 3rd-gen cephalosporin (oral)
Men; symptoms >1 week; recent antimicrobial use; diabetes; age >65 y	Consider 7-day treatment • tmp/smx 160/800 mg bid[a] • tmp 100 mg bid[a] • ciprofloxacin 250 mg bid • ciprofloxacin XR 500 mg daily • levofloxacin 250 mg daily • amoxicillin 250 mg tid or 500 mg bid[b] (amoxicillin/clavulanate can be used empirically if amoxicillin resistance suspected)

Pregnancy	3-day treatment preferred • amoxicillin 250 mg tid or 500 mg bid[b] (amoxicillin/clavulanate can be used empirically if amoxicillin resistance suspected) • nitrofurantoin monohydrate macrocrystals 100 mg bid[c] • nitrofurantoin macrocrystals 50-100 mg qid[c] • cefpodoxime 100 mg bid • cephalexin 250 mg qid Note • Avoid use of tmp/smx (pregnancy category C) in 1st and 3rd trimesters of pregnancy • Avoid use of fluoroquinolone in pregnancy

[a] Empiric use of trimethoprim-sulfamethoxazole (tmp/smx) or tmp alone acceptable only if there is <20% tmp/smx resistance in community.

[b] Use empiric amoxicillin with caution, because many common urinary pathogens are resistant; patients should be followed closely.

[c] Avoid nitrofurantoin in patients with any renal insufficiency or Cl_{Cr} <60 mL/min.

Table 49. Empiric Therapy for Acute Pyelonephritis

Host considerations	Empiric antimicrobial selection[a]
Outpatient (uncomplicated)	ciprofloxacin 500 mg bid for 7-14 days; ciprofloxacin XR 1 g daily for 7-14 days; levofloxacin 500 mg daily for 7-14 days; tmp/smx 160/800 mg bid for 14 days[b] If *Enterococcus* sp suspected by Gram stain: • amoxicillin 500 mg tid or 875 mg bid for 14 days or • amoxicillin/clavulanate 875 mg/125 mg bid for 14 days
Inpatient (uncomplicated): Initial therapy (pending urine culture results): Treat 14 days total IV and oral	ciprofloxacin 400 mg IV q12h; levofloxacin 500 mg IV q24h; ceftriaxone 1 g IV q24h; cefotaxime 1 g IV q8h; cefepime 1 g IV q12h; aztreonam 1 g IV q8h; If *Enterococcus* sp suspected by Gram stain, options include: • ampicillin 1-2 g IV q6h • ampicillin/sulbactam 1.5-3 g IV q6h • piperacillin/tazobactam 3.375 g IV q6h • vancomycin (after recent penicillin use) 15 mg/kg IV q12h

Inpatient (complicated[c]): Uroseptic or hemodynamically unstable	Empiric coverage against more common organisms, including the Enterobacteriaceae and *Enterococcus* sp and *S saprophyticus* **Community-acquired UTI** ampicillin 1-2 g IV q6h plus ciprofloxacin 400 mg q8-12h or levofloxacin 500-750 mg q24h; ampicillin/sulbactam 1.5-3 g IV q6h; piperacillin/tazobactam 3.375 g IV q6h; For penicillin allergy: vancomycin 15 mg/kg IV q12h plus ceftriaxone 1-2 g IV q24h or cefotaxime 1-2 g IV q8h or ciprofloxacin 400 mg q8-12h or levofloxacin 500-750 mg q24h **Catheter-associated and health care facility–acquired UTI (also include activity against *Pseudomonas aeruginosa*)** ampicillin 1-2 g q6h IV plus ciprofloxacin 400 mg q8-12h or levofloxacin 500-750 mg q24h; piperacillin/tazobactam 3.375-4.25 g q6h; cefepime 1-2 g q12h plus ampicillin 1-2 g q6h; meropenem 1 g IV q8h; imipenem 500 mg IV q6h; Consider adding vancomycin if penicillin- or ampicillin-resistant *Enterococcus* sp is a concern[a]

[a] Note: Urine culture recommended for directing targeted effective therapy; urine Gram stain can assist in initial selection of antimicrobial agent.

[b] Empiric use of trimethoprim-sulfamethoxazole (tmp/smx) or tmp alone acceptable only if there is <20% tmp/smx resistance in community.

[c] Complicated urinary tract infection (nosocomial or concomitant with structural or functional abnormalities or nursing home exposure).

Table 50. Empiric Therapy for Special Conditions

Syndrome	Empiric antimicrobial selection[a]
Acute bacterial prostatitis	ciprofloxacin 500 mg bid for 4 weeks; levofloxacin 500 mg daily for 4 weeks; tmp/smx DS bid for 4 weeks[b]
Chronic bacterial prostatitis	ciprofloxacin 500 mg bid for 6-12 weeks; levofloxacin 500 mg daily for 6-12 weeks; tmp/smx DS bid for 6-12 weeks[b]; Relapse: Treat for 12 weeks Failures: Consider suppression with tmp/smx SS daily or nitrofurantoin 50 mg daily
Candiduria	Removal of Foley catheter resolves infection in 40% of cases; treat with fluconazole 200-400 mg daily for 7-14 days only if patient is symptomatic or neutropenic, or has renal allograft or urologic instrumentation
Candida pyelonephritis	fluconazole 400 mg (6 mg/kg) daily for 14 days; fluconazole-resistant *Candida* sp: Consider amphotericin with or without 5-flucytosine

[a] Urine or prostate fluid cultures recommended for directing targeted effective therapy; urine Gram stain can assist in initial selection of antimicrobial agent.

[b] Empiric use of trimethoprim-sulfamethoxazole (tmp/smx) or tmp alone acceptable only if there is <20% tmp/smx resistance in community.

Table 51. Pathogen-Directed Therapy of Urinary Tract Infections

Common pathogens	Preferred antimicrobial therapy[a]	
	First-line treatment	Alternate treatment
Enterobacteriaceae (*Escherichia coli; Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter*, *Serratia*, *Salmonella*, and *Providencia* spp)	fluoroquinolone[b,c]; 2nd-, 3rd-, or 4th-gen cephalosporin (except for *Enterobacter*, *Citrobacter*, and some *Serratia* spp; may have inducible β-lactamase production); tmp/smx[c,d]	aztreonam; β-lactam/β-lactamase inhibitor combinations[e]; carbapenem[f]
Enterococcus sp		
penicillin- or ampicillin-susceptible	penicillin, amoxicillin, ampicillin	β-lactam/β-lactamase inhibitor combinations[d] (except ticarcillin/clavulanate); carbapenem[f] (except ertapenem)
penicillin- or ampicillin-resistant	vancomycin	daptomycin, nitrofurantoin[g]
VRE	daptomycin; nitrofurantoin[g]	linezolid
Staphylococcus saprophyticus	1st-, 2nd-, 3rd-, or 4th-gen cephalosporin; tmp/smx[d]; fluoroquinolone[b]	β-lactam/β-lactamase inhibitor combinations[e]; carbapenem[f]

Common pathogens	Preferred antimicrobial therapy[a]	
	First-line treatment	Alternate treatment
Pseudomonas aeruginosa	ciprofloxacin; levofloxacin; cefepime; ceftazidime; aztreonam	carbapenem[f] (except ertapenem); piperacillin/tazobactam
Staphylococcus aureus[h]		
MSSA	cefazolin, cephalexin, and other 1st-gen cephalosporins; tmp/smx[d]	β-lactam/β-lactamase inhibitor combinations[e]; carbapenem
MRSA	vancomycin; tmp/smx[d]	daptomycin
Candida albicans	fluconazole	amphotericin with or without 5-flucytosine

[a] Urine or prostate fluid cultures recommended for directing effective therapy; urine Gram stain can assist in initial selection of antimicrobial agent.

[b] Fluoroquinolone: levofloxacin or ciprofloxacin but **not** moxifloxacin, as it does not penetrate urinary tract well.

[c] Most communities have >20% trimethoprim-sulfamethoxazole (tmp/smx) resistance; in these circumstances, particularly with upper UTI, fluoroquinolone is preferable. For lower UTI, the 7-day course of nitrofurantoin may help stem fluoroquinolone resistance and overuse.

[d] Empiric use of tmp/smx or tmp alone acceptable only if there is <20% tmp/smx resistance in community.

[e] β-Lactam/β-lactamase inhibitors: piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, amoxicillin/clavulanate.

[f] Carbapenem: imipenem, meropenem, ertapenem.

[g] Nitrofurantoin: Use only for lower urinary tract infections.

[h] Remove catheter in cases of catheter-associated infection. In noncatheter-associated cases, evaluate patients for hematogenous *S aureus* dissemination.

Soft-Tissue Infections: Nontoxigenic

(See also section on Soft-Tissue Infections: Necrotizing or Toxigenic, page 184)

Elements of Diagnosis

Clinical Diagnosis

- Largely based on history and physical examination
- Recurrent cellulitis common (≥20% of patients)
- Leukocytosis may or may not be found
- Blood cultures are low yield (about 2-4%)
- Radiologic procedures are not generally needed except to evaluate for osteomyelitis (eg, chronic infections, postsurgical, diabetic foot, plantar puncture wounds with prolonged symptoms), abscess, or necrotizing process
- Epidemiologic findings dictate microbiology and choice of antibiotic therapy
- For cellulitis, elevate involved area if feasible

Table 52. Treatment of Nontoxigenic Soft-Tissue Infections

Syndrome and common pathogens	First-line treatment	Alternate treatment
CELLULITIS OR ERYSIPELAS		
Uncomplicated cellulitis, no exposure issues (β-hemolytic streptococci and *Staphylococcus aureus*)	cefazolin, nafcillin, oxacillin, dicloxacillin, cephalexin, cefadroxil	clindamycin, vancomycin, doxycycline, tmp/smx
CA-MRSA likely (eg, spider bite–like lesions, abscesses, exposure to others with CA-MRSA, nonresponding or recurrent furuncles or impetigo)	minocycline, doxycycline, clindamycin (if negative inducible-resistance test) Moderate to severe infection: vancomycin Incision and drainage important for purulent lesions	tmp/smx Moderate to severe infection: linezolid, daptomycin, tigecycline

Syndrome and common pathogens	First-line treatment	Alternate treatment
Erysipelas (β-hemolytic streptococci, usually group A)	penicillin	cefazolin, cephalexin, cefadroxil, nafcillin, oxacillin, dicloxacillin, clindamycin, vancomycin
Immunocompromised (β-hemolytic streptococci, *S aureus, Pseudomonas aeruginosa* and other gram-negative bacteria, fungi, viruses)	Empiric therapy depends on clinical presentation; modify on basis of established etiology and cultures and sensitivities	
IMPETIGO		
S aureus, group A streptococci	cefazolin, nafcillin, oxacillin, dicloxacillin, cephalexin, cefadroxil, topical mupirocin	β-lactam allergic or MRSA: vancomycin, linezolid, clindamycin (if negative inducible-resistance test)
WOUND INFECTION		
Bite wounds (often polymicrobial: *Pasteurella* sp, *Capnocytophaga* sp, anaerobes, viridans group streptococci, *Eikenella* sp, *Haemophilus* sp)	ampicillin/sulbactam, amoxicillin/clavulanate Wound cleaning is important; give tetanus vaccination if not up to date	Combination therapy with one of the following: levofloxacin, ciprofloxacin, tmp/smx, 3rd- or 4th-gen cephalosporin, or doxycycline plus either metronidazole or clindamycin; piperacillin/tazobactam; ticarcillin/clavulanate; carbapenem[a]; moxifloxacin

Syndrome and common pathogens	First-line treatment	Alternate treatment
Postsurgical Clean procedures: *Staphylococcus* and *Streptococcus* spp GI procedures: Intestinal flora Rapidly progressive infection in first 48 hours after surgery: *Clostridium* sp and *Streptococcus pyogenes*	Debridement plus antimicrobials based on surgical site and culture results (see Stevens et al*)	
Plantar puncture (*S aureus*, group A streptococci, gram-negative bacteria, including *Pseudomonas aeruginosa*)	Antibiotics should optimally be based on cultures Empiric therapy: cefepime, levofloxacin, ciprofloxacin Tetanus shot (if not up to date)	moxifloxacin (if *Pseudomonas* sp not found or suspected)
DIABETIC FOOT OR DECUBITIS ULCER		
Diabetic foot infection (often mixed aerobic and anaerobic infection)	β-lactam/β-lactamase inhibitor[b] plus glucose control	carbapenem[a]; metronidazole plus either moxifloxacin or levofloxacin; tigecycline
Pressure (decubitis) ulcers (often mixed aerobic and anaerobic infection; may include MRSA or VRE)	β-lactam/β-lactamase inhibitor[b] or carbapenem	fluoroquinolone plus metronidazole; tigecycline MRSA: vancomycin, linezolid, daptomycin, dalfopristin/quinupristin VRE: linezolid, daptomycin, tigecycline

[a] Carbapenems include meropenem, imipenem, and ertapenem.

[b] β-Lactam/β-lactamase inhibitors include piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, and amoxicillin/clavulanate.

*Stevens et al. Clin Infect. Dis. 2005 Nov 15;41:1373-406. Epub 2005 Oct 14. Erratum in: Clin Infect Dis. 2005;41:1830; Clin Infect Dis. 2006;42:1219.

Marine or Water Exposure

β-Hemolytic streptococci and staphylococci are possible pathogens or copathogens of nontoxigenic soft-tissue infections related to marine or water exposure. Base treatment on exposure history and culture data.

- **Salt water or brackish water:** *Vibrio vulnificus*
- **Freshwater:** *Aeromonas*, *Pseudomonas* (also common with hot tubs), *Plesiomonas*, *Edwardsielleae*, and *Erysipelothrix* spp
- **Fish tank or saltwater fish–related injury:** *Mycobacterium marinum*

Table 53. Treatment of Nontoxigenic Soft-Tissue Infections Due to Marine or Water Exposure

Type of therapy	First-line treatment	Alternate treatment
Empiric therapy	Newer fluoroquinolone (moxifloxacin or gemifloxacin) or a 3rd- or 4th-gen cephalosporin; add metronidazole for exposure to sewage Salt water: Add tetracycline Fish tank: Consider rifampin plus ethambutol, with or without fluoroquinolone	Carbapenem,[a] β-lactam/β-lactamase inhibitor,[b] or (if *Aeromonas*, *Plesiomonas*, or *Edwardsielleae* spp) tmp/smx Salt water: Add tetracycline Fish tank: doxycycline, minocycline, tmp/smx, clarithromycin (with or without rifampin)
Pathogen-directed therapy	See section on Bacteria: Preferred and Alternate Treatment Options (page 121) and section on Nontuberculosis Mycobacterial Infections (page 230)	

[a] Carbapenems include meropenem, imipenem, and ertapenem.

[b] β-Lactam/β-lactamase inhibitors include piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, and amoxicillin/clavulanate.

Other Considerations

- **Use of macrolides:** Not as useful today as empiric therapy in penicillin-allergic patients, because resistance to these drugs is found in some strains of β-hemolytic streptococci
- **CA-MRSA:** Should be considered if the patient does not respond to oral β-lactam therapy or if other close contacts have been infected with this organism, or if purulent presentation
- **Referral for management:** Lymphedema, refractory tinea pedis, chronic dermopathies, venous insufficiency
- **Additional measures:** May be required in cases of frequent recurrence, including possible chronic daily suppressive therapy with antibiotics; elimination or prevention of interdigital tinea is important
- **Osteomyelitis:** Consider evaluation for chronic infections, postsurgical infections, pressure ulcers, some plantar puncture wounds
- **Plantar puncture wounds:** Clean thoroughly, remove foreign bodies, and administer a tetanus vaccination; surgical drainage or debridement may also be needed

Soft-Tissue Infections: Necrotizing or Toxigenic

Necrotizing or Toxigenic Soft-Tissue Infections

Elements of Diagnosis

- A high index of suspicion is critical to the diagnosis of necrotizing or toxigenic soft-tissue infections.
- Minor or major trauma can predispose patients to necrotizing soft-tissue infections, which are more common in patients with diabetes mellitus, immunosuppression, or obesity.*
- Necrotizing or toxigenic soft-tissue infections should be considered in the differential diagnosis of patients with presumed cellulitis and extreme pain disproportionate with appearance.
- Symptoms include swelling, erythema, and pain. These may progress to tense edema, blisters, necrosis, crepitus, or subcutaneous gas.*
- Systemic symptoms include tachycardia, fever, and hypotension progressing to shock.* Ultrasonography, computed tomography, and magnetic resonance imaging can be helpful in making a diagnosis, but **immediate surgical consultation** should be obtained when necrotizing fasciitis is suspected.

* Anaya et al. Clin Infect Dis. 2007 Mar 1;44:705-10. Epub 2007 Jan 22.

Table 54. Treatment of Soft-Tissue Infections

Syndrome and common pathogens	First-line treatment	Alternate treatment
TOXIC SHOCK SYNDROME		
Staphylococcus aureus, β-hemolytic streptococci, viridans group streptococci	nafcillin or cefazolin plus clindamycin	vancomycin, linezolid, daptomycin, or tigecycline (any of these 4 drugs, especially for suspected MRSA)
NECROTIZING FASCIITIS		
EMPIRIC THERAPY		
Target mixed flora (various anaerobic and aerobic bacteria), β-hemolytic streptococci (groups A, B, C, F, G), and CA-MRSA	Broad-spectrum empiric coverage until pathogen is identified should include ampicillin/sulbactam, piperacillin/tazobactam, or ticarcillin/clavulanate; or carbapenem[a]; or, for patients allergic to penicillin, tigecycline or clindamycin plus fluoroquinolone Use vancomycin if CA-MRSA is prevalent in local community Consider adding clindamycin for its toxin-inhibiting properties	Alternates for MRSA are linezolid, daptomycin, or tigecycline
PATHOGEN-DIRECTED THERAPY		
Type I Mixed aerobic and anaerobic infection; often seen in patients with severe trauma or diabetes mellitus (eg, Fournier gangrene)	piperacillin/tazobactam or ticarcillin/clavulanate; or carbapenem[a]; or, for patients allergic to penicillin, newer fluoroquinolone plus metronidazole	tigecycline

Syndrome and common pathogens	First-line treatment	Alternate treatment
Type II β-Hemolytic streptococci (usually *Streptococcus pyogenes*)	penicillin G plus clindamycin; or, for patients allergic to penicillin, vancomycin plus clindamycin	cefazolin can be used when penicillin allergy does not produce an immediate reaction (eg, anaphylaxis, hives)
Type III Clostridial myonecrosis due to *Clostridium* sp, especially *C perfringens*	penicillin plus clindamycin	penicillin plus tetracycline; or carbapenem[a]
Type IV CA-MRSA	vancomycin	linezolid, daptomycin, tigecycline, or, if susceptible by double-disk diffusion test, clindamycin

[a] Carbapenems include meropenem, imipenem, and ertapenem.

Other Considerations

- Necrotizing fasciitis and clostridial myonecrosis often require immediate and serial surgical debridement.
- Complications include multiple organ failure or metastatic foci of infection.
- Intraoperative findings of necrotizing fasciitis include gray necrotic tissue, lack of bleeding, thrombosed vessels, dishwater pus, and lack of resistance to finger dissection.*
- Initial histopathologic findings of surgically resected tissues may be of prognostic importance. A poor neutrophilic response with numerous organisms seen on routine stains suggests a poor prognosis.
- Despite aggressive treatment, as many as 15-30% (or more) of patients affected by necrotizing fasciitis and clostridial myonecrosis may die.
- Hyperbaric oxygen as a treatment has not been fully defined and is not routinely recommended.
- Case cohort studies and case reports have suggested some benefit to treatment with intravenous immunoglobulin in specific circumstances (eg, streptococcal toxic shock). However, due to the lack of randomized controlled trials, intravenous immunoglobulin should probably be reserved for select patients.
- Surgical exploration of the incision is needed when toxic shock syndrome occurs.
- Viridans group streptococci can cause toxic shock syndrome in severely immunocompromised patients (eg, bone marrow transplant patients with prolonged neutropenia).

* Anaya et al. Clin Infect Dis. 2007 Mar 1;44:705-10. Epub 2007 Jan 22.

Surgical Prophylaxis

Common Pathogens Targeted by Prophylaxis Regimens

Surgical prophylaxis should be directed toward the microorganism likely to cause infection after the operation.

- **Type I operations:** Involving skin but not body tracts; staphylococci are primary target
- **Type II operations:** Involving both skin and body tracts; various organisms from both sites are possible; reasonable coverage of common gram-negative bacilli and anaerobes may be added to staphylococcal prophylaxis

Table 55. Prophylactic Regimens

Type of surgery	First-line treatment[a]	Alternate treatment
Type I (eg, cardiothoracic, vascular, orthopedic, craniotomy)	cefazolin before incision and q8h for 24-hour max after procedure (48-hour max after cardiac procedures) If <80 kg: 1 g If ≥80 kg: 2 g	cefuroxime
Severe penicillin allergy, cephalosporin allergy, or high-risk for MRSA surgical site infection	vancomycin 15 mg/kg before incision and q12h for 24-hour max (48-hour max after cardiac surgery)	clindamycin
Type II (eg, colorectal, hysterectomy, appendectomy)	cefazolin before incision and q8h for 24-hour max after procedure If <80 kg: 1 g If ≥80 kg: 2 g **plus** metronidazole 500 mg (weight-based dosing: 15 mg/kg once then 7.5 mg/kg) before incision and q8h for 24-hour max after procedure	cefotetan, cefoxitin, or ampicillin/sulbactam For colorectal surgeries, additional alternates are ertapenem alone or an oral regimen of neomycin plus either erythromycin or metronidazole
Severe penicillin or cephalosporin allergy	levofloxacin 750 mg once before incision and q12h for 24-hour max after procedure **plus** metronidazole 500 mg before incision and q8h for 24-hour max after procedure	metronidazole plus either gentamicin or an alternate fluoroquinolone **or** clindamycin plus gentamicin, fluoroquinolone, or aztreonam

[a] Suggested doses are for adults with normal organ function.

Other Considerations

- Infusion just before incision is critical to success but continuation beyond a 24-hour maximum is not necessary (48-hour maximum for cardiac surgery); resistance and complications may result from prolonged use of prophylaxis
- Surgical prophylaxis guidelines and quality indicators specify that antibiotics be started within 1 hour of incision; prophylactic agents that require a longer infusion time (eg, vancomycin and fluoroquinolone) should be started within 1-2 hours of surgery, and infusions should optimally be completed before incision
- Treatment of active infection or spillage is not prophylactic and can be continued as indicated
- Most patients with mild penicillin allergy can receive cephalosporin prophylaxis depending on allergy history or skin testing
- Type I surgery in institutions with a high rate of methicillin-resistant *Staphylococcus aureus* infection may require vancomycin as the primary agent (although increased efficacy is unproven)
- Dosages may require adjustment for renal or hepatic dysfunction
- For extended procedures, a repeat intraoperative dose of antibiotics with a short half-life may be required
- Surgical prophylaxis regimens are currently being updated due to shortages or unavailability of some drugs (eg, cefoxitin, cefotetan) recommended in guidelines*
- Recommendations to improve adherence to guidelines and core measures include
  1) Stocking only the appropriate doses in the operating room
  2) Assigning responsibility for administration of medications to nurses in the preoperative holding area or in anesthesia (rather than administering medications before patients transfer to operating room)
  3) Using preprinted order sets
  4) Involving infection control, infectious diseases, and pharmacy staff as resources
  5) Using visible reminders such as checklists and stickers
- See also Bratzler et al.*

*Bratzler et al. Clin Infect Dis. 2004 Jun 15;38:1706-15. Epub 2004 May 26.

Osteomyelitis

Elements of Diagnosis

- **Clinical:** Localized pain and tenderness of the involved bone; systemic signs and symptoms present in acute hematogenous osteomyelitis
- **Radiology:** Bone destruction or sequestrum in chronic cases
- **Laboratory:** White blood cell count is often normal; erythrocyte sedimentation rate and C-reactive protein are usually elevated

Table 56. Treatment of Osteomyelitis in Adults With Normal Organ Function

Clinical feature	First-line treatment	Alternate treatment
	EMPIRIC THERAPY	
Acute pain, swelling with fever, leukocytosis	cefazolin 1-2 g IV q8h[a,b]	vancomycin 15 mg/kg IV q12h[b]
Wound drainage, painful surgical site, prior surgery	vancomycin 15 mg/kg IV q12h[b]	daptomycin 6 mg/kg IV q24h[b]; or linezolid 600 mg IV or oral q12h[b]
Chronic pain, ulceration, or swelling without systemic symptoms (eg, foot ulceration in patient with diabetes mellitus)	Establish diagnosis; define microbiology before determining treatment options	

Clinical feature	First-line treatment	Alternate treatment
	PATHOGEN-DIRECTED THERAPY	
Staphylococcus sp oxacillin-sensitive	nafcillin or oxacillin 1.5-2.0 g IV q4h for 4-6 weeks; or cefazolin 1-2 g IV q8h for 4-6 weeks	vancomycin 15 mg/kg IV q12h for 4-6 weeks
oxacillin-resistant	vancomycin 15 mg/kg IV q12h for 4-6 weeks	linezolid 600 mg oral or IV q12h for 4-6 weeks; or daptomycin 6 mg/kg IV q24h for 4-6 weeks
β-Hemolytic *Streptococcus* sp or penicillin-sensitive *S pneumoniae*	penicillin G 20 x 10^6 units per day IV either continuously or in 6 equally divided doses for 4-6 weeks; or ceftriaxone 2 g IV or IM q24h for 4-6 weeks; or cefazolin 1-2 g IV q8h for 4-6 weeks	vancomycin 15 mg/kg IV q12h for 4-6 weeks
Enterobacteriaceae	ceftriaxone 2 g IV q24h for 4-6 weeks; or ciprofloxacin 500-750 mg oral q12h for 4-6 weeks	imipenem 500 mg IV q6h for 4-6 weeks; or meropenem 1 g IV q8h for 4-6 weeks; or ertapenem 1 g IV q24h for 4-6 weeks; or aztreonam 1 g IV q8h for 4-6 weeks

Clinical feature	First-line treatment	Alternate treatment
Pseudomonas sp, *Enterobacter* sp	meropenem 1 g IV q8h for 4-6 weeks; or cefepime 2 g IV q12h for 4-6 weeks	ciprofloxacin 750 mg oral q12h for 4-6 weeks; or ceftazidime 2 g IV q8h for 4-6 weeks[c]; or aztreonam 1-2 g IV q8h for 4-6 weeks
Polymicrobial infection (eg, diabetic foot infection)	Treatment depends on type and severity; refer to published guidelines in Lipsky et al*	

[a] Consider using vancomycin in clinical situations with a high risk of methicillin-resistant *S aureus*.

[b] Consider addition of gram-negative coverage in ill-appearing, hemodynamically unstable patients.

[c] Avoid use for organisms that produce extended-spectrum β-lactamases or for organisms that may have inducible β-lactamases.

*Lipsky et al. Clin Infect Dis. 2004 Oct 1;39:885-910. Epub 2004 Sep 10.

Other Considerations

Therapy for Specific Scenarios

- **Hardware retained:** Consider chronic suppression until fusion
- **Vertebral osteomyelitis**: Medical management alone is often sufficient
- **Sternal osteomyelitis (eg, poststernotomy):** Surgical debridement is often required

Management of Complications

- **No clinical or laboratory improvement:** Reassess diagnosis, reassess adequacy of surgical debridement
- **Recurrence of infectious syndrome:** Consider suboptimal medical treatment; reassess adequacy of surgical debridement; consider removal of any hardware

Acute Native Joint Infections

Elements of Diagnosis

- **Clinical:** Acute monoarticular swelling, typically of a large joint, with fever and pain
- **Radiology:** Normal osseus structures (early) with soft-tissue swelling
- **Laboratory:** Elevated leukocytes, erythrocyte sedimentation rate, and C-reactive protein
- **Arthrocentesis:** >100,000 leukocytes (predominately neutrophils), absence of crystals, Gram stain often negative

Table 57. Treatment of Acute Joint Infections

Clinical feature or pathogen	First-line treatment	Alternate treatment
	EMPIRIC THERAPY[a]	
Acute joint swelling with fever, leukocytosis, and joint pain; no prior surgery	cefazolin 1-2 g IV q8h[b,c]	vancomycin 15 mg/kg IV q12h[c]
Wound drainage, painful joint, prior surgery	vancomycin 15 mg/kg IV q12h[c]	daptomycin 6 mg/kg IV q24h[c] or linezolid 600 mg IV or oral q12h[c]
Polyarticular synovitis with rash in young, sexually active patient (eg, disseminated *Neisseria gonorrhoeae*)	ceftriaxone 2 g IV q24h	ciprofloxacin 500 mg oral q12h or 400 mg IV q12h[d] or cefotaxime 1 g IV q8h
Chronic monoarticular swelling without systemic symptoms	Establish diagnosis before determining treatment	
Gram stain positive	Treat as for *Staphylococcus* sp if gram-positive cocci Treat as for *Pseudomonas* sp if gram-negative bacilli	

Clinical feature or pathogen	First-line treatment	Alternate treatment
	PATHOGEN-DIRECTED THERAPY[a]	
Staphylococcus aureus		
oxacillin-sensitive	nafcillin or oxacillin 1.5-2.0 g IV q4h for 3-4 weeks **or** cefazolin 1-2 g IV q8h for 3-4 weeks	vancomycin 15 mg/kg IV q12h for 3-4 weeks
oxacillin-resistant	vancomycin 15 mg/kg IV q12h for 3-4 weeks	linezolid 600 mg oral or IV q12h for 3-4 weeks **or** daptomycin 6 mg/kg IV q24h for 3-4 weeks
β-Hemolytic streptococci or penicillin-sensitive pneumococci	penicillin G 20,000 units per day IV either continuously or in 6 equally divided doses for 2-3 weeks **or** ceftriaxone 2 g IV q24h for 2-3 weeks **or** cefazolin 1-2 g IV q8h for 2-3 weeks	vancomycin 15 mg/kg IV q12h for 2-3 weeks
Enterobacteriaceae	ceftriaxone 2 g IV q24h for 3-4 weeks[e] **or** ciprofloxacin 500-750 mg oral q12h for 3-4 weeks	ertapenem 1 g IV q24h for 3-4 weeks **or** aztreonam 1 g IV q8h for 3-4 weeks

Clinical feature or pathogen	First-line treatment	Alternate treatment
Pseudomonas sp, *Enterobacter* sp	cefepime 2 g IV q12h for 3-4 weeks **or** meropenem 1 g IV q8h for 3-4 weeks	ciprofloxacin 750 mg oral q12h for 3-4 weeks **or** ceftazidime 2 g IV q8h for 3-4 weeks[e]

[a] Adult doses for normal organ function.

[b] Consider using vancomycin in clinical situations with a high risk of methicillin-resistant *S aureus*.

[c] Consider the addition of gram-negative coverage in ill-appearing, hemodynamically unstable patients.

[d] Resistance in *N gonorrhoeae* is increasing in several regions and in men who have sex with other men; susceptibility testing suggested.

[e] Avoid use for organisms that produce extended-spectrum β-lactamases or for organisms that may have inducible β-lactamases.

Table 58. Management of Complications

Complicating factors	Management
No clinical or laboratory improvement	Reassess diagnosis, consider noninfectious etiology, rule out concomitant crystal arthritis, consider atypical organisms
Periarticular osteomyelitis	Consider surgical debridement
Recurrence of infectious syndrome	Consider suboptimal medical treatment, reassess adequacy of surgical debridement, rule out periarticular osteomyelitis
Long-term postseptic degenerative arthritis	Consider total joint arthroplasty

Table 59. Therapy for Specific Scenarios

Scenario	Management
Presence of prosthetic joint	Typically caused by oxacillin-resistant staphylococci; consider vancomycin therapy
Septic arthritis after animal bites	Consider using piperacillin/tazobactam 3.375 IV q6h or ampicillin/sulbactam 3 g IV q6h
Immunocompromised host or standard bacterial cultures that are negative	Consider fungal or mycobacterial organisms

Gastrointestinal Infections

Orofacial Infections, Esophagitis, and Gastritis

Elements of Diagnosis

Orofacial Infections

- **Ludwig angina:** Acute soft-tissue infection usually of dental origin; spreads rapidly and is bilateral; involves submandibular and sublingual spaces and can spread to neck; may include respiratory obstruction from edema
- **Acute necrotizing ulcerative gingivitis (eg, Vincent angina, trench mouth):** Mixed bacterial infection with gingival ulcerations and gingival breakdown, usually due to poor dental hygiene
- **Lemierre syndrome:** Suppurative jugulovenous thrombophlebitis, pharyngitis, and bacteremia, with potential for abscess formation and extension to mediastinum or septic pulmonary emboli; caused most commonly by *Fusobacterium necrophorum*
- **Peritonsillar abscess (quinsy):** Usually due to group A streptococci, often with anaerobic bacteria; often results in enlarged displaced tonsils, severe pharyngeal pain, dysphagia

Esophagitis

- **More common in immunocompromised patients:** HIV infection, hematologic malignancies, postchemotherapy, organ transplantation
- **Most common pathogens:** *Candida* sp (especially *C albicans*), herpes simplex virus (HSV), cytomegalovirus (CMV)
- **Less common pathogens:** *Histoplasma capsulatum, Blastomyces dermatitidis, Mycobacterium tuberculosis*, and other *Mycobacterium* sp, *Actinomyces* sp
- **Noninfectious causes:** Gastroesophageal reflux disease, radiotherapy, antineoplastic chemotherapy, aphthous ulcers (in 5% of AIDS patients and also in some patients with acute human immunodeficiency virus [HIV] infection)
- **Symptoms:** Odynophagia, dysphagia, and substernal chest pain; oral thrush common with HIV-associated candidal esophagitis; pain common with HSV and CMV esophagitis

***Helicobacter pylori* Gastric and Peptic Ulcer Disease**

- *H pylori* colonization and infection are more common with increasing age and in developing countries
- *H pylori* gastric colonization is associated with a 3- to 4-fold increase in the risk for development of either gastric or duodenal ulceration; more than 90% of duodenal ulcerations are associated with *H pylori* infection (in the absence of drug-associated causes)
- *H pylori*–associated chronic gastritis is considered a risk factor for development of gastric carcinoma and gastric mucosa-associated lymphoid tumors (MALT)
- Diagnosis of *H pylori* infection can be made by endoscopy and biopsy or by noninvasive techniques such as serologic analysis, breath test, or fecal antigen analysis

Table 60. Treatment of Gastrointestinal Infections: I. Oropharyngeal Infections, Esophagitis, and Gastritis

Syndrome or common pathogen	First-line treatment	Alternate treatment
TREATMENT OF OROPHARYNGEAL INFECTIONS		
Ludwig angina Viridans group streptococci, other streptococci, *Fusobacterium* sp, *Bacteroides* sp, *Actinomyces* sp	ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, or carbapenem	penicillin G plus metronidazole; or clindamycin
Acute ulcerative or necrotizing gingivitis *Bacteroides* sp, *Fusobacterium* sp, spirochetes, viridans group streptococci, other streptococci	See above	See above
Lemierre syndrome *F necrophorum*, *Bacteroides* sp	See above	See above
Peritonsillar abscess Group A streptococci, anaerobes	See above	See above

Syndrome or common pathogen	First-line treatment	Alternate treatment
TREATMENT OF ESOPHAGITIS*		
Candida sp[a]	fluconazole	itraconazole, echinocandin,[b] voriconazole, amphotericin B, or lipid amphotericin product
Herpes simplex virus[a]	acyclovir, valacyclovir, famciclovir	foscarnet (for acyclovir-resistant strains)
CMV	IV ganciclovir, valganciclovir	foscarnet
Aphthous ulcers	prednisone	thalidomide
TREATMENT OF GASTRITIS		
H pylori	Proton pump inhibitor plus amoxicillin and clarithromycin For penicillin allergy: Proton pump inhibitor plus metronidazole and clarithromycin For macrolide allergy: Proton pump inhibitor plus amoxicillin and metronidazole	bismuth, metronidazole, and tetracycline with proton pump inhibitor; or proton pump inhibitor plus levofloxacin and amoxicillin; or proton pump inhibitor plus rifabutin and amoxicillin

[a] Suppressive therapy may be needed after treatment in AIDS patients and markedly immunosuppressed patients.

[b] The echinocandin class includes caspofungin, micafungin, and anidulafungin.

* Mandell et al. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Vol 1. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. pp. 1231-6.

Diarrhea

Elements of Diagnosis

Noninflammatory Diarrhea

- **Site:** Small intestine
- **Stool volume:** Large, watery diarrhea
- **Fecal leukocytes:** None
- **Common organisms**
  1) **Bacteria:** *Vibrio cholerae*, enterotoxigenic *Escherichia coli* (ETEC), *Bacillus cereus, Staphylococcus aureus, Clostridium perfringens* (type A enterotoxin)
  2) **Viruses:** Rotavirus, calicivirus, Norwalk-like viruses, adenovirus, astrovirus
  3) **Parasites:** *Giardia lamblia, Cryptosporidium* sp

Inflammatory Diarrhea

- **Site:** Colon
- **Stool volume:** Small
- **Fecal leukocytes:** Yes
- **Common organisms**
  1) **Bacteria:** *Shigella* sp, *Salmonella* sp, *Campylobacter jejuni, Vibrio parahaemolyticus*, enteroinvasive *E coli* (EIEC), *E coli* O157:H7 (enterohemorrhagic), *Clostridium difficile* (cytotoxin), *M tuberculosis*
  - **Viruses:** CMV
  - **Parasites:** *Entamoeba histolytica, Schistosoma japonicum, S mansoni*

Invasive Enteric Infections With Secondary Dissemination

- **Site:** Ileum, colon
- **Stool volume:** Small
- **Fecal leukocytes:** Yes
- **Common organisms**
  1) **Bacteria:** *Salmonella typhi, Yersinia enterocolitica, Vibro vulnificus, Listeria monocytogenes, Brucella* sp, *Tropheryma whippelii* (small-bowel predominance with *T whippelii*)
  2) **Parasites:** *E histolytica, Strongyloides stercoralis, Trichinella spiralis*

Evaluation of Food-Borne Diarrhea*

- **Vomiting:** Primary symptoms, possibly with diarrhea
  1) **Viral gastroenteritis:** Rotavirus, norovirus, other caliciviruses
  2) **Preformed bacterial toxins (short incubation period <6 hours):** *S aureus* toxin, *Bacillus* sp toxin
- **Noninflammatory diarrhea:** Acute watery diarrhea without fever or dysentery; sometimes accompanied by fever
  1) **Viral gastroenteritis:** Astrovirus, noroviruses, other caliciviruses, enteric adenovirus, rotavirus
  2) **Bacteria:** ETEC and *V cholerae*
  3) **Parasites:** *G lamblia, Cryptosporidium* sp, *Cyclospora cayetanensis*
- **Inflammatory diarrhea:** Invasive disease; possibly fever and grossly bloody stools

1) **Bacteria:** *Campylobacter* sp, *Shigella* sp, *Salmonella* sp, EIEC, *V parahaemolyticus, E coli* O157:H7, *Y enterocolitica*
2) **Parasites:** *E histolytica*

- **Seafood ingestion:** *Vibrio* sp, *Anisakis* sp, and other genera
- **Persistent diarrhea:** >14 days (especially in travelers to mountainous regions or areas with untreated water)
  1) **Parasites:** *C cayetanensis, E histolytica, Cryptosporidium* sp, *G lamblia*
- **Neurological manifestations:** Paresthesias, respiratory depression, bronchospasm, cranial nerve palsies
  1) **Bacteria:** *Clostridium botulinum* toxin, campylobacter-associated Guillain-Barré syndrome
  2) **Other:** Organophosphate pesticides, thallium poisoning, fish poisoning
- **Systemic illness:** Fever, weakness, arthritis, jaundice
  1) **Bacteria:** *L monocytogenes, Salmonella typhi* and *S paratyphi, Brucella* sp, *V vulnificus*
  2) **Viral:** Hepatitis A and hepatitis E
  3) **Parasites:** *Trichinella spiralis, Toxoplasma gondii, E histolytica* with extraluminal abscess

* American Medical Association; American Nurses Association-American Nurses Foundation; Centers for Disease Control and Prevention; Center for Food Safety and Applied Nutrition, US Food and Drug Administration; Food Safety and Inspection Service, US Department of Agriculture. MMWR Recomm Rep. 2004;53:1-33.

Traveler's Diarrhea

- **Bacterial causes:** *E coli* (most commonly ETEC), *Shigella* sp, *C jejuni, Salmonella* sp, *Aeromonas* sp, *Plesiomonas* sp, noncholera *Vibrio* sp
- **Nonbacterial causes:** Rotavirus (Mexico), Norwalk agent (Mexico), *Giardia* sp (North America, Russia), *Cryptosporidium* sp, *Cyclospora* sp, and, rarely, *Entamoeba* sp
- **High-risk areas:** Developing countries of Latin America, Asia, Africa, and the Middle East
- **Intermediate-risk areas:** Southern Europe and some Caribbean islands
- **Low-risk areas:** United States, Canada, northern Europe, Australia, New Zealand

Noninfectious Considerations

- **Secretory diarrhea:** Carcinoid syndrome, Zollinger-Ellison syndrome, medullary carcinoma of the thyroid, villous adenoma of the rectum, vasoactive intestinal peptide-secreting pancreatic adenoma
- **Inflammatory diarrhea:** Inflammatory bowel disease, ischemic colitis, radiation enteritis, eosinophilic gastroenteritis

Management and Empiric Therapy of Diarrhea

Community-Acquired Diarrhea

- Rehydration for initial management
- Stool culture (if there is fever, bloody stools, or abdominal pain) for *Salmonella, Shigella, Campylobacter*

spp, and *E coli* O157:H7; consider testing for community-acquired *C difficile*

- Empiric therapy (pending cultures) with a fluoroquinolone or macrolide (if fluoroquinolone-resistant *Campylobacter* sp suspected)
- Avoid antimicrobial therapy if *E coli* O157:H7 is suspected (eg, bloody diarrhea with hemolytic uremic syndrome)

Traveler's Diarrhea

- Rehydration is goal of initial management
- No fever or blood in stool
  1) Mild diarrhea of 1-2 loose stools per day: No treatment or only bismuth or loperamide
  2) Moderate to severe diarrhea of >2 loose stools per day: Hydration plus bismuth or loperamide; can add a fluoroquinolone for high stool output (to shorten duration of diarrhea); rifaximin is also an option
- Fever, blood in stool, abdominal pain: A fluoroquinolone for 3 days; stool culture if possible

Persistent (>7 Days) Diarrhea

- Stool examination for *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Isospora* spp, and for other parasites
- Consider noninfectious causes for culture-negative prolonged inflammatory diarrhea (eg, inflammatory bowel disease)

Hospital-Acquired Diarrhea

- Evaluate for *C difficile*; treat severe cases with oral metronidazole or oral vancomycin pending results of *C difficile* toxin stool assay

Intra-Abdominal Infections

Peritonitis and Polymicrobial Intra-Abdominal Infections

Elements of Diagnosis

Primary Peritonitis (Spontaneous Bacterial Peritonitis)

- Peritoneal infection without an obvious source
- Patients with cirrhosis and ascites (eg, due to alcoholism, chronic viral hepatitis) or, occasionally, congestive heart failure, malignancy, or connective tissue disease
- Ascitic fluid with >250/mm^3 polymorphonuclear neutrophils, fever, diffuse abdominal pain; clinical presentation may be more insidious with progressive ascites

Secondary Peritonitis

- Peritoneal infection commonly by communication with gastrointestinal (GI) or genitourinary (GU) tract (eg, due to perforation, trauma, pelvic inflammatory disease [PID]); suppurative or obstructive biliary tract infections; or abdominal abscess
- Fever, marked abdominal pain, tenderness to palpation (focal or diffuse, often with rebound tenderness and muscle rigidity), peripheral and peritoneal fluid leukocytosis
- Prompt abdominal and pelvic computed tomography (CT) scan is optimal for identification of source and definition of treatment; possible surgical options

Peritoneal, Retroperitoneal, or Pelvic Abscess

- Numerous potential sources such as primary or secondary peritonitis (especially due to enteric perforation), appendicitis, diverticulitis, inflammatory bowel disease, PID, postabdominal or pelvic surgery (eg, repair of an enteric or biliary anastomotic leak; splenectomy)
- Commonly polymicrobial infections (especially from enteric or GU source); monomicrobial infections can occur (eg, hematogenous seeding of devitalized tissue, retroperitoneal extension of vertebral osteomyelitis)
- Clinical presentation typically based on location and source of infection
- Abdominal CT (ideal) or ultrasound can define location and potential source and can assist with drainage

Appendicitis

- Most common in older children and young adults in their teens and 20s
- Early symptoms are nonspecific and may include periumbilical or epigastric pain; when parietal peritoneum becomes inflamed, more focused right lower quadrant pain develops
- Pain in the right flank, right back, or right upper quadrant may occur when the inflamed appendix is retrocecal or when appendicitis occurs during pregnancy (2nd and 3rd trimesters)
- Treatment of acute appendicitis is surgical appendectomy

- More prolonged, broadened antimicrobial therapy is indicated in acute appendicitis with perforation or abscess formation and in chronic and recurring appendicitis

Diverticulitis

- Increased dietary fiber and exercise inversely correlate with incidence of diverticulosis; diverticulitis indicates inflammation from microscopic or macroscopic perforation of a diverticulum into pericolic fat
- Left lower quadrant pain occurs in 70% of patients in Western countries, whereas right-sided diverticulitis occurs in only 1-2% (more common in Asians); bleeding may occur
- Uncomplicated diverticulitis can usually be managed with antibiotics alone, although up to one-third of patients will have another episode
- Complicated diverticulitis includes perforation, obstruction, abscess, or fistula; typical management is with both surgery and antimicrobial therapy
- Surgery is generally advised after a first attack of complicated diverticulitis or after 2 or more episodes of uncomplicated diverticulitis

Table 61. Treatment of Peritonitis and Polymicrobial Intra-Abdominal Infections

Syndrome and common pathogens	First-line treatment	Alternate treatment
Primary peritonitis *Escherichia coli, Klebsiella* sp, *Streptococcus pneumoniae*, other streptococci, and *Enterococcus* sp	Ceftriaxone, cefotaxime, cefepime, or levofloxacin for 10-14 days (shorter durations are often successful); SBP recurrence common	carbapenem, piperacillin/tazobactam (Zosyn), ampicillin/sulbactam (Unasyn), ticarcillin/clavulanate (Timentin), moxifloxacin (use moxifloxacin with caution in patients with ESLD)
Abdominal abscess Depends on location and suspected source (polymicrobial or occasionally monomicrobial)	Percutaneous catheter drainage or surgical debridement to: Evacuate devitalized or avascular infected material, define microbiology, and determine duration of antimicrobial therapy Initial therapy as for secondary peritonitis (see below) Targeted antimicrobial therapy based on culture data and suspected source	
Appendicitis Acute, uncomplicated (with luminal obstruction)	Immediate surgery and perioperative antimicrobial prophylaxis: cefazolin plus metronidazole	Other standard surgical wound prophylaxis regimens

Syndrome and common pathogens	First-line treatment	Alternate treatment
Secondary peritonitis Enteric flora, commonly polymicrobial (eg, Enterobacteriaceae,[a] other aerobic gram-negative bacilli, *Bacteroides* sp, other anaerobic bacteria; occasionally aerobic gram-positive bacteria and *Candida* sp	piperacillin/tazobactam; ticarcillin/clavulanate; carbapenem; fluoroquinolone plus metronidazole; 2nd-, 3rd-, or 4th-gen cephalosporin plus metronidazole; or ampicillin/sulbactam plus fluoroquinolone Surgical debridement or drainage may be required Duration of treatment is variable and based on source and surgical intervention, if any For immunocompromised or unstable patients, or for patients with recent antibacterial therapy, consider addition of fluconazole (for *Candida* sp) until microbiology is defined	
Appendicitis With perforation or abscess formation (same as above)	Same as above	
Diverticulitis	Consider surgery for repeated episodes, perforation, or fistula; otherwise, treat same as above	

[a] Enterobacteriaceae group includes *E coli* and *Klebsiella, Enterobacter, Citrobacter, Serratia, Yersinia, Salmonella,* and *Shigella* spp, and others.

Hepatobiliary Infections

Elements of Diagnosis

Cholecystitis and Cholangitis

- Gallstone disease is the most common cause of cholecystitis in the United States
- Cholangitis is commonly associated with obstruction or strictures of the biliary tract
- Symptoms include fever and continuous right upper quadrant abdominal pain
- Murphy sign (ie, inhibition of inspiration by pain during palpation over gallbladder) is often present
- Abdominal ultrasound frequently establishes diagnosis; HIDA scan or abdominal CT is helpful when ultrasound is nondiagnostic

Viral Hepatitis

- **Hepatitis A virus (HAV):** Fecal-oral spread (by contaminated food or water); usually self-limiting; acute viral hepatitis in 40-60% of infections (more common in adults); fulminant disease in 8% of patients; no chronic infection; HAV vaccine and HAV immunoglobulins available
- **Hepatitis B virus (HBV):** Transmission typically by intravenous (IV) route or contaminated needle-stick exposure, perinatal, or by sexual contact; acute hepatitis in 30-40% of infections; chronic disease in 10-25% of infections; risk of cirrhosis and hepatocellular carcinoma with chronic HBV disease; HBV vaccine and HBV immunoglobulins are available
- **Hepatitis C virus (HCV):** Transmission typically by IV or contaminated needle-stick exposure; sexual transmission less common but possible; chronic HCV disease in 85%, with cirrhosis developing in 20% of those patients within 20 years; hepatocellular carcinoma risk increased with HCV-mediated cirrhosis; no HCV vaccine or immunoglobulins currently available
- **Hepatitis D virus (HDV):** A defective RNA virus that uses hepatitis B surface antigen as its structural shell (requires HBV coinfection or superinfection in patients with chronic HBV infection); more aggressive liver disease occurs when HDV superinfects patients with chronic HBV infection, with development of chronic hepatitis in ≥75% and cirrhosis in 70-80%
- **Hepatitis E virus:** Fecal-oral transmission (usually by contaminated water); no chronic disease; 15-25% mortality in pregnant women, especially in 3rd trimester

Hepatosplenic Candidiasis

- More common in patients with hematologic malignancies after prolonged chemotherapy-associated neutropenia
- Common presentation includes persistent fever despite antibacterial agents, especially with recovering neutrophils; occasional right upper quadrant abdominal pain and nausea
- Abdominal CT or magnetic resonance imaging shows characteristic multiple small nodular hypolucent lesions throughout the liver and spleen during neutrophil

recovery; lesions commonly absent with neutropenia

Hepatic Abscess

- Sources include intestinal infections with portal circulation, biliary duct system infections, and contiguous infections
- Bacterial or pyogenic hepatic abscesses generally with acute fever and right upper quadrant abdominal pain
- Abdominal CT or ultrasound for diagnosis and to define treatment options

Splenic Abscess

- Sources include hematogenous seeding (eg, infective endocarditis and other endovascular infections, often in the presence of emboli or hemoglobinopathy), trauma, or contiguous extension from adjacent infected tissue
- Clinical presentation quite variable; fever, abdominal pain, and splenomegaly may all be present
- Abdominal CT or ultrasound for diagnosis and to define treatment options

Table 62. Treatment of Hepatobiliary Infections

Common pathogens	First-line treatment	Alternate treatment
Cholecystitis and cholangitis Enterobacteriaceae, other aerobic gram-negative bacilli, enterococci and other gram-positive bacteria, occasionally *Bacteroides* sp and other anaerobes Less common (biliary tract): *Clonorchis sinensis, Opisthorchis felineus, O viverrini, Fasciola hepatica*	piperacillin/tazobactam; ticarcillin/clavulanate; carbapenem; fluoroquinolone plus metronidazole; a 2nd-, 3rd-, or 4th-gen cephalosporin plus metronidazole; or ampicillin/sulbactam plus a fluoroquinolone Timing of cholecystectomy for cholecystitis debatable; cholecystotomy preferred for unstable patients Drainage of biliary tract in cholangitis by ERCP or percutaneous transhepatic cholangiography	2nd-, 3rd-, or 4th-gen cephalosporin or fluoroquinolone monotherapy
Viral hepatitis HAV HBV HCV	 HAV: Supportive care HBV: pegylated IFN, entecavir, lamivudine, emtricitabine, adefovir, tenofovir HCV: pegylated IFN plus ribavirin	 HBV: IFN HCV: IFN plus ribavirin; pegylated IFN monotherapy
Hepatosplenic candidiasis *Candida albicans* most common	amphotericin product (with or without 5-flucytosine), fluconazole, echinocandin	itraconazole, voriconazole

Common pathogens	First-line treatment	Alternate treatment
Hepatic abscess Commonly polymicrobial: Enterobacteriaceae,[a] other aerobic gram-negative bacilli, *Enterococcus* sp and other gram-positive bacteria, *Bacteroides* sp and other anaerobes; *Entamoeba histolytica*	Pyogenic liver abscess: Surgical drainage; antimicrobial therapy covering suspected pathogens while awaiting microbiology results (see section above on "Cholecystitis and Cholangitis") Amebic liver abscess (*E histolytica*): Typically does not require drainage; metronidazole and an agent (eg, paromomycin) to eliminate enteric carrier state	
Splenic abscess *Staphylococcus aureus*, *Streptococcus* sp, *E coli*, *Salmonella* sp Other: Fungi (*Candida* sp, *Aspergillus* sp) in immunocompromised patients; *Mycobacterium tuberculosis*	Empiric antibiotic selection depends on suspected source and should cover common pathogens; consider splenectomy for complex multifocal or multiloculated bacterial abscess and percutaneous drainage for localized abscess; antifungal therapy is often sufficient for *Candida* abscesses	

[a] Enterobacteriaceae group includes *E coli* and *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Yersinia*, *Salmonella*, and *Shigella* spp, and others.

Neutropenic Fever Empiric Management

Elements of Diagnosis

- **Fever:** Single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) for ≥1 hour
- **Neutropenia:** Neutrophil count of <500 cells/mm^3 or a count of 1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3

Common Pathogens

- Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella* sp)
- Nonfermenting gram-negative bacilli (eg, *Pseudomonas aeruginosa*, *Acinetobacter* sp, *Stenotrophomonas maltophilia*)
- Gram-positive cocci (eg, *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, enterococci)
- Gram-positive bacilli (eg, *Bacillus* sp, *Corynebacterium* sp)[a]

Diagnostic Evaluation

- Review exposure history, recent anti-infective therapy, medications
- Conduct physical examination with particular attention to the pharynx, skin, intravenous access sites, lungs, sinuses, mouth, esophagus, and perianal area
- Run laboratory tests, including complete blood cell count, liver function tests, and creatinine
- Obtain blood and urine cultures
- Order other cultures on the basis of clinical circumstances
- Obtain chest radiographs
- Conduct site-specific imaging studies, as indicated

Initial Impiric Therapy

- **Initial therapy:** Direct at aerobic and facultative gram-negative bacilli
  1) **Monotherapy:** cefepime, ceftazidime,[b] carbapenem,[c] or piperacillin/tazobactam
  2) **Combination therapy:** aminoglycoside or ciprofloxacin plus ceftazidime, an antipseudomonal penicillin (eg, piperacillin), or carbapenem
- **Add vancomycin[d] if**
  1) Clinically suspected catheter-associated infection
  2) Known colonization with methicillin-resistant *S aureus*, penicillin- or cephalosporin-resistant pneumococci
  3) Blood culture positive for gram-positive organisms
  4) Hypotension or other signs of severe sepsis
  5) Prior fluoroquinolone prophylaxis
- **Include coverage for anaerobic bacteria (eg, metronidazole, meropenem, imipenem, piperacillin/tazobactam) if**
  1) Evidence of perianal infection
  2) Presence of necrotizing gingivitis
  3) Recovery of anaerobic bacteria in culture
  4) Potential intraabdominal infection

- **Lower-risk patients**
  1) Consider cautious outpatient management
  2) Use combination oral antibiotic therapy (eg, ciprofloxacin plus amoxicillin/clavulanate)

Pathogen-Directed Therapy

- Base antibiotic selection on in vitro susceptibility data
- Consider combination therapy (eg, β-lactam plus aminoglycoside) for severe infection due to *P aeruginosa* or other resistant gram-negative organisms

Persistent Fever Despite Empiric Antibiotic Therapy

- **Reassess response to treatment on day 3**
  1) If patient is stable, continue with same antibacterial program
  2) Discontinue vancomycin if cultures are negative for gram-positive organisms
  3) If patient is clinically worsening, change or augment antibacterial regimen
- **Persistent fever and neutropenia by day 5**
  1) Add an antifungal agent (eg, voriconazole, amphotericin B product,[e] or caspofungin) with or without a change in the antibiotic regimen; for patients who have been receiving antifungal prophylaxis with an azole, use either an amphotericin B product or caspofungin[f]
  2) Repeat diagnostic clinical examination (with or without radiographs, as indicated)

Duration of Antibiotic Therapy

- Stop antibiotic therapy when neutrophil count is ≥500 cells/mm^3 for 2 consecutive days and patient is afebrile for ≥48 hours if
  1) No evidence of focal infection
  2) Cultures are negative
- Continue antibiotic therapy for 4-5 days after neutrophil count is ≥500 cells/mm^3 if fever persists
- If patient remains febrile and neutropenic with no other evidence of infection, continue anti-infective agents for 2 weeks, followed by clinical reassessment and consideration of discontinuation of antibiotic therapy

Other Considerations

- In patients with a history of a type 1 allergic reaction to penicillin, consider use of aztreonam or ciprofloxacin, or aminoglycoside for coverage of gram-negative organisms
- For patients with a history of vancomycin allergy, consider use of linezolid or daptomycin
- Guide choice of empiric anti-infectives by local or institutional antibiotic resistance profiles
- Consider removal of vascular catheter in patients with fungi or mycobacteria isolated in blood culture, or in patients with bacterial cultures that are persistently positive, or in hemodynamically unstable patients with positive cultures
- Consider granulocyte transfusions only in unusual circumstances (eg, disseminated *Fusarium* sp infection)

[a] Recovery of these organisms in blood culture usually suggests an intravenous catheter infection.

[b] Prolonged use of ceftazidime may induce or select for β-lactamase production, leading to antibiotic resistance in certain gram-negative organisms such as *Enterobacter* sp, *E coli*, or *Klebsiella* sp.

[c] Appropriate carbapenems include meropenem or imipenem/cilastatin; ertapenem does not have reliable activity against *Pseudomonas* sp or other nonfermenting gram-negative bacilli.

[d] In patients known to be colonized with vancomycin-resistant enterococci, linezolid should be used in place of vancomycin.

[e] Liposomal amphotericin B, amphotericin B lipid complex, or amphotericin B deoxycholate.

[f] An amphotericin product is preferable for patients who have been receiving voriconazole prophylaxis or if the clinical situation suggests possible zygomycosis.

Sexually Transmitted Diseases*

Elements of Diagnosis

Urethritis

- Abrupt-onset, purulent urethral discharge and dysuria more common with *Neisseria gonorrhoeae* than with *Chlamydia trachomatis* and other nongonococcal urethritis (NGU) pathogens
- Mucopurulent or purulent urethral discharge and dysuria can occur with any pathogen, which often impedes clinical distinction
- Gram stain of urethral discharge shows >5 leukocytes per high-power field (HPF)
- Positive leukocyte esterase test on first-void urine
- Presence of gram-negative diplococci on stain or culture does not exclude coinfection with other pathogens
- Coinfection with *N gonorrhoeae* and *C trachomatis* or *Ureaplasma urealyticum* occurs in 15-20% of heterosexual men with urethritis

Cervicitis

- Mucopurulent or purulent endocervical discharge
- Gram stain of cervical discharge shows >10 leukocytes per HPF
- Most common in adolescent females
- Commonly presents without symptoms
- Coinfection common with *N gonorrhoeae* and *C trachomatis* or *U urealyticum*
- Abdominal pain and adnexal tenderness may signify pelvic inflammatory disease

Vaginitis

- Clinical clues include vaginal discharge, vulvar pruritus, dyspareunia
- Microscopic examination with cover slip can reveal motile trichomonads and clue cells
- KOH (potassium hydroxide) preparation enables identification of *Candida* sp as yeast or pseudohyphae
- Positive whiff test with KOH is characteristic of trichomoniasis and bacterial vaginosis (BV)
- Vaginal fluid pH is >4.5 in trichomoniasis and BV

Genital Ulcerative Diseases

- **Syphilis:** Average incubation period 21 days; painless ulcers (chancres); nontender, nonfluctuant adenopathy in primary syphilis
- **Chancroid:** Incubation period 2-7 days; painful ulcers; fluctuant adenopathy
- **Genital herpes:** Incubation period 2-7 days; multiple vesicles; painful ulcers; can recur
- **Lymphogranuloma venereum:** Variable incubation period; characteristic "groove sign"; fluctuant buboes that can rupture
- **Donovanosis (granuloma inguinale):** Variable incubation period; painless ulcers; scar formation

* Centers for Disease Control and Prevention, et al. MMWR Recomm Rep. 2006;55:1-94. Erratum in: MMWR Recomm Rep. 2006;55:997.

Common Pathogens and Clinical Characteristics

Urethritis: Urethral Discharge and Dysuria (Common)

- **NGU:** Symptoms less abrupt; more mucoid discharge; more common than gonorrhea in the US and developed countries
  1) ***C trachomatis:*** Most common NGU pathogen (30-50% of cases)
  2) ***U urealyticum:*** 20-25% of cases
  3) **Less common (1-5%)**
     a) Herpes simplex virus
     b) *Trichomonas vaginalis*
     c) *Mycoplasma genitalium*

Cervicitis: Possible Cervical Discharge or Asymptomatic

- Same pathogens as urethritis
- Human papillomavirus (HPV)

Vaginitis: Vaginal Discharge, Vaginal Irritation

- **BV:** 30-45% of cases; replacement of normal vaginal hydrogen peroxide–producing lactobacilli with anaerobic bacteria (eg, *Bacteroides*, *Mobiluncus*, and *Peptostreptococcus* spp), *Gardnerella vaginalis*, and *Mycoplasma hominis*
  1) **Vaginal discharge:** Moderate amount; gray or white; homogeneous and adherent; pH >4.5
  2) **Addition of KOH (whiff test):** Positive (fishy odor)
  3) **Microscopy examination (wet mount):** Clue cells present; few leukocytes
- ***Candida* sp:** 20-25% of cases; controversial vaginal sexually transmitted disease (STD) pathogen
  1) **Vaginal discharge:** Scant or moderate; white, clumped, adherent; pH 4.0-4.5
  2) **Whiff test:** No odor
  3) **Microscopy examination (KOH wet mount):** Pseudohyphae often present; few leukocytes
- ***Trichomonas vaginalis:*** 15-20% of cases
  1) **Vaginal discharge:** Profuse; green-yellow; homogeneous; frothy; pH 5.0-6.0
  2) **Whiff test:** Usually fishy odor
  3) **Microscopy examination (KOH wet mount):** Motile trichomonads; many leukocytes

Genital Ulcerative Diseases: Cutaneous Ulcerations, Commonly With Adenopathy

- *Treponema pallidum:* Syphilis
  1) **Lesions:** Usually painless and single; occasionally multiple; sharply demarcated border; indurated with red or smooth base
  2) **Lymphadenopathy:** Unilateral or bilateral; nontender, firm
- *Haemophilus ducreyi:* Chancroid
  1) **Lesions:** Multiple, painful, nonindurated or mildly indurated; erythematous border with rough yellow-gray base
  2) **Lymphadenopathy:** Usually unilateral; tender; may suppurate

- **Herpes simplex virus**
  1) **Lesions:** Multiple painful lesions; may coalesce; nonindurated, smooth, erythematous lesions
  2) **Lymphadenopathy:** Usually bilateral; firm and tender
- **L1, L2, L3 serovars of *C trachomatis*:** Lymphogranuloma venereum
  1) **Lesions:** Usually single; variable pain; nonindurated
  2) **Lymphadenopathy:** Unilateral or bilateral; firm, tender; frequently suppurative; "groove sign" common (lymphadenopathy above and below inguinal ligament)
- ***Calymmatobacterium granulomatis:*** Donovanosis
  1) **Lesions:** Single or multiple rolled or elevated rough lesions; usually nontender
  2) **Lymphadenopathy:** Pseudoadenopathy; inguinal swelling

Table 63. Pathogen-Directed Therapy

Clinical situation	First-line treatment	Alternate treatment
Urethritis and cervicitis (unless excluded by laboratory testing, treat for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis*)		
N gonorrhoeae[a]	ceftriaxone 125 mg IM once **or** cefixime 400 mg oral once Note: fluoroquinolone no longer recommended for treatment of gonococcal infections in US because of widespread resistance	spectinomycin 2 g IM once ceftizoxime 500 mg IM once cefotaxime 500 mg IM once
C trachomatis and other NGU pathogens	azithromycin 1 g oral once **or** doxycycline 100 mg oral bid for 7 days	erythromycin base 500 mg oral qid for 7 days **or** erythromycin ethylsuccinate 800 mg oral qid for 7 days **or** ofloxacin 300 mg oral bid for 7 days **or** levofloxacin 500 mg oral q24h for 7 days

Clinical situation	First-line treatment	Alternate treatment
Recurrent or persistent urethritis or cervicitis (ensure that both *N gonorrhoeae* and NGU pathogens were treated appropriately)		
Ureaplasma urealyticum (tetracycline-resistant)	azithromycin or erythromycin regimen (dosing above for NGU)	
Trichomonas vaginalis	metronidazole 2 g oral once **or** tinidazole 2 g oral once	

Clinical situation	First-line treatment	Alternate treatment
Vaginitis		
Bacterial vaginosis	metronidazole 500 mg oral bid for 7 days **or** metronidazole gel 0.75% 5 g intravaginal daily for 5 days **or** clindamycin cream 2% 5 g intravaginal for 7 days	metronidazole 2 g oral once **or** clindamycin 300 mg oral bid for 7 days **or** clindamycin ovules 100 mg intravaginal daily for 3 days
Candida sp	Intravaginal agents: butoconazole, clotrimazole, miconazole, nystatin, tioconazole, terconazole Oral systemic agents: fluconazole 150 mg once; itraconazole 200 mg once	Boric acid (intravaginal)
T vaginalis	metronidazole 2 g oral once **or** tinidazole 2 g oral once **or** metronidazole 500 mg bid for 7 days	

Clinical situation	First-line treatment	Alternate treatment
Genital ulcerative disease		
Primary syphilis	benzathine penicillin G 2.4 million units IM once	doxycycline 100 mg oral bid for 14 days **or** tetracycline 500 mg oral qid for 14 days **or** ceftriaxone 250 mg q24h IV or 1 g IV or IM every other day for 8-10 days **or** azithromycin 2 mg oral once (failures and increasing resistance reported)
Chancroid	azithromycin 1 g oral once **or** ceftriaxone 250 mg IM once **or** ciprofloxacin 500 mg oral bid for 3 days **or** erythromycin base 500 mg oral qid for 7 days	

Clinical situation	First-line treatment	Alternate treatment
HSV		
First episode	acyclovir 400 mg oral tid for 7-10 days **or** valacyclovir 1 g oral bid for 7-10 days **or** famciclovir 250 mg oral tid for 7-10 days	
Recurrent disease	acyclovir 400 mg tid or 800 mg bid for 5 days **or** valacyclovir 500 mg to 1 g oral once daily for 3-5 days **or** valacyclovir 1 g daily or q24h oral for 5 days **or** famciclovir 250 mg oral bid for 5 days	
Suppressive therapy	acyclovir 400 mg oral bid **or** valacyclovir 500 mg to 1 g oral once daily **or** famciclovir 250 mg oral bid	
Severe disease or complications (eg, disseminated infection, pneumonitis, hepatitis, meningitis, encephalitis)	acyclovir IV 5-10 mg/kg q8h	

Clinical situation	First-line treatment	Alternate treatment
LGV	doxycycline 100 mg oral bid for 21 days	erythromycin base 500 mg oral qid for 21 days **or** azithromycin 1 g oral once weekly for 3 weeks
Donovanosis	doxycycline 100 mg oral bid >3 weeks **or** tmp/smx 1 DS tab bid >3 weeks	ciprofloxacin 750 mg oral bid for >3 weeks **or** erythromycin base 500 mg oral qid for >3 weeks **or** azithromycin 1 g oral once per week for >3 weeks

[a] Nondisseminated.

Other Conditions

Human Papillomavirus

- Types 6 and 11: Condyloma acuminatum (anogenital warts); most common viral STD in US
- Types 16, 18, 31, 33, and 35: Cervical infection; oncogenic association with cervical cancer
- Most HPV infections are clinically asymptomatic; gynecologic examinations with Papanicolaou test recommended

Molluscum Contagiosum: Benign Disease Caused by Poxviridae Virus

- Classically 2- to 10-mm dome-shaped papules, often with central umbilication
- Treatment is local curettage or cryotherapy

Pelvic Inflammatory Disease: Endometriosis, Salpingitis, Tubo-Ovarian Abscess, Pelvic Peritonitis

- Clinical diagnosis with findings of cervical motion tenderness; uterine or adnexal tenderness
- When associated with cervicitis, *N gonorrhoeae* and *C trachomatis* are primary pathogens
- Anaerobic bacteria and *Streptococcus* sp may contribute
- Treatment: Intravenous (IV) regimen
  1) First-line treatment
     a) cefotetan 2 g IV q12h or cefoxitin 2 g IV q6h plus doxycycline 100 mg IV or oral q12h
     b) clindamycin 900 mg IV q8h plus gentamicin 2 mg/kg IV load then gentamicin 1.5 mg/kg IV q8h
  2) Alternate treatment
     a) ampicillin/sulbactam 3 g IV q8h plus doxycycline 100 mg IV q12h
- Treatment: Non-IV regimen
  1) ceftriaxone 250 mg intramuscular (IM) once or cefoxitin 2 g IM plus probenecid 1 g oral once plus doxycycline 100 mg oral bid for 14 days with or without metronidazole 500 mg oral bid for 14 days
  2) Other select 3rd-generation cephalosporin (eg, ceftizoxime or cefotaxime) plus doxycycline 100 mg oral bid for 14 days with or without metronidazole 500 mg oral bid for 14 days
  3) levofloxacin 500-750 mg with or without metronidazole 500 mg q8h
  4) fluoroquinolone (eg, levofloxacin or ofloxacin) with or without metronidazole may be considered in select cases with documented susceptibility data

Note

- Avoid fluoroquinolone and doxycycline during pregnancy
- Avoid metronidazole during 1st trimester of pregnancy; metronidazole may cause a disulfiram-like reaction with alcohol

Tuberculosis

New Diagnostic Tests

- **Serum interferon-γ release assay (IGRA):** *Mycobacterium tuberculosis* antigen-specific interferon (IFN)-γ release assays: Serum QuantiFERON-TB Gold (Cellestis, Ltd, Melbourne, Australia) and T-SPOT.TB (Oxford Immunotec, Ltd, Oxford, United Kingdom)
  1) Detect IFN-γ release from specific, previously sensitized, memory T-cells by in vitro stimulation by *M tuberculosis*–specific proteins (eg, ESAT-6 and CFP10)
  2) Identify patients infected with *M tuberculosis* (either active or inactive disease)
  3) Differentiate *M tuberculosis* infection from previous bacille Calmette Guérin vaccination and most nontuberculosis mycobacteria infections
  4) False-positive results possible with *M marinum*, *M kansasii*, and *M szulgai* infections
  5) IGRAs may be used in the same setting as the tuberculosis (TB) skin test (also called TST, PPD [purified protein derivative], or Mantoux test); as with the TST, if active TB is suspected, additional diagnostic testing (eg, chest radiograph, sputa collection for appropriate stains and cultures, human immunodeficiency virus [HIV] testing) should be performed before IGRA results are available
- **Nucleic acid amplification (NAA) assays:** Amplicor MTB test (*Mycobacterium tuberculosis* polymerase chain reaction test) (Roche Diagnostic Systems, Inc, Nutley, New Jersey) and the Amplified *Mycobacterium tuberculosis* Direct Test (MTD; Gen-Probe, San Diego, California)
  1) Both NAA assays are approved for direct detection of *M tuberculosis* in smear-positive respiratory specimens; the MTD is also approved for smear-negative respiratory specimens of suspect patients
  2) Both NAA assays are intended to complement acid-fast bacillus (AFB) smear and mycobacterial culture and to offer a more sensitive and rapid early detection method for active TB

Treatment of Latent Tuberculosis Infection in Adults With No Clinical or Radiologic Evidence of Active Disease

- isoniazid 5 mg/kg q24h (300 mg maximum) oral for 9 months
- rifampin 10 mg/kg q24h (600 mg maximum) oral for 4 months
- Alternate treatment or select regimens
  1) isoniazid 900 mg twice weekly (by directly observed therapy [DOT]) for 9 months
  2) No longer recommended: rifampin plus pyrazinamide for 2 months

Treatment of Pulmonary Tuberculosis

- General rules for drug-susceptible *M tuberculosis* isolates
  1) All 6-month regimens should contain isoniazid,

rifampin, and (initially, for 2 months) pyrazinamide
2) All 9-month regimens should contain isoniazid and rifampin
3) DOT strongly recommended for all patients

Standard Therapy for Drug-Susceptible Pulmonary *M tuberculosis*

Option 1

- **Initiation:** isoniazid, rifampin, pyrazinamide, and ethambutol[a] daily for 8 weeks (56 doses)
- **Continuation options**
  1) isoniazid and rifampin daily for 18 weeks (126 doses)
  2) isoniazid and rifampin twice weekly for 18 weeks (36 doses)[b]
  3) isoniazid[b] and rifapentine[c] once weekly for 18 weeks (18 doses)

Option 2

- **Initiation:** isoniazid, rifampin, pyrazinamide, and ethambutol[a] daily for 2 weeks (14 doses); then isoniazid, rifampin, pyrazinamide, and ethambutol[a] twice weekly for 6 weeks (12 doses)[b]
- **Continuation options**
  1) isoniazid and rifampin twice weekly for 18 weeks (36 doses)[b]
  2) isoniazid[b] and rifapentine[c] once weekly for 18 weeks (18 doses)

Option 3

- **Initiation:** isoniazid, rifampin, pyrazinamide, and ethambutol[a] 3 times weekly for 8 weeks (24 doses)[b]
- **Continuation:** isoniazid and rifampin 3 times weekly for 18 weeks (54 doses)[b]

Option 4 (for Pregnant Patients or Those Intolerant of pyrazinamide[d,e])

- **Initiation:** isoniazid, rifampin, and ethambutol daily for 8 weeks (56 doses)
- **Continuation options**
  1) isoniazid and rifampin daily for 31 weeks (217 doses)
  2) isoniazid and rifampin twice weekly for 31 weeks (62 doses)[b]

Treatment Duration (Pulmonary Disease With Susceptible *M tuberculosis* Isolate)

- 2-month induction phase of treatment
- 4-month continuation phase for most patients (6-month total treatment)
- 7-month continuation phase recommended for 3 groups of patients (9-month total treatment)
  1) Patients with cavitary disease caused by drug-susceptible organisms whose sputum culture at end of 2-month initial treatment period is positive
  2) Patients whose initial phase of treatment did not contain pyrazinamide
  3) Patients treated with once-weekly isoniazid plus

rifapentine whose sputum culture at end of 2-month initial treatment period is positive

Special Circumstances

- **HIV coinfection**
  1) rifampin-based regimens generally not recommended with most protease inhibitors or nonnucleoside reverse transcriptase inhibitors[f]
  2) rifabutin causes less hepatic cytochrome P-450 induction than rifampin and may be used in place of rifampin (with dosing adjustments); information about rifamycin and select antiretroviral drug dosing can be found on the Web site of the Centers for Disease Control and Prevention*
  3) The once-weekly isoniazid plus rifapentine continuation phase is contraindicated for HIV-positive patients because of an unacceptably high rate of relapse or failure (often with rifamycin-resistant organisms)
  4) Twice-weekly treatment, as part of either an initial phase or a continuation phase, is not recommended for HIV-positive patients with a CD4 count <100 cells/mcL
  5) Consultation with HIV expert recommended
- **Drug-resistant TB:** Consultation with TB expert recommended
- **Culture-negative TB (2 treatment options)**
  1) isoniazid, rifampin, pyrazinamide, and ethambutol daily for 6 months (preferred)
     a) Using all 4 drugs for duration of therapy is justified because of possible drug resistance
     b) If source patient (index case) is known to have a drug-susceptible isolate, then pyrazinamide and ethambutol may possibly be stopped after 2 months
  2) isoniazid, rifampin, pyrazinamide, and ethambutol for first 2 months, followed by isoniazid and rifampin for 2 more months (4 months total)

[a] Can discontinue ethambutol if susceptibility data are available and isolate is sensitive to isoniazid, rifampin, and pyrazinamide. If pyrazinamide is not used, continue ethambutol for first 2 months for susceptible *M tuberculosis* isolate.

[b] When isoniazid, pyrazinamide, and ethambutol are given 2-3 times weekly instead of daily, their doses must be increased. The rifampin dose is the same whether given daily or intermittently.

[c] Note: Continuation phase of treatment may consist of isoniazid plus rifapentine once weekly for 4 months (by DOT) for HIV-negative patients with noncavitary pulmonary TB and negative sputum smears at completion of initial 2-month treatment.

[d] Use of pyrazinamide not recommended, and streptomycin should be avoided during pregnancy. Streptomycin can be harmful to fetus; effects of pyrazinamide on fetus not well studied.

[e] Pregnant women taking isoniazid should also receive vitamin B_6.

[f] Exceptions to this rule include ritonavir and efavirenz.

*TB/HIV Drug Interactions. Available from: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm. Updated January 20, 2004.

Table 64. Indications for Use of Vitamin B_6 (Pyridoxine) With Isoniazid

Alcoholism	Preexisting peripheral neuropathy
Diabetes mellitus	Pregnancy (includes 2 months postpartum)
HIV infection	Seizure disorder
Malnutrition	Uremia

Table 65. Treatment of Extrapulmonary Tuberculosis

Location	Length of treatment for drug-susceptible disease	Role of steroids
Lymph node	6 mo	No
Bone and joint	6-9 mo	No
Vertebral	9-12 mo	No
Pleural disease	6 mo	No
Pericarditis	6 mo	Recommended[a]
CNS	9-12 mo	Recommended[b,c]
Disseminated		
Adults	6 mo	No
Children	9 mo	No
Genitourinary	6 mo	No
Peritoneal	6 mo	No

[a] Usual prednisone dosing for pericarditis (adults): 60 mg daily for 4 weeks, followed by 30 mg daily for 4 weeks, then 15 mg daily for 2 weeks, then 5 mg daily for 1 week.

[b] Adjunctive dexamethasone is recommended for all patients with central nervous system (CNS) tuberculosis (TB), particularly those with a decreased level of consciousness or TB meningitis.

[c] Usual dexamethasone dose for CNS TB is 12 mg daily (adults) for 3 weeks, which is then gradually tapered over the following 3 weeks.
Modified from Blumberg et al. Am J Respir Crit Care Med. 2003;167:603-62. Used with permission.

Nontuberculosis Mycobacterial Infections

Mycobacteria Classification, Identification, and Diagnosis

Runyon Classification of Nontuberculosis Mycobacteria (NTM)

- **Group I (photochromogens):** Produces pigment in light: *M kansasii, M marinum, M simiae*
- **Group II (scotochromogens):** Produces pigment in dark: *M scrofulaceum, M szulgai, M xenopi, M gordonae*
- **Group III (nonphotochromogens):** No pigment: *M avium-intracellulare* complex (MAC), *M haemophilum, M ulcerans, M malmoense, M terrae* group
- **Group IV (rapidly growing mycobacteria):** *M fortuitum, M chelonae, M abscessus*

Laboratory or Diagnostic Testing

- Microbial stains
  1) **Acid-fast bacilli (AFB) stain (Ziehl-Neelsen or Kinyoun carbolfuchsin):** Red-staining mycobacteria on blue-green background
     a) Beaded ("barber pole") appearance with *M kansasii*
     b) *Nocardia* and *Rhodococcus* spp will also stain weakly AFB positive
  2) **Auramine-rhodamine stain (fluorescence microscopy):** More sensitive than AFB stain; less specific
- Culture: Both broth and solid media
- Rapid mycobacteria identification tests
  1) **HPLC:** Identifies differing species by specific mycolic acid fingerprint patterns
  2) **DNA probes:** Available for identifying *M tuberculosis, M gordonae, M kansasii*, and MAC
  3) **BACTEC NAP test (BD, Franklin Lakes, NJ):** Inhibits growth of *M tuberculosis* but not NTM strains
- Interferon-γ release assays may be useful pending diagnostic microbial testing to help exclude *M tuberculosis* infection from most NTM infections

Specialized Diagnostic Criteria for NTM Pulmonary Disease

- **Note:** All 4 criteria are required, because many NTM can be isolated as environmental contaminant or airway commensal or as minimal disease
  1) Clinical pulmonary symptoms
  2) Radiographic findings include nodular or cavitary opacities on chest radiographs or computed tomography (CT) scans with multifocal bronchiectasis and multiple small nodules
  3) Two or more sputa samples or one bronchial wash or lavage or biopsy with NTM growth
  4) Exclusion of other diagnoses

Major Syndromes of Select NTM Mycobacteria

Pulmonary Disease

- **Most common:** MAC, *M kansasii*
- **Less common:** *M abscessus, M fortuitum, M szulgai,*

M xenopi (in areas of Canada, United Kingdom, and Europe), *M malmoense* (in Scandinavia and other areas of northern Europe), *M celatum*, *M asiaticum*, and *M shimodii*

Skin, Soft-Tissue, and Bone or Joint Disease

- **Cutaneous disease:** *M marinum*, rapidly growing mycobacteria (ie, *M fortuitum*, *M chelonae*, *M abscessus*), *M ulcerans*
- **Tenosynovitis of hand:** *M marinum*, MAC, rapidly growing mycobacteria, *M kansasii*, *M terrae*, *M szulgai*, *M malmoense*, *M xenopi*
- **Postsurgical wound infections:** Commonly caused by rapidly growing mycobacteria

Lymphadenitis

- **Note:** Localized head and neck NTM lymphadenitis is predominantly a disease of children aged 1-5 years caused primarily by MAC, *M scrofulaceum*, and, in northern Europe, *M malmoense*
- **Note:** *M tuberculosis* accounts for 90% of mycobacterial lymphadenitis in adults and for many cases in children living in regions where tuberculosis (TB) is endemic

Disseminated Disease (Typically in Immunosuppressed Patients)

- **Corticosteroid use, transplant recipients, hematologic malignancies**
  1) **Fever of unknown origin:** MAC
  2) **Multiple skin or subcutaneous abscesses:** *M kansasii*, *M chelonae*, *M abscessus*, *M haemophilum*, *M scrofulaceum*
- **Human immunodeficiency virus (HIV):** Typically CD4 counts <50 cells mcL
  1) **Bacteremia:** MAC (most common bacterial bloodstream pathogen in AIDS patients)
  2) *M kansasii* (associated with pulmonary disease), *M haemophilum* (associated with skin, soft-tissue, bone, and joint infections)

Select Nontuberculosis Mycobacteria

M avium-intracellulare Complex (MAC)

General Information: Pulmonary Disease

- **Risk factors or associations with pulmonary MAC disease**
  1) α_1-Antitrypsin deficiency
  2) Ciliary dyskinesia
  3) Cystic fibrosis
  4) Gastroesophageal reflux disease
  5) Prior pulmonary histoplasmosis
  6) Slender body habitus with pectus excavatum
- **Course:** High variability in pulmonary disease and rates of disease progression; patients with minimal pulmonary disease may not require treatment
- **Diagnosis:** Pulmonary MAC diagnosed by composition of active symptoms, radiologic findings on chest radiograph (or CT scan), and positive MAC cultures
- **Posttreatment–recurring MAC disease:** Not uncommon, especially with chronic lung disorders (eg,

bronchiectasis)

Clinical Disease

- Immunocompetent patients
  1) Pulmonary disease
     a) **Fibrocavitary ("TB") type:** Can appear similar to TB with predominance of upper lobe cavitary disease; about 50% of cases
        - Typically men; heavy smoking, alcoholism; aged <60 years
        - Higher MAC organism burden; AFB stain commonly positive
        - Monomicrobial MAC infection more common
     b) **Nodular bronchiectasis type:** Presence of bronchiectasis with nodular disease; 40% of cases
        - Typically women; nonsmoking, no alcoholism; mean age, 70 years
        - Lower MAC organism burden; AFB smear commonly negative
        - Polymicrobial infections common (ie, coexisting MAC, *P aeruginosa*, rapidly growing NTM, *Aspergillus* sp, *Nocardia* sp, and other MAC substrains)
  2) Hypersensitivity-like pulmonary disease
     a) **Common association with hot tubs:** Especially common with indoor hot tubs ("hot tub lung")
     b) **Patients:** Often relatively young and healthy; chest CT scan may show diffuse infiltrate with ground-glass opacities
  3) Head or neck lymphadenitis (ie, cervical); predominantly a pediatric infection in children aged 1-5 years
  4) Cutaneous disease with external hypersensitivity reactions; rarely disseminated
- HIV, AIDS, or immunosuppressed patients
  1) **Disseminated disease:** With positive blood cultures
  2) **Enteric disease:** Enteritis, colitis, malabsorption
  3) **Pulmonary disease:** Less common

Treatment of Pulmonary MAC Disease

- Combination therapy for at least 12 months of negative sputum cultures while undergoing treatment
  1) **First-line treatment:** Use clarithromycin (or azithromycin) plus ethambutol and plus rifampin (or rifabutin)
     a) Daily therapy (for cavitary or severe disease) or thrice-weekly therapy
     b) Consider addition of thrice-weekly amikacin or streptomycin for first 2-3 months for severe and extensive (especially cavitary) disease
     c) Susceptibility testing recommended initially only for clarithromycin; no other susceptibility testing is correlated with clinical outcome
     d) Follow monthly mycobacteria sputum cultures
     e) A 2-drug treatment with clarithromycin (or azithromycin) plus ethambutol may be acceptable

in select mild cases

2) **Alternate treatment:** Consider moxifloxacin, levofloxacin, amikacin, ethionamide, possibly linezolid

3) **Pulmonary hygiene optimization:** With chronic lung disease or bronchiectasis: Flutter valve, postural drainage, β-agonist inhaler; possibly mucolytic agents

Treatment of Hypersensitivity MAC Lung Disease

- Remove source of exposure (eg, avoid contaminated hot tub)
- Moderate to severe cases: Consider corticosteroid taper (4-8 weeks) or combination drug therapy for shorter periods (3-6 months) or both

Treatment of Children With NTM Cervical Lymphadenitis (MAC, *M scrofulaceum*)

- Excisional surgery without chemotherapy
- Combination drug therapy if surgical excision is incomplete

Treatment of Disseminated MAC Disease (Advanced HIV or AIDS Patients)

- Combination therapy with daily clarithromycin (or azithromycin) plus ethambutol with or without rifabutin (or rifampin)
- Duration of therapy in HIV-positive patients: Lifelong or consider discontinuing after at least 12 months in asymptomatic patients with sustained increase in CD4 counts >100 cells/mcL for more than 6 months after highly active antiretroviral therapy
- Avoid adverse drug interactions (eg, rifabutin and select antiretroviral drugs) in HIV patients (for more information, see the Centers for Disease Control and Prevention Web site*)

*TB/HIV Drug Interactions. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Division of Tuberculosis Elimination. Atlanta (GA): Centers for Disease Control and Prevention. [updated 2004 Jan 20; cited 2007 Jul 14]. Available from: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm.

M kansasii

General Information

- **Appearance:** Long, banded or "beaded" on AFB stain
- **Geographic predominance:** Midwestern and southwestern US; isolated from soil, natural water supplies, tap water

Clinical Disease

- **Pulmonary disease:** Thin-walled cavities are common on chest radiographs, although noncavitary and nodular bronchiectasis disease can occur
- **Lymphadenitis:** Especially cervical lymph node involvement
- **Granulomatous skin lesions, erythema nodosum**
- **Bone, joint, and soft-tissue infection**

Treatment

- **First-line treatment:** Use isoniazid plus rifampin plus ethambutol for at least 12 months of negative sputum cultures in pulmonary disease; rifampin is the cornerstone of treatment and the only drug associated

with in vitro resistance and clinical failure

- **Alternate treatment:** Consider clarithromycin, moxifloxacin, rifabutin, amikacin, streptomycin, sulfamethoxazole
- **Note:** *M kansasii* is resistant to pyrazinamide which can be a "non–*M tuberculosis* complex" identifying marker

M marinum

General Information

- Known as "swimming pool granuloma" or "fish tank granuloma"; associated with exposure to salt water, freshwater, fish tanks, and swimming pools
- Infection acquired by skin inoculation; preferential growth in cooler areas of body 27-32°C (ie, extremities)

Clinical Disease

- **Cutaneous disease:** Granulomatous skin lesions; nodules commonly in line of lymphatic drainage ("ascending" appearance similar to that of cutaneous sporotrichosis)
  1) Typically appears on extremities (eg, elbows, knees, dorsum of feet and hands)
  2) May be solitary, grouped, or widespread
- **Tenosynovitis**

Treatment: Variable Approaches (Typically Less Virulent Mycobacteria)

- **Skin and soft-tissue infection:** Use 2 active drugs for 3-4 months (typically 1-2 months after symptoms resolve); single-drug therapy may be an alternate approach for minimal disease in select cases
- **Tenosynovitis and joint disease:** May require debridement with combination drug therapy for 4-6 months
- **First-line drug treatment:** Use clarithromycin (or azithromycin) plus ethambutol; rifampin can be added for bone and other more serious forms of disease
- **Alternate drug treatment:** Consider trimethoprim-sulfamethoxazole (tmp/smx); minocycline or doxycycline; moxifloxacin or ciprofloxacin

M leprae: Leprosy, Hansen Disease

General Information

- *M leprae* grows best at cooler temperatures (33°C) and has a predilection for cooler areas of the body
- Found mainly in the tropics and subtropics; man is its only host and infection is spread by direct contact (eg, close household contact; nasal discharge from infected patient is most common mode of transmission)
- Organism is **not** cultured from laboratory media; diagnosis is made clinically with supporting tissue histology and microbial stains

Clinical Syndromes

- **Lepromatous leprosy:** Symmetric nodules (widely distributed), thickened dermis; cooler areas of body mostly affected; nasal collapse (ie, saddle-nose deformity), ear lobes; skin biopsy shows many bacilli
- **Tuberculoid leprosy:** Few hypopigmented anesthetic macules with distinct borders; distal hypesthesia with

selective loss of pain and temperature most common; peripheral nerves may become large and palpable; prominent neurological involvement; skin biopsy shows only few bacilli

- **Other clinical findings of leprosy**
  1) Peripheral neuritis: Ulnar nerve tropism leading to clawing of 4th and 5th fingers with decreased motor skill ("claw hand") and decreased sensory and fine touch; may be associated with skin lesions
  2) Nasal collapse
  3) Renal amyloidosis
  4) Uveitis, glaucoma
  5) Gynecomastia (due to decreased testosterone)
- **Reversal reactions:** Clinical disease produced by change in host's immune response to *M leprae*
  1) **Type I reactions:** Induced by cell-mediated immunity
     a) **Upgrading reactions:** Typically seen in patients with borderline lepromatous disease who undergo a shift toward more tuberculoid (paucibacillary) forms; may develop after induction of therapy
     b) **Downgrading reactions:** Occur with transformation from tuberculoid to more lepromatous (multibacillary) form; often develop in absence of therapy
     c) **Note:** Both reactions may appear similar clinically and may contain erythema and edema of existing skin lesions with painful neuropathy and ulceration; treat severe reactions with a corticosteroid taper
  2) **Type II reactions:** Immune complex–mediated; including erythema nodosum leprosum
     a) Immune complex–mediated vasculitis; often ulceration with damage to nerves
     b) Treatment options include NSAIDS, corticosteroids, clofazimine, thalidomide

Treatment

- **Paucibacillary disease:** dapsone plus rifampin for 12 months
- **Multibacillary disease:** dapsone plus rifampin plus clofazimine for >24 months

The Rapidly Growing Mycobacteria: M fortuitum, M chelonae, M abscessus

General Information

- Typical growth in liquid media within 3-7 days
- Water, soil, and nosocomial pathogens; flourish in warm humid environments (eg, hot tubs, water piping)
- Typically appear AFB-stain positive, but can be weakly staining or appear AFB-stain negative
- Can infect immunocompetent, healthy patients
- Geographic predominance in southeastern US, along Gulf Coast (from Florida to Texas), Hawaii

Clinical Disease

- Pulmonary disease
  1) Occurs typically in patients with underlying chronic

lung disease; bronchiectasis

2) *M abscessus* is most common and most difficult-to-treat mycobacterial disease

3) Chest radiograph typically shows multilobar, patchy reticulonodular infiltrate with upper lobe predominance; cavitation less common (15% of cases)

- Skin and soft-tissue infections
  1) Usually related to trauma or surgery; develops into wound infection; abscesses common
  2) Cutaneous infections and hypersensitivity reactions can occur (eg, due to contaminated hot tubs or pedicure equipment)
- Bone and joint infections
  1) Secondary to trauma or previous orthopedic surgery
- Less common: Keratitis, lymphadenitis

Treatment

- Selection and duration of combination therapy depend on pathogen, host, syndrome, and available susceptibility drug data
- *M fortuitum* is typically susceptible to more antibiotic options than other rapidly growing mycobacteria
- *M chelonae* is resistant to cefoxitin and usually susceptible to tobramycin, which is more active than amikacin against *M chelonae*
- *M abscessus* is commonly multidrug resistant and difficult to treat successfully (especially pulmonary disease)
- *M abscessus* is more susceptible to amikacin and cefoxitin but relatively resistant to tobramycin
- Drugs active against rapidly growing mycobacteria vary depending on organism and susceptibilities but may include clarithromycin, azithromycin, amikacin (or tobramycin), cefoxitin (or imipenem), moxifloxacin, linezolid, minocycline, and tigecycline
- Other drugs that may possess some activity (especially against *M fortuitum*) include doxycycline and sulfonamide
- Surgery is generally indicated for abscesses, extensive infections, and removal of associated foreign material, and for *M abscessus* pulmonary infections
- Duration of therapy varies, depending on severity and species considerations; 4-6 months for skin and soft-tissue infections, 6 months (with surgical debridement) for bone and joint infections, and 12 months of negative sputum cultures for pulmonary infections (or longer and may require surgery for *M abscessus* pneumonitis)

Other Less Common Rapidly Growing Mycobacteria

- *M smegmatis* group (*M smegmatis, M wolinski, M goodii*)
  1) Clinical disease uncommon; associated with lymphadenitis, osteomyelitis, postsurgical wound infections, intravenous catheter infections
  2) Treatment considerations include amikacin, tmp/smx, doxycycline, moxifloxacin, imipenem, ethambutol, and possibly cefoxitin; characteristic in vitro group resistance to clarithromycin and other

macrolides

- *M immunogenicum*
  1) Typically from contaminated water source
  2) Commonly drug resistant; treatment considerations include clarithromycin and amikacin

M scrofulaceum

Clinical Disease

- Cervical lymphadenitis in young children
- Chronic cutaneous disease
- Pulmonary disease (less common)

Treatment

- Can be multidrug resistant; considerations include clarithromycin, azithromycin, fluoroquinolone
- Surgical excision for localized lymphadenitis and cutaneous disease

M haemophilum

General Information

- Wide geographical distribution (Europe, Israel, Australia, Canada, United Kingdom, Africa, Fiji, and US)
- More common and pronounced disease in immunocompromised patients (eg, transplant recipients, patients taking chronic corticosteroids, HIV-positive or AIDS patients)
- Fastidious in vitro growth; special in vitro growth requirements for hemin- or iron-containing compounds; growth at cooler temperatures (32°C)
- Commonly AFB-stain positive from tissue, but cultures may be negative

Clinical Disease

- Cutaneous lesions (most common), typically over the extremities; can be chronic
- Lymphadenitis can occur in healthy children
- Septic arthritis
- Disseminated disease may occur in immunosuppressed patients

Treatment

- Consider clarithromycin, rifampin, rifabutin, ciprofloxacin, amikacin; variable activity with doxycycline, kanamycin, tmp/smx
- Isolated lymphadenitis in children and immunocompetent patients may be treated with surgical excision alone

M terrae Complex: M terrae, M triviale, M nonchromogenicum, M hiberniae

Clinical Disease

- **Localized tenosynovitis:** Typically affects upper extremities, including hand, wrist, fingers; often in association with trauma
- **Less common:** Pulmonary disease (can produce cavitary disease); genitourinary and gastrointestinal infections

Treatment

- Consider clarithromycin, azithromycin, ethambutol, rifampin, fluoroquinolone, linezolid
- Surgery may be required

M xenopi

General Information

- Obligate thermophile; enhanced growth at 42°C (commonly isolated from hot water taps and showerheads)

Clinical Disease

- Chronic pulmonary disease (common in Canada, the United Kingdom, and other parts of Europe)
- Patients typically have underlying chronic lung disease; upper lobe cavitary disease (common); cavities may be large

Treatment

- Poor correlation between in vitro susceptibility testing and clinical response
- Consider clarithromycin, moxifloxacin, rifampin, and ethambutol; role of isoniazid is unclear and may not be beneficial

M ulcerans

General Information

- Tropical rain forests of Africa, Australia, southwestern Asia, and South and Central America; Papua New Guinea; Malaysia
- Grows at cooler temperatures; predilection for extremities; prolonged incubation period (>3 months); slow growth; optimal growth at temperatures of 28-33°C

Clinical Disease

- African Buruli ulcer or Australian Bairnsdale ulcer; cutaneous necrotic painless ulcer; progressive, granulomatous; may involve large skin areas; can become disfiguring
- Associated with minor penetrating trauma with contaminated soil or water

Treatment

- Difficult in more advanced stages
- Consider clarithromycin often with rifampin, ethambutol, some aminoglycosides; possibly tmp/smx, tetracycline
- Wound debridement with skin grafting may be required

M bovis

General Information

- *M bovis* is a member of *M tuberculosis* complex and a component of bacille Calmette-Guérin (BCG) (live-attenuated *M bovis*) vaccine; significant *M bovis* infection may occur after BCG vaccination in immunosuppressed children or after BCG bladder washings for bladder cancer therapy
- Also found in bovine TB and in contaminated and unpasteurized milk

Clinical Disease

- Similar disease spectrum as TB; pulmonary, genitourinary, and enteric disease common; localized *M bovis* infection can occur at BCG vaccination site in immunosuppressed hosts

Treatment

- Use isoniazid, rifampin, and ethambutol; universal resistance to pyrazinamide

- Isolated persistent bladder infections from BCG instillation can be treated for a few weeks to 3 months
- Most other BCG genitourinary infections (outside the bladder) associated with bladder instillations can be treated with combination therapy for 3-6 months; consider treatment for 6-9 months for more severe or disseminated *M bovis* disease

M szulgai

General Information

- *M szulgai* infections are rare and are generally not considered contaminants; infections usually occur in immunosuppressed patients (eg, HIV-positive patients or transplant recipients); AFB stain may show some banding (similar to that for *M kansasii*)

Clinical Disease

- Pulmonary disease has a presentation similar to that of TB
- Extrapulmonary disease includes osteomyelitis, joint infection, and skin and soft-tissue infections

Treatment

- Use isoniazid, rifampin, and pyrazinamide
- Consider moxifloxacin, clarithromycin, azithromycin

M malmoense

General Information

- Northern Europe (2nd most common NTM isolate from sputum and cervical lymph nodes from children), Finland, Zaire, Japan; rare in US but sometimes found in Florida, Texas, Georgia

Clinical Disease

- Pulmonary disease
- Lymphadenitis
- Other (less common) conditions include tenosynovitis, cutaneous disease, disseminated disease

Treatment

- Poor correlation between in vitro susceptibility testing and clinical response
- Consider combination of isoniazid, rifampin, and ethambutol; possibly add clarithromycin or fluoroquinolone or both

Other *Mycobacteria* sp

M celatum

- Can cross-react with acridinium ester-labeled DNA probe (AccuProbe; Gen-Probe) used to identify *M tuberculosis*
- Respiratory disease (eg, immunosuppressed patients), uncommon isolate
- Typically susceptible to clarithromycin, azithromycin, fluoroquinolone, rifabutin

M genavense

- Disseminated disease in immunosuppressed patients (eg, HIV-positive or AIDS); closely resembles disseminated MAC
  1) Involvement of blood, marrow, liver, spleen, enteric tissue
  2) Splenomegaly common

- Difficult to grow in culture; requires supplemented media
- Usually susceptible to clarithromycin, azithromycin, fluoroquinolone, amikacin, rifampin, rifabutin

M gordonae

- Commonly isolated from tap water ("tap water bacillus")
- Ubiquitous in nature and most commonly regarded as nonpathogenic or specimen contaminant
- Less common pulmonary and disseminated disease reported in immunocompromised and AIDS patients

M mucogenicum

- Central venous catheter infections with secondary bloodstream infections; less common peritoneal dialysis catheter infections
- Common contaminant in isolates from respiratory secretions
- Usually susceptible to amikacin, clarithromycin, cefoxitin, fluoroquinolone, minocycline, doxycycline, tmp/smx, and imipenem

M simiae

- Geographic locales include Israel, Cuba, and southwestern US (Texas, Arizona, New Mexico)
- Clinical disease not common; usually occurs in immunosuppressed patients or those with chronic lung disease; pulmonary disease or (less common) intra-abdominal infections
- Susceptibility drug data may not correlate with clinical outcome
- Consider clarithromycin, moxifloxacin, tmp/smx

Additional Information

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Zoonotic (Animal-Associated) Infections

Table 66. Select Zoonotic (Animal-Associated) Infections

Transmission route	Pathogen	Disease
Direct animal contact	*Bacillus anthracis*	Anthrax
	Brucella sp	Brucellosis
	Coxiella burnetii	Q fever
	Echinococcus sp	Hydatid cyst; alveolar cyst
	Erysipelothrix insidiosa	Erysipeloid; soft-tissue infection
	Francisella tularensis	Tularemia
	Leptospira interrogans	Leptospirosis
	Rhodococcus equi	Respiratory tract infection
	Toxoplasma gondii	Toxoplasmosis
	Yersinia pestis	Plague
Animal bite	*Bartonella henselae*	Cat-scratch disease
	Capnocytophaga canimorsus	Soft-tissue infection
	Pasteurella sp	Soft-tissue infection
	Rabies virus	Rabies

Infections Contracted Through Direct Animal Contact

Brucellosis (B abortus, B canis, B melitensis, B suis)

- **General Information:** 4 species known to cause disease in humans: *B abortus* (cattle), *B canis* (kennel-raised dogs), *B melitensis* (goats and sheep), and *B suis* (pigs)
- **Geographic distribution:** Mediterranean (eg, Spain, Italy, Greece); Latin America, Middle East (eg, Saudi Arabia, Syria, Iraq, Kuwait)
- **Human infection routes**
  1) **Direct animal contact:** Skin abrasions, wound contact, eye inoculation
  2) **Inhalation:** Risk for abattoir workers
  3) **Ingestion:** Contaminated dairy products, unpasteurized milk and cheese, raw meat
- **Clinical disease**
  1) **Acute brucellosis (Malta fever):** Fever, chills, sweats, headache, back pain, splenomegaly (20-30%), adenopathy (10-20%), hepatomegaly (20-30%)
  2) **Subacute and chronic brucellosis:** Indolent, intermittent fever (undulant fever); sacroiliitis and arthritis, granulomatous hepatitis and hepatic abscess, endocarditis, meningitis, bone marrow suppression (ie, anemia, leukopenia, thrombocytopenia); diffuse adenopathy; can involve any organ system
- **Diagnosis:** Serology, culture, polymerase chain reaction (PCR) (investigational)
- **Treatment (duration varies by syndrome from weeks to months):** Combination drug therapy with doxycycline plus rifampin, doxycycline plus gentamicin or streptomycin; trimethoprim-sulfamethoxazole (tmp/smx) plus rifampin

Q Fever (Coxiella burnetii)

- **General information:** Commonly found in urine, stool, birth products, and milk from infected farm animals (eg, cattle, sheep, goats) and other animals (eg, dogs, cats, rabbits, pigeons, rats)
- **Geographic distribution:** Worldwide, common in Nova Scotia, Israel, and southern France
- **Human infection routes**
  1) Inhalation of contaminated aerosol
  2) Contact with body fluids of infected animals; exposure to skin or placenta of infected animals
  3) Consumption of raw milk
- **Clinical disease:** Highly variable
  1) **Acute Q fever:** Can manifest as self-limiting febrile or flulike illness, pneumonia, or hepatitis
     a) **Flulike illness:** Abrupt onset, high-grade fever, myalgias, headache, fatigue
     b) **Pneumonia:** Typically nonproductive cough
     c) **Other:** Rash, pericarditis, myocarditis, aseptic meningitis
  2) **Chronic Q fever:** Symptoms typically persist beyond 6 months

a) **Endocarditis:** Most common syndrome in chronic Q fever
b) **Infected aneurysms and vascular grafts**
c) **Hepatitis:** Elevated transaminases; liver biopsy may show classic doughnut-shaped granulomas (lipid vacuole surrounded by fibrinoid ring); hepatic fibrosis, cirrhosis
d) **Osteomyelitis, osteoarthritis**

- **Diagnosis:** Serology (immunofluorescence assay) with antibody titers >1:200 for antiphase II IgG and >1:50 for antiphase II IgM indicates acute infection; single antiphase I IgG titer >1:800 and IgA titer >1:100 indicate evidence of chronic infection
- **Treatment:** Treat patients who are symptomatic and those with chronic disease
  1) **Acute or chronic Q fever:** doxycycline or tetracycline; alternate treatments include tmp/smx, rifampin, fluoroquinolone
  2) **Q fever endocarditis:** Treat patients who are symptomatic and those with chronic disease; doxycycline plus hydroxychloroquine; alternate treatments include doxycycline plus rifampin or fluoroquinolone or tmp/smx; prolonged duration of combination therapy; valve replacement (common)

Tularemia (Francisella tularensis)

(See information on tularemia in section on Tick-Borne Infections)

Anthrax (Bacillus anthracis)

- **General information:** Soil and herbivores (eg, cattle, goats); zoonotic transmission is more likely in Iran, Iraq, Turkey, Pakistan, and sub-Saharan Africa; spores can survive for long periods in soil
- **Human infection routes:** Direct contact with broken skin; inhalation; enteric exposure
- **Clinical disease**
  1) **Cutaneous anthrax:** Most common form; infection by direct contact with infected animals, hides or wool from infected animals, or infected soil; painless papules develop into vesicles, which lead to ulcers, which then lead to black eschars surrounded by gelatinous haloes and nonpitting edema; painful regional adenopathy
  2) **Respiratory anthrax:** Infection by inhalation of spores (ie, woolsorter's disease); typically biphasic clinical pattern with hemorrhagic mediastinitis, hemoptysis, and respiratory distress; high mortality
  3) **Gastrointestinal anthrax:** Hemorrhagic enteritis, acute abdominal pain, bloody diarrhea; ileocecal ulcerations common
  4) **Oropharyngeal anthrax:** Cellulitis of neck; oropharyngeal ulcers
- **Diagnosis:** Gram stain of large gram-positive bacillus from infected tissue; culture; serology
- **Treatment (depends on presentation):** Use ciprofloxacin (or doxycycline) plus rifampin; consider adding

clindamycin or vancomycin for respiratory or severe disease; other agents include penicillin (although some isolates may produce β-lactamase), ampicillin, meropenem, tmp/smx

Leptospirosis (Leptospira interrogans)

- **General information:** Worldwide presence with higher prevalence in rural areas; animal sources of infection (eg, rodents, cattle, swine, dogs, horses, sheep, goats)
- **Human infection routes:** Primarily by direct exposure to water or soil contaminated by urine from infected animals, such as during recreational (eg, triathlons, swimming) and occupational (eg, dairy farmers, sewer workers) activities
  1) *Leptospira* sp can penetrate abraded skin and intact mucous membranes (eg, conjunctiva, nasopharyngeal and genital epithelium) and progress to hematologic dissemination
- **Clinical disease:** Ranges from subclinical to life-threatening; infections produce small-vessel vasculitis with multisystem disease; distinct biphasic course
  1) **Acute "septicemic" phase**
     a) Sudden headache, retro-ocular pain, myalgias, fever, nausea and vomiting, conjunctival suffusion, transient and mucosal rashes
     b) Patients may improve for a few days, then have recurring fever with immunologic sequelae
  2) **Immunologic phase:** Organisms generally cleared from blood and cerebrospinal fluid
     a) Aseptic meningitis
     b) Myositis (elevated creatine kinase)
     c) Respiratory insufficiency (eg, pulmonary edema, acute respiratory distress syndrome, hemoptysis) may develop
     d) Cardiomyopathy, myocarditis
     e) Thrombocytopenia leading to coagulopathy
     f) Exanthematous rash with pretibial skin lesions
     g) Weil syndrome: More severe disease with hepatic insufficiency (with jaundice) and renal insufficiency
- **Diagnosis:** Bacterial culture of blood (early) or urine (later); serology
- **Treatment**
  1) Mild disease (often self-limiting): Oral amoxicillin or doxycycline
  2) More severe disease: Intravenous (IV) penicillin, ampicillin, doxycycline, ceftriaxone or cefotaxime

Plague (Yersinia pestis)

- **General information:** Rodents (eg, squirrels, prairie dogs) and the fleas that feed on them
- **Human infection routes:** Direct contact by handling animal tissues; from animal bites or scratches or from bites of fleas; human-to-human transmission by pneumonic plague; aerosol inhalation (bioterrorism hazard)

- **Clinical disease**
  1) **Bubonic plague (febrile lymphadenitis)**
     a) Rapidly tender, enlarged, infected lymph node (bubo) with fever
     b) Inguinal and femoral nodes most commonly involved; cervical and axillary less common; buboes may further suppurate and drain
  2) **Septicemic plague**
     a) Disseminated infection; any organ can be involved; no buboes
     b) Hemorrhagic tissue necrosis and gangrenous lesions of skin and digits
  3) **Pneumonic plague**
     a) Inhalation or hematogenous seeding to lungs
     b) High mortality and highly contagious to other humans (aerosolized droplets)
- **Diagnosis:** Watson or Gram stain of infected tissue shows classic bipolar "safety-pin" morphology; culture and serology; PCR (investigational)
- **Treatment:** Either streptomycin or gentamicin for 10 days; alternate drugs include doxycycline, chloramphenicol, tmp/smx

Rhodococcus equi

- **General information:** Found in intestinal tracts of herbivores and contaminated soil of horse farms; organism is gram positive and also partially acid-fast staining
- **Clinical disease:** Typically affects immunocompromised patients (eg, human immunodeficiency virus [HIV] infection or AIDS; patients with low cell-mediated immunity)
  1) **Pulmonary infection (most common):** Subacute onset, necrotizing cavitation in >50% of cases, consolidation; pleural effusions and empyema
  2) **Central nervous system infections:** Brain abscess, meningitis, encephalopathy
  3) **Skin and soft-tissue infections**
  4) **Bloodstream infection:** Hematogenous seeding of multiple organs and joints
  5) **Enteric infections:** Localized and mesenteric adenitis
- **Diagnosis:** Organism grows well in culture; blood cultures commonly positive
- **Treatment (2-6 months with combination drug therapy for immunocompromised patients):** Use azithromycin or clarithromycin, fluoroquinolone, rifampin, vancomycin, imipenem, gentamicin or amikacin

Erysipeloid (E rhusiopathiae)

- **General information:** Infects domestic animals such as swine (major reservoir) but also found in sheep, horses, cattle, chickens, crabs, fish, dogs, and cats; occupational exposure in abattoir workers, butchers, fishermen, farmers, and veterinarians
- **Clinical disease**
  1) **Localized infection (erysipeloid):** Localized

cellulitis; fingers most commonly involved, violaceous skin infection; highly painful; local lymphangitis and adenitis in about 30% of cases

2) **Diffuse cutaneous disease:** Less common; fever and arthralgias (common)

3) **Bacteremia:** Usually associated with severe illness; often complicated by endocarditis with extensive valve destruction; more common with alcoholism and chronic liver disease

- **Treatment:** Local disease often resolves without specific treatment but treatment quickens healing; penicillin, carbapenem, cephalosporin, clindamycin, doxycycline, or macrolide; and resistant to vancomycin, sulfonamides, and aminoglycosides

Echinococcus sp (E granulosus and E multilocularis)

- **General information:** Worldwide (southwestern US, Africa, southern Europe, Latin America, Mediterranean, North and East Africa, Australia, New Zealand, western China
- **Human infection routes:** Humans ingest eggs, then oncospheres penetrate the gut wall and travel by blood and lymphatics to liver (80%), lungs (18%), or (less commonly) kidneys, bones, brain, eyes
- **Clinical disease**

1) *E granulosus* (dogs and sheep or wolves and moose); association with livestock and working dogs fed slaughtered animals

a) **Cystic or unilocular hydatid:** Expands as a discrete fluid-filled mass with fibrous capsule

b) **Hydatid cysts:** May be found in almost any site; liver affected in about two-thirds of patients, lungs in 25%; less common in brain, muscles, kidneys, bones, heart, pancreas

c) **Appearance:** Cysts have characteristic internal septate (representing daughter cysts) and prominent wall

2) *E multilocularis* (foxes and rodents)

a) Alveolar or multilocular hydatid does not form discrete capsule

b) Tumor-like growth can "metastasize" to other parts of the body

- **Treatment**

1) **Surgical resection:** With preoperative and postoperative medical therapy (albendazole or mebendazole; possible combination of either with praziquantel)

2) **Percutaneous aspiration:** With scolicidal agent and reaspiration (PAIR) with pre- and postprocedure medical therapy

3) **Medical therapy alone:** For inoperative, multiple, or very small cysts

Toxoplasmosis (Toxoplasma gondii)

- **General information:** Domestic cats are primary reservoir; also found in lambs and pigs, and in bears and other carnivores

- **Human infection routes**
  1) Ingestion of raw or undercooked meat containing tissue cysts; ingestion of food, water, or soil contaminated with cat feces containing infective oocysts
  2) Transplacental passage of infective tachyzoites (in mothers with primary infection)
  3) Transfusion of infected white blood cells or transplantation of infected organ
- **Clinical disease in immunocompetent patients**
  1) **Acute toxoplasmosis:** Resembles mononucleosis syndrome in immunocompetent patient (eg, cervical adenopathy, atypical lymphocytes); monospot test negative
  2) **Congenital toxoplasmosis:** Classic triad of hydrocephalus, cerebral calcification, and chorioretinitis; most infants with congenital toxoplasmosis appear healthy at birth but have a high incidence of serious ophthalmologic and neurological sequelae that develop during the next 20 years
  3) **Ocular toxoplasmosis:** Retinitis with yellowish cotton-wool spots with atrophic black pigmentation
- **Clinical disease in immunosuppressed patients**
  1) **Encephalitis:** Multiple small, ring-enhancing lesions at corticomedullary junction and basal ganglia; especially common in patients with advanced HIV infection or AIDS; reactivated (nonprimary) disease
  2) **Pneumonitis (severe):** Fever, nonproductive cough; chest radiograph typically with interstitial infiltrate
  3) **Visceral organ disease:** Transplant recipients
  4) **Chorioretinitis**
- **Diagnosis**
  1) **Serology:** Variable interpretation based on specific assays (often more helpful when applied with head imaging for suspicion of toxoplasma encephalitis, such as in AIDS patients)
  2) **Direct tissue examination:** Tachyzoites; immunoperoxidase stain
  3) **Tissue culture**
  4) **PCR (investigational):** Body fluid or tissue
- **Treatment:** See Table 80 in section on Select Opportunistic Infections in Adult HIV Patients

Infections Through Animal Bites

Rabies

- **General information:** Transmission can be significantly reduced by preemptive measures
  1) Good wound care (immediate soap and water) can reduce rabies risk by 90%
  2) Postexposure immunization during incubation period before virus enters central nervous system (CNS) (before onset of neurological symptoms)
- **Animal vectors**
  1) **US:** Bats (most common), skunks, raccoons, some

foxes; dogs (rarely)

2) **Third-world or developing nations:** Dogs (most common); wild animals

- **Clinical disease:** Highly neurotropic virus
  1) Infection by animal bite eventually enters peripheral nerves (sensory and motor); viral replication occurs with retrograde axoplasmic flow transport to CNS; after spread throughout CNS, virus moves anterograde down peripheral nerves
  2) Once symptoms start (eg, pain and paresthesias at wound site), virus has reached spinal ganglion and progressive or rapid encephalitis follows, with mortality approaching 100%
  3) Stages of infection
     a) **Incubation period (variable):** Typically 1-3 months (range, 10 days to several years); 75% of untreated patients become ill within 3 months, 95% within 1 year
     b) **Prodrome:** Pain or paresthesia at site of inoculation; early anxiety, apprehension, or irritability
     c) **Acute neurological period:** Autonomic dysfunction (eg, increased salivation and fever): 2 types
        - **Furious rabies (encephalitic rabies):** Hyperreaction, disorientation, hydrophobia (pharyngeal spasms), aerophobia
        - **Paralytic rabies (dumb rabies):** Paralysis; salivary drooling due to paralysis of swallowing muscles

     d) **Coma:** Usually occurs within 10 days of onset of symptoms; respiratory arrest
- **Diagnosis**
  1) **Testing from multiple sources (direct fluorescent antibody staining, PCR, culture):** Skin biopsy from nape of neck, saliva, serum, cerebrospinal fluid, and cornea (consult state health department and Centers for Disease Control and Prevention for specific testing)
  2) **Brain biopsy (often postmortem):** For Negri bodies (eosinophilic cytoplasmic inclusions)
- **Treatment:** Wash wound and administer postexposure prophylaxis (PEP) treatment
  1) **Evaluate for rabies PEP treatment:** See Table 67
  2) **Rabies PEP treatment:** Vigorously clean wound in all cases
     a) **Previously vaccinated:** Vaccinate with 2 doses (on days 0 and 3); no rabies immunoglobulin needed
     b) **Not previously vaccinated**
        - Give rabies immunoglobulin 20 international units/kg once (one-half in wound, one-half deep in intramuscular site)
        - Vaccinate for 5-6 doses (days 0, 3, 7, 14, 28, and possibly 90)

Table 67. Recommended Postexposure Prophylaxis for Rabies

Animal	Condition of animal	PEP recommendations
Dogs and cats	Healthy and available for 10-day observation Known or suspected rabid Unknown (escaped or animal not available)	Do not begin PEP unless quarantined animal develops signs or symptoms of rabies[a] Immediate PEP Consult local public health officials
Bats, skunks, raccoons, foxes, most other carnivores	Regard as rabid unless geographic area is known to be free of rabies or animal tests negative for rabies	Immediate PEP[b]
Livestock, rodents, rabbits	Consider each case individually	Consult local public health officials

[a] If animal shows signs of rabies during 10-day holding period, begin postexposure prophylaxis (PEP) treatment immediately. Exception for bites to head and neck: Begin PEP immediately, as rabies incubation period can be <10 days, but stop PEP if animal is healthy after 10 days.

[b] Wild animals such as skunks, raccoon, and bats should be killed and tested immediately for rabies, if possible, rather than being held for observation.

Capnocytophaga canimorsus

- **General information:** Infections typically occur by dog bites (canine oral flora) or scratches
- **Clinical disease:** More severe disease in immunosuppressed patients
  1) Soft-tissue infection; wide spectrum of disease from mild to fulminant; can be rapid and severe in asplenic patients; digital gangrene may occur
  2) Bacteremia and multiorgan involvement (eg, meningitis, endocarditis, pneumonia, cellulitis, bone and joint infections)
- **Treatment:** Use penicillins, carbapenems, clindamycin, 3rd-generation cephalosporin, doxycycline, fluoroquinolone

Pasteurella sp

- **General information:** *Pasteurella* sp are part of normal oral flora of many animals (eg, cats [*P multocida*], dogs [*P canis*], rats, cattle, horses, pigs, sheep, birds)
- **Clinical disease:** Typically by animal bite wounds
  1) **Soft-tissue infection:** Very rapid onset (within 24 hours); pain and swelling prominent; purulent drainage in 40% of patients, lymphangitis in 20%, and regional adenopathy in 10%
  2) **Bone, joint, and tendon infections**
  3) **Respiratory tract infection:** Patients usually have underlying chronic lung disease
  4) **Disseminated infection:** Hematogenous spread (usually from wound)
- **Treatment (wounds commonly polymicrobial):** Use penicillin, amoxicillin/clavulanate, β-lactam/β-lactamase inhibitors, carbapenem, doxycycline, most 2nd- and 3rd-generation cephalosporins

Cat-Scratch Disease (Bartonella henselae)

- **General information:** Domestic cat is primary carrier and vector; transmission by cat bite or scratch (or flea bite)
- **Clinical disease**
  1) **Primary cutaneous lesion:** Develops 3-10 days at site of bite or scratch
  2) **Regional adenopathy:** Tender initially; solitary adenopathy more common but multifocal adenitis can occur
     a) **Most common sites:** Axillary, epitrochlear, cervical, supraclavicular, and submandibular lymph nodes
     b) **Course:** Adenopathy persists for several weeks to months, then spontaneously resolves
  3) **Parinaud oculoglandular syndrome:** Conjunctivitis, conjunctival granuloma, and adjacent ipsilateral preauricular lymphadenopathy
  4) **Other sites (less common) and complications:** Can present as fever of unknown origin
     a) Hepatic (granulomatous hepatitis) and splenic involvement

b) Painful arthropathy
c) Osteolytic lesions
d) Neuroretinitis, encephalopathy

- **Diagnosis:** Serology, Warthin-Starry staining of node or infected tissue, culture and PCR
- **Treatment:** Usually none required for isolated cutaneous disease or limited adenopathy; treat severe symptoms, severe adenitis; azithromycin, clarithromycin, tmp/smx, rifampin, ciprofloxacin, gentamicin, doxycycline (avoid localized debridement of suppurative lesions, which can cause chronic sinus tract formation)

Tick-Borne Infections

Tick Vectors

Table 68. Tick Vectors

Family	Genus/species	Common name	Distribution
Hard ticks (Ixodidae)	*Amblyomma americanum*	Lone Star tick	Southern and eastern US
	Dermacentor andersoni	Rocky Mountain wood tick	Southern and western US
	D variabilis	American dog tick	Southern and eastern US
	Ixodes holocyclus	Australian paralysis tick	Australia
	I pacificus	Western black-legged tick	Western US
	I ricinus	Sheep tick	Europe
	I scapularis	Black-legged tick, deer tick	Northeastern and eastern US
	Rhipicephalus sanguineus	Brown dog tick	US, Australia, Europe
Soft ticks (Argasidae)	*Ornithodoros coriaceus*	Pajaroello tick	Southern US and Mexico
	O moubata	African hut tampan	Eastern and southern Africa

Ixodidae Family

General Information

- Consists of the hard ticks that transmit nearly all tick-borne human diseases; 2-30 mm
- Ixodids do not cause pain while feeding; immature stages are frequently not detected because of their small size

Types of Ticks

- ***Ixodes* sp:** *I scapularis, I pacificus, I ricinus*
  1) Black; female has red dorsal posterior
  2) Can attach to humans during all 3 stages of development: Larva, nymph, adult (3-host life cycle)
- ***Dermacentor variabilis*:** American dog tick
  1) Brown and white; larger than deer tick
  2) Attaches to humans predominantly in adult stage
- ***Amblyomma americanum*:** Lone Star tick
  1) Oval and black with white spot near center
  2) Can attach to humans during all 3 stages of development

Argasidae Family

General Information

- Soft ticks; predominantly found in arid environments
- Transmits only a single human disorder (ie, endemic-relapsing fever; *Borrelia hermsii* and *B duttonii*)

Types of Infections Spread by Tick Bites

Lyme Disease (Borrelia burgdorferi)

Geographic Distribution

- Southern New England; eastern Mid-Atlantic states, upper Midwest, northern Pacific Coast

Tick Vectors

- *Ixodes scapularis* (eastern and midwestern US); *I pacificus* (northwestern US)
  1) Tick must feed for about 36-48 hours (to become engorged) before transmission of *B burgdorferi* can occur

Clinical Symptoms or Syndromes

- Erythema chronicum migrans (ECM): Circular erythematous skin lesion, often with central clearing; usually appears 7 days after tick bite (range, 3-10 days); relatively rapid expansion of outer margins, if untreated (erythematous margin contains organisms seen on biopsy)
- Early disseminated Lyme disease
  1) Multiple ECM lesions
  2) Migratory arthralgias
  3) Cranial nerve palsies (especially facial nerve palsy or Bell palsy)
  4) Meningitis, transverse myelitis, mononeuritis multiplex
  5) Carditis with variable degrees of atrioventricular nodal block

- Late Lyme disease
  1) Oligoarticular arthritis, usually in large joints (eg, hips, knees); can be relapsing
  2) Encephalitis, encephalopathy, axonal polyneuropathy
  3) Acrodermatitis chronica atrophicans

Diagnosis

- Skin biopsy and culture of edge of ECM lesion
- Serum enzyme-linked immunosorbent assay (ELISA; can be negative during early Lyme disease with ECM); Western blot assay to confirm positive ELISA

Treatment (see Table 69 below)

Table 69. Treatment of Lyme Disease[a,b]

Disease category	Antimicrobial therapy
Recognized tick bite	doxycycline 200 mg single dose for high-risk criteria[c]
Early localized disease	
Adults and children ≥8 y	doxycycline 100 mg oral bid for 14-21 days Alternate: amoxicillin 500 mg oral tid for 14-21 days
Children <8 y	amoxicillin oral 50 mg/kg/24h in 3 divided doses (max 500 mg pre-dose)
Early disseminated disease	
Multiple ECM	Same as for early localized disease
Isolated facial nerve palsy	Same as for early localized disease
Facial nerve palsy with evidence of CNS involvement[d,e]	Same as for meningitis
Carditis	
Mild	Same as for early localized disease
Severe	Same as for meningitis
Meningitis[e]	ceftriaxone: 2 g IV daily for 14-28 days Alternate: cefotaxime 2 g IV q8h for 14-18 days, penicillin G 18-24 million units IV divided q4h Children: ceftriaxone: 75-100 mg/kg IV daily (max 2 g once daily) for 14-21 days Alternate: penicillin 300,000 units/kg/24h divided q4h (max 20 million units per day) for 14-21 days
Late disease	
Arthritis	Same as for early localized disease but treat for 28 days
Persistent or recurrent arthritis	Same as for meningitis
Neurological disease (eg, encephalitis,[e] polyneuropathy)	Same as for meningitis

[a] Jarisch-Herxheimer reaction occurs occasionally (eg, elevated temperature, myalgia); treat with nonsteroidal anti-inflammatory drugs; reaction usually lasts 1-2 days.

[b] Prolonged antimicrobial therapy demonstrates no clinical benefit for any manifestation of Lyme disease.

[c] A single preventive dose of doxycycline after a tick bite may be given when all criteria are met: 1) identified tick is a nymphal or an adult *I scapularis* that has been attached for >36 hours (based on tick engorgement and time of exposure); 2) doxycycline dose can be given within 72 hours of tick removal; 3) geographic endemic prevalence of *Ixodes* sp tick infection with *B burgdorferi* is at least 20%; and 4) doxycycline treatment is not contraindicated (eg, by pregnancy or in children aged <8 years).

[d] Perform cerebrospinal fluid (CSF) evaluation if there is facial palsy accompanied by other abnormal neurological findings (eg, severe headache, nuchal rigidity). With CSF pleocytosis, consider intravenous (IV) antibiotics.

[e] Oral doxycycline can be a safe, effective treatment for Lyme disease meningitis, cranial neuritis, and radiculitis, with IV therapy reserved for patients with parenchymal central nervous system Lyme disease or with severe or unresponsive neurological disease. Halperin et al. Neurology. 2007 Jul 3;69:91-102. Epub 2007 May 23.

Ehrlichiosis

Types of Infection

- Human granulocytic ehrlichiosis (HGE): *Anaplasma phagocytophilia* and *Ehrlichia ewingii* (less common)
  1) Geographic distribution: Northeastern US, upper midwestern US
  2) Tick vector: *I scapularis*
  3) Coinfection with *B burgdorferi* (Lyme disease) and *Babesia* sp may occur by similar tick vector
- Human monocytic ehrlichiosis (HME): *E chaffeensis*
  1) Geographic distribution: South-central and southeastern US
  2) Tick vector: *Amblyomma americanum* (Lone Star tick)

Clinical Symptoms

- Nonspecific; range from mild to severe: Fever, myalgias, headache, arthralgias, nausea, cough; skin rash uncommon; respiratory insufficiency and neurological symptoms may occur
- Laboratory findings commonly include leukopenia, thrombocytopenia; elevated aspartate aminotransferase or alanine aminotransferase

Diagnosis

- Intracytoplasmic morulae (more common in HGE) on peripheral blood smear; morulae within neutrophils in HGE and within monocytes in HME
- Serology (note symptoms may precede seroconversion)
- Polymerase chain reaction (PCR)

Treatment

- Use doxycycline 100 mg bid for 7-14 days as first-line treatment
- Alternate treatment is with rifampin

Babesiosis (Babesia microti)

Geographic Distribution

- Northeastern US, upper midwestern US, Washington state

Tick Vector

- *I scapularis* (possible coinfection with *B burgdorferi* [Lyme disease] or *A phagocytophilia* [HGE])

Clinical Symptoms

- Nonspecific; can be severe in asplenic patient: Fever, arthralgias, nausea, vomiting, headache, weakness
- More severe cases involve hepatosplenomegaly, jaundice, renal failure, respiratory insufficiency
- Mild-to-severe hemolytic anemia may be present

Diagnosis

- Peripheral blood smear (Wright-Giemsa stain): Intraerythrocytic parasites (ring forms); distinguishing features of *Babesia* sp infection compared with *Plasmodium* sp (malaria) smear:
  1) *Babesia* sp organisms usually form tetrads ("Maltese cross") of merozoites
  2) No hemoglobin-derived pigments within infected red blood cells
  3) Larger ring forms contain central white vacuoles

4) Presence of extracellular merozoites

- Serology immunofluorescence assay
- PCR

Treatment

- Use clindamycin IV plus quinine, or atovaquone plus azithromycin, or trimethoprim/sulfamethoxazole
- Exchange transfusion in severe cases

Rocky Mountain Spotted Fever (Rickettsia rickettsii)

Geographic Distribution

- Atlantic and south-central US; also Idaho and Montana; Canada, Central America, and parts of South America

Tick Vectors

- *D variabilis* (dog tick) predominantly in eastern and southeastern US
- *D andersoni* (wood tick) in western US; *A americanum*

Clinical Symptoms

- *Rickettsia* sp infect the endothelial lining of the small vessels, producing vasculitis
- Typically abrupt onset of fever, headache, and rash (classic triad)
- 90% of patients have rash that typically involves the ankles, wrists, palms, and soles; digital gangrene may occur (10% of patients have no rash; "Rocky Mountain spotless fever")
- More severe cases result in renal failure, pulmonary infiltrate, hypotension, hepatic insufficiency, splenomegaly, neurological symptoms, and disseminated intravascular coagulation with thrombocytopenia

Diagnosis

- No reliable test early in disease; diagnosis commonly based on clinical signs and symptoms (test for confirmation)
- Serology (eg, indirect fluorescent antibody, enzyme immunoassay), typically after first 1-2 weeks of disease
- Skin biopsy with immunohistochemical staining (early in disease) has 70% sensitivity

Treatment

- Usually started empirically before laboratory testing confirmation
- Use doxycycline 100 mg bid for 7-10 days; alternate treatment is chloramphenicol

Other Rickettsial Infections

- *R prowazekii* (epidemic or louse-born typhus) from body louse and flying squirrel
- *R typhi* (murine typhus) with rats as primary reservoir; transmitted by fleas; common in portions of Texas and southern California; worldwide distribution
- *R conorii* (Boutonneuse fever; Mediterranean spotted fever); found in various hard ticks; common in Africa, Middle East, India, Mediterranean basin; infection is common in travelers
- *Orientia tsutsugamushi* (scrub typhus) transmitted by chigger bite; common in Southeast Asia, Australia,

Japan, India, and Pakistan

- *R akari* (rickettsial pox) with house mouse as reservoir; transmitted by mites; found in urban areas of US, Russia, South Africa, Korea
- *R africae* (African tick bite fever; tick typhus); common to endemic regions of Africa and the eastern Caribbean
- *R japonica* (Japanese spotted fever)
- *R slovaca* (tick-borne lymphadenopathy)

Tularemia (Francisella tularensis)

Geographic Distribution

- Western, central, and southern US

Tick Vector

- *A americanum* (Lone Star tick)
- *D andersoni* (Rocky Mountain wood tick)
- *D variabilis* (American dog tick)
- Note: *F tularensis* is also transmitted by deer flies, other biting insects, and animals (eg, rabbits, deer, cats, squirrels, muskrats)

Clinical Symptoms: 6 Well-Described Clinical Presentations

- Ulceroglandular: Most common form; 80% of cases; tender ulcer with painful regional adenopathy
- Glandular: Tender regional adenopathy without (or with minimal) skin lesions
- Oculoglandular: Painful conjunctivitis
- Pharyngeal: Exudative pharyngitis
- Typhoidal: More systemic symptoms (eg, fever, abdominal pain)
- Pneumonic: Pulmonary infiltrate, hilar adenopathy, pleural effusions

Diagnosis

- Serology (ie, tube agglutination or ELISA), PCR, and culture in reference laboratories

Treatment

- Use streptomycin as first-line treatment
- Alternate treatment includes gentamicin, tetracycline, chloramphenicol

Other Tick-Borne Infections

Tick-Borne Encephalitis

- Powassan virus in northeastern US and eastern Canada
- Transmitted by *Ixodes* sp ticks
- Clinical symptoms: Biphasic course (20-30% cases), initially with fever and myalgias, followed later by central nervous system symptoms

Colorado Tick Fever

- Virus is found at elevations of 4,000-10,000 feet in the Rocky Mountains and in the Pacific states
- Transmitted by *D andersoni* (Rocky Mountain wood tick)
- Clinical symptoms include high fever, retro-orbital pain, abdominal pain, biphasic illness in 50% of patients; leukopenia (common)

Tick Paralysis

- Caused by salivary toxins and produced by various ticks; affects humans and animals, often after prolonged

tick attachment or feeding

- *D andersoni* (Rocky Mountain wood tick) is most common tick in US and Canada; other ticks include *D variabilis, A americanum, I scapularis,* and *I pacificus*
- Clinical symptoms include symmetric paralysis in lower extremities with ascending progression; typically no fever
- Treatment includes removal of tick, which typically leads to rapid resolution

Fungal Infections

Select Taxonomy

Yeasts

- *Candida* sp
- *Cryptococcus neoformans*

Dimorphic Fungi

Two different growth forms: Outside the body (25°C), they grow as a mold, producing hyphae and having asexual reproduction of spores; inside the body (37°C), they grow in a nonmycelial form

- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Coccidioides immitis* and *C posadasii*
- *Paracoccidioides brasiliensis*
- *Sporothrix schenckii*

Filamentous Fungi

- *Aspergillus* sp
- Zygomycetes

Select Fungi

Candida sp

Risk Factors for Localized, Mucocutaneous Candidiasis, and Invasive or Disseminated Disease

- Folliculitis
- Prolonged intensive care unit stay with *Candida* sp colonization of multiple nonsterile sites
- Prolonged use of antibacterial antibiotics
- Central venous catheters
- Parenteral nutrition
- Bowel perforations and surgery involving the intestinal wall
- Diabetes mellitus, corticosteroid use, and immunosuppressive conditions
- Burn wounds
- Estrogen use, oral contraceptives, pregnancy (vaginal candidiasis)

Clinical Diseases

- **Oral thrush:** More typical in immunosuppressed patients (eg, human immunodeficiency virus [HIV], corticosteroids)
  1) **Pseudomembranous:** White, creamy plaques on inflamed base (eg, palate, tongue, buccal mucosa)
  2) **Hyperplastic:** Candidal leukoplakia; white lesions that do not wipe off but respond to therapy
  3) **Erythematous (atrophic):** Spotty or confluent red patches (often underdiagnosed)
  4) **Angular cheilitis (perlèche):** Erythema and fissures at corner of mouth
- **Esophagitis:** More typical in immunosuppressed patients
- **Vaginitis (vaginal candidiasis):** Associated with pregnancy, high-estrogen oral contraceptive agents, uncontrolled diabetes, tight-fitting clothing, antibiotics, and dietary factors

1) Affects 75% of childbearing women
2) 40% of affected women have a 2nd episode; 5% have recurrent disease (>4 episodes per year)

- **Cutaneous syndromes**
  1) **Intertriginous infection:** In warm moist areas in diabetic and obese patients
  2) **Folliculitis**
  3) **Balanitis:** May involve scrotum
  4) **Paronychial infection:** Swelling, tenderness, erythema around nail
  5) **Disseminated:** Macronodular lesions; lesions resembling ecthyma gangrenosum
- **Urinary candidiasis:** Colony count not predictive of disease; clinical judgment required
- **Disseminated disease (acute or subacute)**
  1) **Ocular candidiasis:** Up to 30% of patients with fungemia may develop endophthalmitis
  2) **Candidemia:** Only 25% of patients with extensive organ disease have positive blood cultures
  3) **Meningitis:** Especially in patients with intravenous drug abuse; postneurosurgery and central nervous system (CNS) shunt infections
  4) **Osteomyelitis:** Usually from hematogenous dissemination
  5) **Peritonitis:** From peritoneal dialysis, bowel surgery, or perforated bowel
  6) **Endocarditis:** Most common form of fungal infective endocarditis; large vegetations
- **Hepatosplenic candidiasis:** Chronic disseminated candidiasis
  1) Typically seen in hematologic malignancies; postchemotherapy with prolonged neutropenia
  2) May present as neutropenic fever without focal signs or symptoms and fail to respond to antibacterials; ultrasound and computed tomography (CT) may be normal initially during the period of neutropenia
  3) During neutropenic recovery, fever continues with elevation of liver enzymes (especially alkaline phosphatase); abdominal ultrasound, CT, or magnetic resonance imaging commonly shows multiple small round hypoechoic or low-attenuated lesions scattered throughout the liver and spleen; lesions can later calcify
  4) Predominantly a clinical and radiographic diagnosis as liver biopsy is commonly false-negative; blood cultures are usually negative

Treatment: Depends on Syndrome and Type of *Candida* sp

- **Oral thrush:** Oral nystatin, clotrimazole troches, oral fluconazole
- **Esophagitis:** Oral fluconazole, other azoles,[a] or echinocandin[b]; amphotericin B product for refractory disease
- **Vaginitis:** Topical or oral azole[a] therapy
- **Candidemia:** Use fluconazole, voriconazole, or

echinocandin[b]; amphotericin B product for refractory disease (treat for 2 weeks after last positive blood culture and improved symptoms)

- **Chronic disseminated candidiasis:** Use fluconazole or amphotericin B product; alternate treatments include other azoles[a] and echinocandins[b]; treatment duration is typically months for clinical response and radiographic maturation (multiple scattered low-attenuation foci can persist despite successful therapy, because of focal scarring and chronic inactive granulomatous changes)
- Additional treatment information: See guidelines for treatment of candidiasis*

*Pappas et al. Clin Infect Dis. 2004 Jan 15;38:161-89. Epub 2003 Dec 19.

[a] Azole class of antifungal agents: fluconazole, itraconazole, voriconazole, ketoconazole, posaconazole.

[b] Echinocandin class of antifungal agents: caspofungin, anidulafungin, micafungin.

Cryptococcus neoformans

General Information

- Encapsulated, round yeast 4-6 mcm; neurotropic fungal infection
- Common sources include pigeon droppings and contaminated soil

Endemic Areas

- *C neoformans* distributed worldwide
- *C gattii* more focused in southern California

Clinical Disease: Typically in Immunosuppressed Patients

- **Pulmonary cryptococcosis:** Lungs are the portal of entry and most common site of infection; *C neoformans* can disseminate to other organs (especially CNS)
- **CNS disease:** Includes meningitis, meningoencephalitis, cerebral cryptococcomas; clinical symptoms may be present as acute (eg, headache, fever, nuchal rigidity) or chronic (eg, altered mental status, headache)
  1) **Hydrocephalus or high opening cerebrospinal fluid (CSF) pressure:** >20 cm common; serial lumbar punctures or ventriculoperitoneal shunts often help reduce spinal and ventricular fluid pressure
  2) **Negative prognostic factors:** Abnormal or reduced mental status; CSF cryptococcal antigen titer >1:1,024; CSF leukocytes <20 cells/mcL
- **Cutaneous:** Wide variation in presentation (eg, papules, plaques, cellulitis, tumors); cutaneous cryptococcal lesions signal dissemination; *Cryptococcus* skin papules can resemble molluscum contagiosum
- **Other:** Bone and joint disease; renal disease

Diagnosis

- **Cryptococcal antigen (serum and CSF):** About 95% sensitive for disseminated or meningeal cryptococcal disease; false-positive results can occur with *Trichosporon beigelii* and with *Stomatococcus* and *Capnocytophaga* spp infections
- **India ink:** Visualization of polysaccharide capsule; 75% sensitivity in CSF cryptococcal disease
- **Cultures:** Blood, CSF, urine

- **Note:** Any patient with a positive serum cryptococcal antigen or positive blood or urine culture should have a lumbar puncture to rule out CSF cryptococcal disease

Treatment: Selection and Duration of Antifungal Therapy Depend on Location of Disease and Immune Status of Host

- **HIV-negative or immunocompetent patients**
  1) **Pneumonia**
     a) Usual treatment: Either fluconazole 200-400 mg q24h or itraconazole 200-400 mg q24h for 6-12 months;
     b) Severe disease: Use amphotericin B product and treat as for CNS disease
  2) **CNS disease:** For therapy for cryptococcal meningitis, see section IV on "Central Nervous System Infection" (Table 46).
     a) Monitor CSF opening pressure, as repeat lumbar punctures may be needed
- **Note:** Follow-up monitoring of cryptococcal antigen during therapy not consistently helpful in predicting outcome
- **Additional treatment information:** See guidelines for management of cryptococcal disease, including treatment of HIV-positive patients†

†Saag et al. Clin Infect Dis. 2000 Apr;30:710-8. Epub 2000 Apr 20.

Histoplasma capsulatum

General Information

- Intracellular yeast 1-2 x 3 mcm; calcium deposits in tissue (eg, lungs, liver, spleen) common
- *H capsulatum* prevalence associated with chicken coops, bird roosts, soil, bat droppings

Endemic Areas

- Found worldwide, but more common in the Mississippi and Ohio river valleys and in the south-central United States, as well as in parts of Central and South America and in southeast Asia

Clinical Disease

- *Acute pulmonary histoplasmosis:* Often self-limiting patchy pneumonitis; hilar and mediastinal adenopathy common; lung infiltrate can be diffuse, with heavier exposures or immunosuppression; erythema nodosum may be present
- *Histoplasmoma:* Small calcified lung nodules (inactive), often with hilar calcification; may persist after resolution of primary infection
- **Chronic pulmonary histoplasmosis:** Usually upper lobes, often cavities; can radiologically mimic tuberculosis; cavitary findings often called "marching cavity," as the cavities gradually enlarge in >50% of cases
- **Granulomatous mediastinitis:** Active inflammation and enlargement of mediastinal lymph nodes; can produce secondary airway compression or superior vena cava syndrome
- **Fibrosing mediastinitis:** Exaggerated inflammatory response leads to extensive fibrotic tissue deposition in

mediastinum; can result in hypoxemia, dysphagia, and superior vena cava syndrome; treatment options, including surgery, are limited

- **Disseminated histoplasmosis (ie, extrapulmonary spread, progessive):** Can involve multiple sites
  1) **Adrenal gland disease:** May lead to adrenal insufficiency
  2) **Hepatosplenomegaly:** Lesions may later calcify
  3) **Cutaneous lesions:** Erythematous maculopapular lesions
  4) **Ocular disease:** Chorditis
  5) **Bone marrow disease:** Leukopenia, anemia, thrombocytopenia
  6) **Infective endocarditis, pericarditis**
  7) **CNS disease:** Can present as basilar meningitis or cerebral mass lesions
  8) **Oropharyngeal ulcers:** Usually with disseminated disease

Diagnosis

- **Culture**
- **Serology:** Serologic testing is insensitive and commonly negative with active disease; low serology titers are less specific for disease but may be helpful if >1:32 or positive for H or M bands
- **Tissue staining**
- ***Histoplasma* antigen:** From urine, blood, CSF

Table 70. Treatment of Histoplasmosis

Type of histoplasmosis	Severe disease	Mild to moderate disease
Acute pulmonary	amphotericin B product then itraconazole for a total of 12 weeks Supplementation with corticosteroids optional[a]	Symptoms <4 weeks: No treatment Persistent symptoms ≥4 weeks: itraconazole[b] for 6-12 weeks
Chronic cavitary pulmonary	itraconazole for 12-24 months	itraconazole[b] for 12-24 months
Disseminated	amphotericin B product then itraconazole for at least 12 months[c,d]	itraconazole[b] for at least 12 months[d]
Meningitis	amphotericin B product for 4-6 weeks, then fluconazole for at least 12 months	Same as for severe disease
Mediastinal granuloma	itraconazole for 6-12 weeks	None or itraconazole for 6-12 weeks in symptomatic patients
Fibrosing mediastinitis	Treatment not usually indicated or itraconazole for 3 months[e]	Same as for severe disease
Pericarditis	Corticosteroids and itraconazole for 6-12 weeks Pericardial drainage if hemodynamic compromise	NSAIDs for 2-12 weeks
Rheumatologic	prednisone plus itraconazole for 6-12 weeks	NSAIDs

[a] Effectiveness of corticosteroids is controversial.

[b] Alternate azoles with either less activity or less published clinical data include voriconazole and posaconazole.

[c] Therapy should be continued until *Histoplasma* antigen concentration is <2 units/mL in urine or serum.

[d] Lifelong suppresive therapy may be needed in immunosuppressed patients if immunosuppression cannot be reversed.

[e] Therapy is controversial and probably ineffective except in cases of granulomatous mediastinitis that are misdiagnosed as fibrosing mediastinitis.

Modified from Wheat et al. Clin Infect Dis. 2007;45:807-25. Used with permission.

Blastomyces dermatitidis

General Information

- Thick-walled, broad-based budding yeasts 5-15 mcm; common association with riverbanks, soil, decaying matter, wood

Endemic Areas

- South-central and midwestern US, especially Wisconsin; St. Lawrence river basin

Clinical Disease

- **Pulmonary disease:** Chronic pneumonia that can last 2-6 months with weight loss, night sweats, and occasional cavitation
- **Skin disease:** Most common extrapulmonary finding; can present as verrucous or ulcerative lesions; subcutaneous nodules or "cold abscesses," black pepper-like lesions, or eschar forming
- **Osteomyelitis:** Occurs in up to 25% of extrapulmonary cases; noncaseating granulomas with suppuration and necrosis
- **Genitourinary infection:** Prostatitis, epididymo-orchitis

Diagnosis

- **Culture**
- **Tissue staining:** Characteristic broad-based budding yeasts
- **Serology:** Insensitive
- ***Blastomyces* antigen:** Urine, blood

Treatment

- **Pulmonary blastomycosis:** Spontaneous cure can occur in some immunocompetent patients with mild disease
  1) **Severe disease:** Start with amphotericin B product
  2) **Mild to moderate disease:** Treat with itraconazole for minimum of 6 months
- Disseminated blastomycosis
  1) **CNS disease:** Treat with amphotericin B product; alternate treatment is high-dose fluconazole
  2) **Non-CNS disease:** Treat severe cases with amphotericin B product; can change to itraconazole when patients are stable; treat moderate cases with itraconazole for at least 6 months
- **Osteomyelitis:** At least 1 year of azole therapy
- **Immunocompromised hosts:** Patients with HIV or AIDS; transplant patients
  1) **Treatment:** Use amphotericin B product or, in stable patients, itraconazole; consider suppressive therapy with itraconazole
- **Note:** Other azoles with either less activity or less published clinical data include fluconazole, voriconazole, and posaconazole

Coccidioides immitis and C posadasii

General Information

- Large, round spherules 20-80 mcm containing many small endospores
- *Coccidioides* sp flourish just below the surface of the

desert soil, and outbreaks have been associated with dust storms and construction projects
- Africans, Filipinos (probable), and immunosuppressed patients are at increased risk for disseminated disease

Endemic Areas
- Desert Southwest US, Mexico and Central America, Argentina

Clinical Disease
- **Acute coccidioidomycosis or primary disease:** Often self-limiting
  1) **Pulmonary disease:** See below
  2) **Immune-mediated syndromes**
     a) Migratory polyarthralgia (nondeforming), "desert rheumatism"
     b) Erythema nodosum (more frequent in women than in men), and erythema multiforme ("the bumps")
  3) **Valley fever:** Symptoms same as above, with fever, myalgias, malaise, peripheral blood eosinophilia
- **Pulmonary disease:** Cough, pleurisy, fever, and weight loss 1-3 weeks after exposure; hilar adenopathy, pleural effusions, or, in 5% of cases, cavitation
  1) **Residual pulmonary nodules:** Affect about 4% of patients after primary pneumonia
  2) **Coccidioidal pulmonary cavities:** Typically thin-walled cavities (2-8% of adults)
  3) **Ruptured cavities:** Bronchopleural fistula can form; dyspnea and chest pain common; can occur in young, healthy patients; not associated with immunosuppression
  4) **Chronic fibrocavitary pneumonia:** Can occur in patients whose primary pneumonia fails to resolve
  5) **Diffuse, reticulonodular pneumonia:** Affects immunosuppressed patients
- **Extrapulmonary disease**
  1) **Cutaneous disease:** Most common site of dissemination; granulomas, subcutaneous abscesses; plaques with wart-like appearance
  2) **Osteomyelitis and joint infections:** Typically in weight-bearing joints
  3) **Meningitis and CNS disease:** Basilar disease; hydrocephalus common; CSF eosinophilia common
  4) **Other (less common) sites:** Endocrine glands, eyes, liver, kidneys, genital organs, prostate, peritoneal cavity

Diagnosis
- **Culture**
- **Tissue staining:** Identify characteristic spherules containing endospores
- **Serology:** Can be false-negative early in disease
  1) **Complement fixation:** Height of complement fixation titer can correlate with disease extent and response to therapy; serial or longitudinal complement fixation testing should be consistently done in same

laboratory
2) Immunodiffusion
3) Enzyme immunoassay

Treatment

- Relapse is common, especially for meningitis and extrapulmonary disease
- **Pulmonary disease**
  1) **Acute, uncomplicated pulmonary disease:** May be observed without treatment
     a) **Immunosuppression or complement fixation titer >1:16:** Usually warrants fluconazole or itraconazole treatment for 3-6 months
  2) **Diffuse or progressive pulmonary disease:** Administer amphotericin followed by fluconazole or itraconazole for a total period of at least 1 year
  3) **Pulmonary nodule (asymptomatic):** Monitor without treatment
  4) **Pulmonary cavity**
     a) **Asymptomatic:** Most authorities would not treat
     b) **Symptomatic:** Antifungal therapy; surgery considered in select cases
     c) **Ruptured coccidioidal cavity into pleural space:** Well-recognized complication; surgical resection and antifungal therapy
  5) **Chronic fibrocavitary pneumonia:** Antifungal therapy for >1 year and surgery for refractory lesions or hemoptysis
- **Osteoarticular disease:** Antifungal therapy with surgical debridement; variable treatment duration (eg, 6-12 months), depending on disease location, extent, and response to therapy (ie, follow erythrocyte sedimentation rate, C-reactive protein, and anti-*Coccidioides* sp complement fixation serologic titers)
- **Meningitis and CNS disease**
  1) Therapy with amphotericin B product or fluconazole is preferable; alternate treatments include voriconazole and itraconazole
  2) For patients who respond to azole therapy, consider azole treatment indefinitely
  3) Patients who do not respond initially to systemic treatment may be candidates for intrathecal amphotericin B therapy

Paracoccidioides brasiliensis

General Information

- Reproduces by multiple, budding "pilot wheel" (South American blastomycosis)
- Most cases are found in men (15:1)

Endemic Areas

- Latin America from Mexico to Argentina; especially Brazil, Colombia, Argentina, and Venezuela

Clinical Disease

- **Lungs:** Usual portal of entry; patchy or confluent infiltrate; bullae can form; 2 types
  1) **Juvenile form:** More chronic course; more severe

prognosis; minimal respiratory symptoms
2) **Adult form:** More significant respiratory symptoms; better outcome

- **Mucosal ulcerations:** Mouth, lips, gums, tongue, palate (granulomatous appearance), nose
- **Skin:** Warty, ulcerative lesions, crusting; granulomatous
- **Lymphadenopathy:** Cervical, axillary, mesenteric, mediastinal

Treatment

- Either itraconazole or ketoconazole for >6 months
- sulfonamides
- amphotericin B product (in combination therapy)

Sporothrix schenckii

General Information

- Oval- or cigar-shaped budding yeast at 37°C
- Common in soil, plants, or plant products such as straw, wood, sphagnum moss, and thorny plants
- Infection commonly occurs due to mild skin trauma (eg, rose thorn scratches) with potential lymphatic or hematogenous spread) or by inhalation (less common)

Clinical Disease

- **Cutaneous infection:** By contact with plants, rose thorns, gardening
  1) **Plaque sporotrichosis:** Nontender plaque
  2) **Lymphocutaneous sporotrichosis:** Multiple nodular lesions following path of lymphatics
- **Extracutaneous disease**
  1) **Osteoarticular disease:** *S schenckii* infection has a distinct predilection for joints (chronic arthritis)
  2) **CNS involvement:** Typically produces chronic meningitis
  3) **Pulmonary disease:** Subacute or chronic; cavitation usually in upper lobes

Treatment

- **Lymphocutaneous and cutaneous disease:** First-line treatment is itraconazole for 3-6 months; alternate treatments include saturated solution of potassium iodide, fluconazole (less effective), and local hyperthermia
- **Pulmonary sporotrichosis:** Chronic cavitary fibronodular disease
  1) Treat with amphotericin or itraconazole
  2) Surgical resection may be required, especially with cavitary disease
- **Osteoarticular disease:** First-line treatment is itraconazole; alternate treatments include amphotericin or fluconazole
- **Meningeal disease:** Treat with amphotericin B product

Aspergillus sp

General Information

- Filamentous branching at 45° angles with septate hyphae
- Angioinvasive pattern

- **Cultures:** Blood and CSF cultures rarely yield *Aspergillus* sp
- **Definitive diagnosis:** Requires both histopathologic evidence (eg, invasive, acute-angle, branching, septate, or nonpigmented hyphae) and positive *Aspergillus* sp cultures
- **Branching, septated hyphae:** Not specific for *Aspergillus* sp and also characteristic of *Fusarium* sp, *Pseudallescheria boydii*, and agents of phaeohyphomycosis; Zygomycetes may have similar appearance with minimal septae
- **Antifungal treatment options (depends on syndrome):** voriconazole, amphotericin B product, posaconazole, itraconazole, echinocandin
  1) Combination antifungal therapy is under investigation and may have a role in select cases
  2) *Aspergillus terreus* is less susceptible to amphotericin therapy and more responsive to voriconazole, posaconazole, itraconazole, or echinocandin

Clinical Disease and Treatment

- **Pulmonary infections**
  1) **Allergic bronchopulmonary aspergillosis:** A type of hypersensitivity pneumonitis
     a) **Characteristic signs:** Asthma, eosinophilia, increased immunoglobulin E and *Aspergillus* precipitins in serum
     b) **Chest radiographs:** May show transient areas of consolidation, more commonly in upper lobes; "fleeting shadows" commonly described
     c) **First-line treatment:** Corticosteroids; oral antifungal therapy may be useful
  2) ***Aspergillus* colonization of airways:** Common in patients with chronic lung disease, chronic obstructive pulmonary disease, bronchiectasis; does not require treatment
  3) **Aspergilloma:** Noninvasive or minimally invasive fungal mass that exists in lung cavity (eg, in old tuberculosis cavities); patients usually have chronic pulmonary disease; overlap exists between fungal colonization and tissue invasion
  4) **Invasive pulmonary aspergillosis:** Almost exclusively in immunosuppressed patients (eg, postchemotherapy neutropenic and granulocytopenic patients)
     a) **Angioinvasive pulmonary disease:** Hemoptysis and pulmonary hemorrhage common
     b) **Chest radiograph (variable):** Nodular or wedge-shaped pleural densities; cavities may occur later
     c) **Chest CT (variable):** Nodular lesions; halo sign may be present early (area of low attenuation surrounding nodular lung lesion); later a "crescent sign" can appear (air crescent near periphery of lung nodule caused by contracted lung tissue)
  5) Treatment of invasive aspergillosis: voriconazole, amphotericin B product, posaconazole, itraconazole, echinocandin
     a) Optimal duration of invasive pulmonary

aspergillosis variable although typically months

b) Consider continuation of antifungal therapy through chemotherapy and neutropenic period or resumption of therapy in patients about to receive additional (induction or consolidation) chemotherapy

c) Surgical resection of isolated lesion (eg, large size or cavitary) considered in select patients who require additional chemotherapy or transplantation

- **Sinonasal infections:** Invasive and noninvasive disease
  1) **Acute invasive infection:** Usually occurs in immunocompromised patients
     a) **Mucosal invasion with infarction:** Can spread to contiguous structures, including eyes and brain (high mortality)
     b) **Presentation:** Patients often present with epistaxis, naso-orbital pain, sinus congestion with headache
     c) **Diagnosis:** Endoscopic inspection, biopsy, and culture of suspicious mucosal lesions to 1) document tissue invasion and 2) identify invasive fungus type
     d) **Treatment:** Combined medical and surgical approach
  2) **Chronic indolent invasive infection:** Usually occurs in immunocompetent patients
     a) **Course:** Progresses over months to years (usually in areas with high levels of spores)
     b) **Treatment:** Surgical debridement and drainage are usually sufficient; use of antifungals is secondary
  3) ***Aspergillus* fungus ball (mycetoma):** Usually remains confined to a single sinus cavity for months to years
     a) **Course:** Usually little tissue reaction and no invasion
     b) **Treatment:** Surgical debridement and drainage usually sufficient
  4) **Allergic fungal sinusitis:** Usually affects immunocompetent young adults
     a) **Bone destruction:** 30-50% of cases
     b) **Treatment:** Conservative surgical drainage with antibacterial agents (as needed for secondary bacterial infection); systemic antifungal therapy not needed without definite evidence of tissue invasion or orbital or intracranial extension
- **Ear infections:** Both colonization (common) and invasion can occur (immunosuppression)
  1) **No tissue invasion:** Local cleaning measures, cerumen removal, topical therapy
  2) **Tissue invasion:** Systemic antifungal therapy with surgical evaluation
- **Ocular infections:** By direct extension, trauma, surgery, hematogenous spread

1) **Diagnosis:** Culture of vitreous or aqueous humor
2) **Treatment:** Intravitreal amphotericin, usually after pars plana vitrectomy

- **CNS disease:** Abscess, meningitis, epidural abscess, subarachnoid hemorrhage
  1) **Diagnosis and treatment:** Surgery for diagnosis; debride as much of the lesion as possible
  2) **Systemic antifungal therapy:** amphotericin, voriconazole, itraconazole
- **Endocarditis (large vegetations):** Blood cultures rarely positive
- **Treatment:** Systemic antifungal therapy with surgical evaluation

Zygomycetes

General Characteristics

- **Appearance:** Fungi grow as mycelium and possess broad nonseptate (or rarely septate) hyphae with right-angle branches
- **Angioinvasive organism:** Leads to tissue infarction and necrosis (eg, in sinus or lungs)
- **Course:** Grows best in low-pH, high-glucose environment (eg, diabetic ketoacidosis) and has association with deferoxamine treatment
- **Species common with human infection:** *Rhizopus*, *Cunninghamella*, *Mucor*, *Syncephalastrum*, *Rhizomucor*, *Apophysomyces*, *Absidia*, and *Saksenaea* spp

Clinical Disease (Usually in Immunocompromised Patients)

- **Infarction and necrosis of tissue:** From invasion of vasculature by hyphae; usually fast paced
- **Rhinocerebral infection:** Most common clinical presentation of mucormycosis
  1) Initial acute sinusitis with necrosis of nasal septum and turbinates; rapid spread to contiguous structures (eg, palate, orbits, brain)
  2) Secondary CNS infection common with 80-90% mortality
- **Pulmonary:** Angioinvasive disease of pulmonary vessels with secondary necrosis and hemorrhage
- **Other organ system involvement:** Cutaneous (eg, skin trauma or inoculation, tissue necrosis, black eschar); gastrointestinal mucormycosis (less common) with involvement of stomach (58%) and colon (32%); renal mucormycosis; isolated involvement of CNS

Treatment

- High-dose amphotericin or oral posaconazole
- Surgical debridement required for rhinocerebral disease; ideal for other sites, if possible

Antiretroviral Therapy for HIV Infection

Elements of Diagnosis and Clinical Issues Related to Starting Therapy

- Obtain confirmatory human immunodeficiency virus (HIV) testing by rapid test or enzyme-linked immunosorbent assay (ELISA); optimally repeat HIV viral load (VL) and CD4 T-cell (CD4) count 2 times before initiation of therapy; a substantial change in CD4 count is generally >30%
- Perform VL immediately before treatment initiation (or change in therapy) and again 2-8 weeks later; for the latter, there should optimally be a decrease of at least 1 log
- Consider resistance testing for acute HIV infection, for chronic HIV infection before initiation of therapy, and for virologic failure or suboptimal response (if HIV VL >1,000 copies/mL)
- Include baseline testing of HIV VL, CD4 count, complete blood cell count (CBC), chemistries (eg, renal and liver function, lipids, glucose), urinalysis, sexually transmitted disease testing, serologies (for cytomegalovirus, toxoplasmosis, and hepatitis), tuberculin test, chest radiograph, Papanicolaou test, and specific opportunistic infection testing as appropriate
- Obtain patient history of vaccinations, HIV risk factors, exposure issues, allergies, substance abuse, psychiatric history, opportunistic infections, cardiac risk factors, pregnancy or lactation status, current medications (including alternative or herbal medications), history of previous antiretrovirals, results of previous resistance testing, adherence issues, and social issues that may affect adherence
- Perform extensive counseling about implications of the diagnosis, transmission risk factors, prognosis, and the critical importance of adherence, optimally before initiation of therapy (except when therapy must be initiated promptly due to life-threatening complications)
- Review potential drug interactions before initiating therapy and when adding any new medication
- Focus on treatment goals of reducing HIV-related morbidity or mortality, improving quality of life, restoring or preserving immune function, and maximally and durably suppressing HIV VL

Table 71. Indications for Antiretroviral Therapy

Clinical category	CD4 T-cell count	Plasma viral RNA, copies/mL	Recommendation
Symptomatic (eg, AIDS-defining illness, severe symptoms)	Any value	Any value	Treat
Asymptomatic	CD4 ≤200	Any value	Treat
Asymptomatic	CD4 >200 but ≤350	Any value	Individualized decision; discuss pros and cons of treatment with patient
Asymptomatic	CD4 >350	≥100,000	Most clinicians recommend deferring therapy, but some clinicians will treat
Asymptomatic	CD4 >350	<100,000	Defer therapy
In a pregnant patient regardless of symptoms	Any value	Any value	Treat pregnant patients to prevent mother-to-child transmission; refer to USDHHS guidelines* for detailed information

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

*Perinatal HIV Guidelines. Rockville (MD): Department of Health and Human Services [cited 2007 Jul 23]. Available from: http://aidsinfo.nih.gov.

Table 72. Recommended Antiretroviral Agents for Treatment-Naïve HIV Patients

(Choose one option from column A and one option from column B [selection of an antiretroviral regimen should be individualized on the basis of patient- and drug-specific factors].)

Type of treatment	Column A: PI or NNRTI	Column B: 2 NRTI
First-line (in alphabetical order)	atazanavir plus ritonavir; or efavirenz; or fosamprenavir plus ritonavir bid; or lopinavir/ritonavir (coformulated) bid	tenofovir/emtricitabine (coformulated); or zidovudine/lamivudine (coformulated)
Alternate (in alphabetical order)	atazanavir; or fosamprenavir (unboosted); or fosamprenavir plus ritonavir once daily; or lopinavir/ritonavir (coformulated) once daily; or nevirapine	abacavir/lamivudine (coformulated); or didanosine plus lamivudine

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

Table 73. Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs): Select Characteristics

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
abacavir (Ziagen)	300 mg bid or 600 mg once daily No dose adjustment needed for renal dysfunction	Take with or without food Alcohol increases abacavir levels	Hypersensitivity reaction can be severe or fatal (usually within days to 6 weeks after initiation). Symptoms may include fever, malaise, abdominal cramping, nausea, diarrhea, possible rash, elevated transaminases and creatine kinase, and possible respiratory symptoms Rechallenge after hypersensitivity reaction is contraindicated and can have severe or fatal consequences GI intolerance, fever, malaise, headache, increased transaminases NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (infrequent) Pregnancy category C	Hepatic metabolism by alcohol dehydrogenase or glucuronyl transferase, with renal excretion of metabolites May inhibit or be affected by other drugs that inhibit alcohol dehydrogenase or UDP-glucuronyl transferase Alcohol increases abacavir levels
abacavir 600 mg plus lamivudine 300 mg (coformulated; Epzicom)	1 tab once daily Cl_{Cr} <50 mL/min: Give separately in dosing as per individual agents	Take without regard to food	See individual agents	See individual agents

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg (coformulated; Trizivir)	>40 kg: 1 tab bid Cl_{Cr} <50 mL/min: Give separately in dosing as per individual agents	Take without regard to food	See individual agents	See individual agents
didanosine (Videx EC)	≥60 kg: EC capsules: 400 mg once daily With tenofovir: 250 mg once daily <60 kg: EC capsules: 250 mg once daily With tenofovir: 200 mg once daily Cl_{Cr} <60 mL/min: Reduce dose	Take on empty stomach	Pancreatitis, peripheral neuropathy, GI intolerance Fatal lactic acidosis reported in pregnant patients receiving stavudine plus didanosine; avoid combination in pregnancy, if possible NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (higher frequency with didanosine) Pregnancy category B	50% renally cleared tenofovir can significantly increase didanosine concentrations; reduce didanosine dose ribavirin can increase didanosine exposure and risk of toxicity; use combination with caution methadone can decrease didanosine levels; consider dose increase hydroxyurea can increase potential for toxicity; avoid concomitant use
efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir 300 mg (coformulated; Atripla)	1 tab once daily Cl_{Cr} <50 mL/min: Give separately in dosing as per individual agents	Do not take with high-fat meal Take at bedtime at least to start with	See individual agents	See individual agents

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
emtricitabine				
emtricitabine (Emtriva)	200 mg once daily Cl_{Cr} <50 mL/min: Reduce dose	Take without regard to food	Generally well tolerated; headache, diarrhea, nausea, rash; generally mild skin discoloration (hyperpigmentation on palms or soles) Active against HBV; may see flare on discontinuation NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (infrequent) Pregnancy category B	Renal excretion
emtricitabine 200 mg plus tenofovir 300 mg (coformulated; Truvada)	1 tab once daily	Take without regard to food	See individual agents	See individual agents

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
lamivudine (Epivir)	≥50 kg: 150 mg bid or 300 mg once daily <50 kg: 2 mg/kg bid Cl_{Cr} <50 mL/min: Reduce dose	Take without regard to food	Generally well tolerated; headache, nausea, diarrhea, abdominal pain, rash, pancreatitis in pediatric patients (rare in adults) Active against HBV; may see flare on discontinuation NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (infrequent) Pregnancy category C	Renal excretion
lamivudine 150 mg plus zidovudine 300 mg (coformulated; Combivir)	1 tab bid Cl_{Cr} <50 mL/min: Give separately in dosing as per individual agents	Take without regard to food	See individual agents	See individual agents

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
stavudine (Zerit)	≥60 kg: 40 mg bid <60 kg: 30 mg bid Cl_{Cr} <50 mL/min: Reduce dose	Take without regard to food	Peripheral neuropathy, GI intolerance, headache, insomnia, pancreatitis, hyperlipidemia, ascending neuromuscular weakness Fatal lactic acidosis reported in pregnant patients receiving stavudine plus didanosine; avoid combination in pregnancy if possible NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (higher frequency with stavudine) Pregnancy category C	50% renally cleared Possible increased risk of pancreatitis, neuropathy, hepatotoxicity, and lactic acidosis when combined with didanosine or hydroxyurea

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
tenofovir (Viread)	300 mg once daily Cl_{Cr} <50 mL/min: Reduce dose	Take without regard to food	Mild GI complaints, asthenia, headache; renal dysfunction; osteomalacia Active against HBV; may see flare on discontinuation NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis (infrequent with tenofovir) Pregnancy category B	Renally cleared Can substantially increase didanosine levels; reduce didanosine dose Can decrease atazanavir levels; use atazanavir in combination with ritonavir Concomitant therapy with ritonavir, lopinavir, atazanavir, or didanosine can increase tenofovir levels and toxicity; monitor closely cidofovir, ganciclovir, and valganciclovir can compete for tubular secretion; monitor closely
zidovudine (Retrovir)	300 mg bid Cl_{Cr} <15 mL/min: Reduce dose	Take without regard to meals	Macrocytic anemia or neutropenia; malaise, GI intolerance, insomnia, asthenia; myopathy NRTI class side effects: Fat redistribution; lactic acidosis and hepatomegaly with steatosis Pregnancy category C	Hepatic metabolism with renal clearance of metabolites ribavirin can inhibit phosphorylation and activation of zidovudine

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.

[b] See package insert and other resources for specific drug interactions.

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

Table 74. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Select Characteristics

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
delavirdine (Rescriptor)	400 mg tid	Take without regard for food	Skin rash (common); can usually treat through but can be serious in some cases Mild headache, fatigue, GI complaints, increased transaminases Pregnancy category C	Hepatic metabolism Substrate for CYP 3A4[c,d] and CYP 2D6 Can inhibit CYP 3A4,[e] CYP 2D6, CYP 2C9, and CYP 2C19 Avoid H_2–receptor agonists or proton pump inhibitors

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
efavirenz (Sustiva)	600 mg once daily (preferably at bedtime to start)	Take with or without food (high-fat meal can increase bioavailability up to 50% and should be avoided)	Rash (can usually treat through if mild) CNS symptoms (eg, dizziness, light-headedness, nightmares, feeling of disengagement, impaired concentration, agitation) can be minimized by taking at bedtime and often subside after 2-4 weeks Case reports of psychosis, delusional thoughts, suicidal ideation, and depression (more frequent in patients with mental illness history) Increased transaminases, especially in patients with hepatitis Mild increase in cholesterol and triglycerides in some patients False-positive urine screening test for marijuana Pregnancy category D (avoid in pregnant patients)	Hepatic metabolism Substrate for CYP 3A4[c,d] Can induce or inhibit CYP 3A4[e] Can decrease methadone levels or effects; titrate dose
efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir 300 mg (coformulated; Atripla)	1 tab once daily Cl_{Cr} <50 mL/min: Give separately in dosing as per individual agents	Take on an empty stomach (or at least not with high-fat meal); take at bedtime to start with	See individual agents	See individual agents

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
nevirapine (Viramune)	200 mg once daily for 14 days then 200 mg bid	Start with 2-week lead-in of reduced dose to reduce incidence of rash Autoinduction occurs and stabilizes at 2-4 weeks Take with or without food	Rash (can usually treat through if mild); rare serious cutaneous reactions (eg, Stevens-Johnson syndrome) Severe and fatal cases of hepatitis reported, particularly in first 18 weeks Risk of hepatotoxicity may increase with elevated transaminases, history of hepatitis B or C, CD4 >250 in women and CD4 >400 in men If hepatitis occurs, discontinue nevirapine permanently During first 8 weeks, monitor patients intensively for serious cutaneous reactions and signs of hepatoxicity Nausea, headache, diarrhea Pregnancy category C	Hepatic metabolism Substrate for CYP 3A4[c,d] Induces CYP 3A4[e] Decreases methadone levels Decreases oral contraceptive levels; use alternate method of birth control

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.

[b] See package insert and other resources for specific drug interactions.

[c] Abbreviated list of CYP 3A4 **inducers** that can decrease serum levels of substrates for CYP 3A4 (eg, PIs, NNRTIs): rifampin, rifabutin, rifapentine, carbamazepine, phenobarbital, phenytoin, nevirapine, efavirenz, St. John's wort.

[d] Abbreviated list of CYP 3A4 **inhibitors** that can potentially increase serum level of substrates for CYP 3A4 (eg, PIs, NNRTIs): PIs, erythromycin, clarithromycin, azole antifungals, amiodarone, cimetidine, grapefruit juice.

[e] Abbreviated list of CYP 3A4 **substrates** (serum levels can be increased by CYP 3A4 inhibitors such as PIs and decreased by CYP 3A4 inducers such as nevirapine or efavirenz): benzodiazepines (avoid midazolam or triazolam; can use lorazepam with PIs); statins (avoid use of lovastatin or simvastatin with PIs; pravastatin and rosuvastatin do not significantly interact and atorvastatin can be used with caution and

monitoring); dihydropyridine calcium channel blockers; ergot alkaloids (avoid with PIs); sildenafil, vardenafil, and tadalafil (dose reduction of erectile dysfunction drugs needed with PIs); some antiarrhythmics (eg, amiodarone, lidocaine, quinidine); warfarin; pimozide (avoid with PIs); rifabutin (may need dose alterations of one or both drugs); some antidepressants and anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital); immunosuppressants (eg, cyclosporine, tacrolimus, sirolimus); azole antifungals.

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

Table 75. Select Characteristics of Protease Inhibitors

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
atazanavir (Reyataz)	400 mg once daily; or 300 mg atazanavir plus 100 mg ritonavir, both once daily Use boosted regimen with ritonavir when combined with tenofovir, efavirenz, or nevirapine	Take with food	Increased indirect bilirubin (usually asymptomatic), jaundice, GI effects, rash Prolonged PR interval, 1st-degree heart block in some patients PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia; atazanavir has less effect on glucose and lipids than other PIs Pregnancy category B	Hepatic metabolism Substrate for CYP 3A4[c,d] Can inhibit CYP 3A4,[e] CYP 1A2, and CYP 2C9 Levels decreased by tenofovir; use atazanavir plus ritonavir; atazanavir can also increase tenofovir levels (monitor for adverse effects) Space apart from antacids, avoid use with H_2 receptor and proton pump inhibitors, if possible

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
darunavir (Prezista)	600 mg with 100 mg ritonavir, both bid	Take with food	Diarrhea, nausea, and headache; elevated transaminases; rash (contains a sulfonamide moiety, so use with caution in patients with sulfonamide allergy) PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category B	Hepatic metabolism Substrate for CYP 3A4[c,d] Inhibitor of CYP 3A4[e] Decreases oral contraceptive levels; use alternate method of birth control

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
fosamprenavir (Lexiva)	Naïve patients: fosamprenavir 1,400 mg bid; or fosamprenavir 1,400 mg plus ritonavir 200 mg, both once daily; or fosamprenavir 700 mg plus ritonavir 100 mg, both bid PI-experienced patients: fosamprenavir 700 mg plus ritonavir 100 mg, both bid Coadministration with efavirenz: Use boosted regimen with ritonavir	Take with or without food	Nausea, vomiting, diarrhea, headache, rash (including rare Stevens-Johnson syndrome); amprenavir is a sulfonamide and theoretically has cross-allergenicity with other sulfa drugs Elevated transaminases PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category C	Rapidly converted to amprenavir by cellular phosphatases in the gut amprenavir is a substrate for CYP 3A4[c,d] and can inhibit CYP 3A4[e]

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
indinavir (Crixivan)	800 mg q8h With ritonavir: indinavir 800 mg plus ritonavir 100 mg or 200 mg, both given bid With efavirenz or nevirapine: indinavir 1,000 mg q8h	Take on empty stomach or with light meal, unless given with ritonavir Drink >48 ounces water daily to decrease nephrolithiasis	Nephrolithiasis (can decrease risk by drinking >48 ounces of water daily) Increased bilirubin (usually asymptomatic) Headache, nausea, vomiting, diarrhea, rash, increased hepatic transaminases, thrombocytopenia, dry skin and lips, ingrown toenails PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category C	Hepatic metabolism Substrate for CYP 3A4[c,d] Inhibits CYP 3A4[e]

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
lopinavir 200 mg/ ritonavir 50 mg (coformulated; Kaletra)	lopinavir 400 mg plus ritonavir 100 mg (2 tab) bid; or lopinavir 800 mg plus ritonavir 200 mg (4 tab once daily); use the once-daily regimen only in treatment-naïve patients Treatment-experienced patients also on efavirenz or nevirapine: lopinavir 600 mg plus ritonavir 150 mg bid	Take with food	GI intolerance, diarrhea, headache, skin rash, asthenia Higher incidence of elevated triglycerides and cholesterol than with other PIs Increased transaminases PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hematolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category C	Hepatic metabolism Substrate for CYP 3A4[c,d] Both lopinavir and ritonavir are potent inhibitors of CYP 3A4[e] Decreases methadone levels Decreases oral contraceptive levels; use alternate method of birth control Oral solution contains alcohol—avoid with metronidazole or disulfiram
nelfinavir (Viracept)	1,250 mg bid or 750 mg tid	Take with food	Diarrhea, soft stool, nausea, flatulence, rash PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category B	Hepatic metabolism Substrate for CYP 3A4[c,d]; inhibits CYP 3A4[e] (induces CYP 3A4 occasionally) Decreases oral contraceptive levels; use alternate method of birth control

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
ritonavir (Norvir)	When used as the only PI: 600 mg bid When used as a boosting agent with another PI: 100-400 mg in 1 or 2 divided doses	Take with meals when used as the sole PI	GI intolerance (dose-related; may resolve with continued therapy); less common when used in low-dose boosting regimen Taste changes, dizziness, headache, somnolence, paresthesias (circumoral and extremities), hepatotoxicity PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, spontaneous bleeding or hematomas with hemophilia; increased lipids may be more severe with ritonavir vs other PIs Pregnancy category B	Hepatic metabolism Substrate for CYP 3A4[c,d] Very potent inhibitor of CYP 3A4[e] Inhibits or competes for CYP 2C9, CYP 2C19, and CYP 2D6 Induces CYP 1A2 (decreases theophylline levels) Decreases methadone levels Decreases oral contraceptive levels; use alternate method of birth control
saquinavir (Invirase)	saquinavir 1,000 mg with ritonavir 100 mg, both bid	Take with a full meal (or within 2 hours of eating)	GI intolerance (may subside with continued therapy), diarrhea, headache, asthenia, rash, increased transaminases PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category B	Hepatic metabolism Substrate for CYP 3A4[c,d] Inhibits CYP 3A4[e] Levels decreased by dexamethasone

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
tipranavir (Aptivus)	tipranavir 500 mg with ritonavir 200 mg	Take with food	Hypersensitivity (especially in young women); possible cross-allergy with sulfonamide Hepatotoxicity; contraindicated in patients with moderate to severe liver disease Fatal and nonfatal intracranial hemorrhages reported PI class side effects: Increased lipids, lipodystrophy, hyperglycemia, hemolytic anemia, and spontaneous bleeding or hematomas with hemophilia Pregnancy category C	Substrate for CYP 3A4[c,d] Inhibitor of CYP 3A4[e] Decreases oral contraceptive levels; use alternate method of birth control

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.

[b] See package insert and other resources for specific drug interactions.

[c] Abbreviated list of CYP 3A4 **inducers** that can decrease serum levels of substrates for CYP 3A4 (eg, PIs, NNRTIs): rifampin, rifabutin, rifapentine, carbamazepine, phenobarbital, phenytoin, nevirapine, efavirenz, St. John's wort.

[d] Abbreviated list of CYP 3A4 **inhibitors** that can potentially increase serum level of substrates for CYP 3A4 (eg, PIs, NNRTIs): PIs, erythromycin, clarithromycin, azole antifungals, amiodarone, cimetidine, grapefruit juice.

[e] Abbreviated list of CYP 3A4 **substrates** (serum levels can be increased by CYP 3A4 inhibitors such as PIs and decreased by CYP 3A4 inducers such as nevirapine or efavirenz): benzodiazepines (avoid midazolam or triazolam; can use lorazepam with PIs); statins (avoid use of lovastatin or simvastatin with PIs; pravastatin and rosuvastatin do not interact and atorvastatin can be used with caution and monitoring); dihydropyridine calcium channel blockers; ergot alkaloids (avoid with PIs); sildenafil, vardenafil, and tadalafil (dose reduction of erectile dysfunction drugs needed with PIs); some antiarrhythmics (eg, amiodarone, lidocaine, quinidine); warfarin; pimozide (avoid with PIs); rifabutin (may need dose alterations of one or both drugs); some antidepressants and anticonvulsants (eg, carbamazepine, phenytoin, phenobarbital); immunosuppressants (eg, cyclosporine, tacrolimus, sirolimus); azole antifungals.

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

Table 76. Fusion Inhibitor: Select Characteristics

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
enfuvirtide	90 mg SQ bid	Each 108-mg vial should be reconstituted 1:1 with sterile water before injection Reconstituted injection should be refrigerated and used within 24 hours	Local injection site reactions Possible increased rate of bacterial pneumonia Hypersensitivity reaction, nausea and vomiting, diarrhea, peripheral neuropathy Pregnancy category B	Thought to undergo catabolism to constituent amino acids Unlikely to have significant CYP-450–related drug interactions

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.

[b] See package insert and other resources for specific drug interactions.

Modified from Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville (MD): Department of Health and Human Services [cited 2007 Jun 07]. Available from: http://aidsinfo.nih.gov.

Table 77. Integrase Inhibitor: Select Characteristics

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
raltegravir (Isentress)	400 mg bid	Take with or without food	Diarrhea, nausea, and headache were most commonly reported in studies Rare myopathy and rhabdomyolysis have been reported Rare hepatic toxicity has been reported, potentially preceded by symptoms of an allergic reaction	Metabolized by glucuronidation Does not affect P-450 enzymes Rifampin and other UGT1A1 inducers can decrease raltegravir levels; use with caution

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.

[b] See package insert and other resources for specific drug interactions.

Table 78. CCR5 Coreceptor Antagonist: Select Characteristics

Medication	Usual adult dose (without organ dysfunction)	Dosing instructions	Toxicities	Metabolism or excretion route and pharmacokinetic drug interaction potential[a,b]
maraviroc (Selzentry)	300 mg bid For CCR5-tropic virus only: Administer a tropism test before use	Take with or without food	Cough, fever, upper respiratory infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness most commonly reported in studies Rare cardiovascular effects have been noted Rare hepatic toxicity has been reported, potentially preceded by symptoms of an allergic reaction	Substrate for CYP 3A4 and P-glycoprotein (Pgp)

[a] Drug interactions listed here are not all-inclusive and do not include drugs with overlapping toxicities.
[b] See package insert and other resources for specific drug interactions.

Select Opportunistic Infections in Adult HIV Patients

***Pneumocystis jiroveci* (formerly *P carinii*)**

- **Risk factors:** Ubiquitous organism, CD4 count <200/mcL, chronic corticosteroid or other immunosuppressive drug therapy
- **Clinical disease**
  1) Exertional dyspnea, fever, nonproductive cough, and chest discomfort that gets worse over days to weeks
  2) Hypoxemia; chest radiographs vary (most commonly show diffuse bilateral, symmetrical interstitial infiltrate but may be relatively normal early in course and can have atypical presentation)
  3) Fulminant pneumonia less common in HIV patients
  4) Concomitant respiratory pathogen not uncommon
  5) Immune reconstitution syndrome can be seen (corticosteroids or nonsteroidal anti-inflammatory drugs [NSAIDS] may help)
- **Criteria for starting primary prophylaxis:** CD4 <200/mcL (or history of AIDS-defining illness)
- **Criteria for stopping primary or secondary prophylaxis:** Adequate response to highly active antiretroviral therapy (HAART) with CD4 >200/mcL for ≥3 months

Table 79. Treatment and Prophylaxis of *Pneumocystis jiroveci* Infections in HIV Patients

Antimicrobial therapy	First-line treatment	Alternate treatment
Treatment of active disease (usually 21-day duration)	tmp/smx IV 15 mg/kg/24h (tmp component) in divided doses q6-8h for 21 days; consider serum level monitoring If PaO_2 <70 mm Hg or alveolar-arterial oxygen gradient >35 mm Hg, add prednisone 40 mg bid for 5 days, then 40 mg q24h for 5 days, then 20 mg q24h for 11 days	**Severe disease:** pentamidine 3-4 mg/kg IV q24h **Mild to moderate disease:** clindamycin 600-900 mg IV q8h (or clindamycin 300-450 mg oral tid or qid) plus primaquine 15-30 mg oral q24h; or dapsone 100 mg oral q24h plus tmp 5 mg/kg oral q8h; or atovaquone 750 mg oral bid; or trimetrexate 1.2 mg/kg IV q24h plus leucovorin 0.5 mg/kg oral qid; or tmp/smx DS 2 tab tid
Prophylaxis (primary or secondary)	tmp/smx 1 DS (or SS) tab daily	dapsone 100 mg oral q24h or 50 mg oral bid; or dapsone 50 mg oral q24h plus pyrimethamine 50 mg oral once weekly plus leucovorin 25 mg oral weekly; or dapsone 200 mg oral weekly plus pyrimethamine 75 mg oral weekly plus leucovorin 25 mg oral weekly; or atovaquone 1,500 mg oral q24h; or tmp/smx 1 DS tab 3 x/wk; or pentamidine 300 mg Inh monthly

Toxoplasma gondii Encephalitis

- **Risk factors:** CD4 <100/mcL (greatest risk with CD4 <50/mcL), usually represents reactivation (IgG seropositive); primary disease risk factors are undercooked meat and exposure to cat feces
- **Clinical disease**
  1) Most common presentation is focal encephalitis
  2) Computed tomogram (CT) or magnetic resonance imaging (MRI) typically shows multiple contrast-enhancing lesions
  3) Immune reconstitution syndrome can be seen (corticosteroids or NSAIDS may help)
- **Criteria for starting primary prophylaxis:** Initiate with CD4 <100/mcL and IgG antibody positive for *Toxoplasma gondii*
- **Criteria for stopping prophylaxis:** Adequate response to HAART and
  1) **For primary prophylaxis,** CD4 >200/mcL for ≥3 months
  2) **For secondary prophylaxis,** completion of treatment course, resolution of symptoms, and CD4 >200/mcL for ≥6 months

Table 80. Treatment and Prophylaxis of *Toxoplasma gondii* Encephalitis in HIV Patients

Antimicrobial therapy	First-line treatment	Alternate treatment
Treatment of active disease (at least 6-week duration)	pyrimethamine 200 mg oral once then 50-75 mg oral q24h plus sulfadiazine 1,000-1,500 mg oral q6h plus leucovorin 10-20 mg oral q24h	pyrimethamine 200 mg oral once then 50-75 mg oral q24h plus leucovorin 10-20 mg oral q24h plus clindamycin 600 mg IV or oral q6h; or tmp/smx 5 mg/kg oral bid; or atovaquone 1,500 mg oral bid plus pyrimethamine and leucovorin in above doses; or atovaquone 1,500 mg oral bid plus sulfadiazine 1,000-1,500 mg oral q6h; or pyrimethamine and leucovorin in above doses plus azithromycin 900-1,200 mg oral q24h
Primary prophylaxis	tmp/smx DS 1 tab daily	tmp/smx SS tab daily; or dapsone 50 mg oral q24h plus pyrimethamine 50 mg oral weekly plus leucovorin 25 mg oral weekly; or dapsone 200 mg oral weekly plus pyrimethamine 75 mg oral weekly plus leucovorin 25 mg oral weekly; or atovaquone 1,500 mg oral q24h with or without pyrimethamine 25 mg oral q24h plus leucovorin 10 mg oral q24h

Antimicrobial therapy	First-line treatment	Alternate treatment
Secondary prophylaxis (chronic maintenance therapy)	sulfadiazine 500-1,000 mg oral qid plus pyrimethamine 25-50 mg oral q24h plus leucovorin 10-25 mg oral q24h	clindamycin 300-450 mg oral q6-8h plus pyrimethamine 25-50 mg oral q24h plus leucovorin 10-25 mg oral q24h atovaquone 750 mg oral q6-12h with or without pyrimethamine 25 mg oral q24h plus leucovorin 10 mg oral q24h

Mycobacterium avium Complex

- **Risk factors:** Ubiquitous organism; CD4 <50/mcL is greatest risk; can occur at CD4 <100/mcL
- **Clinical disease**
  1) Usually disseminated, affecting multiple organs
  2) Common symptoms usually include fever, night sweats, weight loss, fatigue, diarrhea
  3) Disease can be localized
  4) Immune reconstitution syndrome common
- **Criteria for starting primary prophylaxis:** CD4 <50/mcL
- **Criteria for stopping prophylaxis:** Adequate response to HAART, and
  1) **For primary prophylaxis,** CD4 >100/mcL for ≥3 months
  2) **For secondary prophylaxis,** completion of ≥12-month treatment course, resolution of symptoms, and CD4 >100/mcL for ≥6 months

Table 81. Treatment and Prophylaxis of *Mycobacterium avium* Complex in HIV Patients

Antimicrobial therapy	First-line treatment	Alternate treatment
Treatment of active disease (typically ≥12-month duration) Use at least 2 drugs for initial therapy; consider 4-8 weeks of corticosteroids for persistent symptoms	clarithromycin 500 mg oral bid plus ethambutol 15 mg/kg oral q24h with or without rifabutin[a,b] 300 mg oral q24h	azithromycin 500-600 mg oral q24h (make effort to include either clarithromycin or azithromycin in drug regimen) Other 3rd or 4th drug: rifampin (as active as rifabutin but with significant antiretroviral drug interactions); or newer fluoroquinolone (levofloxacin 500-700 mg oral q24h or moxifloxacin 400 mg oral q24h); or amikacin 10-15 mg/kg IV q24h
Primary prophylaxis	azithromycin 1,200 mg oral weekly or clarithromycin 500 mg oral bid	rifabutin[a,b] 300 mg oral q24h; or azithromycin 1,200 mg oral weekly plus rifabutin[a,b] 300 mg oral q24h
Secondary prophylaxis (chronic maintenance therapy)	clarithromycin 500 mg oral bid plus ethambutol 15 mg/kg oral q24h with or without rifabutin[a,b] 300 mg oral q24h	azithromycin 500 mg oral q24h plus ethambutol 15 mg/kg oral q24h with or without rifabutin[a,b] 300 mg oral q24h

[a] Reduce rifabutin dose to 150 mg every other day or 3 x/wk in combination with ritonavir, lopinavir/ritonavir, ritonavir/saquinavir, fosamprenavir/ritonavir, atazanavir (with or without ritonavir), tipranavir/ritonavir, or darunavir/ritonavir.

[b] Decrease rifabutin dose to 150 mg q24h or 300 mg 3 x/wk in combination with indinavir, nelfinavir, amprenavir, or fosamprenavir (without ritonavir).

Cytomegalovirus (CMV) Retinitis

- **Risk factors:** CD4 <50/mcL is greatest risk; can occur at CD4 <100/mcL
- **Clinical disease**
  1) Retinitis most common (in AIDS patients)
  2) Colitis, esophagitis, pneumonitis, neurological disease also possible
  3) Immune reconstitution syndrome can be seen (worsening); corticosteroids or NSAIDs may help
- **Criteria for starting primary prophylaxis:** Primary prophylaxis not recommended
- **Criteria for stopping secondary prophylaxis:** Completion of treatment course and sustained CD4 >100-150/mcL (eg, for ≥6 months) with no evidence of active disease; should undergo routine eye examinations

Table 82. Treatment and Prophylaxis of Cytomegalovirus Retinitis in HIV Patients

Antimicrobial therapy	First-line treatment	Alternate treatment
Treatment of active disease	Sight threatening: valganciclovir 900 mg oral bid or ganciclovir 5 mg/kg IV q12h for 2-3 weeks; then valganciclovir 900 mg oral daily or ganciclovir 5 mg/kg oral q24h plus ganciclovir ocular implant with either regimen (change every 6-8 months) Peripheral lesions: valganciclovir 900 mg oral bid for 14-21 days then daily	ganciclovir 5 mg/kg IV q12h for 2-3 weeks then 5 mg/kg IV q24h; or ganciclovir 5 mg/kg IV q12h for 2-3 weeks then valganciclovir 900 mg oral q24h; or foscarnet 60 mg/kg IV q8h or 90 mg/kg q12h for 2-3 weeks then 90-120 mg/kg IV q24h; or cidofovir 5 mg/kg IV weekly for 2 weeks then 5 mg/kg IV every 2 weeks with probenecid and saline hydration; or Repeated intravitreal injections of fomivirsen (for relapses only—not primary therapy)
Primary prophylaxis	Not routinely recommended	
Secondary prophylaxis	valganciclovir 900 mg oral q24h	foscarnet 90-120 mg/kg IV q24h; or cidofovir 5 mg/kg IV every other week plus oral probenecid 2 g at 3 hours before and 1 g at 2 hours and at 8 hours after cidofovir dose (4 g total); or fomivirsen 1 vial into vitreous and repeat every 2-4 weeks

Additional Information

- For treatment of non-CNS *Cryptococcus* and other fungal infections, see section on Fungal Infections, page 261.
- For treatment of CNS *Cryptococcus*, see section on Central Nervous System Infections, page 161.
- For treatment of *Mycobacterium tuberculosis*, see section on Tuberculosis, page 225.

Table 83. Recommended Vaccines for Prevention of Opportunistic Infections in Adult HIV Patients

Vaccine	Candidates	Comments
Streptococcus pneumoniae	All patients; consider delaying until CD4 ≥200/mcL	23-valent *S pneumoniae* vaccine; consider 1 repeat dose in 5 years
Influenza	All patients annually before influenza season	Yearly inactivated influenza vaccine only
Hepatitis A	Consider for all patients who are not immune (especially illegal drug users, men who have sex with other men, patients with hemophilia, and patients with liver disease including hepatitis B or C)	Hepatitis A vaccine in 2 doses (or combination hepatitis A and hepatitis B vaccine in 3 doses)
Hepatitis B	All patients who are not immune	Hepatitis B vaccine in 3 doses (or combination hepatitis A and hepatitis B vaccine in 3 doses)

Data from Guidelines for the prevention of opportunistic infections among HIV-infected persons-2002. Rockville (MD): Department of Health and Human Services. [cited 2007 Jul 14]. Available from: http://aidsinfo.nih.gov.

Occupational Postexposure Prophylaxis and Management

Important Information for Postexposure Prophylaxis Decisions

Risk of Viral Transmission

Percutaneous Needlestick Exposure From Infected Source

- Hepatitis B virus (HBV) for nonvaccinated persons when blood from source is
  1) HBsAg (hepatitis B surface antigen) positive **and** HBeAg (hepatitis B e antigen) positive: HBV transmission risk is about 37-62%
  2) HBsAg positive **and** HBeAg negative: HBV transmission risk is about 23-37%
- Hepatitis C virus (HCV) transmission risk is about 1.8-3% (range, 0-7%)
- Human immunodeficiency virus (HIV) transmission risk is about 0.3% (about 1 in 300)
  1) About 0.1% after mucous membrane exposure
  2) <0.1% after exposure to nonintact skin

Body Fluids

- Fluids that pose some degree of risk of HIV, HBV, or HCV transmission: Blood, semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, amniotic fluid
- Fluids that do **not** pose a risk of HIV, HBV, or HCV transmission: Urine, stool, saliva (not containing blood), emesis, nasal secretions, tears, sweat

Counseling and Prophylaxis

- Persons exposed to HIV, HBV, or HCV should be offered counseling to promote a full understanding of the risks of viral transmission
- HIV postexposure prophylaxis (PEP) should be started as soon as possible (within hours); any benefit of PEP is significantly decreased when started more than 48 hours after exposure

Information to Document Immediately After Exposure

Clinical Information About Exposure Source

- Known positive HIV, HBV, or HCV source?
- In patients known to be HIV positive: Most recent HIV viral load (VL), current and previous HIV treatment, response to HIV treatment (eg, failing treatment), or suspected drug-resistant virus
- In patients with unknown HIV status: Any clinical findings or previous opportunistic infections to suggest possible HIV infection

Types of Exposure

- Percutaneous (ie, needlestick) vs mucous membrane or broken skin exposure to blood
- Direct laboratory contact with concentrated virus (eg, in laboratory workers)
- If needlestick injury: Hollow-bore or solid suture needle? Visible blood on needle?
- If mucous membrane or broken skin exposure: Type of infectious fluid (eg, blood) and quantity (eg, a few drops or a splash)

Characteristics of the Exposure

- Date and time of exposure
- Puncture directly into blood vessel?
- Depth of puncture? Was bleeding produced?
- Were any protective barriers (eg, gloves) being worn?

Clinical Information About Exposure Recipient

- HBV vaccination status
- Was wound washed promptly with soap and water?
- Potential for pregnancy, current medications, allergies, and medical conditions

HIV PEP Management

Table 84. Recommended PEP for HIV-Associated Percutaneous Injuries

Type of exposure	Infection status of source				
	HIV positive, class 1[a]	HIV positive, class 2[b]	HIV status of source unknown	Unknown source	HIV negative
Less severe[c]	Basic 2-drug PEP	Expanded ≥3-drug PEP	No PEP needed generally; consider 2-drug PEP if source has HIV risk factors	No PEP needed generally; consider 2-drug PEP if exposure to HIV-positive person is likely	No PEP needed
More severe[d]	Expanded ≥3-drug PEP	Expanded ≥3-drug PEP	No PEP needed generally; consider 2-drug PEP if source has HIV risk factors	No PEP needed generally; consider 2-drug PEP if exposure to HIV-positive person is likely	No PEP needed

[a] Human immunodeficiency virus (HIV) positive, class 1: Asymptomatic HIV infection or known HIV viral load (VL) <1,500 copies/mL.

[b] HIV positive, class 2: Symptomatic HIV infection, AIDS, acute seroconversion; known high HIV VL.

[c] Examples: Solid needle or superficial injury.

[d] Examples: Large, hollow-bore needle; deep puncture; visible blood on device; needle used in artery or vein of patient.

Modified from Centers for Disease Control and Prevention. MMWR. 2005;54(RR-9):1-17.

Table 85. Recommended PEP for HIV-Associated Mucous Membrane Exposures and Nonintact Skin Exposures

Type of exposure	Infection status of source				
	HIV positive, class 1[a]	HIV positive, class 2[b]	HIV status of source unknown	Unknown source	HIV negative
Small volume[c]	Consider basic 2-drug PEP	Basic 2-drug PEP	No PEP needed generally	No PEP needed generally	No PEP needed
Large volume[d]	Basic 2-drug PEP	Expanded ≥3-drug PEP	No PEP needed generally; consider 2-drug PEP if source has HIV risk factors	No PEP needed generally; consider 2-drug PEP if exposure to HIV-positive person is likely	No PEP needed

[a] Human immunodeficiency virus (HIV) positive, class 1: Asymptomatic HIV infection or known HIV viral load (VL) <1,500 copies/mL.

[b] HIV positive, class 2: Symptomatic HIV infection, AIDS, acute seroconversion; known high HIV VL.

[c] Example: A few drops.

[d] Example: A blood splash.

Modified from Centers for Disease Control and Prevention. MMWR. 2005;54(RR-9):1-17.

HIV PEP Drug Regimens

Basic 2-Drug Regimens

- Combivir (zidovudine 300 mg/lamivudine 150 mg) 1 tab oral bid
- zidovudine 300 mg oral bid plus lamivudine 300 mg oral once daily or lamivudine 150 mg oral bid (higher pill burden)
- zidovudine 300 mg oral bid plus emtricitabine 200 mg once daily
- tenofovir 300 mg oral once daily plus lamivudine 300 mg oral once daily
- Truvada (emtricitabine 200 mg/tenofovir 300 mg) 1 tab oral once daily
- **Note:** Combination drugs such as Combivir and Truvada decrease pill burden and may improve patient compliance

Alternate Basic 2-Drug Regimens

- stavudine 40 mg oral bid plus one of the following: lamivudine 300 mg oral once daily (or lamivudine 150 mg oral bid [higher pill burden]) or emtricitabine 200 mg oral once daily
- didanosine 400 mg oral once daily plus either lamivudine 300 mg oral once daily (or lamivudine 150 mg oral bid [higher pill burden]) or emtricitabine 200 mg oral once daily

Expanded (3rd-Drug) Options With 2-Drug Regimen Above

- Kaletra (lopinavir 200 mg/ritonavir 50 mg) 2 tab oral bid
- atazanavir 300 mg oral once daily plus ritonavir 100 mg oral once daily or atazanavir 400 mg once daily without ritonavir
- fosamprenavir 1,400 mg oral bid
- fosamprenavir 1,400 mg oral once daily plus ritonavir 200 mg oral once daily (or fosamprenavir 700 mg oral bid plus ritonavir 100 mg oral bid)
- efavirenz 600 mg oral once daily (typically at bedtime)

Other Drug Combinations

- Consider using other drug combinations (eg, abacavir, nevirapine, indinavir, nelfinavir, saquinavir) if source had drug-resistant HIV or if exposure recipient has drug intolerance, but consider obtaining an expert consultation (see section on additional resources)

HBV PEP Management

Table 86. Recommended PEP for HBV Exposure

Vaccination status of exposed HCP[a]	HBV antigen or antibody status of source		
	Source HBsAg positive	Source HBsAg negative	Source HBV status unknown (or not available for testing)
Not previously vaccinated	HBIG once and initiate HBV vaccine series	Initiate HBV vaccine series	Initiate HBV vaccine series
Previously vaccinated			
Known responder[b]	No treatment	No treatment	No treatment
Known nonresponder[c]	HBIG once and initiate revaccination or HBIG twice[b]	No treatment or consider revaccination	If source has known high HBV risk, treat as HBsAg positive
HBV antibody response unknown	Test exposed HCP for anti-HBs: If adequate, no treatment necessary If inadequate, administer HBIG once and vaccine booster	No treatment	Test exposed HCP for anti-HBs: If adequate, no treatment necessary If inadequate, administer vaccine booster and recheck anti-HBs titer in 1-2 mo

[a] Persons previously infected with hepatitis B virus (HBV) are immune to reinfection and do not require postexposure prophylaxis.

[b] Appropriate protective response to HBV vaccine defined by quantitative anti-HBs ≥10 milliunits/mL (adequate antibody level).

[c] Inadequate protective response to vaccine defined by quantitative anti-HBs <10 milliunits/mL (inadequate antibody level).

Modified from Centers for Disease Control and Prevention. MMWR. 2001;50(RR-11):1-42.

HCV Postexposure Management

- There is currently no postexposure immunoglobulin or vaccine recommended for HCV exposure
- Patients with symptomatic acute HCV infection may benefit from antiviral therapy administered after expert consultation

Postexposure HIV, HBV, and HCV Laboratory Monitoring

Source of Exposure

- Test immediately for HIV serology (if HIV positive, check VL and possibly conduct resistance testing if virus is poorly controlled), HBsAg, anti-HBs, and HCV serology

Exposure Recipient

- **HIV serology:** At baseline, 6 weeks, 3 months, and 6 months (consider extending HIV serology testing to 1 year if HCV seroconversion occurs)
- **If antiretroviral therapy started for HIV PEP:** Complete blood cell count, liver function tests, and creatine (glucose if protease inhibitor used) at baseline and again after 2 weeks of antiretroviral PEP
- **HBV serology:** At baseline, 4-6 weeks, 3 months, and 6 months (consider alanine aminotransferase [ALT], HBsAg, or HBV DNA if symptoms are consistent with acute infection)
- **HCV serology:** At baseline, 3 months, and 6 months (consider ALT and HCV RNA testing if symptoms are consistent with acute infection)

Additional Resources for HIV, HBV, and HCV Postexposure Management

HIV Exposure

- National HIV/AIDS Clinicians' Consultation Center. Available from: http://www.uscf.edu/hivcntr/PEPline (PEPline Hotline 1-888-448-4911)
- HIV/AIDS Prevention at CDC. Atlanta (GA): Centers for Disease Control and Prevention. [updated 2007 Mar 20; cited 2007 Jul 21]. Available from: http://www.cdc.gov/hiv/aboutDHAP.htm
- AIDSinfo. Rockville (MD): AIDSinfo. [cited 2007 Jul 21]. Available from: http://aidsinfo.nih.gov/

HBV and HCV Exposure

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Vaccine Schedule for Ages 0-18

Table 87. Recommended Immunization Schedule for Children 0-6 Years of Age[a]

Birth	1 Month	2 Months	4 Months	6 Months	12 Months	15 Months	18 Months	19-23 Months	2-3 Years	4-6 Years
HBV	HBV[b]		[c]	HBV[b]				HBV series[d]		
		Rota	Rota	Rota						
		DTaP	DTaP	DTaP		DTaP[b]				DTaP[b]
		Hib	Hib	Hib[e]	Hib[b]		Hib[d]			
		PCV	PCV	PCV	PCV[b]				PCV[f]	
									PPV[f]	
		IPV	IPV	IPV[b]						IPV[b]
				Influenza (yearly)[b]						[f]
					MMR[b]					MMR[b]
					Varicella[b]					Varicella[b]
					HAV (2 doses)[b]				HAV series[f]	
									MPSV4[f]	

[a] Recommended ages for routine administration of currently licensed childhood vaccines as of December 1, 2006, for children 0-6 years of age (see also http://www.cdc.gov/nip/recs/child-schedule.htm). For detailed recommendations, consult the respective Advisory Committee on Immunization Practices statement.

[b] Range of recommended ages (shaded throughout).

[c] Administer monovalent hepatitis B virus (HBV) vaccine to newborns before hospital discharge, then complete series with either monovalent HBV vaccine or combination vaccine, with 2nd dose at age 1-2 months and final dose at age ≥24 weeks. If combination vaccines are administered after the birth dose, 4 doses of HBV vaccine are permissible. If monovalent HBV vaccine is used for doses after the birth dose, a dose at age 4 months is not necessary.

[d] Catch-up immunization age ranges.

[e] If PRP-OMP is administered at age 2 months and at age 4 months, a dose at age 6 months is **not** required. The combination product DTaP/Hib should **not** be used for primary immunization but can be used as a booster after any Hib vaccine in children aged ≥12 months.

[f] Certain high-risk groups.

From Centers for Disease Control and Prevention. MMWR. 2007;55:Q1-4. Please see full document for footnotes and additional information.

Table 88. Catch-Up Vaccination Schedule for Children 4 Months to 6 Years of Age Who Start Late or Are More Than 1 Month Behind

Vaccine	Minimum age for dose 1	Minimum interval between doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
HBV	Birth	4 wk	8 wk (16 wk after first dose)		
Rota	6 wk	4 wk	4 wk		
DTaP	6 wk	4 wk	4 wk	6 mo	6 mo[a]
Hib	6 wk	4 wk (if 1st dose given at age <12 mo) 8 wk (as final dose if 1st dose given at age 12-14 mo) No further doses needed (if 1st dose given at age ≥15 mo)	4 wk[b] if current age <12 mo 8 wk (as final dose)[b] if current age ≥12 mo and second dose given at age <15 mo No further doses needed (if previous dose given at age ≥15 y)	8 wk (as final dose) necessary **only** for children 12 mo to 5 y who received 3 doses before age 12 mo	

Vaccine	Minimum age for dose 1	Minimum interval between doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
PCV	6 wk	4 wk if 1st dose given at age <12 mo and current age <24 mo 8 wk (as final dose) if 1st dose given at age ≥12 mo or current age 24-59 mo No further doses needed for healthy children given 1st dose at age ≥24 mo	4 wk if current age <12 mo 8 wk (as final dose) if current age ≥12 mo No further doses needed for healthy children if previous dose given at age ≥24 mo	8 wk (as final dose) necessary **only** for children 12 mo to 5 y who received 3 doses before age 12 mo	
IPV	6 wk	4 wk	4 wk	4 wk[c]	
MMR	12 mo	4 wk			
Varicella	12 mo	3 mo			
HAV	12 mo	6 mo			

[a] A 5th dose of DTaP is **not** necessary if 4th dose was given at age ≥4 years. DTaP is **not** indicated for children aged ≥7 years.

[b] Minimum age: 6 weeks. Hib vaccine not generally recommended for children aged ≥5 years. If age <12 months and 1st 2 doses were PRP-OMP, 3rd dose should be given at age 12-15 months at least 8 weeks after 2nd dose. If 1st dose was given at age 7-11 months, give 2 doses 4 weeks apart plus booster at age 12-15 months.

[c] Minimum age: 6 weeks. If all-inactivated poliovirus (IPV) or all-oral poliovirus (OPV) series was given with 3rd dose at age ≥4 years, no 4th dose necessary. If both IPV and OPV given as part of series, a total of 4 doses should be given regardless of current age.

Table 89. Recommended Immunization Schedule for Persons 7-18 Years of Age[a]

<table>
<tr><th>7-10 Years</th><th>11-12 Years</th><th>13-14 Years</th><th>15 Years</th><th>16-18 Years</th></tr>
<tr><td>[b]</td><td>Tdap[c]</td><td colspan="3">Tdap[d]</td></tr>
<tr><td>[e]</td><td>HPV (3 doses)[c]</td><td colspan="3">HPV series[d]</td></tr>
<tr><td rowspan="2">MPSV4[f]</td><td rowspan="2">MCV4[c]</td><td></td><td>MCV4[c,g]</td><td></td></tr>
<tr><td colspan="2">MCV4[f,g]</td></tr>
<tr><td colspan="5">PPV[f]</td></tr>
<tr><td colspan="5">Influenza (yearly)[f]</td></tr>
<tr><td colspan="5">HAV series[f]</td></tr>
<tr><td colspan="5">HBV series[d]</td></tr>
<tr><td colspan="5">IPV series[d]</td></tr>
<tr><td colspan="5">MMR series[d]</td></tr>
<tr><td colspan="5">Varicella series[d]</td></tr>
</table>

[a] Recommended ages for routine administration of currently licensed childhood vaccines as of December 1, 2006, for children aged 7-18 years (see also http://www.cdc.gov/nip/recs/child-schedule.htm). For detailed recommendations, consult the respective Advisory Committee on Immunization Practices statement.

[b] Give Tdap at age 11-12 years if childhood DTP/DTaP series completed but no Td booster dose received or at age 13-18 years if childhood DTP/DTaP series completed but no Td/Tdap booster administered at age 11-12 years.

[c] Range of recommended ages (shaded throughout).

[d] Catch-up immunization age range.

[e] Give 1st dose of human papillomavirus (HPV) series in females at age 11-12 years, 2nd dose 2 months later, and 3rd dose 6 months after 1st dose. Give HPV series to females at age 13-18 years if not administered previously.

[f] Certain high-risk groups.

[g] Give MCV4 at age 11-12 years and to previously unvaccinated adolescents at high school entry about age 15 years. Give MCV4 to previously unvaccinated college freshmen living in dormitories; MPSV4 is acceptable alternate vaccine. Give to high-risk groups at age ≥2 years (eg, with terminal complement deficiencies or anatomical or functional asplenia).

From Centers for Disease Control and Prevention. MMWR. 2007;55:Q1-4. Please see full document for footnotes and additional information.

Table 90. Catch-Up Vaccination Schedule for Children 7-18 Years of Age Who Start Late or Are More Than 1 Month Behind

Vaccine	Minimum age for dose 1	Minimum interval between doses		
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4
Td, Tdap	7 y[a]	4 wk	8 wk if 1st dose administered at age <12 mo 6 mo if 1st dose given at age ≥12 mo	6 mo if 1st dose administered at age <12 mo
HPV	9 y	4 wk	12 wk	
HAV	12 mo	6 mo		
HBV	Birth	4 wk	8 wk (and 16 wk after 1st dose)	
IPV	6 wk	4 wk	4 wk	4 wk[b]
MMR	12 mo	4 wk		
Varicella	12 mo	4 wk if 1st dose given at age ≥13 y 3 mo if 1st dose given at age <13 y		

[a] Minimum ages: 7 years for Td, 10 years for BOOSTRIX (tetanus toxoid, diphtheria toxoid, and pertussis antigens [Tdap]), and 11 years for ADACEL (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis absorbed [Tdap]). Substitute Tdap for single dose of Td in primary catch-up series or as booster if age appropriate; use Td for other doses. Five-year interval recommended between last Td dose and Tdap booster. Give booster (4th dose) if any previous doses given at age <12 months.

[b] Minimum age: 6 weeks. If all-inactivated poliovirus (IPV) or all-oral poliovirus (OPV) series was given with 3rd dose at age ≥4 years, no 4th dose necessary. If both OPV and IPV given as part of series, a total of 4 doses should be given regardless of current age.

Vaccine Schedule for Adults

Table 91. Recommended Adult Immunization Schedule by Vaccine and Age Group

Vaccine	Age group		
	19-49 Years	50-64 Years	≥65 Years
Td/Tdap[a]	1 dose Td booster every 10 y[b] (substitute 1 dose Tdap for Td for persons aged 19-64 y)		
HPV[a]	3 doses (females)[b]		
MMR[a]	1 or 2 doses[b]	1 dose[c]	
Varicella virus[a]	2 doses (0 and 4-8 wk)[b]	2 doses (0 and 4-8 wk) if not immune[c]	
Influenza[a]	1 dose annually[c]	1 dose annually	
PPV	1-2 doses[c]		1 dose[b]
HAV[a]	2 doses (0 and 6-12 mo or 0 and 6-18 mo) if not immune[c]		
HBV[a]	3 doses (0, 1-2 mo, and 4-6 mo) if not immune[c]		
MCV4 (or MPSV4)	1 or more doses[c]		

[a] Covered by the Vaccine Injury Compensation Program.

[b] For all persons who meet age requirements and lack evidence of immunity (eg, no documentation of vaccination or no evidence of prior infection) (shaded throughout).

[c] Recommended if some other risk factor is present (eg, on basis of medical, occupational, or lifestyle indication).

From Centers for Disease Control and Prevention. MMWR. 2006. 55:Q1-4. Please see full article for footnotes and additional information on specific vaccines.

Table 92. Recommended Adult Immunization Schedule by Vaccine and Medical and Other Indications

Vaccine	Condition							
	Pregnancy	Immuno-deficiency[a]	Chronic medical conditions[b]	Asplenia[c]	Chronic liver disease[d]	Kidney failure	HIV infection	Health care workers
Td/Tdap[e]	1 dose Td booster every 10 years[f] (substitute 1 dose of Tdap for Td for all indications **except** pregnancy)							
HPV		3 doses for women ≤26 y (0, 2, and 6 mo)[f]						
MMR[e]	g	g	1 or 2 doses[f]					
Varicella[e]	g	g	2 doses (0 and 4-8 wk)[f]				g	2 doses[f]
Influenza[e]	1 dose annually			1 dose annually[h]	1 dose annually			
PPV	1-2 doses[h]	1-2 doses						1-2 doses[h]
HAV[e]	2 doses (0 and 6-12 mo or 0 and 6-18 mo)[h]				2 doses[f]	2 doses (0 and 6-12 mo or 0 and 6-18 mo) if not immune[h]		
HBV[e]	3 doses (0, 1-2, and 4-6 mo)[h]				3 doses (0, 1-2, and 4-6 mo) if not immune[f]			
MCV4 (or MPSV4)	1 dose[h]			1 dose[f]	1 dose[h]			

[a]Congenital immunodeficiency, leukemia, lymphoma, generalized malignancy, cerebrospinal fluid leaks, therapy with alkylating agents, antimetabolites, radiotherapy, or high-dose long-term corticosteroids.

[b]Diabetes, heart disease, chronic pulmonary disease, chronic alcoholism.

[c]For example, elective splenectomy or terminal complement component deficiencies.

[d]Also includes recipients of clotting factor concentrates.

[e]Covered by the Vaccine Injury Compensation Program.

[f]For all persons who meet age requirements and lack evidence of immunity (eg, no documentation of vaccination or no evidence of prior infection) (shaded throughout).

[g]Contraindicated.

[h]Recommended if some other risk factor is present (eg, on basis of medical, occupational, or lifestyle indication).

Travel Medicine/Prophylaxis

Travel Prophylaxis

Malaria Prophylaxis

- The risk of contracting malaria exists to varying degrees in some countries in specific regions of the world
  1) Countries that put travelers at risk are located in Africa, Asia, Southeast Asia, Central and South America, the Middle East, and the Caribbean
  2) Prophylaxis choice depends on the traveler's itinerary, which **must** be reviewed with the physician before departure; prophylaxis is recommended if a stay in a high-risk area lasts longer than 2 nights

Malaria Medications

- The type of prophylaxis depends on the **geographic area of travel and the patient's medical history**; medications include:
  1) chloroquine
  2) atovaquone
  3) doxycycline
  4) mefloquine

Table 93. General Geography-Based Vaccine and Malaria Prophylaxis for Higher-Risk International Travel[a,b,c]

Vaccines appropriate for all adults prior to travel	Travel only to Western Europe, Japan, Australia, New Zealand	Travel to countries in South America, Africa, the Middle East	Travel to Eastern Europe, the former USSR, Asia
HAV: Series of 2 doses Immunity: About 25 years after 2 doses	No additional special vaccines; keep routine adult vaccinations updated; give annual influenza vaccine	Meningococcal vaccination is needed before travel to some countries in Africa and the Middle East; immunity lasts 3-5 years	For Asia only: Japanese encephalitis vaccination before extensive (>4 weeks) rural travel
HBV (repeated trips or prolonged travel): Series of 3 doses Immunity: Lifelong after 3 doses	In some areas of Europe, for prolonged stay (especially with prolonged outdoor exposure): Vaccination for tick-borne encephalitis may be needed (not available in US)	Yellow fever vaccination is required **10 days before** departure for travel to or from a country that has yellow fever; immunity lasts 10 years	Proof of yellow fever vaccination may be required **before** flying directly from an infected or endemic country in South America or Africa
Influenza vaccine: Annually for age ≥50 y		Poliomyelitis vaccine for some countries; one-time adult booster if childhood series completed	
Td or Tdap (as appropriate) vaccine booster required every 10 years		Typhoid (oral or IV); immunity lasts 5 years (oral) or 2 years (IV)	
Complete 2 MMR vaccine doses if born after 1957		Rabies vaccination if regularly spending time outdoors (eg, jogging, hiking) in developing countries; immunity lasts 3-5 years	
Pneumococcal vaccine if underlying chronic medical condition (eg, diabetes, renal insufficiency, cardiovascular disease, immunosuppressive condition, asplenia) or age ≥65 y	If there is any likelihood of frequent travel without advance notice to South America, Africa, Eastern Europe, the former USSR, or Asia, it may be best to complete typhoid, poliomyelitis, and yellow fever vaccinations in advance to prevent travel without protection		

[a] These are general guidelines for healthy persons and do **not** apply to immunocompromised persons.

[b] Defined as travel to most areas in Central and South America, the Caribbean, Asia, Africa, the Middle East and parts of Eastern Europe, and the former USSR.

[c] Before any vaccination is administered, patients should consult with a health professional to review their personal medical history and discuss the contraindications and risks of vaccines.

Notes:

I. Antimicrobial Agent Fundamentals

II. Antimicrobial Dosing—Adult and Pediatric

III. Treatment of Specific Organisms

IV. Infectious Syndromes in Adults

ISBN 978-142008518-1

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