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Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

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PREFACE

The *2004 Pocket Book of Infectious Disease Therapy* is intended for physicians and other care providers who manage adult patients with infectious diseases. These include internists, generalists, surgeons, obstetricians, gynecologists, medical sub-specialists, and surgical subspecialists.

This book has the same lofty goals as the first eleven editions: to provide standards of care for the management of infectious disease with particular emphasis on antimicrobial agents, their selection, dosing regimens, costs, and side effects. As with prior editions, there is extensive use of recommendations from various authoritative sources such as the Centers for Disease Control and Prevention (CDC) and the *Medical Letter on Drugs and Therapeutics* and from official statements of learned societies such as the American College of Physicians/American Society of Internal Medicine (ACP/ASIM), the American Heart Association (AHA), the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), and the Surgical Infection Society (SIS).

The 2004 edition has extensive additions, deletions, and revisions. Tabular material has been updated to account for recently approved antibiotics and new recommendations for management. This edition includes topical issues such as severe acute respiratory syndrome (SARS), West Nile Virus, hepatitis C virus (HCV), and bioterrorism. It also contains the new guidelines for intraabdominal sepsis, IV catheter-associated sepsis, fever of unknown origin, fever in the neutropenic cancer patient, and HCV management. Antimicrobials introduced since the tenth edition that are now included are peginterform, valganciclovir, adefovir, caspofungin, voriconazole, cefditoren, ertapenem, and nitazoxanide.

The HIV/AIDS section has been deleted because of space constraints and the availability of an alternative resource: *Medical Management of HIV Infection* by this author.

The reader is encouraged to notify the author (1830 Monument Street, Room 437, Baltimore, MD 21205, 410-955-7634) if there are errors,

differences of opinion, or suggested additions.

The reader is also encouraged to visit the Johns Hopkins website for updated information. For material related to HIV/AIDS: http://www.hopkins-aids.edu; for maaterial related to general infectious diseases: http://www.hopkins-id.edu. Use for management guidance http://www.hopkins-abxguide.org, which is also availaable with hand-held devices.

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Preparations and Recommended Dosing Regimens for Antimicrobial Agents

(Adapted from Drug Information 03, American Hospital Formulary Service, 2003; Physicians' Desk Reference, 57th Edition, 2003; and Drug Information for the Health Care Professional, USP DI, 23rd Edition, 2003)

Agent (generic) Pregnancy category*	***Trade names***	***Dosage form***	***Usual adult regimen and AWP***
Acyclovir Category C***	Zovirax	5% ointment; 2 & 15 g tubes 200 mg cap 400 & 800 mg tabs 200 mg/5 mL susp 500 & 1000 mg vials (IV)	Topical q3h • 2 g @ $35.28 200 mg po; × 3–5/d • 200 mg @ $1.12 400 mg po bid 800 mg po × 5/d • 800 mg @ $4.21 200–800 mg po × 3–5/d 15–30 mg/kg/d IV over 1 hr q8h • 1 g @ $35.00
Adofovir Category C	Hepsera	10 mg tab	10 mg po qd × 48–92 wks • 10 mg @ $17.60
Albendazole Category C	Albenza	200 mg tabs	400 mg po bid • 200 mg @ $1.49
Amantadine Category C	Symmetrel Symadine	100 mg cap 50 mg/5 mL soln	200 mg qd or 100 mg bid (treatment

			or prophylaxis); 100 mg/d age > 65 yr • 100 mg @ $0.62
Amikacin Category D	Amikin	0.1, 0.5 & 1 g vials	15 mg/kg/d IV × 1/d or q8–12h • 500 mg @ $119.60
Aminosalicylic acid*	Paser granules	4 g packet	150 mg/kg/d po q6–12h
Amoxicillin Category B	Amoxil, Trimox, Wymox	250 & 500 mg caps 125 & 250 mg/5 mL susp	250–500 mg po tid • 250 mg @ $0.25 • 500 mg @ $0.43
Amoxicillin + clavulanate Category B	Augmentin	125/31 & 250/62 mg/5 mL susp 125/31 & 250/62 mg chewable tab 250–250/125 & 500/125 mg tab 875/125 mg tab	250–500 mg po tid (amoxicillin) • 875/15 mg @ $5.84 • 500/125 mg @ $4.22 • 875/125 mg po bid
Amphotericin B Category B	Fungizone	50 mg vial	0.3–1 mg/kg/d IV over 4–6 hr • 50 mg @ $10.94
Amphotericin B	Abelcet (ABLC)	100 mg vials	5 mg/kg/d IV • 100 mg @ $230.00

lipid complex Category B			
	Amphotec (ABCD)	50 & 100 mg vials	3–4 mg/kg/d IV • 100 mg @ $160.00
Amphotericin BM liposomal Category B	AmBisome	50 mg vials	3–5 mg/kg/d IV Usually 5 mg/kg/d • 50 mg @ $196.25
Ampicillin Category B	Omnipen Totacillin	250 & 500 mg caps 125, 250 & 500 mg/5 mL susp	250–500 mg po qid • 250 mg @ $0.23 • 500 mg @ $0.40
Ampicillin sodium Category B	Omnipen-N Polycillin-N Totacillin-N	0.125, 0.25, 0.5, 1, 2 & 10 g vials	1–2 g IV q4–6h (up to 8 g/d) • 2 g @ $4.69
Ampicillin + sulbactam Category B	Unasyn	1:0.5 & 2:1.0 g vials (amp:sulbactam)	1–2 g IV q6h (ampicillin) • 2:1 g @ $15.85
Atovaquone Category C	Mepron	750 mg/5 mL susp	750 mg po bid w/food • 210 mL (21 day supply) @ $738.64
Atovaquone + proguanil	Malarone 100	250 mg atovaquone ×	Malaria treatment—4 tabs/d × 3 days (single daily dose) • 250/100 mg @ $4.70
		62.5 mg atovaquone + 25 mg proguanil tabs (pediatrics)	Malaria prevention—1 tab/day Take with food

	mg proguanil tabs	Category C	
Azithromycin Category B	Zithromax	250 & 600 mg tab Z Pak with 6 250 mg tabs	500 mg po first day, then 250 mg q24h × 4 or 500 mg po qd • 250 mg @ $7.83 • 600 mg @ $15.66
		500 mg vial	500 mg IV qd • 500 mg @ $27.83
Aztreonam Category B	Azactam	0.5, 1 & 2 g vials	0.5–2.0 g q 6–8 h • 1 g @ $23.35
Bacitracin*	Baci-IM Baciguent	50,000 unit vial 500 units/g ointment 15, 30, 120 & 454 g	10,000–25,000 units IM q6h; 25,000 units po q6h (*C. difficile* colitis) • 50,000 units @ $10.00
Butoconazole	Femstat	2% vaginal cream, 3 single doses	1 dose hs × 3 • 5 g @ $34.62
Capreomycin Category D	Capastat	1 g vial	1 g/day IM or IV • 1 g @ $26.60
Carbenicillin indanyl sodium Category B	Geocillin	382 mg tab (with 118 mg indanyl sodium)	382–764 mg po q6h • 382 mg @ $2.37
Caspofungin Category C	Cancidas	50 & 70 mg vials	70 mg IV (initial dose) 50 mg/d IV (daily dose) • 50 mg @ $283.71
Cefaclor	Ceclor	250 & 500 mg caps	250–500 mg po tid

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Prefered Antimicrobial Agents for Specific Pathogens

Organism	*Usual disease*	*Preferred agent(s)*	*Alternatives (in random order)*
Acinetobacter baumanii (CID 2003;37:214;AAC 2003;47:1681)	Sepsis (esp line sepsis) Pneumonia-ventilator Burn wound sepsis	Imipenem/meropenem; amikacin; ampicillin-sulbactam; cefepime; fluoroquinolone (6) ± amikacin or ceftazidime	Fluoroquinolone (6); ceftazidime; tetracycline (4); antipseudomonad penicillin (2); aztreonam; colistin/polymyxin Note: Some sensitive only to polymyxin
Actinobacillus actinomycetemcomitans	Actinomycosis	Penicillin; amoxicillin	Clindamycin; tetracycline (4); erythromycin; cephalosporins (5);
	Endocarditis	Penicillin + aminoglycoside (1)	Cephalosporin (5) + aminoglycoside (1)
Actinomyces israelii (also *A. naeslundii, A. odontolyticus*, and *Arachnia proprionica*)	Actinomycosis	Penicillin G; amoxicillin	Clindamycin; tetracycline (4); macrolide (8)
Aeromonas hydrophila (CID	Diarrhea (see p 271)	Fluoroquinolone (6); sulfa-trimethoprim × 3d	Tetracycline (4); gentamicin
	Bacteremia	Cephalosporin (3rd gen) Fluoroquinolone (6)	Sulfa-trimethoprim; imipenem/meropenem; cephalosporin (3rd generation) (5)

2001;32:331)			
	Cellulitis/myositis/osteomyelitis	Fluoroquinolone (6) Sulfa-trimethoprim	
Afipia felix (see *Bartonella henselae*)			
Alcaligenes xylosoxidans (AAC 1996;40:772)	Meningitis, septicemia	Imipenem/meropenem Antipseudomonad penicillin (2)	Ceftazidime; sulfa-trimethoprim; doxycycline; ticarcillin-clavulanic acid
Areanobacterium haemolyticum (Clin Micro Rev 1997;10:125)	Pharyngitis, chronic ulcers	Penicillin; macrolides (2)	Clindamycin; doxycycline
Babesia microti (NEJM 2000;343:1454;AAC 2002;46:1163)	Babesiosis	Atovaquone (750 mg po q12h) + azithromycin (500 mg × 1, then 250 mg/d × 7) Quinine (650 mg po tid × 7 d) plus clindamycin (600 mg po qid × 7 d)	
Bacillus anthracis (JAMA 2002;287:2236)	Inhalation anthrax	Ciprofloxacin IV or doxycycline IV plus 1–2 other agents: vancomycin, clindamycin, rifampin, penicillin, imipenem, clarithromycin, chloramphenicol; then oral ciprofloxacin (500 mg bid) or oral doxycycline (100 mg bid) to complete 60 days	In vitro sensitivity of strain for bio-terrorism will dictate recommendations Other fluoroquinolones are probably comparable to ciprofloxacin Steroids: Role is unclear; some treat 100 days Duration based on presumed inhalation exposure
	Cutaneous anthrax	Ciprofloxacin 500 mg bid or doxycycline 100 mg bid × 60 days	
	Prophylaxis	Ciprofloxacin 500 mg bid or	

		doxycycline 100 mg bid × 60 days	
Bacillus cereus	Food poisoning	Not treated	
	Endophthalmitis	Intravitreal clindamycin 450 µg and/or gentamicin 200–400 µg	Imipenem; fluoroquinolones (6)
Bacillus species (Medicine 1987;66:218)	Septicemia (comp host) Endocarditis	Vancomycin	Imipenem/meropenem; fluoroquinolones (6); clindamycin
Bacteroides bivius (Prevotella bivia)	Female genital tract infections	Metronidazole; clindamycin; cefoxitin; cefotetan; beta-lactam-BLT (7)	Chloramphenicol; antipseudomonad penicillin (2); imipenem/meropenem
"*B. fragilis* group" (*B. distasonis, B. fragillis, B. ovatus, B. thetaio-tamicron, B. vulgatus*) (CID 2002;35:S126)	Abscesses Bacteremia Intra-abdominal sepsis	Metronidazole; beta-lactamase-BLT (7); imipenem/meropenem/ertapenem	Clindamycin; antipseudomonad penicillin (2); cefoxitin; moxifloxacin; gatifloxacin
"*B. melaninogenicus* group" (*Prevotella melaninogenicus, P. intermedius*)	Oral-dental, pulmonary, and female genital tract infections	Metronidazole; clindamycin; beta-lactam-BLI (7)	Imipenem/meropenem cefoxitin
Bartonella bacilliformis	Bartonellosis (Oroya fever)	Chloramphenicol 2 g/d × 7 d	Doxycycline; ampicillin
Bartonella henselae (PIDJ 1998;17:447)	Cat-scratch disease	Azithromycin	Ciprofloxacin, sulfa-trimethoprim; gentamicin; rifampin
Bartonella henselae and *B.*	Bacillary angiomatosis Trench fever	Erythromycin 500 mg po qid × 2–4 mo	Doxycycline 100 mg po q12h

quintana (NEJM 1997;337:1876)			
	Peliosis hepatis, osteomyelitis, endocarditis	Erythromycin plus rifampin IV	Doxycycline × rifampin IV
Bordetella pertussis	Pertussis	Erythromycin 2g/d × 14 days	Sulfa-trimethoprim; clarithromycin; azithromycin
Borrelia burgdorferi (see p 216)	Lyme disease, erythema migrans	Doxycycline 200 mg/d × 10 d (Ann Intern Med 2003;138:697) Amoxicillin	Penicillin G po or IV; cefuroxime axetil; cefotaxime
	Lyme disease-late	Ceftriaxone	Penicillin G IV
	Prophylaxis	Doxycycline 200 mg × 1 within 72 hrs (NEJM 2001;345:79)	
Borrelia recurrentis (Ann Intern Med 1985;102:397)	Louse-borne relapsing fever	Tetracycline (0.5 g × 1)	Erythromycin (0.5 g × 1)
	Tick borne relapsing fever	Doxycycline (200 mg/d × 5–10 d)	Erythromycin (0.5 g qid × 5–10 d)
Brucella (Ann Intern Med 1992;117:25; CID 1992;15:582)	Brucellosis	Doxycycline (200 mg/d) × 6 wks + streptomycin (1 g/d IM) or gentamicin × 3 wks	Doxycycline (200 mg/d) + rifampin (600–900 mg/d) × 6 wks; sulfa-trimethoprim + gentamicin
	Brucella meningitis, endocarditis	Doxycycline + rifampin + sulfa-trimethoprim × months	
Burkholderia cepacia (*Pseudomonas cepacia*) (AAC 1999;43:213)	Septicemia Pneumonia	Sulfa-trimethoprim, minocycline, meropenem	Ceftazidime; meropenem; fluoroquinolone (6)
Burkholderia pseudomallei (Pseudomonas pseudomallei) (CID		Meliodosis Septicemia	Ceftazidime (120 mg/kg/d up to 6 g/d by continuous infusion (AAC 39:2356, 1995) ± TMP-SMX	Sulfa-trir chloramp imipenem

1999;29:381)		(40 mg/kg/d trimethoprim) (CID 2001;33:29)	TMP-SMX resistance in Thailand
	Localized	TMP-SMX; amoxicillin-clavulanate	Tetracycline; chloramphenicol; sulfisoxazole
Calymmatobacterium granulomatis (MMWR 2002;51 RR-6)	Granuloma inguinale Donovanosis	Doxycycline 200 mg/d ≥ 21 days TMP-SMX 1 DS/d × ≥ 21 days	Ciprofloxacin 750 mg bid ≥ 21 days; erythromycin 500 mg bid × ≥ 21 days; fluoroquinolones (6)
Campylobacter fetus	Septicemia, vascular infections, meningitis	Imipenem	Gentamicin; chloramphenicol; fluoroquinolone (6)
Campylobacter jejuni (CID 2001;32:331)	Diarrhea (see p 271)	Erythromycin 500 mg bid × 5 d	Tetracycline (4); furazolidine; fluoroquinolone (6)
Capnocytophaga canimorus (CDC group DF-2) (AAC 1988;32:78)	Dog and cat bites	Amoxicillin; clindamgcin	Doxycycline; amoxicillin-clavulanate; macrolides (8)
	Bacteremia (asplenia)	Clindamycin; penicillin	Cephalosporins (3rd generation) (5); imipenem/meropenem; fluoroquinolones (6); beta-lactam-BLI (7)
Capnocytophaga ochracea (CDC group DF-1) (JID 1985;151:140)	Periodontal disease	Clindamycin; amoxicillin-clavulanic acid; erythromycin; doxycycline	
	Bactermia in neutropenic host	Clindamycin; imipenem/meropenem/ertapenem	Beta-lactam-BLI (7); fluoroquinolone (6)
Cardiobacterium sp.	Endocarditis	Penicillin ± aminoglycoside	Cephalosporin (5) ± aminoglycoside (1)
Cat-scratch disease, (see *Bartonella henselae*)			

Chlamydia pneumoniae	Pneumonia (see p 255)	Doxycycline or macrolide × 10–14 d Telithromycin × 7–10 d	Fluoroquinolone (6) × 10–14 d
Chlamydia psittaci	Psittacosis (see p 255)	Doxycycline	Chloramphenicol
Chlamydia trachomatis (see pp 293–294) (MMWR 2002;51:RR-6)	Urethritis, cervicitis, PID, epididymitis, urethral syndrome	Doxycycline (200 mg/d × 7 d); azithromycin (1 g po × 1)	Erythromycin (500 mg qid × 7d); ofloxacillin (300 mg bid × 7d)
	Lymphogranuloma venereum	Doxycycline 200 mg/d × 21 d	Erythromycin 500 mg qid × 21 d
	Trachoma	Azithromycin 20 mg/kg × 1 (CID 1997;24:363)	Doxycycline 200 mg/d × 14 d
	Inclusion conjunctivitis	Doxycycline 200 mg/d × 7 d	Erythromycin; azithromycin
Citrobacter diversus	Urinary tract infections, pneumonia	Cephalosporin (2nd, 3rd gen) (5); cefepime; sulfa-trimethoprim	Fluoroquinolone (6); imipenem/meropenem; aztreonam
Citrobacter freundii	Urinary tract infection, wound infection, septicemia, pneumonia	Imipenem/meropenem; fluoroquinolone (6); TMP-SMX; aminoglycoside	Cefepime; antipseudomonad penicillins; aztreonam
Clostridium difficile (NEJM 2002; 346:334)	Antibiotic-associated colitis and diarrhea (see p 271)	Metronidazole 250 mg po qid × 10 d	Vancomycin 125 mg po qid × 10 d or vancomycin 500 mg by nasogartic or rectal tube (patients unable to take po drugs)
Clostridium sp.	Gas gangrene Sepsis	Penicillin G (all systemic clostridial infections) + Clindamycin (JID 1987;155:220)	Chloramphenicol; metronidazole; ampicillin; clindamycin; imipenem/meropenem
	Tetanus	Metronidazole (Lancet	Penicillin; cephalosporins;

		1989;2:1216) + tetanus toxoid + tetanus Immune globulin (500 IU IV)	imipenem; macrolides; tetracycline
	Botulism	Penicillin + A/B or E equine antitoxin (10 mL IV) (available from the CDC at 404-639-3670)	
Corynebacterium diphtheriae	Diphtheria	Erythromycin (250–500 mg qid) or penicillin (IM or po) × 14 d + antitoxin (20,000–40,000 units IM for pharyngeal disease ≤ 48 hrs; 80,000–120,000 units IV/IM for severe disease) (available from CDC at 404-639-3670)	Clindamycin; tetracycline (4)
Corynebacterium jeikeium (CDC group JK)	Septicemia	Vancomycin	Penicillin G + gentamicin; daptomycin; fluoroquinolone (6); macrolide (8)
Corynebacterium minutissimum	Erythrasma	Erythromycin	
Corynebacterium ulcerans	Pharyngitis	Erythromycin	
Coxiella burnetii (MMWR 2002;51:924)	Q fever	Doxycycline (200 mg/d × 2–3 wks)	Chloramphenicol; erythromycin; fluoroquinolone (6)
	Q fever endocarditis	Doxycycline (100 mg bid + hydroxychloroquine 200 mg tid × 18 mo–4 yr) (Arch Intern Med 1999;159:167)	Doxycycline × rifampin or fluoroquinolone (6) × 2 yrs.
Dysgonic fermenter type-2 (DF-2)	See *Capnocytophaga canimoris*		

Ehrlichia chaffeensis E. phagocytophia (Emerg Infect Dis 1996;2:18; AAC 1997;41:76)	Ehrlichiosis–human monocyte ehrlichiosis (EMH) and human granulocyte ehrlichiosis (HGE)	Doxycycline (100 mg bid po or IV × 7–14 days)	Rifampin; fluoroquinolones (AAC 1997;41:76)
Eikenella corrodens (AAC 1988;32:1143)	Oral infections, bite wounds	Ampicillin; amoxicillin Penicillin G	Tetracycline (4); amoxicillin-clavulanic acid; ampicillin-sulbactam; cephalosporin (2nd & 3rd gen) (5); fluoroquinolone (6); TMP-SMX
Enterobacter aerogenes, E. cloacae (JAMA 2003;298:885)	Sepsis, pneumonia, wound infections	Imipenem/meropenem; cefepime; aminoglycoside (1); fluoroquinolone (6); ciprofloxacin; antipseudomonad penicillin (2)	
	Urinary tract infection	Sulfa-trimethoprim Cephalosporin (3rd generation) (5)	Antipseudomonad penicillin (2); aminoglycoside; fluoroquinolone (6); imipenem
Enterococcus (E. faecalis and *E. faecium)*	Urinary tract infection	Ampicillin/amoxicillin Nitrofurantoin; fosfonomycin	Penicillin + aminoglycoside (1); vancomycin; fluoroquinolone (6)
	Wound infections, intra-abdominal sepsis, bacteremia	Ampicillin ± aminoglycoside (1)	Vancomycin; daptomycin; linezolid; penicillin ± aminoglycoside (1); imipenem (*E. faecalis*)
	Endocarditis	Penicillin G/ampicillin + gentamicin or streptomycin	Vancomycin + gentamicin or streptomycin
Enterococcus faecium	Urinary tract infection	Nitrofurantoin; fosfonomycin	
	Bacteremia and other systemic infections	Linezolid; daptomycin Some strains sensitive to chloramphenicol, tetracycline, or fluoroquinolones; clinical results are variable (CID 1995;20:1137) Nitrofurantoin (UTI)	

(vancomycin-resistant)			
	Endocarditis	Daptomycin	
Erysipelothrix rhusiopathiae (AAC 1990;34:2038)	Localized cutaneous (erysipeloid)	Amoxicillin; fluoroquinolone (6)	Clindamycin; imipenem
	Endocarditis/disseminated	Penicillin 12–20 mil units/d × 4–6 wks	Cephalosporins—1st generation (5); fluoroquinolone
E. coli (JAMA 2003;289:885)	Septicemia, intra-abdominal sepsis, wound infection	Cephalosporin (3rd gen) (5) Ampicillin (if sensitive) Sulfa-trimethoprim (if sensitive)	Imipenem/meropenem/ertapenem; fluoroquinolone (6); cefepime; cephalosporin (1st or 2nd gen) (5); aztreonam; antipseudomonad penicillin (2); beta-lactam-BLI (7) aztreonam
	Urinary tract infection	TMP-SMX (if sensitive); fluoroquinolone	Cephalosporin (5); imipenem/meropenem
	Diarrhea ETEC (travelers' diarrhea) (see p 272)	Ciprofloxacin (500 mg bid × 3d); TMP-SMX (DS bid × 3d) (CID 2001;32:331)	
Francisella tularensis (CID 1994;19:42)	Tularemia	Streptomycin (1 g 1M bid × 10 days); gentamicin (5 mg/kg/d × 10 days)	Tetracycline (4); chloramphenicol; ciprofloxacin × ≥ 14 days
Fusobacterium	Oral/dental/pulmonary infection, liver abscess, female genital tract	Penicillin G; metronidazole; clindamycin; amoxicillin-clavulanate	Cefoxitin/cefotetan; imipenem/meropenem/ertapenem
Gardnerella vaginalis (MMWR 2002;51:RR-6) (see p 303)	Bacterial vaginosis	Metronidazole (500 mg bid × 7 d); clindamycin 2% 5 g topical qd × 7; metronidazole gel 0.75% 5 g bid × 5 d	Metronidazole (2 g po × 1); clindamycin (300 mg po bid × 7 d)

Haemophilus aphrophilus	Sepsis, endocarditis	Penicillin G + aminoglycoside (1)	Cephalosporin (3rd gen) (5) + aminoglycoside (1)
H. ducreyi (MMWR 2002;51:RR-1)	Chancroid (see p 296)	Ceftriaxone (250 mg IM × 1) Erythromycin (500 mg qid × 7 d) Azithromycin (1 g po × 1)	
H. influenzae (AAC 1997;41:292)	Meningitis (see p 237) Epiglottis, pneumonia (see p 253); arthritis; cellulitis	Cefotaxime; ceftriaxone	Fluoroquinolones; cefuroxime (not meningitis); beta-lactamase-BLT
	Otitis, sinusitis, exacerbations of exacerbations of chronic bronchitis	Sulfa-trimethoprim; azithromycin Cephalosporin (2nd or 3rd gen); clarithromycin	Tetracycline (4); beta-lactamase-BLT (7); fluoroquinolone (6)
	Pneumonia, acute sinusitis, acute bacterial exacerbations of chronic bronchitis	Telithromycin; azithromycin; cephalosporin (2nd + 3rd gen); clarithromycin	Fluoroquinolone; beta-lactamase-BLT
Hafnia alvei (See *Enterobacter*)			
Helicobacter pylori (Med Lett 1997;39:1 Ann Intern Med 1997;157:87 BMJ 2001;232:1047; NEJM 2002;347:1175) (see p 270)	Peptic ulcer disease	Omeprazole (20 g) + amoxicillin (1 g bid) + clarithromycin (500 mg bid) × 14 d Bismuth subsalicylate (2 tabs bid) + tetracycline (500 mg qid) + metronidazole (500 mg tid) + omeprazole (20 mg bid) × 14 d Omeprazole + amoxicillin (1 g bid), + clarithromycin (500 mg bid) × 1 wk	Omeprazole or ranitidine + clarithromycin Omeprazole or lansoprazole + clarithromycin + metronidazole
Kingella sp.	Endocarditis	Penicillin + aminoglycoside	Cephalosporin (5) + aminoglycoside (1)
	Septic arthritis	Penicillin; cephalosporin	TMP-SMX; doxycycline; macrolides

			(8); fluoroquinolone (6)
Klebsiella pneumoniae K. oxytoca (JAMA2003;289:885)	Septicemia, nosocomial pneumonia, intra-abdominal sepsis, urinary tract infection	Cephalosporin (3rd gen) (5) Imipenem/meropenem; beta-lactam-BLI (7); aztreonam; cefepime; fluoroquinolone (6)	Aminoglycoside (1); sulfa-trimethoprim
Legionella sp (J Resp Dis 2002;23:229)	Legionnaires' disease (see p 255)	Gatifloxacin, moxifloxacin, or levofloxacin × 10–14 d Azithromycin × 7–10 d	Erythromycin; doxycycline; clarithromycin; sulfa-trimethoprim
Leptospira spp (CID 1995;21:1)	Leptospirosis Mild disease	Doxycycline 200 mg/d Amoxcillin 500 mg qid	
	Serious disease	Penicillin G 1.5 mil units q6h Ampicillin 0.5–1 g IV q6h	
Leuconostoc (AAC 1990;34:543)	Bacteremia Wound infection	Penicillin/ampicillin	Erythromycin; aminoglycosides (1); clindamycin
Listeria monocytogenes (JCM 2003;41:483)	Meningitis (see p 237) Septicemia	Ampicillin or penicillin ± gentamicin	Sulfa-trimethoprim
Moraxella catarrhalis (Branhamella catarrhalis) (AAC 1996;40:2884)	Otitis, sinusitis, pneumonitis	Sulfa-trimethoprim; doxycycline; cephalosporin (2nd or 3rd gen) (5); amoxicillin-clavulanate macrolides (8)	Doxycycline; fluoroquinolone (6)
	Acute bacterial exacerbations of chronic bronchitis	Telithromycin; azithromycin; cephalosporin (2nd + 3rd gen); clarithromycin	Doxycycline; fluoroquinolone
Morganella morganii	Bacteremia, pneumonia, urinary tract infection, wound infection	Fluoroquinolone (6); imipenem/meropenem; cephalosporin (3rd gen) (5);	Sulfa-trimethoprim; aztreonam; antipseudomonad penicillin (2); aminoglycoside (1);

		cefepime	beta-lactam-BLI
Mycobacterium abscessus	Cutaneous pulmonary	Amikacin + cefoxitin or imipenem	Clarithromycin ± clofazimine
M. avium-intracellulare (see p 170)	Pulmonary infection	Clarithromycin or azithromycin, Ethambutol, ± rifampin or ciprofloxacin (6)	Azithromycin; ethionamide; amikacin; cycloserine; ciprofloxacin/ofloxacin/levofloxacin; streptomycin
	Disseminated infection (AIDS)	Clarithromycin + ethambutol ± rifabutin or ciprofloxacin (6)	Ethionamide; cycloserine; rifampin/rifabutin; amikacin
M. chelonae (see p 171)	Skin and soft tissue	Tobramycin + cefoxitin or imipenem	Clofazimine or clarithromycin, then sulfonamide, rifampin, doxycycline, or erythromycin
M. fortuitum (see p 170)	Soft tissue and wound infections Pulmonary	Amikacin + cefoxitin or imipenem × 2–4 wk, then clarithromycin, ciprofloxacin, or doxycycline	Sulfonamide
M. genavense (AIDS) (see p 171)	Disseminated disease	Clarithromycin + other agents	INH; ethambutol; rifampin; ciprofloxacin; pyrazinamide
M. haemophilum (AIDS) (see p 171)	Disseminated disease (skin, bone, gut, nodes) Pulmonary	Rifampin or rifabutin + amikacin + ciprofloxacin	Cycloserine
M. kansasii (see p 170)	Pulmonary infection	INH + rifampin + ethambutol	Clarithromycin; ciprofloxacin; rifabutin; ethionamide; streptomycin; amikacin; cycloserine; sulfa-trimethoprim
M. leprae		Paucibacillary	Rifampin 600 mg/mo (supervised) plus dapsone 100

		mg/d	
	Multibacillary	Rifampin 600 mg/mo (supervised) + dapsone 100 mg/d + clofazimine 100 mg/mo (supervised) or 50 mg/d	Rifampin 600 mg/d plus dapsone 100 mg/d ± clofazimine 50 mg/d ≥ 24 mo
M. marinum (see p 171)	Soft tissue infections	Rifampin + ethambutol Sulfa-trimethoprim Minocycline or doxycycline	Clarithromycin
M. tuberculosis (see pp 162)	Tuberculosis	INH + rifampin + pyrazinamide + ethambutol or streptomycin	Capreomycin, kanamycin or amikacin; ciprofloxacin, ofloxacin or moxifloxacin Ethionamide; PAS; nitroimidazoles Cycloserine; aerosolized aminoglyco-sides
M. ulcerans (see p 171)	Pulmonary	Rifampin + ethambutol Amikacin + sulfa-trimethoprim	
Mycoplasma hominis (CID 1996;23:671)	Genital tract infections	Doxycycline 200 mg/d × 7 d	
Mycoplasma pneumoniae	Pneumonia (see p 255)	Macrolide (8); doxycycline × 10–14 d; telithromycin × 7–10 d	Fluoroquinolones (6) × 10–14 d
Neisseria gonorrhoeae (see	Genital tract infections	Ceftriaxone (125 mg IM × 1); ciprofloxacin (500 mg × 1); ofloxacillin (400 mg × 1) (each with doxycycline or azithromycin)	Spectinomycin (2 g IM × 1); azithromycin (2 g po × 1); cefoxitin 2 g IM probenecid 1 g po
	Disseminated gonococcal infection	Ceftriaxone 1 g IV or IM/d until asymptomatic 24–48 hr, then oral Rx to complete 1 wk	Cefotaxime 1 g IV q8h

pp 288–289) (MMWR 2002;51:RR-6)			
N. meningitidis (see p 237)	Meningitis (see p 237), bacteremia, pericarditis, pneumonia	Penicillin G (up to 24 mil units/d IV) × 10–14 d	Ampicillin; cefotaxime; ceftriaxone; chloramphenicol; sulfa-trimethoprim
	Prophylaxis	Ciprofloxacin (500 mg × 1)	Rifampin (600 mg bid × 2 d) Ceftriaxone (250 mg IM × 1)
Nocardia asteroides (Clin Microbiol Rev 1994;7:357)	Nocardiosis: pulmonary infection, abscesses—skin, lung, brain	Sulfonamide (usually sulfadiazine or sulfisoxazole) (3–6 g/d) Sulfa-trimethoprim (5–10 mg/kg/d trimethoprim po or IV up to 15 mg/kg/d)	Minocycline ± sulfonamide Amikacin ± imipenem, ceftriaxone, cefuroxime, amoxicillin-clavulanate, or sulfa-trimethoprim Imipenem + cefotaxime or sulfa-trimethoprim
Pasteurella multocida (AAC 1988; 32:213)	Animal bite wound	Penicillin G; ampicillin; amoxicillin	Tetracycline (4); fluoroquinolones; Cephalosporins (2nd and 3rd gen) (5) Amoxicillin-clavulanic acid; macrolides
	Septicemia, septic arthritis/osteomyelitis	Penicillin G	Cephalosporins (3rd gen) (5); beta-lactam-BLI (7); imipenem/meropenem
Peptostreptococcus	Oral/dental/pulmonary infection; intra-abdominal sepsis; gynecologic infection	Penicillin G; ampicillin; amoxicillin; clindamycin	Cephalosporin (1st gen) (5); chloramphenicol; macrolides (8); moxifloxacin, gatifloxacin; vancomycin; Imipenem/meropenem/ertapenem
Plesiomonas shigelloides	Diarrhea (usually not treated) (see p 273)	Sulfa-trimethoprim (IDS bid × 3 d) Fluoroquinolone (6) × 3 d	

(CID 2001;51:331)			
	Extra-intestinal infection	Cephalosporin (3rd gen) (3) Aminoglycoside (1)	Aztreonam; sulfa-trimethoprim; imipenem/meropenem; fluoroquinolone (6)
Propionibacterium acnes	Acne	Tetracycline (4)	Clindamycin (topical); clindamycin
Proteus mirabilis (JCM 2002;40:1549)	Septicemia, urinary tract infection, intra-abdominal sepsis, wound infection	Ampicillin Cephalosporins (1st, 2nd, 3rd generation) (5)	Aminoglycosides (1); sulfa-trimethoprim; tetracycline Antipseudomonad penicillin (2); aztreonam; fluoroquinolone (6); beta-lactam-beta-lactamase inhibitor (7)
Proteus vulgaris	Septicemia Urinary tract infection	Cephalosporin (3rd gen) (5) Imipenem; beta-lactam-BLT (7)	Aminoglycoside (1); TMP-SMX; antipseudomonad penicillin (2); cefepime; aztreonam; fluoroquinolone (6)
Providencia	Septicemia Urinary tract infection	Cephalosporin (3rd gen) (5) Imipenem; amikacin	Aminoglycoside (1); aztreonam; antipseudomonad penicillin (2); cefepime; ticarcillin-clavulanate; TMP-SMX; fluoroquinolone (6)
Pseudomonas aeruginosa (JAMA 2003;289:885)	Septicemia, pneumonia Intra-abdominal sepsis	Aminoglycoside (tobramycin) and/or antipseudomonad penicillin (2); ceftazidime; cefepime; imipenem/meropenem; aztreonam	Ciprofloxacin (6); piperacillin-tazobactam, ticarcillin-clavulanate
	Urinary tract infections	Aminoglycoside (1); ciprofloxacin; antipseudomonad penicillin (2)	Imipenem/meropenem; ceftazidime; cefepime; cefoperazone; aztreonam
P. cepacia(see *Burkholderia cepecia*)			

Rhodococcus equi (CID 2002;34:1379)	Localized + immunocompetent	2 oral agents: rifampin, erythromycin, or ciprofloxacin	
	Disseminated, severe, or immunosuppressed	2 parenteral agents: vancomycin, imipenem/meropenem/ertapenem, ciprofloxacin, aminoglycoside, rifampin, or erythromycin	
Rickettsia spp (MMWR 2000;49:888)	Rocky Mountain spotted fever, Q fever, tick-bite fever, murine typhus, scrub typhus, typhus, trench fever	Doxycycline (100 mg po or IV bid × 7 days)	Chloramphenicol (2 g/d × 7 d) fluoroquinolone (6)
Rochalimaea quintana and *R. henselae* (See *Bartonella henselae* and *B. quintana*)			
Salmonella typhi (AAC 1999;43:1441; CID 2001;32:331)	Typhoid fever (see p 273)	Ceftriaxone 1–2 g/d × 10–14 d Ciprofloxacin 500 mg bid × 10 d If severely ill: Steroids (RID 1991;13:85)	Ampicillin/amoxicillin (preferred if sensitive); chloramphenicol (4 g IV/d); sulfa-trimethoprim (1 DS bid)
	Carriers (see p 274) (Lancet 1987;2:162)	Ciprofloxacin (× 4–6 wks) Amoxicillin (× 6 wks) TMP-SMX (× 6 wks)	
Salmonella sp. (other) (CID 2001;32:331)	Gastroenteritis (See indications p 274)	Ciprofloxacin (500 mg bid × 5–7 d) Ceftriaxone (100 mg/kg/d × 5–7 d) TMP-SMX (1 DS bid × 5–7 d)	Olfloxacin and norfloxacin
	Bacteremia	Ceftriaxone or quinolone (IV × 7–14 d)	
	Endovascular infection	Ceftriaxone, ampicillin, or ciprofloxacin (IV × 6 wks ± surgery)	
	Carrier	As for *S. typhi* (above)	
Serratia marcescens	Septicemia, urinary tract	Cephalosporin (3rd gen) (5) ±	Aztreonam; pip/tazobactam;

	infection, pneumonia	gentamicin; imipenem/meropenem; fluoroquinolone (6); antipseudomonad penicillin (2) + amikacin	Ticar/sulbactam
Shigella spp (CID 2001;32:331)	Colitis (see p 274)	Sulfa-trimethoprim (1 DS bid × 3 d) Ciprofloxacin 500 mg bid × 3 d)	Ofloxacillin; nalidixic acid; azithromycin
Spirillum minus	Rat-bite fever	Penicillin G (IV × 5–7 d) then amoxicillin × 7 days	Tetracycline (4); streptomycin Possibly effective: clindamiycin; erythromycin; ceftriaxone
Staphylococcus aureus Methicillin-sensitive	Septicemia, pneumonia, cellulitis, wound infection	Penicillinase-resistant penicillin (3)	Cephalosporins (1st gen) (5); cefepime; vancomycin; sulfa-trimethoprim; macrolide (8); beta-lactam-BLT (7); fluoroquinolone (6) (increasing resistance); clindamycin
	Acute sinusitis	Telithromycin; amoxicillin; cephalosporin (2nd + 3rd gen)	Sulfa-trimethoprim; macrolide; clindamycin
Methicillin-resistant	As above	Vancomycin	Daptomycin (except pneumonia); linezolid Community-acquired MRSA are often sensitive to clindamycin, fluoroquinolones, TMP-SMX
Vancomycin-intermediate sensitive *S. aureus* (NEJM 1999;340:493)	As above	Vancomycin *plus* oxacillin, nafcillin, cefazolin, or cefotaxime (NEJM 1999;340:517); linezolid; daptomycin (except pneumonia)	Quinupristin-dalfopristin
Vancomycin-resistant *S.*	As above	Linezolid; daptomycin (except	Quinupristin-dalfopristin; some

aureus(NEJM 2003;348:1342; MMWR 2002;51:565)		pneumonia)	strains sensitive to tetracycline, TMP-SMX, chloramphenicol
S. saprophyticus	Urinary tract infections	Sulfa-trimethoprim Ampicillin/amoxicillin Fluoroquinolone (6)	Cephalosporins (5); tetracycline (4)
Methicillin-resistant	Septicemia Infected prosthetic devices	Vancomycin ± gentamicin or rifampin	Daptomycin; linezolid; (possibly effective—chloramphenicol, rifampin, tetracycline)
Stenotrophomonas maltophilia (Xanthomonas maltophilia)	Septicemia, pneumonia, UTI	Sulfa-trimethoprim	Ceftazidime; fluoroquinolone (6);minocycline Ticarcillin-clavulanate
Streptobacillus moniliformis	Rat-bite fever Haverhill fever	Penicillin G IV × 5–7 d, then amoxicillin × 7 d	Tetracycline (4); erythromycin; clindamycin; streptomycin
Streptococcus, groups B, C, G; *S. bovis, S. milleri, S. viridans*, anaerobic streptococci (*Peptostreptococcus*) and	Pharyngitis Soft tissue infection Pneumonia (see p 253) Abscesses	Penicillin G or V (if penicillin-resistant *S. pneumoniae*— see below)	Cephalosporin (1st gen), cefuroxime, cefotaxime, ceftriaxone; Erythromycin, clarithromycin, azithromycin Vancomycin; clindamycin
penicillin-sensitive strains *S. pneumoniae (S. pyogenes*—see pp 241, 245) (CID 2002;35:113)	Endocarditis	Penicillin G ± streptomycin or gentamicin	Cephalosporin: Parenteral—see above vancomycin
S. iniae	Bacteremia, cellulitis	Penicillin, clindamycin	Beta-lactams
S. pneumoniae (see p 253)	Meningitis (see p 237) Ocular infections	Vancomycin + cefotaxime or ceftriaxone	Cefotaxime; ceftriaxone (activity variable)

S. pneumoniae Penicillin-sensitive (mic ≤ 1.0 µg/mL)	Pneumonia (see p 253)	Penicillin G; amoxicillin; cefotaxime or ceftriaxone	Telithromycin;† macrolides (8); cephalosporins—cefpodoxime, ceftibutin, cefprozil; fluoroquinolone (6); clindamycin; doxycycline; pip-tazobactam; amoxicillin ± clavulanate
	Meningitis	Penicillin; ceftriaxone; cefotaxime	Vancomycin; chloramphenicol
Penicillin-intermediate sensitive (MIC 2 µg/mL)	Pneumonia	As for penicillin-sensitive strains (see above) OR telithromycin†	Most active beta-lactams—amoxicillin; cefotaxime; ceftriaxone; ceftibutin; cefpodoxime Other options—fluoroquinolone; clindamycin; beta-lactam-BLI's (7)—but not ticarcillin
	Meningitis	Vancomycin	
Penicillin-resistant (mic ≥ 4.0 µg/mL)	Pneumonia	Telithromycin;† fluoroquinolone (6); vancomycin; linezolid	Quinupristin-dalfopristin; daptomycin
S. pyogenes	Pharyngitis (CID 2002;35:113) Soft tissue Toxic shock syndrome	Penicillin V 500 mg bid × 10 d Benzathine penicillin 1.2 mil units IM × 1 Penicillin; amoxicillin Clindamycin + penicillin	Erythromycin 250 mg po tid × 10 d
Treponema pallidum	Syphilis (see pp 289–292)	Penicillin G	Tetracycline (4); ceftriaxone
Tropheryma whippelii (Lancet 2003;361:231)	Whipple's disease	Induction: ceftriaxone (2 g IV/d) or penicillin (1.2 mil units/d) + strep (1 g/d) × 2 wks Maintenance: TMP-SMX (1 DS/d) or doxycycline/minocycline (200 mg/d × 1 yr)	

Ureaplasma urealyticum	Genital tract infection	Doxycycline (200 mg/d × 7 d)	Macrolides (8)
Vibrio cholerae (Lancet 2003;361:231)	Cholera (see p 274)	Doxycycline (300 mg × 1); tetracycline (500 mg qid × 3 d)	Fluoroquinolone-single dose
Vibrio parahaemolyticus (CID 2001;32:331)	Diarrhea (usually not treated) (see p 275)	Tetracycline (4) Fluoroquinolone (6)	
Vibrio vulnificus (CID 2003;37:272)	Septicemia Wound infection Gastroenteritis	Tetracycline (4)	Cefotaxime/Ceftriaxone Chloramphenicol Aminoglycoside
Xanthomonas maltophilia (see *Stenotrophomonas maltophila*)			
Yersinia enterocolitica (CID 2001;32:331)	Enterocolitis and mesenteric adenitis (usually not treated)	Sulfa-trimethoprim; gentamicin; fluoroquinolone (6); doxycycline	Cephalosporin (3rd gen) (5)
	Septicemia	Aminoglycoside (gentamicin)	Chloramphenicol; ciprofloxacin; sulfa-trimethoprim
Yersinia pestis (JAMA 2000;283:2281)	Plague treatment	Streptomycin; gentamicin	Chloramphenicol; tetracycline (4); ciprofloxacin
	Prevention	Doxycycline Ciprofloxacin	Chloramphenicol
Yersinia pseudo-tuberculosis	Mesenteric adenitis (usually not treated) Septicemia	Aminoglycoside (1) Ampicillin	Sulfa-trimethoprim; tetracycline (4)

1 . Aminoglycosides: gentamicin, tobramycin, amikacin, netilimicin. Netilmicin is no longer available in the U.S.
2 . Antipseudomonad penicillin: ticarcillin, piperacillin.
3 . Penicillinase-resistant penicillins: nafcillin, oxacillin, methicillin, cloxacillin, dicloxacillin.
4 . Tetracycline: Tetracycline, doxycycline, minocycline.
5 . Cephalosporins and miscellaneous beta-lactams

1st generation: Cefadroxil*, cefazolin, cephalexin,* cephapirin, cephradine*
2nd generation: Cefaclor,* cefaclor ER, cefamandole, ceforanide, cefotetan, cefoxitin, cefuroxime,* cefprozil,* loracarbef*
3rd generation: Cefotaxime, ceftizoxime, ceftazidime, cefoperazone, ceftriaxone, moxalactam, cefixime,* cefpodoxime,* cefdinir,* cefditoren,* ceftibuten*
4th generation: Cefepime
Cephamycins: Cefoxitin, cefotetan
Monobactam: Aztreonam
Carbapenem: Imipenem, meropenem, ertapenem
Carbacephem: Loracarbef*

6 . Fluoroquinolones: Norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, levofloxacin, trovafloxacin, gatifloxacin, gemifloxacin, and moxifloxacin. Systemic infections are usually treated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, or moxifloxacin; all may be used for urinary tract infections. With regard to spectrum:*P. aeruginosa*—ciprofloxacin and trovafloxacin;*Mycobacterium*—ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, or ofloxacin;*C. trachomatis*—ofloxacin; *S. pneumoniae*—levofloxacin, gatifloxacin, or moxifloxacin; anaerobes—gatifloxacin and moxifloxacin are most active; ciprofloxacin and levofloxacin are least active; side-effects: trovafloxacin has a FDA-mandated black box warning about hepatotoxicity and revised indications in 1999 that restrict use to infections for which alternative antibiotics are unavailable.

7 . Beta-lactam-beta-lactamase inhibitor. Amoxicillin + clavulanate (Augmentin), ticarcillin + clavulanate (Timentin), ampicillin + sulbactam (Unasyn), and piperacillin + tazobactam (Zosyn).

8 .Macrolides: Erythromycin, clarithromycin, azithromycin, dirithromycin.

* Oral cephalosporins; cefuroxime has both oral and parenteral formulations.

† Telithromycin is also active agent against multi-drug resistant *Streptococcus pneumoniae.*

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Antimicrobial Dosing Regimens in Renal Failure

A. **GENERAL PRINCIPLES**

1. Initial dose is not modified in renal failure.
2. Initial dose is not modified in renal failure.
3. Adjustments in subsequent doses for renally excreted drugs may be accomplished by *a*) giving the usual maintenance dose at extended intervals, usually three half-lives (extended interval method); *b*) giving reduced doses at the usual intervals (dose reduction method); or *c*) a combination of each.

$$\text{Male: } \frac{\text{weight (kg)} \times (140 \text{ minus age in yr})}{72 \times \text{serum creatinine (mg/dL)}}$$

Female: Above value × 0.85

Pitfalls and notations with calculations follow.

a. **Elderly patient**: Serum creatinine may be deceptively low (with danger of overdosing) because of reduced muscle mass.
b. **Pregnancy, ascites, and other causes of volume expansion**: GFR may be increased (with danger of underdosing) in third trimester of pregnancy and patients with normal renal function who receive massive parenteral fluids.
c. **Obese patients**: Use lean body weight.
d. **Renal failure**: Formulas assume stable renal function; for patients with anuria or oliguria assume creatine clearance (CCr) of 5–8 mL/min.

B. AMINOGLYCOSIDE DOSING

1. **GUIDELINES OF THE JOHNS HOPKINS HOSPITAL CLINICAL PHARMACOLOGY DEPARTMENT**

Agent	***Loading dose, regardless of renal function*** [b,c]	***Subsequent doses (before level measurements)***		***Therapeutic levels (1 hr after start of infusion over 20–30 min)***
		CCr > 70 mL/min	**CCr < 70 mL/min**[d]	
Gentamicin[a]	2 mg/kg	1.7–2 mg/kg/8 h	0.03 × CCr = mg/kg/8 h	5–10 µg/mL
Tobramycin[a]	2 mg/kg	1.7–2 mg/kg/8 h	0.03 × CCr = mg/kg/8 h	5–10 µg/mL

Amikacin[a]	8 mg/kg	7.5–8 mg/kg/8 h	0.12 × CCr = mg/kg/8 h	20–40 µg/mL

[a] Doses for gentamicin and tobramycin should be written in multiples of 5 mg; doses of amikacin and kanamycin should be written in multiples of 25 mg.
[b] Seriously ill patients with sepsis often need higher loading doses to achieve rapid therapeutic levels despite third spacing, e.g., 3 mg/kg for gentamicin and tobramycin.
[c] Obese patients: use calculated lean body weight plus 40% of excess fat.
[d] Patients who are oliguric or anuric: use CCr of 5–8 mL/min.

2. **MAYO CLINIC GUIDELINES** (Mayo Clin Proc 47:519, 1999)
   a. Initial dose: Gentamicin, tobramycin, netilmicin: 1.5–2 mg/kg; amikacin: 7.5–15 mg/kg. This is based on ideal body weight (IBW) calculated for males: 50 kg × 2.3 kg (height in inches–60 inches), and for female patients: 45 kg × 2.3 kg (height in inches–60 inches). For obese patients (>30% above ideal body

   weight) calculate dosing weight is IBW × 0.4 (actual weight in kg -IBW).
   b. Maintenance dose: Cockcroft-Gault equation.
3. **MONITORING**: Measure peak levels at 1 hr after start of 20- to 30-min infusion. Goal with q8h dosing is 5–10 µg/mL for gentamicin and tobramycin or 20–40 µg/mL for amikacin; peak levels when using low doses of gentamicin or tobramycin for synergy vs staph, strep or enterococcus is 3 µg/mL. Monitor for nephrotoxicity with serum creatinine qd or qod. **Monitor for ototoxicity when feasible in patients treated >3 days with periodic Romberg's sign and with reading an eye chart after rapid head movements.**

ONCE DAILY AMINOGLYCOSIDES

Rationale: see Infect Dis Clin Pract 5:12, 1996; AAC 39:650, 1995; Eur J Clin Microbiol Infect Dis 14:1029, 1995; Ann Intern Med 124:717, 1996

Clinical trials: 24 published trials (Eur J Clin Microbiol Infect Dis 14:1029, 1995): Showed comparable results with once daily versus multiple daily doses for therapeutic response and toxicity.

Contraindication: Patients receiving aminoglycosides for synergy with beta-lactam agents for streptococcal endocarditis or enterococcal infections should receive standard thrice daily dosing regimens.

Monitoring: Some authorities suggest monitoring predose levels (18 hr) after second dose, which should show gentamicin or tobramycin levels 0.6–2.0 µg/mL and amikacin levels 2.5–5.0 µg/mL; higher levels should lead to dose reduction. All patients receiving aminoglycosides should be monitored for nephrotoxicity and ototoxicity (see above).

Regimen

1. *Standard dose*

   Gentamicin and tobramycin: 5–6 mg/kg/d (some use 4–7 mg/kg/d)

   Amikacin and streptomycin: 15–20 mg/kg/d

2. *Dose adjustment based on trough levels*

   Gentamicin and tobramycin:≤0.5 µg/mL

   Amikacin:<5 µg/mL

3. Dose adjustment based on renal function (Mayo Clin Proc 1999;47:519.)

Creatinine clearance (mL/min)	Dose (mg/kg) q24h Gentamicin tobramycin	Amikacin
>80	5.0	15.0
60–79	4.0	12.0
50	3.5	7.5
40	2.5	4.0
<30	Conventional dosing	

C. **DRUG THERAPY DOSING GUIDELINES**

(Adapted in part from Drug Information for the Health Care Professional, USP DI, 23rd Edition, 2003; Physicians' Desk Reference, 57th Edition, 2003)

Drug	Major excretory Route	Half-life (hr)*		Usual regimen		Maintenance regimen renal failure		
		Normal	Anuria	Oral	Parenteral	GFR 50–80 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Acyclovir	Renal	2–2.5	20	200 mg 3–5×/d 400 mg bid 800 mg 5×/d —	— — — 5–10 mg/kg q8h	Usual Usual Usual Usual	Usual Usual 800 mg q8h 5–12 mg/kg q12–24h	200 mg q12h 200 mg q12h 800 mg q12h 2.5–6 mg/kg q24h
Adofovir	Renal	1.6 IC-16	↑	10 mg q24h	—	Usual	10 mg q48–72h	10 mg q wk
Albendazole	Hepatic	8	8	400–800 mg bid	—	Usual	Usual	Usual

Amantadine	Renal	15–20	170	100 mg bid	—	100–150 mg q day	100–200 mg 2–3 ×/wk	100–200 mg q wk
Amdinocillin	Renal	1	3.3	—	10 mg/kg/q4–6h	Usual	10 mg/kg q6h	10 mg/kg q8h
Amikacin	Renal	2	30	—	7.5 mg/kg	<<<<<<<	See pp 39–40	>>>>>>>
Amoxicillin	Renal	1	15–20	250–500 mg q8h	—	0.25–0.5 g q12h	0.25–0.5 g q12–24h	0.25–0.5 g q12–24h
Amoxicillin clavulanic acid	Renal	1	8–16	250–500 mg q8h	—	Usual	0.25–0.5 g q12h	0.25–0.5 g q24–36h
Amphotericin B	Nonrenal	15 days	15 days	—	0.3–1.4 mg/kg/d	Usual	Usual	Usual
Amphotericin B lipid complex	Nonrenal	7 days (ABLC)	1 day (ABCD)	—	5 mg/kg/d (ABCD) 3–4 mg/kg/d (ABLC)	Usual	Usual	Usual
Amphotericin B liposomal	Nonrenal	4–6 days	4–6 days	—	3–5 mg/kg/d	Usual	Usual	Usual
Ampicillin	Renal	1	8–12	0.25–0.5 g q6h	—1–3 g q4–6h	Usual Usual	usual 1–2 g IV q8h	Usual 1–2 g IV q 12h
Ampicillin-sulbactam	Renal	1	8–12	—	1–2 g q6h	1–2 g IV q8h	1–2 g IV q8h	1–2 g IVq12h
Atovaquone	Gut	70	70	750 mg bid susp	—	Usual	Usual	Unknown
Atovaquone +proguanil	Urinary	70	?	1–4 tabs/day	—	Usual	Usual	Unknown
Azithromycin	Hepatic	68	68	250 mg/d	500 mg/d	Usual	No data—"use caution"	
Aztreonam	Renal	1.7–2	6–9	—	1–2 g q6h	1–2 g q8–12h	1–2 g q12–18h	1–2 g q24hq12–18h

Bacampicillin	Renal	1	8–12	0.4–0.8 g q12h	—	Usual	Usual	Usual
Capreomycin	Renal	4–6	50–100	1 g q day 2×/wk	—	Usual	7.5 mg/kg 1–2 days	7.5 mg/kg 2×/wk
Carbenicillin	Renal	1	13–16	0.5–1 g q6h	—	Usual	0.5–1 g q8h	Avoid
Caspofungin	Metabolized	9–11	9–11	—	70 mg d 1 50 mg qd	Usual	Usual	Usual
Cefaclor	Renal	0.75	2.8	0.25–0.5 g q8h	—	Usual	Usual	Usual
Cefadroxil	Renal	1.4	20–25	0.5–1 g q12–24h	—	Usual	0.5 g q12–24h	0.5 g q36h
Cefamandole	Renal	0.5–2.1	10	—	0.5–2 g q4–8h	0.5–2 g q6h	1–2 g q8h	0.5–0.75 g q12h
Cefazolin	Renal	1.8	18–36	—	0.5–2 g q8h	0.5–1.5 g q8h	0.5–1 g q8–12h	0.25–0.75 g q18–24h
Cefdinir	Renal	1.7	?	300 mg bid		Usual	300 mg qd	300 mg qod
Cefditoren	Renal	1.4	4–5	200–400 mg bid	—	Usual	200 mg q12–24h	200 mg q24h
Cefepime	Renal	2	13	—	0.5–2 g q12h	0.5–2g q24h	0.5–1 g q24h	250–500 mg q24h
Cefixime	Renal (50%)	3–4	12	200 mg q12h	—	Usual	300 mg/d	200 mg/d
Cefmetazole	Renal	1.2	—	—	2 g q6–12h	1–2 g q12h	1–2 g q18–24h	1–2 g q48h
Cefonicid	Renal	4–5	50–60	—	0.5–2 g q24h	8–25 mg/kg q24h	4–8 mg/kg q24h	4 mg/kg q3–5d

Cefoperazone	Gut	1.9–2.5	2–2.5	—	1–2 g q6–12h	Usual	Usual	Usual
Ceforanide	Renal	3	20–40	—	0.5–1 g q12h	Usual	0.5–1 g q24h	0.5–1 g q48–72h
Cefotaxime	Renal	1.1	3	—	1–2 g q4–8h	Usual	1–2 g q6–12h	1–2 g q12h
Cefotetan	Renal	3–4	12–30	—	1–2 g q12h	Usual	1–2 g q24h	1–2 g q48h
Cefoxitin	Renal	0.7	13–22	—	1–2 g q6–8h	1–2 g q8–12h	1–2 g q12–24h	0.5–1 g q12–48h
Cefpodoxime	Renal	2.4	—	200–400 mg q12h	—	Usual q24h	200–400 3× weekly	200–400 mg weekly
Cefprozil	Renal	1.3	5–6	0.25–0.5 g q12h	—	Usual	0.25–0.5 g q24h	0.25 g q12–24h
Ceftazidime	Renal	0.9–1.7	15–25	—	1–2 g q8–12h	Usual	1 g q12–24h	0.5 g q24–48h
Ceftibutin	Renal	2.4	?	400 mg/d	—	Usual	200 mg/d	100 mg/d
Ceftizoxime	Renal	1.4–1.8	25–35	—	1–3 g q6–8h	0.5–1.5 g q8h	0.25–1 g q12h	0.25–0.5 g q24h
Ceftriaxone	Renal and biliary	6–9	12–15	—	1–2 g q24h	Usual	Usual	Usual
Cefuroxime	Renal	1.3–1.7	20	—	0.75–1.5 g q8h	Usual	0.75–1.5 g q8–12h	0.75 g q24h
Cefuroxime axetil	Renal	1.2	20	250 mg q12h	—	Usual	Usual	250 mg q24h
Cephalexin	Renal	0.9	5–30	0.25–1 g q6h	—	Usual	0.25–1 g q8–12h	0.25–1 g q24–48h
Cephalothin	Renal	0.5–0.9	3–8	—	0.5–2 g q4–8h	Usual	1.0–1.5 g q6h	0.5 g q8h

Cephapirin	Renal	0.6–0.9	2.4	—	0.5–2 g q4–6h	0.5–2 g q6h	0.5–2 g q8h	0.5–2 g q12h
Cephradine	Renal	0.7–2	8–15	0.25–1 g q6h —	— 0.5–2 g q4–6h	Usual 0.5–1 g q6h	0.5 g q6h 0.5–1 g q6–24h	0.25 g q12h 0.5–1 g q24–72h
Chloramphenicol	Hepatic	2.5	3–7	0.25–0.75 g q6h	0.25–1 g q6h	Usual	Usual	Usual
Chloroquine	Renal and metabolized	48–120	?	300–600 mg po qd	—	Usual	Usual	150–300 mg po qd
Cidofovir	Renal	17–65	↑	—	5 mg/kg q 2 wk	Usual	Contraindicated	
Cinoxacin	Renal	1.5	8.5	0.25–0.5 g q12h	—	0.25 g q8h	0.25 g q12h	0.25 g q24h
Ciprofloxacin	Renal and hepatic metabolism	4	5–10 slight	0.25–0.75 g q12h —	— 400 mg q12h	Usual Usual	0.25–0.5 g q12h 0.4 g q18h	0.25–0.5 g q18h 0.4 g q24h
Clarithromycin	Hepatic and renal metabolism	4		250–500 mg q12h	—	Usual	Usual	250–500 mg q24h
Clindamycin	Hepatic	2–2.5	2–3.5	150–300 mg q6h	300–900 mg q6–8h	Usual	Usual	Usual
Cloxacillin	Renal	0.5	0.8	0.5–1 g q6h	—	Usual	Usual	Usual
Colistin	Renal	3–8	10–20	—	1.5 mg/kg q6–12h	2.5–3.8 mg/kg/d	1.5–2.5 mg/kg q24–36h	0.6 mg/kg q24h
Cyclacillin	Renal	0.6	—	0.5–1 g q6h	—	Usual	Usual	0.5–1 g q12h
Cycloserine	Renal	8–12	?	250–500 mg bid	—	Usual	250–500 mg qd	250 mg qd

Dapsone	Hepatic metabolism	30	Slight	50–100 mg/d	—	Usual	Usual	No data
Daptomycin	Renal	9.4	30	—	4 mg/kg/d	Usual	4 mg/kg q48h CrCl>30 mL/min	
Dicloxacillin	Renal	0.5–0.9	1–1.6	0.25–0.5 g q6h	—	Usual	Usual	Usual
Dirithromycin	Bile	30–44	30–44	500 mg/d	—	Usual	Usual	Usual
Doxycycline	Renal and gut	14–25	15–36	100 mg bid	100 mg bid	Usual	Usual	Usual
Enoxacin	Renal and hepatic	3–6	—	200–400 mg bid	—	Usual	1/2 usual dose	1/2 usual dose
Ertapenem	Renal and hepatic	4	?	—	1 g q24h	Usual	500 mg qd	500 mg qd
Erythromycin	Hepatic metabolism	1.2–1.6	4–6	0.25–0.5 g q6h	1 g q6h	Usual	Usual	Usual
Ethambutol	Renal	3–4	8	15–25 mg/kg q24h	—	15 mg/kg q24h	15 mg/kg q24–36h	15 mg/kg q48h
Ethionamide	Metabolized	4	9	0.5–1 g/d, 1–3 doses	—	Usual	Usual	5 mg/kg q48h
Famciclovir	Renal	2.3	13	125 mg q12h 500 mg q8h	— —	Usual Usual	125 mg q24h 500 mg q 12–24h	125 mg q48h 250 mg q48h
Fluconazole	Renal	20–50	100	100–200 mg/d	100–400 mg/d	Usual	50% usual dose	25–50 mg/d
Flucytosine	Renal	3–6	70	37 mg/kg q6h q12–24h	—	Usual	37 mg/kg	Adjust to keep 2 hr level at 50–100 µg/mL

Foscarnet induction	Renal	3	8	—	60 mg/kg q8h	40–50 mg/kg q8h	20–30 mg/kg q8h	Contra-indicated (CrCl <20 mL/min)
maintenance					90 mg/kg qd	60–70 mg/kg qd	50–70 mg/kg qd	Contra-indicated (CrCl <20 mL/min)
					120 mg/kg/d	80–90 mg/kg qd	60–80 mg/kg qd	Contra-indicated (CrCl <20 mL/min)
Ganciclovir-induction doses (maintenance—1/2 dose)	Renal	2.5–3.6	10	—	5 mg/kg bid 5 mg/kg/d	2.5 mg/kg bid 2.5 mg/kg/d	2.5 mg/kg qd 1.2 mg/kg/d	1.25 mg/kg 3×/wk 0.6 mg/kg/3×/wk
Ganciclovir—oral	GI	3–7	10	1000 mg tid	—	500 mg tid	500 mg/d	500 mg 3×/wk
Gatifloxacin	Renal	8		400 mg qd	400 mg qd	Usual	400 mg q24–48h	400 mg qod
Gemifloxacin	Renal	5–9	↑	320 mg qd	—	Usual	160 mg qd	160 mg qd
Gentamicin	Renal	2	48	—	1.7 mg/kg q8h	<<<<<<< See pp 39–40 >>>>>>>		
Grepafloxacin	Metabolized	15	15	400–600 mg qd	—	Usual	Usual	Usual
Griseofulvin microsize ultramicrosize	Hepatic metabolism Same	24 24	24 24	0.5–1 g qd 0.33–0.66 g qd	— —	Usual Usual	Usual Usual	Usual Usual
Imipenem- cilastatin	Renal	0.8–1	3.5	—	0.5–1 g q6h	0.5 g q6–8h	0.5 g q8–12h	0.25–0.5 mg q12h
Interferon alpha	Nonrenal	2–3	Same ?	—	3 mil units	Usual	Usual	Usual(?)

					q3d (HCV) 30–35 mil units/wk(HCV)			
Isoniazid	Hepatic	0.5–4	2–10	300 mg q24h	300 mg q24h	Usual	Usual	Slow acety-lators 1/2dose
Itraconazole	Hepatic	20–60	20–60	200–400 mg/d	200 mg/d	Usual	Usual	Usual
Ivermectin	Metabolized	16	16	12–18 mg × 1	—	Usual	Usual	Usual
Kanamycin	Renal	2–3	27–30	—	7.5 mg/kg q12h	<<<<<<< See pp 39–40 >>>>>>>		
Ketoconazole	Hepatic metabolism	1–4	1–4	200–400 mg q12–24h	—	Usual	Usual	Usual
Lamivudine	Renal	5–7 IC-12	↑	100 mg q24h (HBV)	—	Usual	100 mg × 1 50 mg q24h	25–50 mg q24h
Levofloxacin	Renal	6.3	35	500 mg q24h	500 mg q24h	Usual	250 mg q24h	250 mg q48h
Linezolid	Nonrenal	5–7	5–7	600 mg bid	600 mg bid	Usual	Usual	Usual
Lomefloxacin	Renal	8	45	400 mg q24h	—	Usual	400 mg; then 200 mg qd	Unknown
Loracarbef	Renal	1	32	200–400 mg q12h	—	Usual	200–400 mg q24h	200–400 mg 5d
Mefloquine	Hepatic	2–4 wk	2–4 wk	1250 mg × 1 250 mg q wk	—	Usual	Usual	Usual

Meropenem	Renal	1	↑	—	1 g q8h	Usual	500 mg q12h	500 mg q24h
Methenamine hippurate mandelate	Renal Renal	3–6 3–6	? ?	1 g q12h 1 g q6h	— —	Usual Usual	Avoid Avoid	
Methicillin	Renal(hepatic)	0.5	4	—	1–2 g q4–6h	1–2 g q6h	1–2 g q8h	1–2 g q12h
Metronidazole	Hepatic	6–14	8–15	0.25–0.75 g tid	0.5 g q6h	Usual	Usual	Usual
Mezlocillin	Renal	1	1.5	—	3–4 g q4–6h	Usual	3 g q8h	2 g q8h
Miconazole	Hepatic	0.5–1	0.5–1	—	0.4–1.2 g q8h	Usual	Usual	Usual
Minocycline	Hepatic and metabolized	11–26	17–30	100 mg q12h	100 mg q12h	Usual	Usual	Usual or slight decrease
Moxifloxacin	Metabolized	12	12	400 mg qd	400 mg qd	Usual	Usual	Usual
Nafcillin	Hepatic metabolism	0.5	1.2	0.5–1 g q6h	0.5–2 g q4–6h	Usual	Usual	Usual
Nalidixic acid	Renal and hepatic metabolism	1.5	21	1 g q6h	—	Usual	Usual	Avoid
Netilmicin	Renal	2.5	35	—	2.0 mg/kg q8h	<<<<<<< See pp 39–40 >>>>>>>		
Nitazoxanide	Metabolized	1–1.6	1–1.6	500 mg q6–12h	—	Usual	Usual	Usual
Nitrofurantoin	Renal	0.3	1	50–100 mg q6–8h	—	Usual	Avoid	Avoid
Norfloxacin	Renal and hepatic metabolism	3.5	8	400 mg bid	—	Usual	400 mg qd	400 mg qd

Nystatin	Not absorbed	—	—	0.4–1 mil units 3–5 × /d	—	Usual	Usual	Usual
Ofloxacin	Renal	6	40	200–400 mg bid —	— 200–400 mg q12h	Usual Usual	200–400 mg qd 200–400 mg q24h	100–200 mg qd 100–200 mg q24h
Oseltamivir	Renal	6–10 hr	↑	75 mg bid	—	Usual	75 mg qd	Avoid
Oxacillin	Renal	0.5	1	0.5–1 g q6h	1–3 g q6h	Usual	Usual	Usual
Peginterferon	Renal-30%	40	Slight ↑	—	180 mcg/kg SC q wk (Roche) 1.5 mcg/kg SC q wk (Schering)	Usual	Half dose(?)	Half dose(?)
Penicillin G, crystalline benzathine Penicillin V	Renal Renal Renal Renal	0.5 24 10–15 days 0.5–1.0	7–10 — — 7–10	— — 0.4–0.8 mil units q6h	1–4 mil units q4–6h 0.6–1.2 mil units IM q12h 0.6–1.2 mil units IM —	Usual Usual Usual Usual	Usual Usual Usual Usual	1/2 usual dose Usual Usual
Pentamidine	Non-renal	6	6–8	—	4 mg/kg q24h	Usual	4 mg/kg q24–36h	4 mg/kg q48h
Piperacillin	Renal	1	3	—	3–4 g q4–6h	Usual	3 g q8h	3 g q12h
Piperacillin + tazobactam	Renal	1	3	—	3/0.375 g q6h	Usual	2/0.25 g q6h	2/0.25 g q8h
Polymyxin B	Renal	6	48	—	7500–12,500 units/kg/d q12h	7500–12,500 units/kg/d q12h	5625–12,500 units/kg/d q12h	3750–6250 units/kg/d q12h
Praziquantel	Hepatic	0.8–1.5	?	10–25	—	Usual	Usual	Usual

	metabolism			mg/kg tid				
Pyrazinamide	Metabolized	10–16	?	15–35 mg/kg/d	—	Usual	Usual	12–20 mg/kg/d
Pyrimethamine	Hepatic metabolism	1.5–5days	?	25–75 mg/d	—	Usual	Usual	Usual
Quinacrine	Renal	5 days	—	100–200 mg q6–8h	—	Usual	?	?
Quinine	Hepatic metabolism	4–5	4–5	650 mg tid	7.5–10 mg/kg q8h	Usual	Usual	Usual
Quinupristin/delforistin	Hepatic metabolism	1.5	1.5	—	7.5 mg/kg q8–12h	Usual	Usual	Usual
Ribavirin	Hepatic	0.5–2 IC 40	Same	0.8–1.2 g/d	—	Usual	Usual	Half dose
Rifampin Late 2	Hepatic	Early 2–5	2–5	600 mg/d	600 mg/d	Usual	Usual	Usual
Rifapentine	Hepatic	16–19h	—	600 mg 2×/wk	—	Usual	Usual	Usual
Rimantadine	Hepatic	24–30	48–60	100 mg bid	—	Usual	Usual	100 mg/d
Spectinomycin	Renal	1–3	?	—	2 g/d IM	Usual	Usual	Usual
Streptomycin	Renal	2–5	100–110	—	500 mg q12h	15 mg/kg q24–72h	15 mg/kg q72–96h	7.5 mg/kg q72–96h
Sulfadiazine	Renal	8–17	22–34	0.5–1.5 g q4–6h	—	Usual	0.5–1.5 g q8–12h	0.5–1.5 gq12–24h
Sulfisoxazole	Renal	3–7	6–12	1–2 g q6h	—	Usual	1 g q8–12h	1 g q12–24h

Teicoplanin	Renal	6	41	—	6–12 mg/kg/d	Usual	1/2 usual dose	1/3 usual dose
Telithromycin	Hepatic	9.8 hr	↑ sl	800 mg qd	—	Usual	Usual No dose recommendation when GFR<30mL/min	No data
Tetracycline	Renal	8	50–100	0.25–0.5 g q6h		Usual	Use doxycycline	
Ticarcillin	Renal	1–1.5	16	—	3 g q4h	Usual	2–3 g q6–8h	2 g q12h
Ticarcillin + clavulanic acid	Renal	1–1.5	16	—	3 g q4–6h	Usual	2–3 g q6–8h	2 g q12h
Tobramycin	Renal	2.5	56	—	1.7 mg/kg q8h	<<<<<<<See pp 39–40 >>>>>>>		
Trimethoprim	Renal	8–15	T:24	100 mg q12h	—	Usual	100 mg q24h	Avoid
Trimethoprim-sulfamethoxazole	Renal	T:8–15 S:7–12	T:24 S:22–50	2–4 tabs/d or 1–2 DS/d	— 3–5 mg/kg q6–12h	Usual Usual	Half dose 3–5 mg/kg q12–24h	Avoid Avoid
Trovafloxacin	Renal and metabolism	10	10	100–200 mg qd	200–300 mg qd	Usual	Usual	Usual
Valacyclovir	Renal	2.5–3.3	14	1000 mg tid 500 mg bid	— —	Usual Usual	1 g q 12–24 hr 500 mg q 12–24 h	500 mg qd 500 mg qd
Valganciclovir	Renal	4 IC-18	20	900 mg bid × 3 wks 900 mg qd	—	Usual	1/2 dose	450 mg qod 3 wks 450 mg biw
Vancomycin	Renal	6–8	200–250	0.125–0.5	—	Usual	Usual	0.125 g po q6h

				g q6h —	15 mg/kg q12h	1 g q24h	1 g q3–10d	1 g q5–10d
Voriconazole	Hepatic	—	—	200 mg q12h	6 mg/kg q12h ×2, then 4 mg/kg q12h	Usual	po-usual IV-not recommended	po-usual IV-not recommended
Zanamivir	Renal	3	18	10 mg bid inhaled	—	Usual	No data	No data

* Half life in serum
IC = intracellular half life.

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D. **ANTIMICROBIAL DOSING REGIMENS DURING DIALYSIS**

(Adapted from Principles and Practice of Infectious Diseases, 4th Edition, Churchill Livingstone, New York:1995:506–519; American Hospital Formulary Service 1995:37–587)

Drug	Hemodialysis	Peritoneal dialysis
Acyclovir	2.5–5.0 mg/kg/d + extra dose postdialysis	2.5 mg/kg/d
Adofovir	10 mg q7d	—
Amdinocillin	No extra dose	—
Amikacin	2.5–3.75 mg/kg postdialysis	Loading dose predialysis 9–20 mg/L dialysate*

Amoxicillin	0.25 g postdialysis	Usual regimen
Amoxicillin + clavulanic acid	0.50 g (amoxicillin) + 0.125 (CA) halfway through dialysis and another dose at end	Usual regimen
Amphotericin B	Usual regimen	Usual regimen
Amphotericin lipid forms	Usual regimen	Usual regimen
Ampicillin	Usual dose postdialysis	Usual regimen
Ampicillin + sulbactam	2 g ampicillin postdialysis	Usual regimen
Atovaquone	Unknown	Unknown
Azithromycin	Usual regimen	Usual regimen
Aztreonam	1/8 initial dose (60–250 mg) postdialysis	Usual loading dose, then 1/4 usual dose at usual intervals
Carbenicillin	0.75–2.0 g postdialysis	2 g 6–12h
Caspofungin	Usual regimen	Usual regimen
Cefaclor	Repeat dose postdialysis	Usual regimen
Cefadroxil	0.5–1.0 g postdialysis	0.5 g/d
Cefamandole	Repeat dose postdialysis	0.5–1.0 g q12h
Cefazolin	0.25–0.5 g postdialysis	0.5 g q12h
Cefdinir	300 mg plus 300 mg postdialysis	—
Cefditoren	—	—
Cefepime	Standard dose postdialysis	Standard dose q48h

Cefixime	300 mg/d	200 mg/d
Cefonicid	No extra dose	Usual regimen
Cefoperazone	Schedule dose postdialysis	Usual regimen
Cefotaxime	0.5–2.0 g daily plus supplemental dose postdialysis	1–2 g/d
Cefotetan	1/4 usual dose q24h on non-dialysis days and 1/2 dose on dialysis days	1 g/d
Cefoxitin	1–2 g postdialysis	1 g/d
Cefpodoxime	200–400 mg 3×/wk	
Cefprozil	250–500 mg postdialysis	0.25 g q12–24h
Ceftazidime	1 g loading 1 g postdialysis	0.5–1.0 g loading, then 0.5 g/d or 250 mg in each 2 L dialysate
Ceftibutin	400 mg cap postdialysis	—
Ceftizoxime	Scheduled dose postdialysis	1 g/d
Ceftriaxone	No extra dose	Usual regimen
Cefuroxime	Repeat dose postdialysis	15 mg/kg post-dialysis or 750 mg/d
Cephalexin	0.25–1.0 g postdialysis	250 mg po tid
Cephalothin	Supplemental dose postdialysis	Option to add ≤6 mg/dL to dialysate
Chloramphenicol	Schedule dose postdialysis	Usual regimen
Ciprofloxacin	250–500 mg q24h postdialysis	250–500 mg/d
Clindamycin	Usual regimen	Usual regimen

Clofazimine	Usual regimen	Usual regimen
Cloxacillin	Usual regimen	Usual regimen
Daptomycin	4 mg/kg q48h	4 mg/kg q48h
Dicloxacillin	Usual regimen	Usual regimen
Doxycycline	Usual regimen	Usual regimen
Ertapenem	500 mg qd 150 mg supplement postdialysis	—
Erythromycin	Usual regimen	Usual regimen
Ethambutol	15 mg/kg/d postdialysis	15 mg/kg/d
Famciclovir	250 mg (zoster) or 125 mg (genital herpes) postdialysis	—
Fluconazole	100 mg postdialysis	1/2 usual dose
Flucytosine	37.5 mg/kg postdialysis	0.5–1.0 g/d
Ganciclovir—IV	1.25 mg/kg q24h given postdialysis on dialysis days	?
Ganciclovir—po	500 mg postdialysis 3×/wk	—
Gentamicin	1.0–1.7 mg/kg postdialysis	Loading dose predialysis, 2–4 mg/L dialysate*
Imipenem + cilastatin	Supplemental dose postdialysis and q12–24h thereafter	500 mg/d
Interferon	Usual	Usual
Isoniazid	5 mg/kg postdialysis	Daily dose postdialysis or 1/2 usual dose
Itraconazole	Usual regimen	Usual regimen

Kanamycin	4–5 mg/kg postdialysis	3.75 mg/kg/d
Ketoconazole	Usual regimen	Usual regimen
Lamivudine	25–50 mg/d dose postdialysis	25–50 mg/d
Levofloxacin	500 mg, then 250 mg q48h	500 mg, then 250 mg q48h
Linezolid	Usual dose	Usual dose
Metronidazole	Usual regimen	Usual regimen
Mezlocillin	2–3 g postdialysis then 3–4 g q12h	3 g q12h
Minocycline	Usual dose (some suggest reduced dose)	Usual dose (some suggest reduced dose)
Moxalactam	1–2 g postdialysis	1–2 g/d
Moxifloxacin	Usual dose	Usual dose
Nafcillin	Usual regimen	Usual regimen
Netilmicin	2 mg/kg postdialysis	Loading dose predialysis 3–5 mg/L dialysate*
Ofloxacin	200 mg, then 100 mg q24h	?
Oxacillin	Usual regimen	Usual regimen
Peginterferon	—	—
Penicillin G	500,000 units postdialysis	—
Penicillin V	0.25 g postdialysis	—
Pentamidine	Usual regimen	Usual regimen
Piperacillin	1 g postdialysis, then 2 g q8h	3–6 g/d

Piperacillin—tazobactam	2/0.25 g q8h + additional dose postdialysis	3–6 g/d
Pyrazinamide	Usual dose postdialysis	Avoid
Quinupristin—dalfopristin	Usual regimen	Usual regimen
Ribavirin	Usual dose	—
Rifampin	Usual regimen	Usual regimen
Rifapentine	Usual dose	Usual dose
Saquinavir	1200 mg tid	1200 mg tid
Streptomycin	0.5 g postdialysis	
Tetracycline	500 mg postdialysis	Use doxycycline
Ticarcillin	3 g postdialysis, then 2 g q12h	3 g q12h
Ticarcillin + clavulanic acid	3 g (ticarcillin) postdialysis, then 2 g q12h	3 g (ticarcillin) q12h
Tobramycin	1 mg/kg postdialysis	Loading dose predialysis, 2–4 mg/L dialysate*
Trimethoprimsulfa	4–5 mg/kg (as trimethoprim) postdialysis	0.16/0.8 g q48h
Trovafloxacin	Usual regimen	Usual regimen
Valacyclovir	1 g po postdialysis	No supplemental doses
Valganciclovir	Not recommended	—
Vancomycin	1 g/wk	0.5–1.0 g/wk
Vidarabine	Scheduled dose postdialysis	
Voriconazole	IV-not recommended po-standard dose	IV-not recommended po-standard dose

* Aminoglycosides given for prolonged periods to patients receiving continuous peritoneal dialysis have been associated with high rates of ototoxicity. Monitor level after loading dose, and follow for symptoms of ototoxicity with periodic Romberg's sign and reading after rapid head movement.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Use of Antimicrobial Agents in Hepatic Disease

Many antimicrobial agents are metabolized by the liver and/or excreted via the biliary tract. Nevertheless, few require dose modifications in hepatic disease; with few exceptions, doses are usually modified only if there is concurrent renal failure and/or the liver disease is either acute or is associated with severe hepatic failure as indicated by ascites or jaundice. The following recommendations are adapted from *Drug Information for the Health Care Professional*, USP DI, 21st Edition, 2001.

Agent: Recommended Dose Modification

Aztreonam: Some recommend a dose reduction of 20–25%.

Caspofungin: Usual maintenance dose of 50 mg/d is reduced to 35 mg/d with moderate hepatic disease; no data for severe hepatic disease.

Cefoperazone: Maximum dose is 4 g/d; if higher, monitor levels; with coexisting renal impairment maximum dose is 1–2 g/d.

Ceftriaxone: Maximum daily dose of 2 g with severe hepatic and renal impairment.

Chloramphenicol: Use with caution with renal and/or hepatic failure; monitor serum levels to achieve levels of 5–20 µg/mL.

Clindamycin: Dose reduction recommended only for severe hepatic failure.

Daptomycin: No dose adjustment.

Fluoroquinolones: Use standard dose except with trovafloxacin (see below).

Isoniazid: Use with caution and monitor hepatic function for mild-moderate hepatic disease; acute liver disease or history of INH-associated hepatic injury is contraindication to INH.

Itraconazole: Two-fold increase in half-life with cirrhosis; give with caution.

Linezolid: No dose adjustment.

Metronidazole: Modify dose for severe hepatic failure, although specific guidelines are not provided; peak serum levels with 500 mg doses are 10–20 μg/mL.

Mezlocillin: Reduce dose by 50% or double the dosing interval.

Nafcillin: Metabolized by liver and largely eliminated in bile; nevertheless, dose modifications are suggested only for combined hepatic and renal failure.

Penicillin G.: Dose reduction for hepatic failure only when accompanied by renal failure.

Ribavirin: AUC is unchanged wih severe hepatic failure.

Rifampin: Induces hepatic enzymes responsible for inactivating methadone, cortico steroids, oral anti-diabetic agents, digitalis, quinidine, cyclosporine, oral anticoagulants, estrogens, oral contraceptives, and chloramphenicol. Concurrent use of these drugs with rifampin and use in patients with prior liver disease require careful review.

Rimantadine: Severe hepatitis disease use 100 mg/d (half dose).

Telithromycin: No dose adjustment.

Ticarcillin: For patients with hepatic dysfunction and creatinine clearance <10 mL/min, give 2 g/d IV in one or two doses.

Ticarcillin/clavulanate: For patients with hepatic dysfunction and creatinine clearance <10 mL/min give usual loading dose (3.1 g) followed by 2 g once daily.

Trovafloxacin: For hepatic failure, adjust by indicated dose—indicated dose 300 mg/d IV, use 200 mg/d; indicated dose 200 mg/d IV or po, use 100 mg/d; indicated dose 100 mg/d, use 100 mg/d.

Voriconazole: Mild to moderate hepatic insufficiency—6 mg/kg IV q12h × 2, then 2 mg/kg IV q12h.

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Adverse Reactions to Antimicrobial Agents

A. **Adverse Reactions by Class**

Adapted from Medical Letter Handbook of Antimicrobial Therapy, Revised Edition 2000:5–200

Drug	Frequent	Occasional	Rare
Acyclovir (Zovirax)	Irritation at infusion site	Rash—nausea and vomiting; diarrhea; renal toxicity (especially with rapid IV infusion, prior renal disease, and nephro-toxic drugs); dizziness; abnormal liver function tests; itching; headache Topical—local reaction	CNS (especially with high dose in renal failure)—agitation, encephalopathy, lethargy, tremor, transient hemiparesis, disorientation, seizures, hallucina-tions, anemia, hypotension, neutropenia
Adofovir		Asthenia, GI intolerance (nausea, vomiting, diarrhea, abdominal pain), headache, pruritis, rash	Nephrotoxicity; lactic acidosis
Albendazole		Diarrhea, abdominal pain	Leukopenia, alopecia, increased transaminase levels
Amantadine (Symmetrel)	Insomnia, lethargy, dizziness, inability to concentrate (10–15% of adults receiving 200 mg/d)	GI intolerance especially nausea (5–10%), rash, depression, confusion, livedo reticularis	CNS—lethargy, tremor, confusion, obtundation, delirium, psychosis, visual hallucinations, paranoia, mania, seizures (primarily in elderly renal failure and/or seizure disorder), heart failure, eczematoid derma-titis, photosensitivity, oculogyric episodes, orthostatic hypotension,

			peripheral edema, bone marrow suppression, sudden loss of vision, urinary retention
Aminoglycosides Tobramycin Gentamicin Amikacin Netilmicin Kanamycin	Renal failure—related to dose, duration, hepatic function, prior renal function, concurrent nephrotoxic drugs, hydration status, hypotention, increased trough levels, and advanced age (Am J Med 1987;83:1091) (monitor creatinine 3–7×/wk and output). Nephrotoxicity is usually reversible	Vestibular and auditory damage: related to dose and duration, only risk is advanced age (AAC 1987;31:1383)—note dizziness, vertigo, roaring, tinnitis, high tone hearing loss; ototoxicity is irreversible	Fever, rash, blurred vision, neuromuscular blockage especially with myasthenia or Parkinson's—may be reversible with calcium salts, paresthesias, hypotension, allergic reactions—usually caused by sulfites in some preparations
Aminosalicylic acid (PAS)	GI intolerance	Liver damage; allergic reactions, thyroid enlargement, hepatotoxicity	Acidosis, vasculitis, hypoglycemia (diabetes), hypokalemia, encephalopathy, decreased prothrombin activity, myalgias, renal damage, gastric hemorrhage
Amoxicillin + clavulanic acid	Similar to amoxicillin—see penicillins		
Amphotericin B (Fungizone)	Fever (maximal at 1 hr) and chills (at 2 hr)—prevent/reduce with hydrocortisone, ibuprofen, ASA, acetaminophen, meperidine Renal tubular acidosis—dose dependent and usually reversible in absence of prior renal damage and dose <3 g, reduce with hydration and sodium	Hypomagnesemia, nausea, vomiting, metallic taste, headache	Hypotension, rash, pruritus, blurred vision, peripheral neuropathy, convulsions, hemorrhagic gastroenteritis, arrhythmias, diabetes insipidus, hearing loss, pulmonary edema, anaphylaxis, acute hepatic failure, eosinophilia, leukopenia, thrombocytopenia, delirium (especially with intrathecal use)

	supplementations Hypokalemia Anemia (treat severe anemia with erythropoietin) Phlebitis and pain at injection site (add 1,000 units heparin to infusions)		
Amphotericin B lipid complex and liposomal (Amphotec Abelcet AmBisome)	Chills and fever during infusion; infusion-related side effects and nephrotoxicity are significantly less compared with amphotericin B(Amphotec > Abelcet > AmBisome) (CID 2000;31:1155) Dose-related nephrotoxicity (substantially less than with amphotericin B; Abelcet > Amphotec > AmBisome)	GI intolerance, electrolyte abnormalities	Hypotension, anaphylaxis
Ampicillin + sulbactam (Unasyn)	Similar to those for ampicillin alone—see penicillins		
Atovaquone (Mepron)	Rash—20%; rash requiring discontinuation—4%; GI intolerance—20%; diarrhea—20%	Nausea, vomiting, mild diarrhea; headache in comparative trial for PCP—9% required discontinuation because of side effects vs 24% with sulfatrimetho-prim; 7% vs 21% with IV pentamidine	Fever, elevated aminotransferases (generally mild), abdominal pain
Atovaquone + proguanil (Malarone)	Abdominal pain—20%, nausea—12%, vomiting—20%, headache—10%, diarrhea—8%	Dizziness—5%, increased transaminases	

Azithromycin (Zithromax)		GI intolerance (4%), diarrhea, nausea, abdominal pain, vaginitis	Reversible hearing loss (more common with 500 mg × 30–90 days); erythema multiforme; increased transaminase; *C. difficile* colitis
Aztreonam (Azactam)	Eosinophilia	Phlebitis at infusion site, rash, diarrhea, nausea, eosinophilia, abnormal liver function tests	Thrombocytopenia, colitis, hypotension, unusual taste, seizures, chills
Bacitracin	Nephrotoxicity (proteinuria, oliguria, azotemia), pain with IM use		Rash, blood dyscrasia
Bithionol (Bitin)	Photosensitivity, vomiting; diarrhea, abdominal pain, urticaria		Leukopenia, toxic hepatitis
Capreomycin	Renal damage (tubular necrosis especially in patients with prior renal damage): Increased creatinine, proteinuria, cylindruria—monitor UA and creatinine weekly	Ototoxicity (vestibular > auditory—should assess vestibular function before and during treatment); electrolyte abnormalities; pain, induration, sterile abscesses at injection sites	Allergic reactions, leukopenia, leukocytosis, neuromuscular blockage (large IV doses—reversed with neostigmine), hypersensitivity reactions, hepatitis?
Caspofungin		Nausea, vomiting	Histamine-mediated adverse drug reaction with rash, face swelling, pruritis; fever; increased alkaline phosphotase; hypokalemia; proteinuria
Ceftibutin	—	GI intolerance—4%, headache, diarrhea, rash pruritis; 2% in clinical trial discontinued drug due to ADR	*C. difficile*-associated diarrhea, colitis
Cephalosporins	Phlebitis at infusion sites; diarrhea (especially cefoperazone	Allergic reactions (anaphylaxis rare), diarrhea and *C. difficile* colitis, hypoprothrombinemia (cefamandole, cefoperazone, moxalactam), platelet dysfunction	Hemolytic anemia, interstitial nephritis (cephalothin), hepatic

	and cefixime); pain at IM injection sites (less with cefazolin)	(moxalactam), eosinophilia, positive Coombs' test Serum sickness (especially prolonged parenteral use of cefaclor), cholelithiasis (ceftriaxone)	dysfunction, convulsions (high dose with renal failure), neutropenia, thrombocytopenia, confusion, disorientation, hallucinations
Chloramphenicol (Chloromycetin)		GI intolerance (oral), marrow suppression (dose related)	Fatal aplastic anemia (1:40,000), fever, allergic reactions, peripheral neuropathy, optic neuritis, *C. difficile* colitis
Chloroquine (Aralen)		Visual disturbances (related to dose and duration of treatment with ≥100 g as used for rheumatoid arthritis), GI intolerance, pruritus, weight loss, alopecia	CNS—headache, confusion, dizziness, extraocular muscle palsies, psychosis, peripheral neuropathy, cardiac toxicity, hemolysis (G6PD deficiency), marrow suppression, exacerbate psoriasis, eczema and other rashes, photophobia, myalgias, hematemesis
Cidofovir	Nephropathy—dose dependent: Reduce with IV hydration and probenecid; monitor creatinine and urinalysis. Report renal failure to Gilead: 800-GILEAD-5 or the FDA: 800-FDA-1088. Probenecid: Chills, fever, headache, rash, nausea in 30–50%	GI intolerance, neutropenia, metabolic acidosis	Uveitis, ocular hypotony
Ciprofloxacin (Cipro)	See quinolones		
Clarithromycin (Biaxin)		GI intolerance (4%), diarrhea	Headache, transaminase elevation, *C. difficile* colitis, reversible dose-related hearing loss

Clindamycin (Cleocin)	Diarrhea (frequency of *C. difficile* toxin is 5% for all clindamycin recipients and 15–25% for those with clindamycin-associated diarrhea)	Rash, *C. difficile* colitis, GI intolerance (oral)	Blood dyscrasias, hepatic damage, neutropenia, neuromuscular blockade, eosinophilia, fever, metallic taste, phlebitis at IV infusion sites, esophageal ulceration
Colistimethate (Coly-Mycin)	See polymyxins		
Cycloserine (Seromycin)	CNS—anxiety, confusion, depression, somnolence, disorientation, headache, hallucinations, tremor, hyper-reflexia, increased CSF protein, and pressure (dose related and reversible) (contraindicated in active alcoholics; twitching and seizures prevented with large doses of pyridoxine—100 mg tid)	Liver damage, malabsorption, peripheral neuropathy, folate deficiency, anemia	Coma, seizures (contraindicated in epileptics), hypersensitivity reactions, heart failure, arrhythmias
Dapsone	Rash, fever, nausea, anorexia, neutropenia—sufficiently severe to require discontinuation in 30–40% of HIV infected patients	Blood dyscrasias (methemogloblinemia and sulfahemoglobinemia ± G6PD deficiency)—warn patient to observe for cyanosis and dark urine; nephrotic syndrome; blurred vision; photosensitivity, tinnitis; insomnia; irritability; headache (transient)	Hypoalbuminemia, epidermal necrolysis, optic atrophy, agranulocytosis, peripheral neuropathy, aplastic anemia, "sulfone syndrome" (fever, exfoliative dermatitis, jaundice, adenopathy, methemo-globinemia, and anemia—treat with steroids), renal papillary necrosis
Daptomycin (Cubicin)		Dose related elevated CPK with or without symptoms or myopathy (reversible)	Elevated transaminases; neuropathy
Diethylcarbamazine citrate (Hetrazan)	Severe allergic or febrile reactions in patient with		Encephalopathy

	microfilaria in blood or skin, GI intolerance		
Diloxanide (Furamide)		Flatulence, diarrhea, nausea	Dizziness, diplopia, headache, urticaria
Dirithromycin	GI intolerance, abdominal pain, nausea	—	—
Eflornithine (DFMO, Ornidyl)	Anemia, leukopenia	Diarrhea, thrombocytopenia, seizures	Hearing loss
Emetine	Arrhythmias, precordial pain, muscle weakness, phlebitis	Diarrhea, vomiting; neuropathy, heart failure; headache, dyspnea	
Ertapenem		Nausea, vomiting, diarrhea; increased ALT; seizures in 0.5%	
Erythromycins	GI intolerance (related to oral doses); phlebitis (IV)	Diarrhea, stomatitis, cholestatic hepatitis (especially estolate-reversible), generalized rash	Allergic reactions, *C. difficile* colitis, hemolytic anemia, reversible ototoxicity (especially high dose and renal failure), QT prolongation with drug induced torsades de pointes especially in women (JAMA 280:1774, 1998), hypothermia, aggravation of myasthenia gravis
Ethambutol (Myambutol)		Optic neuritis (decreased acuity, reduced color discrimination, constricted fields, scotomata—dose related and infrequent with 15 mg/kg), GI intolerance, confusion, precipitation of acute gout	Hypersensitivity reactions, peripheral neuropathy, thrombocytopenia, toxic epidermal necrolysis, lichenoid skin rash
Ethionamide (Trecator)	GI intolerance (CNS effect)	Allergic reactions, peripheral neuropathy (prevented with pyridoxine), reversible liver damage (9%) with jaundice (1–3%)—monitor transaminase q2–4 wk, gynecomastia, menstrual irregularity	Optic neuritis, gouty arthritis, hypothyroidism, impotence, poor diabetic control, rash, hypotension
Famciclovir (Famvir)			Headache, nausea, fatigue

Fluconazole (Diflucan)	GI intolerance (bloating, nausea, vomiting, pain, anorexia, weight loss) dose related: 8–11% with 400 mg/d, 30% with >400 mg/d. Reversible alopecia in 10–20% receiving ≥400 mg/d × 3 mo (Ann Intern Med 123:354, 1995)	Transaminase elevations to ≥ 8 × normal (1%), headache, rash, diarrhea, prolonged prothrombin time with warfarin	Hepatic necrosis, Stevens-Johnson syndrome, thrombocytopenia, anaphylaxis, possible seizures
Flucytosine (Ancobon) Note: Levels should be <100 µg/mL	GI intolerance—nausea, vomiting, diarrhea	Marrow suppression with leukopenia or thrombocytopenia (dose related, especially with renal failure, serum concentration >100 µg/mL, or concurrent amphotericin); confusion; rash; hepatitis (dose related); enterocolitis headache; photosensitivity reaction	Hallucinations, eosinophilia, blood dyscrasias with agranulocytosis and pancytopenia, fatal hepatitis, anaphylaxis, anemia
Fluoroquinolones—see quinolones			
Foscarnet (Foscavir)	Renal failure (usually reversible; 30% get creatinine >2 mg/dL; monitor serum creatinine 1–3 ×/wk and discontinue if creatinine >2.9 mg/dL)	Mineral and electrolyte changes—reduced calcium, magnesium, phosphorus, ionized calcium, potassium—monitor serum electrolytes 1–2 ×/wk and monitor for symptoms of paresthesias; seizures (10%); fever; GI intolerance; anemia; genital ulceration; neuropathy	Marrow suppression, arrhythmias, nephrogenic diabetes insipidus, hypertension
Fosfomycin	—	Diarrhea (10%), headache, vaginitis, nausea	Angioedema, aplastic anemia, cholestatic jaundice, hepatic necrosis, toxic megacolon
Furazolidone (Furoxone)	GI intolerance	Allergic reactions, pulmonary infiltrates, headache, fever	Hemolytic anemia (G6PD deficiency), hypotension, polyneuropathy, hypoglycemia, agranulocytosis, disulfiram reaction with alcohol
Ganciclovir—IV (Cytovene)	Neutropenia (ANC	Anemia; fever; rash; CNS—headache, seizures,	CNS—psychosis, delirium,

	<500/mm^3 in 15–20%, usually early in treatment and responds within 3–7 days to drug holiday or to G-CSF/GM-CSF); thrombocytopenia (platelet count <20,000/mm^3 in 10%, reversible). Monitor CBC 2–3×/wk and discontinue with ANC <500–750/mm^3 or platelet count <25,000/mm^3	confusion; changes in mental status; abnormal liver function tests (2–3%)	confusion, agitation; neuropathy; impaired reproductive function (?); hematuria; renal failure; nausea; vomiting; GI bleeding or perforation; myocardiopathy; hypotension; ataxia; coma; somnolence; alopecia; pruritis, urticaria
Griseofulvin (Fulvicin)	Headache (often resolves with continued treatment)	Photosensitivity	GI disturbances, allergic reactions, paresthesias, exacerbation of lupus or leprosy, liver damage, lymphadenopathy, blood dyscrasias, thrush, transient hearing loss, fatigue, dizziness, insomnia, psychosis
Halofantrine (Halfan)		Diarrhea, abdominal pain	
Imipenem + cilastatin (Primaxin)		Phlebitis at infusion sites, allergic reactions, nausea, vomiting and diarrhea, eosinophilia, hepatotoxicity (transient), drug fever, transient hypotension during infusion, seizures (increased rates with high doses, renal failure, elderly patient, prior seizure disorder)	Myoclonus, *C. difficile* colitis, bone marrow suppression, renal toxicity
Interferon alfa (Roferon A, Intron)	Flu-like illness (80% with >5 mil units/d); fever; fatigue; anorexia; headache; myalgias Depression GI intolerance with nausea, vomiting, and pain or diarrhea	Marrow suppression—leukopenia, anemia ± thrombocytopenia (3–70%, dose related, usually transient and well tolerated); neuropsychiatric effects—psychosis, confusion, somnolence, anxiety; hepatitis—dose related in up to 40% receiving high doses; alopecia (8%); rash; activation of lupus; proteinuria	Edema, arrhythmias, cardiomyopathy, renal failure, hearing loss, pulmonary infiltrates. Some patients with hepatitis B have increased risk of decompensation with decreasing albumin levels, prolonged prothrombin time,

	(20–65%) Toxic effects start within 6 hr and last 2–12 hr; pretreat with NSAIDs		and increased ALT; delirium, obtundation
Iodoquinol		Rash, acne, GI intolerance—nausea, diarrhea, cramps	Optic atrophy, vision loss, peripheral neuropathy (with use for months), iodine sensitivity
Isoniazid (INH)	Hepatitis—age related <20 yr—nil; 35–6%; 45–11%; 55–18%. Rate of symptomatic hepatitis+ transaminase levels ≥ 5× ULN among patients taking INH prophylaxis by current guidelines is only 0.1% (Ann Intern Med 281:1014, 1999). Patient should be warned of symptoms, and drug should be discontinued if transaminase levels are ≥ 3–5 × normal limit	Allergic reactions; fever; peripheral neuropathy (reduced with pyridoxine) especially with alcoholism, diabetes, pregnancy, malnutrition, glossitis	CNS—optic neuritis, psychosis, agitation, depression, hallucination, paranoia, convulsions; toxic encephalopathy; twitching; coma; blood dyscrasias; hyperglycemia; lupus-like syndrome; keratitis; pellagra-like rash; B-6 and folate deficiency; chronic liver injury
Itraconazole (Sporanox)		Headache; GI intolerance—nausea (10%), vomiting, rash (8%), high dose (600 mg/day)—hypokalemia, adrenal insufficiency, impotence, gynecomastia, leg edema	Hepatitis (1/1000), toxic epidural necrolysis, hypertension
Ivermectin (Stromectol)			Mazzotti reaction in onchocerciasis with hypotension, fever, pruritus, bone and joint pain
IVIG		Hypotension, flushing, fever, chills, headache	Renal failure, hemolysis, aseptic meningitis, hyponatremia, anaphylaxis

Ketoconazole (Nizoral)	GI intolerance (dose related; take with food or at hs to improve tolerance) Temporary increase in transaminase levels (2–5%)	Endocrine—decreased steroid and tes-tosterone synthesis with impotence, gynecomastia, oligospermia, reduced libido; menstrual abnormalities (prolonged use and dose related, usually ≥600 mg/d); headache; somnolence; dizziness; asthenia; pruritus; rash; abdominal pain; photophobia	Abrupt and fulminant hepatitis (1:15,000), rare cases of fetal hepatic necrosis, anaphylaxis, lethargy, arthralgias, fever, marrow suppression, hypothyroidism (genetically determined), hallucinations, thrombocytopenia
Linezolid		Neutropenia, thrombocytopenia, anemia—monitor CBC weekly (see MedWatch—http://www.fda.gov/medwatch/feedback.htm); diarrhea, nausea, headache	Fever, thrush, rash, dizziness
Mebendazole (Vermox)		Diarrhea, abdominal pain	Leukopenia, agranulocytosis, hypospermia
Mefloquine (Lariam)	Vertigo, light-headedness, nausea, nightmares, headache, visual disturbances (dose related), decreased fine motor function	Psychosis and panic attacks, seizures; disorientation (dose related—rare at doses used for prophylaxis); GI intolerance; dizziness	Prolonged cardiac conduction, hypotension, seizures, coma
Melarsoprol (Mel B)	Heart damage, hypertension, colic, encephalopathy, vomiting	Peripheral neuropathy	Shock
Meropenem		Diarrhea (5%), nausea, headache, rash	Anaphylaxis, seizures (especially with CNS disorders or renal failure), thrombocytopenia, pseudomembranous colitis
Methenamine (Mandelamine)		GI intolerance, dysuria (reduced dose or acidification)	Allergic reactions, edema, tinnitus, muscle cramps
Metronidazole (Flagyl)	GI intolerance, metallic taste, headache	Peripheral neuropathy (prolonged use—reversible), phlebitis at injection sites, disulfiram-like reaction with	Seizures, ataxic encephalitis, *C. difficile*

		alcohol, insomnia, stomatitis	colitis, leukopenia, dysuria, pancreatitis, allergic reactions, mutagenic in Ames test (significance is ?), depression, uncontrolled crying, hallucinations, agitation, *C. difficile* colitis
Miconazole (Monistat)		Phlebitis at injection sites; chills; pruritus; rash; dizziness; blurred vision; hyperlipidemia; nausea; vomiting; hyponatremia; hyperlipidemia; irritation with topical use	Marrow suppression—anemia and thrombocytopenia, renal damage, anaphylaxis, hypotension, thrombo-cytosis, psychosis, cardiac arrhythmias or cardiac arrest with initial dose
Nalidixic acid (NegGram)	See quinolones		
Niclosamide (Niclocide)		Nausea, abdominal pain	
Nifurtimox (Lampit)	GI intolerance, loss of memory, sleep disorders, paresthesias, weakness, polyneuritis		Seizures, fever, pulmonary infiltrates
Nitazoxanide		Abdominal pain (give with food), headache	Hypotension
Nitrofurantoin (Macrodantin)	GI intolerance	Hypersensitivity reactions, pulmonary infiltrates (acute, subacute, or chronic ± fever, eosinophilia, rash, or lupus-like reaction)	Peripheral neuropathy, hepatitis, hemolytic anemia (G6PD deficiency), lactic acidosis, parotitis, pancreatitis, pulmonary fibrosis, cholestatic jaundice, trigeminal neuralgia
Nitrofurazone		Local irritation	Allergic reactions, contact dermatitis, renal failure with wound dressing in severe burn patients

Nystatin (Mycostatin)		GI intolerance	Allergic reactions
Ofloxacin (Floxin)	See quinolones		
Ornidazole		Dizziness, headache, GI intolerance	Reversible peripheral neuropathy
Oseltamivir	Nausea, vomiting (nausea usually resolves in 1–2 days and reduced with food)	Dizziness, headache, fatigue, insomnia	
Oxamniquine (Vansil)		Headache, fever, dizziness, somnolence, GI intolerance, hepatitis, insomnia, EEG changes, ECG changes, orange discoloration of urine	Seizures, neuropsychiatric disturbances
Paromomycin (Humatin)	GI intolerance		Ototoxicity and nephrotoxicity (especially with GI absorption plus renal failure)
Peginterferon	See interferon. Side effect profile is identical.		
Penicillins	Hypersensitivity reactions, rash (especially ampicillin and amoxicillin), diarrhea (especially ampicillin)	GI intolerance (oral agents), fever, Coombs' test positive, phlebitis at infusion sites and sterile abscesses at IM sites, Jarisch-Herxheimer reaction (syphilis or other spirochetal infections)	Anaphylaxis; leukopenia; thrombocytopenia; *C. difficile* colitis (especially ampicillin); hepatic damage; renal damage; CNS—seizures, twitching (high doses in patients with renal failure); hyperkalemia (penicillin G infusion); abnormal platelet aggregation with bleeding diathesis (carbenicillin, ticarcillin, piperacillin, nafcillin); thrombocytopenia (methicillin, mezlocillin); sodium overload (ticarcillin, nafcillin); GI bleeding (dicloxacillin)

Pentamidine (Pentam NebuPent)	Nephrotoxicity—in 25%, usually reversible with discontinuation (IV Pentam) Aerosol administration—cough (30%), pretreat with albuterol, 2 puffs	Hypotension (administer IV over 60 min); hypoglycemia (5–10%, usually occurs after day 5 of treatment including past treatment, may last days or weeks, treat with IV glucose); diabetes mellitus, may be insulin dependent; cardiotoxicity; delirium; rash (including Stevens-Johnson syndrome); marrow suppression (common in AIDS patients); GI intolerance with nausea, vomiting, abdominal pain, anorexia, and/or bad taste Aerosol administration—asthma reaction (2–5%)	Hepatotoxicity, leukopenia, thrombocytopenia, pancreatitis, toxic epidermal necrolysis, fever
Polymyxins (Aerosporin)	Pain and phlebitis at injection sites, neurotoxicity (ataxia, paresthesias), nephrotoxicity, dizziness, drowsiness, facial flushing		Allergic reactions, neuromuscular blockade—sometimes reversed with IV CaCl (not neostigmine)
Praziquantel (Biltricide)	Malaise, headache, dizziness	Sedation, abdominal pain, fever, sweating, fatigue	Pruritis, rash
Primaquine		Hemolytic anemia (G6PD deficiency); warn patient to observe for dark urine and cyanosis, or screen for G6PD deficiency; GI intolerance	Headache, pruritus, neutropenia, CNS symptoms, hypertension, arrhythmias, disturbed visual accommodation
Pyrazinamide	Non-gouty polyarthralgia, asymptomatic hyperuricemia	Hepatitis (dose related, frequency not increased when given with INH or rifampin, rarely serious), GI intolerance, gout (treated with allopurinol and probenecid)	Rash, fever, porphyria, photosensitivity
Pyrimethamine (Daraprim)		Folic acid deficiency with megaloblastic anemia and pancytopenia (dose related and reversed with leucovorin), allergic reactions, GI intolerance (nausea, anorexia, vomiting)	CNS—ataxia, tremors, headache, malaise, seizures (dose related), fatigue
Quinacrine (Atabrine)	Dizziness, headache, vomiting, diarrhea	Yellow staining of skin, psychosis, blood dyscrasias, rash, insomnia	Hepatic necrosis, seizures, exfoliative dermatitis, ocular effects like chloroquine

Quinine		GI intolerance, cinchonism (tinnitus, headache, visual disturbances), hemolytic anemia (G6PD deficiency)	Arrhythmias, hypotension with rapid IV infusion, hypoglycemia, hepatitis, thrombocytopenia
Quinolones Ciprofloxacin Enoxacin Gatifloxacin Gemifloxacin Levofloxacin Lomefloxacin Moxifloxacin Nalidixic acid Norfloxacin Ofloxacin Trovafloxacin	Animal studies show arthropathies in weight-bearing joints of immature animals; significance in humans is unknown Contraindicated during pregnancy and in persons <18 yr Gemifloxacin—high rate of apparently inconsequential rash especially with persons < 40 years, women and courses > 7 days	GI intolerance; CNS—headache, malaise, insomnia, restlessness, dizziness; allergic reactions; diarrhea; photosensitivity (especially lomefloxacin and naladixic acid); increased hepatic enzymes; tendon rupture (especially Achilles—over 100 cases reported); prolonged QT interval (rare, but important, especially when combined with other drugs that can cause this)	Papilledema; nystagmus; visual disturbances; diarrhea; C. difficile colitis; marrow suppression; photosensitivity; anaphylaxis; serum sickness; seizures; toxic psychosis; CNS stimulation—tremors, restlessness, insomnia, delirium, psychosis, confusion, hallucinations; encephalopathy with coma; interstitial nephritis; prolonged bleeding time; vasculitis Hepatotoxicity—trovafloxacin implicated in 14 cases of liver failure resulting in liver transplantation or death, which led to revised indications that generally limit the drug to hospital use for patients with infections that cannot be managed with alternative antibiotics
Quinupristin—dalfopristin	Arthralgias and myalgias Hyperbilirubinemia	Phlebitis at IV infusion sites, rash, nausea, headache, transaminase increase	Colitis
Ribavirin + interferon (see interferon)	Hemolytic anemia in wk 1–4; dose related	Cough, dyspnea, fatigue, headache, insomnia, GI intolerance	
Rifabutin (Mycobutin)	Orange discoloration of urine, tears (contact lens), sweat (see drug interactions) Uveitis with eye pain,	Hepatitis, GI intolerance, allergic reactions	Dose-related polyarthralgias, thrombotic thrombocytopenic purpura, hemolysis, myositis, confusion, seizures

	photophobia, redness, and blurred vision—usually high doses (600 mg/d or concurrent use of fluconazole or clarithromycin); usually responsive to topical corticosteroids plus mydriatics (NEJM 330:438, 1994) Major concern is drug interactions because rifabutin accelerates cytochrome p-450 (see drug interactions)		
Rifampin (Rifadin)	Orange discoloration of urine, tears (contact lens), sweat Major concerns are drug interactions because rifampin accelerates cytochrome P-450	Hepatitis—usually cholestatic changes during first month (frequency not increased when given with INH); jaundice (usually reversible with dose reduction and/or continued use); GI intolerance; hypersensitivity reactions; accelerated metabolism of steroids so increase steroid requirement in adrenal insufficiency; may require alternative to oral contraceptives; contraindicated for concurrent use with protease inhibitors (see drug interactions); flu-like syndrome with intermittent use characterized by dyspnea, wheezing	Thrombocytopenia, leukopenia, hemolytic anemia, eosinophilia, renal damage, proximal myopathy, hyperuricemia, anaphylaxis, renal damage, acute organic brain syndrome, *C. difficile* colitis
Rimantadine (Flumadine)		GI intolerance (3–8%); CNS—light headed-ness, insomnia, reduced concentration, nervousness (4–8%, about half the rate with amantadine)	Seizures (primarily in patients with seizure disorder)
Sodium stibogluconate (Pentostam)	Muscle pain, joint stiffness, nausea, T-wave flattening, increased hepatic enzymes	Weakness, colic, hepatic damage, bradycardia, leukopenia	Diarrhea, rash, pruritus, hemolytic anemia, cardiac damage, renal damage, shock, sudden death
Spectinomycin (Trobicin)		Pain at injection site, urticaria, fever, insomnia, dizziness, nausea, headache	Anaphylaxis, fever, anemia, renal failure and abnormal liver function test (multiple doses)

Sulfonamides	Allergic reactions—rash, pruritus, fever (appears to be dose related, usually within 7–10 days of initial dose), cross reactions noted between sulfonamides including thiazide diuretics and oral hypoglycemics	Periarteritis nodosum, lupus, Stevens-Johnson syndrome, serum sickness; crystalluria with renal damage, urolithiasis and oliguria (prevent with increasing urine pH, hydration, and use of sulfonamide-sulfonamide combinations); GI intolerance; thiazide diuretics and oral hypoglycemics photosensitivity; hepatitis	Myocarditis, psychosis, confusion, euphoria, disorientation, neuropathy, dizziness, depression, hemolytic anemia (G6PD deficiency), marrow suppression, agranulocytosis
Suramin	GI intolerance, pruritis, photophobia, hyperesthesia	Peripheral neuropathy, renal damage, blood dyscrasias, optic atrophy	
Telithromycin		GI intolerance—nausea, vomiting, diarrhea; dysgeusia; headache; dizziness	Elevated transaminases, *C. difficile* colitis; blurred vision; exacerbation of myasthenia gravis; potential to prolong QTc interval (similar to clarithromycin)
Terbinafine		GI intolerance—diarrhea, dyspepsia, abdominal pain; rash; taste perversion; hepatitis; pruritis	Anaphylaxis, neutropenia
Tetracyclines Demeclocycline Minocycline Tetracycline	GI intolerance (dose related); stains and deforms teeth in children up to 8 yr; vertigo (minocycline); negative nitrogen balance and increased azotemia with renal failure (except doxycycline; vaginitis)	Hepatotoxicity (dose related, esp pregnant women); esophageal ulcerations; diarrhea; candidiasis (thrush and vaginitis); photosensitivity (esp demeclocycline and doxy- cycline); phlebitis with IV treatment and pain with IM injection	Malabsorption, allergic reactions, visual disturbances, aggravation of myasthenia (reversed with Ca^{++}), hemolytic anemia, *C. difficile* colitis, increased intra-cranial pressure, hemolytic anemia, papilledema
Thiabendazole (Mintezol)	Nausea, vomiting, vertigo	Rash, hallucinations, olfactory disturbances, leukopenia	Stevens-Johnson syndrome, shock, tinnitis, cholestasis, seizures, angioneurotic edema
Ticarcillin + clavulanic acid (Timentin)	Similar to those for ticarcillin alone	See penicillins	

Trifluridine (Viroptic)		Burning at application site	Palpebral edema, hypersensitivity reactions, epithelial keratopathy
Trimethoprim	GI intolerance (dose related), rash, pruritis	Marrow suppression—megaloblastic anemia, neutropenia, thrombocytopenia (hematologic toxicity increased with folate depletion and high doses—treat with leucovorin, 3–15 mg/d × 3 days); reversible hyperkalemia (dose related); photosensitivity	Pancytopenia; erythema multiforme, Stevens-Johnson syndrome, TEN
Trimethoprim-sulfamethoxazole (see sulfonamides and trimethoprim) (Bactrim, Septra)	Fever, leukopenia, rash, and/or GI intolerance in 25–50% of HIV-infected persons; dose related and most tolerate readministration of lower dose after 2 wk discontinuation; reactions noted above for sulfonamides and trimethoprim	*Candida* vaginitis, thrush (AIDS patients); anemia; thrombocytopenia, renal failure; hemolytic anemia with G6PD deficiency; hepatitis including cholestatic jaundice	Ataxia, apathy, ankle clonus, erythema multiforme, Stevens-Johnson syndrome, *C. difficile*-associated colitis, pancreatitis, hepatic necrosis
Trimetrexate	Marrow suppression with neutropenia and thrombocytopenia. Must give with folinic acid (leucovorin) 20–40 mg/m^2 q6h). Must monitor CBC, renal function, and liver function, tests ≥2 times a week	Hepatotoxicity with increased trans-aminase levels (3%), rash (3%); GI toxicity (1%), stomatitis, nephrotoxicity	Seizures— ? relation, anaphylaxis
Tryparsamide	Nausea, vomiting	Impaired vision, optic atrophy, fever, allergic reactions, rash, tinnitus	
Valacyclovir (Valtrex)			GI intolerance—nausea, vomiting, diarrhea, headache, constipation
Valganciclovir (Valtrex)	Neutropenia; anemia; contraindicated with ANC × 500 Hgb × 8 g/dL	Thrombocytopenia; confusion; headache; fever; abnormal LFTs, rash	

	GI intolerance		
Vancomycin (Vancocin)	Phlebitis at injection sites	"Red-man syndrome" (flushing over chest and face) ± hypotension and pruritis (infusion >60 min; may be reversed or prevented with anti-histamine); fever; eosinophilia; allergic reactions with rash	Anaphylaxis, ototoxicity and nephrotoxicity (dose related), peripheral neuropathy, marrow suppression
Voricmazole (Valtrex)	Visual distrubances in 20% (blurring, color distortion, etc)—usually treat through; D/C in × 1%	Increased LFTs D/C for hepatotoxicity in 4–8%; hallucination in 4%; rash in 6%	
Zanamivir		Bronchospasm or reduced expiratory flow rate especially in patients with asthma or chronic lung disease; should have rapidly acting broncho-dilator available in susceptible patients	Dizziness

B. **Penicillin Allergy—** Guidelines based primarily on recommendations of the Joint Council of Allergy, Asthma and Immunology (J Allergy Clin Immunol 1998;101:S465–S528.) and the CDC recommendations for penicillin skin testing (MMWR 2002; 51: RR-6.)

1. **Classification of Penicillin Hypersensitivity Reactions**(JAMA 2001;285:2498.)

Type	*Mechanism*	*Clinical expression*
I	IgE	Urticaria, angioedema, anaphylaxis,* laryngeal edema, asthma frequency—0.02%, mortality—10%
II	Cytotoxic Ab of IgG class	Hemolytic anemia
III	Immune complexes IgG and IgM Ab	Serum sickness
IV	Cell-mediated	Contact dermatitis
Idiopathic	Unknown	Maculopapular rash (common), interstitial nephritis, drug fever, eosinophilia, exfoliative dermatitis, Stevens-Johnson syndrome

* Anaphylaxis is defined as an immediate systemic reaction due to IgE. Anaphylactoid reactions mimic anaphylaxis but are not caused by IgE.

2. **Cross Reactions Among Beta-lactam Agents** (J Allergy Clin Immunol 1998; 101:S465.)
   - Allergy to one penicillin indicates allergy to all.
   - Allergy to penicillins may indicate allergy to cephalosporins and carbapenems (imipenem, meropenem, etc.); it is generally considered safe to give cephalo sporins to patients with non–IgE-mediated reactions to penicillins such as maculopapular rashes. The risk of an allergic reaction to a cephalosporin in a patient with penicillin allergy is >10%; it is greater with first generation cephalosporins than second or third generation agents. Penicillin skin testing is a valid method to test safety of cephalosporins in penicillin-allergic patients.
   - There are rare cross reactions with aztreonam.
   - Ampicillin and amoxicillin cause morbilliform rashes in 5–13% of patients; these do not constitute a reaction meriting skin testing unless the reaction is urticarial or anaphylactic.
   - Serum sickness to cefaclor is caused by a hereditary defect in metabolism and does not indicate risk with other beta-lactams (Immunol Allergy Clin N. Am 1998; 189:745.).
3. **Skin Testing**

   This is considered a safe, rapid, and effective method to exclude an IgE-mediated response with ≥ 97% assurance (MMWR 1993;42(RR-14):45.).

   a. **The indication is a patient who has a history of an allergic reaction** to penicillin or a cephalosporin and who needs penicillin. Morbilliform rashes to amoxi cillin or ampicillin do not count as a positive history. The test may be used for the penicillin allergic patient who requires a cephalosporin as well.

   b. **Patients with a history of severe reactions during the past year** should be tested in a monitored setting in which treatment for anaphylaxis is possible. Antigens should be diluted 100-fold.

   c. **Patients with a history of penicillin allergy** and a negative skin test should receive penicillin 250 mg po and be observed for 1 hr before treatment with therapeutic doses.

      Those with a positive skin test should be desensitized.

d. **Penicillin allergy skin testing**: Patient should not have taken anti histamines in the previous 48 hr.

1. **Reagents** (Ann Allergy Asthma Immunol 1999;83:665.; MMWR 2002;51: RR-6.)

- Major determinants:

  Benzylpenicilloyl-polylysine (Pre-Pen, Kremers-Urban, Milwaukee, WI) as conjugated of benzylpenicillin with poly-L-lysine in concen tration of 6×10^{-5} mEq penicilloyl moieties.

  Benzyl penicilloyl (10^{-2} or 6000 units/mL).

- Minor determinants:

  Freshly diluted aqueous penicillin G.

- Positive control (histamine 1 mg/mL).
- Negative control (buffered saline solution).

  Dilute the antigens 100-fold for preliminary testing if there has been an immediate generalized reaction within the past year.

2. **Procedure**

Epicutaneous (scratch or prick) test: apply one drop of material to volar forearm and pierce epidermis with a 26-gauge needle without drawing blood; observe for 20 min. A wheal of ≥4 mm is a positive test. If there is no wheal ≥4 mm or systemic reaction, proceed to intradermal test. With a positive scratch test, the subsequent intradermal test should be performed with the corresponding reagent diluted 10^2–10^4 fold.

Intradermal test: Inject 0.02 mL intradermally raising a 2- to 3-mm wheal using a 27-gauge short-bevelled needle; observe for 20 min. A wheal of 2 mm larger than original wheal is positive.

3. **Interpretation**

For test to be interpretable, negative (saline) control must elicit no reaction, and positive (histamine) control must elicit a positive reaction.

Positive test: A wheal >2 mm in mean diameter to any penicillin reagent; erythema must be present. A positive history and a positive skin test gives a 50% chance of an immediate reaction if penicillin is given (J Allergy Clin Immunol 1998;101:S465.)

Negative test: Wheals at site of penicillin reagents are equivalent to negative control. A negative test to major and minor determinants gives a 97–99% probability of no immediate reaction if penicillin is given (J Allergy Clin Immunol 1998;101:S465.)

Indeterminate: All other results.

Epicutaneous test	*Histamine*	*Diluent*	*Conclusion*
Neg	Pos	Neg	Do epidermal test; wheal 2 mm larger than original wheal at 15–20 min is positive
Neg	Neg	Neg	False negative. No conclusion.
Pos	Pos	Neg	Avoid penicillin or desensitize
From Ann Intern Med 1987;107:204; JAMA 1993;270:2456			

e. **Experience with test** (JAMA 1993;270:2456.)

Test results in 4977 patients with indication for penicillin therapy

- Results by history of penicillin reaction

Positive history	55*/776 (7.1%)
Negative history	73/4201 (1.7%)
Total	128/4977 (2.6%)
* History of urticaria—34/274 (12.4%), rash—7/166 (4%), other or uncertain—5/284 (1.7%)	

- Reaction pattern with 128 positives

Positive—major determinants	96 (75%)
Positive—minor determinants 13	(10%)
Positive—both	19 (15%)

- Results with penicillin given to 596 patients with positive history and negative skin test

Anaphylaxis	2/596 (0.3%)
Urticaria	15/596 (2.5%)
Rash/pruritis	13/596 (2.1%)

f. **Experience with cephalosporins**

- Literature review of 15,987 patients who received first or second generation cephalosporins showed reactions in 8.1% with a history of penicillin reaction versus 1.9% without this history (Arch Intern Med 1992;152:930.).
- A review of 9388 patients with a history of penicillin allergy showed 2 cases of anaphylaxis (0.02%) with cephalosporin treatment.
- The rate of cephalosporin reactions with a positive penicillin skin test is 6/135 (4.4%) compared to 2/351 (0.6%) in those with a negative skin test (NEJM 2001;345:804.).
- Patients with an allergic reaction to a cephalosporin should not receive the same agent again, but other cephalosporins with different side chains may not cause cross reactions. Animal studies suggest side-chain specific antibodies may dominate the immune response to cephalo sporins (Biochem 1971;123:183.; Ann Intern Med 1987;107:204.).

4. **Testing without Minor Determinant**

   If the full battery of skin test reagents is unavailable (minor determinant is difficult to obtain), testing should be performed with major determinant (Pre-Pen, Taylor Pharmaceutical Co, Decatur, IL) and penicillin G (benzylpenicillin G 6000 units/mL). This testing detects 90–97% of allergic patients; because lack of minor determinants misses 3–10% of allergic patients, caution is necessary. Patients at high risk of anaphylaxis (history of penicillin-induced anaphylaxis, urticaria, asthma etc should be tested with a 100-fold dilution of test reagents before testing full strength. A 10-fold dilution is suggested for other types of immediate, generalized reactions within the past year. Test methods are described above using the epicutaneous (scratch) test followed by the intradermal test.

5. **Penicillin Desensitization** (MMWR 2002;51:RR-6.)

   a. **Penicillin desensitization should be performed in a hospital** because IgE-mediated reactions can occur, although they are rare. Desensitization may be done po or IV, although oral administration is often considered safer, simpler, and easier. Desensitization requires about 4 hr, after which the first dose is given.

   b. **Parenteral desensitization**: Give 1 unit penicillin IV, and then double the dose at 15-min intervals or increase the dose 10-fold at 20- to 30-min intervals.

   c. **Oral desensitization protocol** (NEJM 1985;312:1229.):

		Amount[b]		
Dose[a]	***Penicillin V suspension (units/mL)***	***mL***	***units***	***Cumulative dose (units)***
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300

7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Observation period: 30 min before parenteral administration of penicillin.
[a] Interval between doses, 15 min; elapsed time, 3 hr and 45 min; cumulative dose, 1.3 mil units.
[b] Specific amount of drug was diluted in approximately 30 mL of water and then given po.

6. **Management of Allergic Reactions**
   - Medical facilities should have a protocol for dealing with allergic reactions, especially anaphylaxis. Supplies include oxygen, aqueous epinephrine, injectable antihistamine, IV steroids, airway intubation suppliers, and IV access supplies.
   - **Epinephrine**: IgE-mediated reactions
   - **Antihistamines**: Accelerated and late urticaria, maculopapular rashes
   - **Glucocorticoids**: Severe urticaria, prolonged systemic anaphylaxis, serum sick-ness, contact dermatitis, exfoliative and bullous skin reactions, interstitial nephritis, pulmonary and hepatic reactions
7. **Anaphylactic Shock**

	Epinephrine dose
Initial treatment	
SC (preferred) or IM: Repeat every 20–30 min prn up to 3×	0.3–0.5 mL (1:1000)

Severe shock or inadequate	3–5 mL at 5- to 10-min intervals
response to IM or SC:	(1:10,000)
IV administration	

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Drug Interactions

(Adapted from Medical Letter Handbook of Adverse Drug Interactions, 2000 and Drug Information for the Health Care Professional, USP DI, 21st Edition, 2001)

Drug	Effect of interaction
Acyclovir	
Narcotics	Increased meperidine level
Probenecid	Possible increased acyclovir level
Adofovir	
Ibuprofen	Adofovir AUC increases 23%
Amantadine	

Anticholinergics	Hallucination, confusion, nightmares
Thiazide diuretics	Increased amantadine toxicity with hydrochlorothiazide-triamterene combination
Trimethoprim–sulfamethoxazole	Amantadine toxicity with delirium
Aminoglycosides	
Amphotericin	Increased nephrotoxicity
Bumetanide	Ototoxicity
Cephalosporins	Increased nephrotoxicity
Cisplatin*	Increased nephrotoxicity—avoid
Cyclosporine*	Increased nephrotoxicity—avoid
Enflurane*	Increased nephrotoxicity—avoid
Ethacrynic acid*	Increased ototoxicity—avoid

Furosemide*	Increased oto- and nephrotoxicity—avoid
Gallium	Increased nephrotoxicity
$MgSO_4$	Increased neuromuscular blockage
Malathion	Possible respiratory depression
Methotrexate	Possible decreased methotrexate activity with oral aminoglycosides
Neuromuscular blocking agents	Increased neuromuscular blockade
Vancomycin	Increased nephrotoxicity and possible increased ototoxicity
Aminosalicylic acid (PAS)	
Anticoagulants, oral	Increased hypoprothrombinemia
Digitalis	Decreased digoxin level
Probenecid	Increased PAS toxicity

Rifampin	Decreased rifampin effectiveness (give as separate doses by 8–12 hr)
Amphotericin B	
Aminoglycosides	Increased nephrotoxicity
Capreomycin	Increased nephrotoxicity
Cisplatin	Increased nephrotoxicity
Corticosteroids	Increased hypokalemia
Cyclosporine*	Increased nephrotoxicity (JID 29:106, 1994)—avoid
Digitalis	Increased cardiotoxicity due to hypokalemia—monitor K^+
Diuretics	Increased hypokalemia
Leukocyte transfusions	Acute pulmonary toxicity
Methoxyflurane	Increased nephrotoxicity

Pentamidine	Increased nephrotoxicity
Skeletal muscle relaxants	Increased effect of relaxants
Vancomycin	Increased nephrotoxicity
Atovaquone	
AZT	Increased AZT levels (Clin Pharmacol Ther 59:14, 1996)
Food (fat)	Increased absorption (should be taken with meals)
Metoclopramide	Decreased atovaquone levels
Rifampin and rifabutin	Decreased atovaquone levels
Sulfa-trimethoprim	Slight decrease in TMP-SMX levels
Tetracycline*	Decreased atovaquone levels (40%)—avoid
Azithromycin	

Antacids with Mg^{++} or Al^{++}	Area under curve does not change peak level
Coumadin	Increased prothrombin time
Food	Tablets: No effect Oral suspension: Absorption increases, but area under curve is unchanged
Theophylline	Increased theophylline levels (Pharmacotherapy 17:827, 1997)
Capreomycin	
Aminoglycosides*	Increased oto- and nephrotoxicity—avoid
Theophylline	Increased theophylline effect and toxicity
Caspofungin	
Cyclosporine*	Increases levels of caspofungin 35%—avoid or monitor LFTs
Dexamethasone	May decrease caspofungin levels

Efavireniz	May decrease caspofungin levels
Nelfinavir	May decrease caspofungin levels
Nevirapine	May decrease caspofungin levels
Phenytoin	May decrease caspofungin levels
Rifampin	May decrease caspofungin levels
Tacrolimus	May decrease caspofungin levels
Cephalosporins	
Alcohol	Disulfiram-like reaction for those with tetrazole-thiomethyl side chain: Cefamandole, cefoperazone, cefotetan
Aminoglycosides	Possibly increased nephrotoxicity
Antacids with Al^{++} or Mg^{++} or H^2 blockers	Reduced absorption of cefdinir and cefditoren, take ≥ 2 hr apart

Contraceptives	Decreased contraceptive effect; mechanism unknown—two case reports (Br J Clin Pharmacol 25:527, 1988)
Cyclosporine	Increased cyclosporine levels with ceftriaxone (Nephron 59:681, 1991)
Ethacrynic acid	Increased nephrotoxicity
Food	Most oral agents are unaffected; oral cefuroxime absorption promoted
Furosemide	Increased nephrotoxicity
Probenecid	Increased concentrations of most cephalosporins
Chloramphenicol	
Anticoagulants, oral	Increased hypoprothrombinemia
Chlorpropamide	Increased chlorpropamide activity
Dicumarol	Increased dicumarol activity

Phenobarbital	Decreased concentrations of chloramphenicol
Phenytoin	Increased phenytoin activity
Rifampin	Decreased chloramphenicol levels (NEJM 312:788, 1985)
Tolbutamide	Increased tolbutamide activity
Cidofovir	
Nephrotoxic drugs*	Promotes nephrotoxicity—must avoid concurrent use of aminoglycosides, amphotericin B, foscarnet, IV pentamidine, and nonsteroidal anti-inflammatory agents—avoid all
Probenecid	Reduces nephrotoxicity of cidofovir and must be given before cidofovir infusion. Probenecid increases levels of acetaminophen, acyclovir, aminosalicylic acid, barbiturates, beta-lactam antibiotics, benzodiazepines, bumetanide, clofibrate, methotrexate, furosemide, and theophylline
Ciprofloxacin (see fluoroquinolones)	

Clarithromycin	
Carbamazepine*	Increased carbamazepine levels and possible reduction in clarithromycin effect (Ann Pharmacother 28:1197, 1994)—avoid
Cisapride*	Ventricular arrhythmias—avoid
Disopyramide*	Increased disopyramide levels with cardiac arrhythmia (Lancet 349:326, 1997)—avoid
Pimozide	Increased pimozide levels with cardiac toxicity (Clin Pharmacol Ther 59:189, 1996)
Rifabutin	Increased rifabutin levels with uveitis (Genitourin Med 72:419, 1996)
Seldane*	Ventricular arrhythmias—avoid
Theophylline	Elevated theophylline levels
Clindamycin	
Antiperistaltic agents	Increased risk and severity of *C. difficile* colitis

(Lomotil, loperamide)	
Cycloserine	
Alcohol	Increased alcohol effect or convulsions; warn patients
Ethionamide	Increased CNS toxicity
Isoniazid	CNS toxicity, dizziness, drowsiness
Phenytoin	Increased phenytoin effect (toxicity)
Dapsone	
Coumadin	Increased prothrombin time
ddI	Decreased levels of dapsone
Primaquine	Increased hemolysis with G6PD deficiency
Probenecid	Increased dapsone levels

Pyrimethamine	Increased marrow toxicity (monitor CBC)
Rifampin	Decreased levels of dapsone
Saquinavir	Increased levels of dapsone
Trimethoprim	Increased levels of both drugs
Daptomycin	
HMG-CoA reductase inhibitors (statins)	Caution with concurrent use since both may cause myopathy—recommend temporary discontinuation of statins
Ertapenem	
Dextrose	Incompatible—do not infuse in dextrose
Probenecid	Increased ertapenem AUC 25%
Erythromycins (inhibit cytochrome P-450)	
Anticoagulants, oral	Increased hypoprothrombinemia

Carbamazepine	Increased carbamazepine toxicity
Cisapride (Propulsid)*	Ventricular arrhythmias—avoid
Corticosteroids	Increased methylprednisolone levels
Cyclosporine	Increased cyclosporine toxicity (nephrotoxicity)
Digoxin	Increased digitalis levels
Disopyramide*	Increased disopyramide levels—avoid
Ergot alkaloids	Increased ergot levels
Felodipine	Increased felodipine levels (Clin Pharmacol Ther 60:25, 1996)
Phenytoin	Possible decreased phenytoin levels
Quinidine	Increased quinidine levels with cardiac toxicity (Pharma-cotherapy 117:626, 1997)
Seldane*	Ventricular arrhythmias—avoid

Tacrolimus	Increased tacrolimus levels (Lancet 344:825, 1994)
Theophylline	Increased theophylline levels (Pharmacotherapy 17:827, 1997)
Triazolam	Increased triazolam toxicity
Valproate	Increased valproate levels (Ann Intern Med 116:877, 1992)
Ethionamide	
Cycloserine	Increased CNS toxicity
Isoniazid	Increased CNS toxicity
Famciclovir	
Cimetidine	Increased penciclovir levels
Digoxin	Increased digoxin levels
Probenecid	Increased penciclovir levels

Theophylline	Increased penciclovir levels
Fluconazole (inhibits cytochrome P-450)	
Alprazolam	Increased sedation
Atovaquone	Increased atovaquone levels
Benzodiazepines	Increased benzodiazepine levels
Caffeine	Possible caffeine toxicity
Cisapride (Propulsid)*	Ventricular arrhythmias—avoid
Clarithromycin	Increased clarithromycin levels
Contraceptive	Decreased contraceptive effect—three cases reported
Coumadin	Increased prothrombin time
Cyclosporine	Increased cyclosporine nephrotoxicity

Midazolam	Increased sedation
Nortriptyline	Increased sedation, cardiac arrythmias
Phenytoin	Increased phenytoin levels
Rifabutin*	Increased rifabutin levels with possible uveitis—avoid
Rifampin	Reduced fluconazole absorption
Saquinavir	Increased saquinavir levels
Seldane*	Ventricular arrhythmias—avoid
Sulfonylureas	Increased levels with hypoglycemia
Tacrolimus	Increased nephrotoxicity
Theophylline	Increased levels of theophylline
Triazolam	Increased sedation

Zidovudine	Increased levels of zidovudine (JID 169:1103, 1994)
Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, trovafloxacin, gatifloxacin, moxifloxacin, gemifloxacin, lomefloxacin)	
Antacids	Decreased fluoroquinolone absorption with Mg^{++}, Ca^{++}, or Al^{++} containing antacids or sucralfate; give antacid > 2 hr after fluoroquinolone
Anticoagulants, oral	Increased hypoprothrombinemia
Caffeine	Increased caffeine effect; significance?; not noted with ofloxacin, sparfloxacin, levofloxacin
Cyclosporine	Possible increased nephrotoxicity
Diazepam	Increased diazepam levels with ciprofloxacin (Eur J Clin Pharmacol 44:365, 1993)
Food	Decreased absorption of norfloxacin and ciprofloxacin: Take 1–2 hr before or after meal
Food (dairy products)	Decreased absorption

Foscarnet	Possible seizures with ciprofloxacin (Ann Pharmacother 28:869, 1994)
Iron	Decreased fluoroquinolone absorption—give quinolone >2 hr before or > 6 hr after iron
Nonsteroidal anti-inflammatory agents	Possible seizures and increased epileptogenic potential of theophylline, opiates, tricyclics, and neuroleptics
Pentoxifyline	Headaches with ciprofloxacin
Phenytoin	Possible decrease in phenytoin level
Probenecid	Increased fluoroquinolone levels
Theophylline	Increased theophylline toxicity—especially ciprofloxacin and enoxacin; not noted with ofloxacin, levofloxacin, or sparfloxacin
Zinc	Decreased fluoroquinoline absorption
Foscarnet	

Aminoglycosides	Increased renal toxicity
Amphotericin B	Increased renal toxicity
Pentamidine	Increased hypocalcemia
Ganciclovir	
AZT (Retrovir)	Increased leukopenia: Must monitor CBC and discon-tinue or give G-CSF
Imipenem	Increased frequency of seizures (?)
Myelosuppressing drugs: TMP-SMX, AZT, azathio-prine, pyrimethamine, flucytosine, interferon, doxorubicin, vinblastine, vincristine	Increased leukopenia
Probenecid	Increased ganciclovir levels
Griseofulvin	
Alcohol	Possibly potentiates effect of alcohol

Anticoagulant, oral	Decreased anticoagulant effect
Aspirin	Decreased aspirin effect
Contraceptive	Decreased contraceptive effect
Cyclosporine	Possible decreased cyclosporine effect
Food	Fat increases absorption
Phenobarbital	Decreased griseofulvin levels
Theophylline	Decreased theophylline effect
Imipenem	
Ganciclovir*	Increased frequency of seizures
Probenecid	Increased imipenem levels
Isoniazid	
Alcohol	Increased hepatitis; decreased INH effect in some

Antacids	Decreased INH with AI^{++} containing antacids
Anticoagulants, oral	Possible increased hypoprothrombinemia
Benzodiazepines	Increased effects of benzodiazepines
Carbamazepine*	Increased toxicity of both drugs (NEJM 307:1325, 1982) avoid
Cycloserine	Increased CNS toxicity, dizziness, drowsiness
Diazepam	Increased diazepam levels—reduce diazepam dose
Disulfiram*	Psychotic episodes, ataxia (Am J Psychol 125:1725, 1969)—avoid
Enflurane*	Possible nephrotoxicity—avoid
Ethionamide	Increased CNS toxicity
Food	Decreased absorption INH
Itraconazole	Decreased itraconazole levels

Ketoconazole*	Decreased ketoconazole levels—avoid
Phenytoin	Increased phenytoin toxicity
Rifampin, rifabutin	Possible increased hepatic toxicity
Theophylline	Increased theophylline levels
Tyramine (foods and fluids rich in tyramine)	Palpitations, sweating, urticaria, headache, vomiting, and hypertension with consumption of cheese, wine, some fish (rare reaction to monoamine-rich foods) (Lancet 2:671, 1985)
Vincristine	Increased neurotoxicity
Itraconazole (inhibits cytochrome P-450)	
Alprazolam*	Increased sedation—avoid
Antacids	Decreased itraconazole absorption
Astemizole*	Ventricular arrhythmias—avoid

Carbamazepine (Tegretol)	Decreased itraconazole levels
Cisapride*	Ventricular arrhythmias—avoid
Contraceptives	Decreased contraceptive effect
Coumadin	Increased hypoprothrombinemia
Cyclosporine	Increased cyclosporine levels with nephrotoxicity
ddI	Reduced itraconazole absorption
Digoxin	Increased digoxin levels
Felodipine	Increased felodipine with edema
Food	Increased itraconazole absorption: Give with meal
H_2 antagonists*, antacids*, omeprazole*	Decreased itraconazole absorption—avoid
Hypoglycemics, oral	Severe hypoglycemia

INH	Decreased itraconazole levels
Loratadine	Increased loratadine levels with cardiac arrhythmia
Lovastatin	Large increase in lovastatin levels with possible rhabdomyolysis (NEJM 333:664, 1995)
Midazolam*	Increased midazolam levels—avoid
Nifedipine	Increased nifedipine with edema
Phenobarbital	Decreased itraconazole levels
Phenytoin	Decreased itraconazole levels
Protease inhibitors	Increased level of saquinavir and indinavir
Rifampin, rifabutin	Decreased itraconazole levels (CID 18:266, 1994)
Seldane (terfenadine)*	Ventricular arrhythmias—avoid
Tacrolimus	Increased tacrolimus levels—monitor levels

Triazolam*	Increased triazolam effect—avoid
Sucralfate	Decreased itraconazole absorption
Sulfonylureas	Increased sulfonylurea with hypoglycemia
Ketoconazole (inhibits cytochrome P-450)	
Alcohol	Possible disulfiram-like reaction
Alprazolam	Increased alprazolam with increased sedation
Anticoagulants, oral	Increased hypoprothrombinemia
Astemizole*	Increased astemizole levels—avoid
Chlordiazepoxide	Increased chlordiazepoxide toxicity
Cisapride (Propulsid)*	Ventricular arrhythmias—avoid
Contraceptives	Decreased contraceptive effect
Corticosteroids	Increased methylprednisolone levels

Cyclosporine	Increased cyclosporine levels
ddI	Decreased ketoconazole level—give ≥2 hr apart
Food	Decreased absorption: take 1–2 hr before or after meal
H_2 antagonists, antacids, omeprazole	Decreased ketoconazole effect; use sucralfate or antacids given 2 hr before
Hypoglycemics, oral	Severe hypoglycemia
Indinavir	Increase indinavir levels 70%
Isoniazid*	Decreased ketoconazole levels (NEJM 311:1681, 1984)—avoid
Loratadine (Claritin)	Increased loratadine levels
Midazolam*	Increased midazolam levels—avoid
Phenobarbital	Reduced ketoconazole levels

Phenytoin	Altered metabolism of both drugs; increased phenytoin levels and decreased ketoconazole levels
Rifampin*, rifabutin*	Decreased levels of both drugs—avoid
Ritonavir	Increased ritonavir levels
Saquinavir	Increased saquinavir levels by 150% (often desired)
Seldane (terfenadine)*	Ventricular arrhythmias—avoid
Sucralfate	Possible decreased ketoconazole effect
Tacrolimus	Possible tacrolimus toxicity
Theophylline	Increased theophylline levels
Triazolam*	Increased triazolam toxicity—avoid
Linezolid	
Phenylpropanolamine	Risk of hypertension

Pseudoephedrine	Risk of hypertension
Tyramine > 100 mg/d	Risk of hypertension
Mebendazole	
Phenytoin and carbamazepine	Decreased mebendazole concentrations; clinically significant only for extraintestinal helminthic infections
Mefloquine	
Beta-adenergic blockers*	Increased risk of cardiac toxicity including cardiac arrest—avoid
Chloroquine	Increased risk of seizures
Halofantrine*	QT prolongation—avoid
Quinidine*	Increased risk of cardiac toxicity including cardiac arrest—avoid
Quinine*	Increased risk of cardiac toxicity including cardiac arrest—avoid

Meropenem	
probenecid*	Increases meropenem levels 40%—avoid
Metronidazole	
Alcohol	Disulfiram-like reaction (flushing, headache, nausea ± vomiting, and chest/abdominal pain)
Anticoagulants, oral	Increased hypoprothrombinemia
Barbiturates	Decreased metronidazole effect with phenobarbital
Cimetidine*	Possible increased metronidazole toxicity—avoid
Corticosteroids	Decreased metronidazole levels
Disulfiram*	Organic brain syndrome (NEJM 280:1482, 1969)—avoid
Fluorouracil	Transient neutropenia
Food	Food often reduces gastric irritation

Lithium	Lithium toxicity—monitor lithium levels (JAMA 257:3365, 1987)
Phenobarbital	Decreased metronidazole levels—double metronidazole dose if phenobarbital is essential (NEJM 305:529, 1983)
Miconazole	
Aminoglycosides	Possible decreased tobramycin levels
Anticoagulant, oral	Increased hypoprothrombinemia
Hypoglycemics	Severe hypoglycemia with sulfonylurea
Phenytoin	Increased phenytoin toxicity
Nalidixic acid	
Anticoagulants, oral	Increased hypoprothrombinemia
Nitrofurantoin	

Antacids	Possible decreased nitrofurantoin effect; give 6 hr apart
Food	Increases absorption
Probenecid	Decreased nitrofurantoin effect (for UTIs)
Nitazoxanide	None known
Oseltamivir	
probenecid	Increases levels of oseltamivir
Penicillins	
Allopurinol	Increased frequency of rash with ampicillin
Anticoagulants, oral	Decreased anticoagulant effect with nafcillin and dicloxacillin
Cephalosporins	Increased cefotaxime toxicity with mezlocillin + renal failure

Contraceptives	Possible decreased contraceptive effect with ampicillin or oxacillin
Cyclosporine	Decreased cyclosporine effect with nafcillin and increased cyclosporine toxicity with ticarcillin
Food	Decreased absorption of oral ampicillin, cloxacillin, oxacillin, dicloxacillin, and penicillin G
Lithium	Hypernatremia with ticarcillin
Methotrexate	Possible increased methotrexate toxicity
Probenecid	Increased concentrations of penicillins
Pentamidine	
Aminoglycosides	Increased nephrotoxicity
Amphotericin B	Increased nephrotoxicity
Capreomycin	Increased nephrotoxicity

Foscarnet	Increased nephrotoxicity
Piperazine	
chlorpromazine	Possibly induces seizures
Polymyxin or colistimethate	
Aminoglycoside	Increased nephrotoxicity; increased neuromuscular blockade
Neuromuscular blocking agents	Increased neuromuscular blockade
Vancomycin	Increased nephrotoxicity
Pyrazinamide	
allopurinol*	Failure to decrease hyperuricemia—avoid
Pyrimethamine	
Antacids	Possible decreased pyrimethamine absorption

Dapsone*	Agranulocytosis reported
Kaolin	Possible decreased pyrimethamine absorption
Phenothiazines	Possible chlorpromazine toxicity
Quinolones (see fluoroquinolones)	
Quinupristin-dalfopristin (inhibits cytochrome P-450 3A4) (Synercid)	
Cyclosporine	Increased cyclosporine levels—63% (monitor cyclosporine levels)
Midazolam	Increased midazolam levels—33%
Nifedipine	Increased nifedipine levels
Terfenadine	Increased terfenadine levels—44%
(other drugs metabolized by cytochrome P-450 3A4: Astemizole, diazepam, verapamil, diltiazem, lovastatin, cisapride, protease inhibitors, carbamazepine quinidine)	
Ribavirin	

ddI*	Increased intracellular ddI with risk of pancreatitis, neuropathty, or lactic acidosis—avoid
AZT, 3TC, ABC	Possible in vitro antagonism; significance not known
Rifabutin: Presumed to be identical to rifampin except for clarithromycin and fluconazole, both of which increase rifabutin levels and increase risk of uveitis. Effect on cytochrome P-450 is somewhat less than rifampin. Rifabutin should not be given concurrently with saquinavir; dose with indinavir should be reduced by 50%	
Rifampin (induces cytochrome P-450)	
Aminosalicylic acid (PAS)	Decreased effectiveness of rifampin; give in separate doses by 8–12 hr
Amprenavir	Reduced amprenavir levels
Anticoagulants	Decreased hypoprothrombinemia
Atovaquone	Decreased atovaquone levels
Barbiturates	Decreased barbiturate levels
Beta-adrenergic blockers	Decreased beta-blocker levels

Chloramphenicol	Decreased chloramphenicol levels
Clofazimine	Reduced rifampin levels
Clofibrate	Decreased clofibrate levels
Contraceptives	Decreased contraceptive levels (JAMA 227:608, 1974)
Corticosteroids	Decreased corticosteroid levels (Arch Intern Med 154:1521, 1994); if used together—increase corti-costeroid dose
Cyclosporine*	Decreased cyclosporine levels
Dapsone	Decreased dapsone effect (not significant with treatment of leprosy)
Delavirdine	Reduced delavirdine levels
Diazepam	Decreased diazepam levels
Digitalis	Decreased digitalis levels

Disopyramide*	Decreased disopyramide levels
Doxycycline	Decreased doxycycline levels
Efavirenz	Efavirenz can be used with rifampin in standard doses for both drugs
Estrogens	Decreased estrogen effect—use alternative method of birth control
Fluconazole	Decreased fluconazole levels
Food	Decreased absorption
Haloperidol	Decreased haloperidol levels
Hypoglycemics	Decreased hypoglycemic effect of sulfonylurea
Isoniazid	Increased hepatotoxicity
Ketoconazole*	Decreased effect of ketoconazole and rifampin—avoid

Methadone	Methadone withdrawal symptoms
Mexiletine	Decreased antiarrhythmic levels
Nevirapine*	Combination not recommended
Nifedipine	Decreased antihypertensive effect
Nisoldipine	Decreased nisoldipine antihypersensitive effect
Phenytoin	Decreased phenytoin levels
Progestins	Decreased norethindrone levels
Protease inhibitors	Ritonavir and ritonavir + saquinavir can be used with standard doses; other protease inhibitors should be avoided
Quinidine	Decreased quinidine levels
Theophyllines	Decreased theophylline levels
Triazolam	Decreased triazolam levels (Br J Clin Pharmacol

	42:249, 1997)
Trimethoprim	Decreased trimethoprim levels
Trimetrexate	Decreased trimetrexate levels
Verapamil	Decreased verapamil levels
Sulfonamides	
Anticoagulants, oral	Increased hypoprothrombinemia
Barbiturates	Increased thiopental levels
Digoxin	Decreased digoxin levels with sulfasalazine
Food	Decreased absorption
Hypoglycemics	Increased hypoglycemic effect of sulfonylurea
Methotrexate	Possible increased methotrexate toxicity
Monoamine oxidase inhibitors	Possible increased phenelzine toxicity with

	sulfisoxazole
Phenytoin	Increased phenytoin levels except with sulfisoxazole
Telithromycin	
Cisapride	Prolonged QTc interval—Avoid
Digoxin	Increased digoxin levels
Itraconazole	Increased telithromycin levels
Ketoconazole	Increased telithromycin levels
Metoprolol	Increased AUC of metoprolol
Midazolam	Increased midazolam levels, monitor and adjust dose if necessary
Pimozide	Prolonged QTc interval—Avoid
Rifampin	Decreased AUC of telithromycin

Simvastatin	Increased simvastatin levels with risk of myopathy
Sotalol	Decreased AUC of sotalol
Theophylline	Increased GI intolerance
Tetracyclines	
Alcohol	Decreased doxycycline effect in alcoholics
Antacids*	Decreased tetracycline effect with antacids containing Ca^{++}, Al^{++}, Mg^{++}, and $NaHCO_3$ (give 3 hr apart)
Anticoagulants, oral	Increased hypoprothrombinemia
Antidepressants, tricyclic*	Localized hemosiderosis with amitriptyline
Antidiarrheal agents	Agents containing kaolin and pectin or bismuth subsalicylate decrease tetracycline effect
Barbiturates*	Decreased doxycycline effect (Br Med J 2:470, 1974)—avoid

Bismuth subsalicylate, Pepto-Bismol	Decreased tetracycline effect
Carbamazepine (Tegretol)*	Decreased doxycycline effect—avoid
Contraceptives, oral*	Decreased contraceptive effect—avoid
Digoxin	Increased digoxin level (10% of population)
Food (dairy products)	Decreased absorption (except doxycycline)
Iron, oral	Decreased tetracycline effect (except with doxycycline) and decreased iron effect; give 3 hr before
Laxatives	Agents containing Mg^{++} decrease tetracycline effect
Lithium	Increased lithium toxicity—monitor levels (J Clin Psychopharmacol 17:59, 1997)
Methotrexate	Possible increased methotrexate toxicity
Methoxyflurane anesthesia, Penthrane	Possibly lethal nephrotoxicity

Milk*	Decreased absorption of tetracycline. Does not apply to doxycycline or minocycline
Molindone	Decreased tetracycline levels
Phenformin*	Decreased doxycycline levels—avoid
Phenytoin	Decreased doxycycline levels
Rifampin	Possible decreased doxycycline levels
Theophylline	Possible increased theophylline toxicity
Zinc*	Decreased tetracycline levels—avoid
Thiabendazole	
Theophyllines	Increased theophylline toxicity
Trimethoprim	
Amantadine	Increased levels of both drugs

Azathioprine	Leukopenia
Contraceptives	Decreased contraceptive effect—two case reports (Br J Clin Pharmacol 25:527, 1988)
Cyclosporine*	Increased nephrotoxicity—avoid
Dapsone	Increased levels of both drugs; increased methemoglobinemia
Digoxin	Possible increased digitalis levels
Phenytoin	Increased phenytoin levels
Rifampin	Decreased trimethroprim levels
Thiazide diuretics	Possible increased hyponatremia with concomitant use of amiloride with thiazide diuretics
Trimethoprim-sulfamethoxazole	See trimethoprim
Amantadine	Amantadine toxicity with delirium (Am J Med Sci 298:410, 1992)

Anticoagulants, oral	Increased hypoprothrombinemia
Atovaquone	Slight decrease in TMP-SMX levels
Contraceptives	Decreased contraceptive effect—five case reports (Br J Clin Pharmacol 25:527, 1988)
Mercaptopurine*	Decreased mercaptopurine activity—avoid
Methotrexate*	Megaloblastic anemia
Paromomycin	Increased nephrotoxicity
Phenytoin	Increased phenytoin toxicity
Procainamide	Increased procainamide levels
Tricyclic antidepressants	Recurrence of depression Possible imipramine toxicity Desipramine toxicity
Trimetrexate	

Acetaminophen	Increased trimetrexate levels
AZT	Increased bone marrow suppression
Cimetidine	Increased trimetrexate levels
Erythromycin	Increased trimetrexate levels
Fluconazole	Increased trimetrexate levels
Ketoconazole	Increased trimetrexate levels
Rifampin, rifabutin	Decreased trimetrexate levels
Valacyclovir	
Cimetidine	Increased acyclovir levels
Probenecid	Increased acyclovir levels
Valganciclovir	
Myelosuppressive drugs	Increased risk of anemia, neutropenia, and

	thrombo-cytopenia
Probenecid	Increased ganciclovir levels
Vancomycin	
Aminoglycosides	Increased nephrotoxicity and possible increased ototoxicity
Amphotericin B	Increased nephrotoxicity
Cisplatin	Increased nephrotoxicity
Digoxin	Possible decreased digoxin effect
Neuromuscular blocking agents	Increased succinylcholine and vecuronium effect
Paromomycin	Increased nephrotoxicity
Polymyxin	Increased nephrotoxicity
Voriconazole (Drugs that induce cytochrome P-450 enzymatic activity reduce voriconazole activity; drugs that inhibit cytochrome P-450 increase toxicity. Voriconazole inhibits cytochrome	

P-450 enzymes)	
Astemizole*	Risk ventricular arrhythmia—avoid
Barbiturates	Increase barbiturate levels—avoid long acting barbiturates
Benzodiazepines	Anticipated prolonged sedative effect—avoid midazolam, triazolam, and alprazolam
Calcium channel blockers	May increase calcium channel blocker level—monitor for toxicity
Cisapride*	Risk ventricular arrhythmias—avoid
Cyclosporine	Risk nephrotoxicity—use half cyclosporine dose and monitor levels
Ergot	Risk ergotism
Pimozide*	Risk ventricular arrhythmias—avoid
Quinidine*	Risk ventricular arrhythmias—avoid

Rifampin*	Reduce voriconazole levels—avoid
Rifabutin*	Reduce voriconazole levels—avoid
Sirolimus	Risk sirolimus toxicity—avoid
Statins	Anticipated increase in statin levels—consider lower statin dose
Tacrolimus	Increase tacrolimus levels—reduce dose to 1/3 and monitor
Warfarin	Increase prothrombin time 2×—monitor prothrombin time

* Concurrent use should be avoided if possible.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Adult Immunization Schedule

A. **ADULT IMMUNIZATION SCHEDULE**

MMWR 2002;51;RR-2:1–36.

Vaccine	***19–49 yrs***	***50–64 yrs***	***>65 yrs***
Tetanus, diphtheria	Booster dose every 10 yrs		
Influenza	Medical, occupational, or household contact indication	Annual dose	
Pneumovax	Medical indication		1 dose or revaccination at 5 yrs
Measles, rubella, Mumps	1 dose if hx unreliable		
Varicella	2 doses (0 and 4–8 wks) if susceptible		
Hepatitis A	2 doses (0, 6–12 mo) for indications		
Hepatitis B	3 doses (0, 4, and 6 mo) for indications		

Note: The only true contraindications to vaccinations are a history of severe allergic reaction after a prior dose or a vaccine constituent. Severely immunocompromised persons should not receive live virus vaccines. (MMWR 2002;51 RR-2:8)
Common mistakes which are not contraindications

1. Mild illness ± fever
2. Local reaction ± fever with prior vaccination
3. Current antimicrobial therapy

4. Convalescent phase of illness
5. Fever <40.5°C

B. **VACCINES AVAILABLE IN UNITED STATES**

MMWR 2002;51(RR-2).

Vaccine	***Type and indications (adults)***	***Route and usual regimen[a]***
BCG (bacillus of Calmette-Guérin)	Live bacteria. No longer advocated	Percutaneous or 0.2–0.3 mL
Cholera	Inactivated bacteria. Not recommended by WHO, but sometimes required for international travel	0.5 mL SC × 2 >1 wk apart or intradermal 0.2 mL × 2
DT (diphtheria, tetanus)	Toxoids. Booster dose recommended q10yr	0.5 mL SC
DTP (diphtheria, tetanus, pertussis eIPV (inactivated polio-virus vaccine)	Toxoids and inactivated bacteria; Td or DT preferred for adults Enhanced inactivated viruses of all three serotypes. Travel to epidemic areas and immunocompromised patient or household contact Note: Polio is eradicated in Western hemisphere	0.5 mL IM 0.5 mL SC × 1
Haemophilus influenzae B conjugate (HbCV)	Polysaccharide conjugated to protein. Adult at risk—splenectomy	0.5 mL IM × 1
HB (hepatitis B)	Inactive viral antigen (surface antigen). Increased risk: Public safety workers exposed to blood; health care workers; injection drug users; gay men; household/ sex contacts with HBsAg pos; recent STD; renal disease; multiple sex partners	1.0 mL IM × 3 at 0, 1, and 6 mo
Hepatitis A	Inactivated virus with 1440 ELISA units/mL Travel to or work in endemic areas; gay men; injection drug	1 mL IM (deltoid mm) + booster dose at 6–12 mo

	users; chronic liver disease; HCV infection; persons with occupational risk (lab workers who handle HAV)	
Hepatitis A and B (Twinrix)	Bivalent vaccine with 720 ELISA units HAV Ag (Havrix) and 20 mcg HBsAg (Energix-B). Indications for HAV and HBV vaccine including travelers who can receive two doses before travel	1 mL IM at 0, 1, and 6 mo
Influenza	Inactivated virus or viral components. High risk, age >65, chronic disease; health care workers; pregnant women who will be in second or third trimester during flu season	0.5 mL IM × 1 annually
Japanese B encephalitis	Inactivated JE virus. Travel >1 mo in epidemic area	1 mL SC at days 0, 7, and 30
Measles	Live virus. Unvaccinated adults born after 1956 without measles; unless pos serology or documented vaccination—highest priority are women of childbearing potential, health care workers, international. travelers	0.5 mL SC × 1 with second >1 mo after first
Meningococcal vaccine	Bacterial polysaccharides of serotypes A/C/Y/W-135. Outbreaks of *N. meningitidis* serotype C disease; offer to college freshman in dormatories. Travel to epidemic area	0.5 mL SC × 1
MMR (M, measles; M, mumps; r, rubella)	Live viruses. Usual form for persons susceptible to two of these viruses No link to autism found by IOM (BMJ 2001;322:1083)	0.5 mL SC × 1 or 2 with >1 mo after first
Mumps	Live virus. Unvaccinated adults born after 1956 without mumps	0.5 mL SC × 1
OPV (oral poliovirus vaccine)	Live viruses of all three sero-types. All-IPV schedule recommended in U.S. at 2, 4, 6–18 mos, 4–6 y per CDC-2000	po × 1
Pertussis	Inactivated whole bacteria	IM—Distributed by Biologic Products Program, Michigan Department of Public Health (phone: 517-335-8120)

	Live attenuated strain (Ty21a). Travelers to epidemic area	po × 4 qod, boosters at 5-yr intervals
	Typhim Vi capsular polysaccharide vaccine. Travelers to epidemic areas	0.5 mL IM × 1
Varicella	Live attenuated virus Susceptible adults (negative history of chickenpox ± negative serology) and risk category: Health care workers, household contacts of immunosuppressed patient, persons living or working in high-risk area (schools, day care centers), nonpregnant women of childbearing age, or international travelers	Adults: 0.5 mL SC × 2 separated by 4–8 wk
Yellow fever (17 D strain)	Live virus. Travel to epidemic areas	0.5 mL SC × 1

[a] *Assumes childhood immunizations have been completed*

[b] *Dt, tetanus and diphtheria toxoids for use in children aged <7 yr. Td, tetanus and diphtheria toxoids for use in persons aged ≥7 yr. Td contains the same amount of tetanus toxoid as DPT or DT but a reduced dose of diphtheria toxoid.*

C. **RECOMMENDATIONS BY RISK CATEGORY**

Adapted from Guide for Adult Immunization, American College of Physicians, 3rd Edition, Philadelphia 1994:1–218; MMWR 2002;51(RR-2).

Category/vaccine	***Comments***
AGE	
18–24 yr	
Td[a] (0.5 mL IM)	Booster every 10 yr at mid-decades (age 25, 35, 45, etc) or single dose at midlife (age 50) for those who completed primary series

Measles[b] (MMR, 0.5 mL SC × 1 or 2)	Post-high school institutions should require two doses of live measles vaccine (separated by 1 mo); first dose preferably given before entry
Rubella[c] (MMR, 0.5 mL SC × 1)	Especially susceptible females; pregnancy now or within 3 mo postvaccination is contraindication to vaccination
Influenza	Advocated for young adults at increased risk of exposure (military recruits, students in dorms, etc)
Meningococcus 0.5 mL SC × 1	Military—new recruits Offer to college students—especially freshmen who live in close quarters (JAMA 2001;286:720; CID 2002;35:1376)
25–64 yr	
Td[a]	Booster every 10 yr
Influenza	Optional
Mumps[c]	As above
Measles[b] (MMR, 0.5 mL SC × 1)	Persons born after 1957—need positive serology or proof of vaccination
Rubella[c] (MMR, 0.5 mL SC × 1)	Principally females ≤45 yr of childbearing potential; pregnancy now or within 3 mo after vaccination is contraindication to vaccination
> 65 yr	
Td[a]	Booster every 10 yr
Influenza (0.5 mL IM)	Annually, usually in October–November

Pneumococcal (23 valent, 0.5 mL IM or SC)	Single dose; efficacy for elderly established for preventing invasive pneumococcal infection (bacteremia and meningitis, but not for preventing pneumonia (NEJM 2003;348:1737; NEJM 2003;348:1747)
PREGNANCY	All pregnant women should be screened for hepatitis B surface antigen (HBsAg) and rubella antibody Live virus vaccines[d] should be avoided unless specifically indicated. It is preferable to delay vaccines and toxoids until 2nd or 3rd trimester. Immune globulins are safe; most vaccines are a theoretical risk only
Td[a] (0.5 mL IM)	If not previously vaccinated—dose at 0, 4 wk (preferably second and third trimesters) and 6–12 mo; protection to infant is conferred by placental transfer of maternal antibody
Measles	Risk for premature labor and spontaneous abortion; exposed pregnant women who are susceptible[b] should receive immune globulin within 6 days and then MMR post-delivery at least 3 mo after immune globulin (MMR is contraindicated during pregnancy)
Mumps	No sequelae noted; immune globulin is of no value, and MMR is contraindicated
Rubella	Rubella during first 16 wk carries great risk, e.g., 15–20% rate of neonatal death and 20–50% incidence of congenital rubella syndrome; history of rubella is unreliable indicator of immunity. Women exposed during first 20 wk should have rubella serology and if not immune should be offered abortion. Inadvertent vaccine administration to 300 pregnant women showed no vaccine-associated malformations
Hepatitis A	Immune globulin preferably within 1 wk of exposure
Hepatitis B	All pregnant women should have prenatal screening for HBsAg; newborn infants of HBsAg carriers should receive HBIG and HBV vaccine; pregnant women who are HBsAg negative and at high risk should receive HBV vaccine
Inactivated polio vaccine (0.5 mL po)	Advised if exposure is imminent in women who completed the primary series more than 10 yr ago. Unimmunized women should receive two doses separated by 1–2 mo; unimmunized women at high risk who need immediate protection should receive oral live polio vaccine

Influenza	
Pneumococcal vaccine	Not routinely recommended, but can be given if there are other indications
Varicella (VZIG, 125 units/10 kg IM; maximum 625 units)	Varicella-zoster immune globulin (VZIG) may prevent or modify maternal infection
FAMILY MEMBER EXPOSURE	Recommendations apply to household contacts
H. influenzae type B	*H. influenzae* meningitis: Rifampin prophylaxis for all household contacts in households with another child <4 yr; contraindicated in pregnant women
Hepatitis A Hepatitis B	Immune globulin within 2 wk of exposure HBV vaccine (three doses) plus HBV immune globulin for those with intimate contact and no serologic evidence of prior infection
Influenza A and B	With exposure to influenza A unimmunized high-risk family members should receive prophylactic amantadine, rimantadine, or oseltamivir (×14 days) and vaccine; prevention of influenza B requires oseltamavir or zanamivir
Meningococcal infection	Rifampin, ciprofloxacin, or ceftriaxone for close contacts of meningococcal meningitis
Varicella-zoster	No treatment unless immunocompromised or pregnant: consider VZIG
RESIDENTS OF NURSING HOMES	
Influenza (0.5 mL IM)	Annually for staff and residents; vaccination rates of 80% required to prevent outbreaks; for influenza A outbreaks consider prophylaxis with amantadine or rimantadine
Pneumococcal (23 valent, 0.5 mL IM)	Single dose, efficacy not clearly established in this population

Td[a] (0.5 mL IM)	Booster dose at mid-decades
RESIDENTS OF INSTITUTIONS FOR MENTALLY RETARDED	
Hepatitis B	Screen all new admissions and long-term residents: HBV vaccine for susceptible residents (seroprevalence rates are 30–80%)
PRISON INMATES	
Hepatitis B	As above
HOMELESS	
Td[a]	Most will need primary series or booster
Measles, rubella, mumps	MMR 0.5 mL SC (young adults)
Influenza	Annual
Pneumococcal vaccine (0.5 mL IM)	Give × 1
HEALTH CARE WORKERS	
Hepatitis B (1.0 mL IM × 3)	Personnel in contact with blood or blood products; serologic screening with vaccination only of seronegatives is optional; serologic studies show 5% are non-responders (negative for anti-HBs) even with repeat vaccinations
Influenza (0.5 mL IM)	Annual usually in October–November
Rubella (MMR, 0.5 mL SC)	Personnel who might transmit rubella to pregnant patients or other health care workers should have documented immunity or vaccination

Mumps (MMR, 0.5 mL SC)	Personnel with no documented history of mumps or vaccine should be vaccinated
Measles (MMR, 0.5 mL SC)	Personnel who do not have immunity[b] should be vaccinated; those vaccinated in or after 1957 should receive an additional dose, and those who are unvaccinated should receive two doses separated by at least 1 mo; during outbreak in medical setting vaccinate (or revaccinate) all health care workers with direct patient contact
Polio	Persons with incomplete primary series should receive inactivated polio vaccine
Varicella	Personnel with negative history of chickenpox and/or negative serology (5–10% of adults have negative serology)
IMMIGRANTS AND REFUGEES	
Td[a]	Immunize if not previously done
Rubella, measles, mumps (MMR 0.5 mL SC)	Most have been vaccinated or had these conditions, athough MMR is advocated except for pregnant women
Polio	Adults will usually be immune
Hepatitis B	Screen for HBsAg and vaccinate susceptible family members and sexual partners of carriers; screening is especially important for pregnant women
HOMOSEXUAL MEN	
Hepatitis B Hepatitis A	Prevaccination serologic screening advocated because 30–80% have serologic evidence of HBV markers
IV DRUG ABUSERS	
Hepatitis B Hepatitis A	As above; seroprevalence rates of HBV markers are 50–80%

IMMUNODEFICIENCY	
HIV infection	
Measles	Vaccine is contraindicated. Postexposure prophylaxis with immune globulin for AIDS patients with CD4 count <200/mm^3: Immune globulin—0.5 mL/kg IM (15 mL maximum)
Pneumococcal vaccine (0.5 mL SC)	Recommended for patients with CD4 count > 200/mm^3. Revaccination at 5 yr
Influenza (0.5 mL IM)	Annual
Hepatitis A	All with HCV co-infection (if seronegative)
Hepatitis B	All who have negative screening anti-HBc
Asplenia	
Pneumococcal vaccine (0.5 mL IM)	Recommended, preferably given 2 wk before elective splenectomy; revaccinate those who received the 14 valent vaccine and those vaccinated >6 yr previously
Meningococcal vaccine (0.5 mL SC)	Indicated
H. influenzae B conjugate (0.5 mL IM)	Consider
Renal failure	
Hepatitis B (1.0 mL IM × 3)	For patients whose renal disease is likely to result in dialysis or transplantation; double dose and periodic boosters advocated
Pneumococcal vaccine (0.5 mL SC)	Give × 1

Influenza (0.5 mL IM)	Annual
Bone marrow transplant recipients	At 12 mo post-transplant: Revaccinate with inactivated vaccines including Td, hepatitis B, eIVP, *H. influenza* type B, Pneumovax, and influenza; at ≥ 24 mo—MMR if not immunosuppressed and no graft-vs-host disease (see Vaccine Adults, CDC 3:1).
Alcoholics	
Pneumococcal vaccine (0.5 mL SC)	Give × 1
DIABETES AND OTHER HIGH-RISK DISEASES	
Influenza (0.5 mL IM)	Annually from October to December
Pneumococcal vaccine (0.5 mL SC)	Give × 1
TRAVEL[a] (recommendations of Med Lett 1999;41:39; CDC Health Information for International Travel 1999–2000)	For travelers to developed countries (Canada, Europe, Japan, Australia, New Zealand) the risk of developing vaccine-preventable disease is no greater than for those traveling in the U.S. Each country has its own vaccine requirements Smallpox vaccination is no longer required and should not be given
Yellow fever (0.5 mL SC) (see MMWR 1990; 39(RR6))	Recommended and usually required for endemic area: Tropical South America and most of Africa between 15° North and 15° South. Give 10 days before travel; booster every 10 yr Available only at sites designated by local or state health departments Some African countries require certification of vaccination by all incoming travelers; some countries in Africa, South America, or Asia require certification of vaccination by travelers traveling from or through endemic areas Contraindications: Age <4 mo and hypersensitivity to eggs. Relative contraindications are pregnancy, age 4–9 months and immunosuppression (HIV, leukemia, lymphoma, generalized malignancy, cancer chemotherapy, chronic steroid use) ACIP reported 7 cases of multiple organ failure in recipients of 17D derived yellow fever vaccine; all became ill within 2–5 days of vaccination and six died (MMWR 2001;50:643)

	(http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm).
Cholera	Not recommended because risk is low and vaccine has limited effectiveness (Lancet 1990;1:270)
Typhoid fever	Recommended for travel to rural areas of countries where typhoid fever is endemic or any area of an outbreak, primarily travelers outside the usual tourist routes in Latin America, Asia, and Africa Live oral vaccine—Vivotif (1 cap every other day × 4 starting at least 2 wk before travel)—is preferred over the parenteral killed bacterial vaccine because of comparable efficacy, longer protection, and better tolerance (Lancet 1990;336:891); available from Berna Prod (800-533-5899). New polysaccharide vaccine (Typhim Vi, Connaught 800-822-2463) is also effective and requires only one IM dose (J Infect Dis 1992;25:63; MMWR 1994;43(RR-14); Clin Infect Dis 1995;4:186)
Hepatitis A	Susceptibility may be determined with tests for IgG antibody that are widely available (Lancet 1988;1:1447) Vaccine (Havrix, SmithKline Beecham; VAQTA, Merck) is recommended for travel outside U.S., Canada, Western Europe, Japan, Australia, or New Zealand. Protective. Consult CDC advisory (NEJM 1992;327:453; JAMA 1994;271:1328; Ann Intern Med 1996;124:35) Protective levels of antibody are usually achieved 2–4 wk after a single dose. A booster is recommended at 6–12 mo, but a single dose is considered adequate protection if given at least 2–4 wk before travel. Twinrix requires two doses separated by 1 month prior to travel, otherwise the monovalent vaccine is preferred. Alternative is immune globulin (0.02 mL/kg IM) available from 800-843-7477. This has established efficacy and is sometimes required for patients who need immediate protection
Hepatitis B (1 mL IM × 3)	HBV vaccine if travel to endemic areas, and there is risk of need for medical or dental care, travel >6 mo, sexual contact with local persons is likely, or if contact with blood is likely. Major risk areas are China, Korea, all of Africa, Middle East, Southern and Pacific Islands, Amazon region of South America, Haiti, Dominican Republic, and Southeast Asia (Med Letter 2001;43:67). (All of these are high risk areas for HAV as well) Accelerated schedule is dosing at 0, 1, and 2 mo with a fourth dose at 12 mo Twinrix is available for patients at risk for HAV and HBV
Rabies	Consider human diploid cell rabies vaccine (HDCV), rabies vaccine absorbed (RVA), or purified chick embryo cell vaccine (PCEC) for travelers with occupational risk and those with extended travel to endemic area

Japanese encephalitis (JE-Vax, 1 mL SC × 3 in 2–4 wk)	Vaccine recommended endemic areas with stays of >1 mo in rural rice-growing areas with extensive exposure to mosquitoes. Potential problem countries include Bangladesh, Cambodia, Indonesia, Laos, Malasia, Myanmar (Burma), Pakistan, China, Korea, Taiwan, Thailand, Singapore, eastern Russia, Vietnam, India, Nepal, Sri Lanka, and the Philippines (NEJM 1988;319:641) JE Vax is Formalin-inactivated, purified, mouse-brain-derived vaccine that causes urticaria, angioedema, or other serious reactions in 0.5% of recipients (MMWR 1993;42(RR-1):12) Attack rate is low: <10 cases in U.S. travelers over 1985–95
Influenza	Indicated for persons at risk traveling to Southern Hemisphere April–September or at any time of year for travelers to tropics or travelers in large tourist groups including cruise ships Need vaccination ≥ 2 wk before travel
Measles (MMR 0.5 mL SC × 1)	Susceptible persons[b] should receive a single dose before travel
Meningococcal vaccine with serogroups A, C, Y, and W 135 (0.5 mL SC × 1)	Recommended for travel to areas of epidemics, most frequently sub-Saharan Africa (December–June) Saudi Arabia requires certificate of vaccination for pilgrims to Mecca or Medina Vaccine is single dose and provides protection for 3 yr
Polio	Travelers to developing countries outside the Western Hemishere should receive a primary series and inactivated polio vaccine if not previously immunized If protection is needed within 4 wk, single dose eIPV or trivalent (live) OPV recommended. Previously immunized travelers should receive one booster of OPV or eIPV

[a] Diphtheria and tetanus toxoids adsorbed (for adult use). Primary series is 0.5 mL IM at 0, 4 wk and 6–12 mo; booster doses at 10-yr intervals are single doses of 0.5 mL IM. Adults who have not received at least three doses of Td should complete primary series. Persons with unknown histories should receive series.

[b] Persons are considered immune to measles if there is documentation of receipt of two doses of live measles vaccine after first birthday, prior physician diagnosis of measles, laboratory evidence of measles immunity, or birth before 1957.

[c] Persons are considered immune to mumps if they have a record of adequate vaccination, documented physician diagnosed disease, or laboratory evidence of immunity. Persons are considered immune to rubella if they have a record of vaccination after their first birthday or laboratory evidence of immunity. (A physician diagnosis of rubella is considered nonspecific.)

[d] Live virus vaccines: measles, rubella, yellow fever, oral polio vaccine.

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D. SPECIFIC VACCINES

1. INFLUENZA VACCINE

Recommendations of Advisory Committee on Immunization (MMWR 2003;52:RR-8.).

Preparations: Inactivated egg-grown viruses that may be split (chemically treated to reduce febrile reactions in children) or whole. The 2003–04 trivalent vaccine contains A/Moscow/10/99 (H3H2), A/New Caledonia/20/90 (H1N1) and B/Hong Kong/330/2001. Product information available from Connaught 800-822-2463 and, Parke Davis 800-543-2111.

Flu mist: This is the first nasally administered vaccine in the U.S. It consists of live viruses including two strains of influenza A and one strain of influenza B. This was FDA approved in June 2003 for use in persons

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5–49 years; a single dose is advocated for persons 9–49 years, persons >50, those with medical conditions that constitute indications for the vaccine, and persons with immunosuppression should use standard influenza vaccine since FluMist is a live virus vaccine and has not been tested in high risk populations. The cost is $46/dose.

Administration (older than 12 yr): Whole or split virus vaccine, 0.5 mL × 1 IM in the deltoid muscle, preferably mid-October to mid-November. Recommendations for the 2003–04 season are for preferential immunization of high risk persons in October to assure an adequate supply for this group. This includes: Age >50 years, children 6–23 mo., persons 2–49 years with medical indications, healthcare workers and household contacts of high risk persons. The needle should be ≥1 inch. Protection begins 2 wk post-vaccination and may last 6 mo, but antibody titers may fall below protective levels within 4 mo in elderly patients.

Effectiveness: At least 70–90% effective in preventing influenza in healthy persons (MMWR 1993;42(RR-5):1., Drugs 1997;54:841.) when there is a good match between the vaccine antigens and the prevalent strain(s) of influenza. This has been achieved in 12 of the last 13 seasons. In elderly nursing home residents, the vaccine is 30–40% effective in preventing influenza and up to 80% effective in preventing influenza-related mortality (JAMA 1985;251:1136.). Population-based studies show influenza vaccinations of persons >65 years are associated with a 20–30% reduction in hospitalization for heart disease and pneumonia and a 50% reduction in all-cause mortality (NEJM 2003;348:1322.).

Target Group for Influenza Vaccine

Note: This list defines the two categories that should have the highest priority for initial vaccination in the event that supplies are limited.

Groups at increased risk for influenza-related complications

1. Persons > 50 yrs
2. Residents of nursing homes and other chronic care facilities housing persons of any age with chronic medical conditions
3. Persons with chronic disorders of the pulmonary or cardiovascular system, including those with asthma
4. Adults and children who required regular medical follow-up or hospitalization during the prior year due to chronic metabolic diseases (diabetes), renal dysfunction, hemoglobinopathies, or immunosuppression (including HIV infection)
5. Children and teenagers who are receiving long-term aspirin therapy (risk of Reye's syndrome)

6. Women who will be in the second or third trimester of pregnancy during influenza season
7. Elderly and other high-risk persons embarking on international travel: Tropics—all year; Southern Hemisphere—April–September

Groups that can transmit influenza to high-risk patients

1. Physicians, nurses, and other personnel who have contact with high-risk patients
2. Employees of nursing homes and chronic care facilities who have contact with patients or residents
3. Employees of assisted living and other residences for persons at high risk
4. Providers of home care to high-risk persons
5. Household family members of high-risk persons

Contraindications

1. Severe allergy to eggs
2. Persons with acute febrile illness (delay until symptoms abate); persons with minor illnesses such as URIs may be vaccinated
3. Pregnancy: There has been no significant excess in the influenza-associated mortality among pregnant women since the 1957–58 pandemic (Am J Obstet Gynecol 1959;78:1172.). Influenza vaccine is not routinely recommended, but pregnancy is not viewed as a contraindication in women with other high-risk conditions. A study of more than 2000 pregnant women who received influenza vaccine showed no adverse fetal effects (Int J Epidemiol 1973;2:229.). Some experts prefer to vaccinate in the second trimester to avoid a coincidental association with spontaneous abortions unless the first trimester corresponds to the influenza season

Adverse Reactions for Influenza Vaccine

1. Soreness at the vaccination site for up to 2 days in about one-third
2. Fever, malaise, etc—infrequent and most common in those not previously exposed to influenza antigens, e.g., young children. Reactions begin 6–12 hr postvaccination and persist 1–2 days
3. Allergic reactions—rare and include hives, angioedema, asthma, anaphylaxis; usually allergy to egg protein
4. Guillain-Barré syndrome: 1976–77 influenza vaccine was associated with a statistically significant risk of Guillain-Barré syndrome. A review of the influenza vaccine for 1992–93 and 1993–94 showed the odds ratio for Guillain-Barré with vaccination was 1.8; this represents a risk of 1–2 cases/1 million persons vaccinated (MMWR 1998;47(RR–6).; NEJM 1998;339:1797.)

2. **MEASLES PREVENTION**

Revised recommendations of the Advisory Committee on Immunization Practices (MMWR 1991;40(RR-12):20–21.)

Category	*Recommendations*
Routine childhood schedule	Two doses[a]: first at 12 mo (high-risk area) or 15 mo (most areas); second dose at 4–6 yr

Adults	Single dose unless documentation of at least one dose of live measles vaccine ≥1 yr[b] or other evidence of immunity[c]
Colleges and other educational institutions	Two doses[a] unless documentation of receipt of two doses[b] live measles vaccine at ≥1 yr or other evidence of immunity[c]
Medical personnel beginning employment	Two doses[a] for all persons who do not have proof of two doses[b] live measles vaccine at ≥1 yr or other evidence of immunity[c]
Outbreaks in institutions or medical facilities	Two doses[a] for all persons born after 1956 who do not have proof of two doses[b] live measles vaccine at ≥1yr or other evidence of immunity[c]
Exposures	Vaccine preferred if given <72 hr after exposure. Alternative is immune globulin (0.25 mL/kg IM, maximum 15 mL), acceptable if given within 6 days. Live measles vaccine should be given 3 mo after IG

[a] Usually MMR (0.5 mL SC). Two doses in adults should include second dose ≥1 mo after first

[b] Single dose of live measles vaccine given at age ≥1 yr should provide long-lasting immunity in 95%. In some settings a 5% rate of susceptibility provides enough non-immune persons to sustain an epidemic. Persons vaccinated with killed measles vaccine (1963–67) are considered unvaccinated.

[c] Born before 1957, physician-diagnosed measles or laboratory evidence of immunity (measles-specific antibody). Serologic studies in health care workers showed 9% of persons born before 1957 were not immune, and 29% of health care workers who acquired measles (1985–89) were born before 1957. Therefore, vaccine should be offered to those born before 1957 if there is reason to consider them susceptible.

3. **RABIES PREVENTION**

Recommendation of Advisory Committee on Immunization Practice (MMWR 1999; 48:(RR–1.))

Experience: From 1980 to 1997 there were a total of 36 cases of human rabies in the U.S.—12 from dogs outside the U.S. and 21 from bats. Rabies in wildlife (primarily racoons, skunks, and bats) account for gt;85% of animal rabies in the U.S. The major animal source in Asia, Africa, and Latin America is dogs. Rabies is now rare in domestic animals in the U.S., although gt;80% of exposures that qualify for post-exposure rabies prevention treatment are dog and cat contacts (JAMA 2000;284:1001.). **Greatest risk is bats including bat exposure with no clear bite; these account for all five rabies cases acquired in the U.S. from 1998–2000** (MMWR 2000;49:1111.). **A review of 26 cases of bat variant rabies indicated that only two were associated with known bat bites** (CID 2002;35:738.). **The revised recommendations are for rabies prophylaxis for a bat bite, but also for situations where there is a reasonable possibility that a bite has occurred** (MMWR 2002;51:828.).

Rabies biologics

1. Vaccines: Neutralizing antibodies are produced in 7–10 days and persist ≥2 yr

Vaccine	*Name*	*Source*
Human diploid cell vaccine (HDCV) IM Intradermal	 Imovax Rabies Imovax Rabies ID	Pasteur Merieux Connaught 800-822-2463
Rabies vaccine absorbed (RVA) IM	Rabies Vaccine Adsorbed (RVA)	Bio Port Corp 517-327-1500
Purified chick embryo cell vaccine (PCEC) IM	Rab Avert Rabipur	Chiron Corp 800-244-7668

2. Rabies immune globulin (RIG): Provides rapid passive immunity with a half-life of 21 days

Rabies immune globulin product	*Source*
Imogam Rabies-HT	Pasteur-Merieux Connaught 800-822-2463
BayRab	Bayer Corp 800-288-8370

Cost: AWP cost for five doses of any of the three vaccines is $735–$760; for rabies immune globulin the cost is about $700 for a 70-kg patient.

RABIES POSTEXPOSURE PROPHYLAXIS—UNITED STATES, 1999

Note: In reality, the major risk for rabies is from a dog bite that takes place in the developing world or a bat exposure (with or without a bite) in the U.S. These recommendations do not account for the latter experience.

Animal type	*Evaluation and disposition of animal*	*Postexposure prophylaxis recommendations*
Dogs and cats	Healthy and available for 10 days' observation	Should not begin prophylaxis unless animal develops symptoms of rabies[a]
	Rabid or suspected rabid Unknown (escaped)	Immediate vaccination Consult public health officials
Skunks, raccoons, bats, foxes, and most other carnivores	Regarded as rabid unless animal proven negative by laboratory test[b]	Consider immediate vaccination
Livestock, small rodents and lagomorphs (rabbits and hares), large rodents (wood-chucks and beavers), and other mammals	Consider individually	Consult public health officials. (Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, chucks and beavers), and hares almost never require antirabies treatment

[a] During the 10-day holding period, begin postexposure prophylaxis at the first sign of rabies in the dog, cat, or ferret that has bitten someone. If animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.
[b] Animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of animal are negative.

RABIES POSTEXPOSURE PROPHYLAXIS SCHEDULE

MMWR 1998;47:4.

Vaccination status	*Treatment*	*Regimen*[a]	
Not previously		Local wound	Postexposure treatment should begin with immediate thorough cleansing of all wou

vaccinated	cleaning	with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds (J Am Acad Dermatol 1995;33:1019)
	RIG	20 IU/kg body weight. If anatomically feasible, full dose should be infiltrated around wound and the rest should be given IM at a site distant from vaccine administration. RIG and vaccine should not be administered in the same syringe. Because RIG may partially suppress active production of antibody, no more than recommended dose should be given
	Vaccine	HDCV, RVA—1.0 mL or PCEC IM (deltoid area),[b] one each on days 0, 3, 7, 14, and 28
Previously vaccinated[c]	Local wound cleaning	All post-exposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds.
	RIG	RIG should **not** be administered
	Vaccine	HDCV, RVA, or PCEC 1.0 mL IM (deltoid area); one each on days 0 and 3

[a] Regimens are applicable for all age groups, including children.
[b] Deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in gluteal area.
[c] Any person with a history of pre-exposure vaccination with HDCV, RVA, or PCEC; prior post-exposure prophylaxis with HDCV, RVA, or PCEC; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response in the prior vaccination.

4. **TETANUS-DIPHTHERIA VACCINE**

Recommendations of Advisory Committee on Immunization Practices (MMWR 1991;40(RR-10).

Vaccine: Inactivated toxoid vaccine tetanus and diphtheria toxoids adsorbed (Td) are preferred to tetanus toxoid because most adults who need tetanus toxoid are susceptible to diphtheria (Mayo Clin Proc 1999;74:381.). The primary series is 0.5 mL IM doses at 0 time, 1–2 mo, and 6–12 mo. Doses should not be repeated if the schedule is delayed. Booster doses are recommended at 10-yr intervals.

Cost: Td adsorbed, 0.5 mL—$9.75.

Susceptibility: Antigenic response is good but is reduced in elderly

patients. Current estimates are that 27% of U.S. persons >70 yr are unprotected against diphtheria and tetanus (NEJM

1995;332:761.)

Adverse reactions: Pain and tenderness at injection site; systemic reactions are rare. The frequency of local reactions increases with increases in the number of doses given.

Contraindications: Anaphylactic reaction or neurologic reaction to prior Td dosing. Persons with a history of an Arthrus reaction or fever > 39.4°C should not receive Td more than once every 10 yr. Persons who report reactions to a "tetanus shot" before 1938 probably received equine antitoxin and can receive the current vaccine tetanus prophylaxis.

TETANUS PROPHYLAXIS

MMWR 1991;40(RR-12):1–94.

History of tetanus toxoid	Clean, minor wounds		Other[b]	
	Td[a]	TIG[a]	Td[a]	TIG[a]
Unknown or <3 doses	Yes	No	Yes	Yes
≥3 doses[c]	No unless >10 yr since last dose	No	No, unless >5 yr since last dose	No

[a] Td. tetanus toxoid; TIG. tetanus immune globulin.
[b] Wounds contaminated with dirt, stool, soil, saliva, etc; puncture wounds; avulsions; from missiles, crushing, burns and frostbite.
[c] If only three doses of toxoid, a fourth should be given.

5. **PNEUMOCOCCAL VACCINE**

Advisory Committee on Immunization Practices, CDC (MMWR 1997;46(RR-8)..

Vaccine: 23 valent polysaccharide vaccine for the *S. pneumoniae* contains antigens responsible for 87% of bacteremic pneumococcal disease in the U.S. The 23 types (Danish nomenclature) follow: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. Six serotype (6B, 9V, 14, 19A, 19F, 23F) account for most antibiotic resistance and are included in the vaccine. Most adults show a 2 × rise in type-specific antibody at 2–3 wk after vaccination.

Efficacy: Seven systematic reviews of Pneumovax between 1994 and 2002 show no decrease in mortality or in rates of pneumococcal pneumonia in high risk patients (elderly or immunosuppressed) who are the target of current vaccine policies (see below) (BMJ 2002;325:292.). A more recent report shows efficacy in reducing invasive pneumococcal disease (primarily pneumococcal bacteremia), but not pneumonia or pneumococcal pneumonia (NEJM 2003;348:1747.)

Preparation and cost: Pneumovax (Merck Human Health) — $7.66/ dose.

Recommendations for adults:

1. Immunocompetent adults at increased risk of pneumococcal disease or its complications because of chronic illness (e.g.,

cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, or cerebrospinal fluid

leaks) or who are ≥65 yr old. Current recommendations are to review risks for pneumococcal disease at the 50th birthday because 30–40% have medical conditions that merit vaccine.

2. Immunocompromised adults at increased risk of pneumococcal disease or its complications (e.g., splenic dysfunction or anatomic asplenia, lymphoma, Hodgkin's disease, multiple myeloma, chronic renal failure, nephrosis organ transplant recipients, HIV infection, and other conditions associated with immunosuppression).
3. Persons in special environments or social settings with identified risk of pneumococcal disease (Native Americans, homeless, etc).
4. Patients with HIV infection should be given vaccine early during disease for adequate antibody response.

Note: 1) Vaccine should be given at least 2 wk before elective splenectomy; 2) vaccine should be given as long as possible before planned immunosuppressive treatment; 3) hospital discharge is a convenient time for vaccination because two-thirds of patients with serious pneumococcal infections have been hospitalized within the prior 5 yr; 4) may be given simultaneously with influenza vaccine (separate injection sites).

Adverse reactions:

1. Pain and erythema at injection site: 50%.
2. Fever, myalgia, severe local reaction: <1%.
3. Anaphylactoid reactions: 5/million; severe reactions: Estimated frequency of anaphylactoid reactions is 5/million. A meta-analysis of 7531 pneumococcal vaccine recipients in nine trials showed no patients had severe fever or anaphylactic reactions. There have been no cases of Guillain-Barré syndrome. Arthrus reactions are more common with revaccination at <4 yr.
4. Frequency of severe reactions is increased with revaccination <13 mo after primary vaccination; severe reactions are no more frequent when revaccination occurs >4 yr after primary vaccination.

Revaccination: This is recommended at 5 yr for adults who are immunosuppressed or have asplenia and those who were <65 yr when first vaccinated. Frequency of local reactions is 3.3× higher with revaccination (JAMA 1999;281:243.).

Pneumococcal conjugate vaccine (Prevnar): 7 valent conjugate vaccine with antigens for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These account for 80% of invasive pneumococcal disease in children < 6 yr in the U.S. Use is currently restricted to pediatrics.

6. **VARICELLA VACCINE**

Recommendations of Advisory Committee on Immunization Practice (MMWR 1996;45(RR-11).; MMWR 1999;48(RR-6).)

Morbidity in adults: Approximately 5–8% of adults are susceptible; about 75% of adults with a negative history for chickenpox have antibody indicating prior exposure (JAMA 1991;266:2724.). Chickenpox is more severe in young adults; risks are greatest in pregnant and immunocompromised hosts (Ann Intern Med 1980;93:414.). About 15% of adults develop herpes zoster. The rate of zoster in vaccine recipients was 2.6/100,000 person-yr in vaccine recipients compared with 68/100,000 persons-yr in a general population of persons age <20 yr, but these numbers are not necessarily comparable (MMWR 1999;48(RR-6).)

Vaccine: VARIVAX—live attenuated virus vaccine

Note: Vaccine must be stored frozen at < - 15°C to maintain potency. Once reconstituted it must be used within 30 min

Dose: Adult—0.5 mL SC × 2 separated by 4–8 wk

Cost: $65.40/dose

Efficacy: Seroconversion rate in adults is 78% with one dose; 99% with two doses. Protection at 7–10 yr is 70–90% against infection and 95% against severe disease. Impact in rates of zoster is unknown. It is speculated that reactivation of the vaccine strain causes mild disease and boosted immunity (Nature Med 2000;6:451.). **There are recent reports of vaccine failure that are expected to occur more frequently as the period of time from vaccination increases** (NEJM 2002;347:1909.). **A concern is the possible confusion with smallpox** (NEJM 2002;347:1962.)

Indications: Susceptible adults in rank order are in the following categories (Ann Intern Med 1996;124:35.).

1. Health care workers
2. Susceptible household contacts of immunosuppressed persons
3. Persons living or working in areas where transmission of VZV is likely—teachers of young children, day care employees, staff members in institutional settings
4. Young adults in closed or semiclosed populations—military personnel, college students, inmates and staff of prisons and jails
5. Nonpregnant women of childbearing potential
6. International travelers
7. Adolescents or adults living in households with children

Cost effective analysis: Serologic testing in adults and vaccinating seronegatives would be cost effective only for those 20–29 yr. Assumptions were cost of vaccination—$78, cost of serology—$20, cost for outpatient treatment of chickenpox—$80 plus acyclovir at $124 (Am J Med 2000;108:723.)

Contraindictions:

1. Pregnancy or this possibility within 1 mo

2. Immunosuppressed patients
3. Miscellaneous: Active tuberculosis; persons who have received blood products within 6 mo (passive immunity precludes antibody response); persons with anaphylactic reactions to gelatin or neomycin

Adverse reactions:

Fever >100°F: 10%

Local reaction at injection site: 30% in 0–2 days

Varicella-like rash at injection site: In 6–20 days reported in 37/100,000 vaccine doses; 3% in clinical trials

Generalized varicella rash: 10% in 7–21 days; this usually consists of <10 lesions fasting ≥3 days and may be source of

VZV transmission to susceptible contacts

Transmission: Transmission of the vaccine strain is a theoretical risk but is documented in only three cases out of 15 million vaccine doses distributed; all three were mild (MMWR 1999;48(RR-6).).

Post-exposure prophylaxis: Should be given within 3 days of exposure. Comparative cost and efficacy with other postexposure strategies follow:

Strategy	*Time from exposure*	*Cost*	*Efficacy*
Vaccine	3 days	$40	70–90%
Acyclovir 40–80 mg/kg	7–9 days	$120	80–85%
ZIG 625 units IM	4 days	$400	90%

7. **HEPATITIS A VACCINE**

Recommendations of Advisory Council on Immunization Practices (MMWR 1996;45(RR-15):1–30.; Ann Intern Med 1996;124:35.; NEJM 1997;336:196.; Med Letter 2001;43:67.)

Vaccine: HAVRIX-killed, formalin-inactivated (SmithKline Beecham) and VAQTA (Merck & Co); Twinrix (Glaxo SmithKline) (HBV + HAV vaccines)

Dose (adult): 1440 ELISA units (Havrix) (1 mL) IM × 1 or 2 (separated by ≥6 mo); 50 units/1.0 mL (VAQT). Twinrix—720 units HAV vaccine and 20 mcg HBV vaccine/1.0 mL to be given at 0, 1 and 6 mo

Cost: $59.45—1440 units Havrix; $62.94—50 units VAQTA; $92.00/dose—Havrix and HBV vaccine (Twinrix)

Adverse reactions: Local reactions in 20–50%, fever in 4% and rare severe reactions: Anaphylaxis, Guillain-Barré syndrome and other neurologic syndromes

Efficacy: 80% seroconvert in 15 days; >96% at 30 days, with booster dose—100% respond. Duration of immunity expected to be at least 10 years

Indications: Travelers to countries with endemic HAV (Note: Unnecessary in northern and western Europe, New Zealand, Australia, Canada, and Japan. Also note that immune globulin is a less expensive

alternative for short term protection); gay men; injection drug users; persons with clotting disorders; persons >30 yr with chronic liver disease (including persons with chronic HCV infection); lab workers handling HAV; persons working with nonhuman primates. Twinrix is recommended for adults with indications. Indications for both vaccines, especially travelers

Consideration: Day care workers, food handlers, staff of institutions for institutionally disabled

Hepatitis A: Immune globulin: Available from Michigan Department of Public Health (517-335-8120). May be given with HAV at

separate injection sites.

Indication	Dose	Duration of coverage
(1) Travelers to developing countries <3 mo	0.02 mL/kg	1–2 mo
Visit >3 mo	0.06 mL/kg	3–5 mo
Concurrent administration with vaccine (owing to late initiation)	0.02 mL/kg	—
(2) Post-exposure (must be given within 2 wk of exposure)		
Close personal contacts and sexual partners		
Day care centers: Staff and attendees when one case or at least two cases in families of attendees		
Institutions for custodial care		
Residents and staff with close contact with cases		0.02 mL/kg (up to 2 mL)
Common source exposure: Food and waterborne outbreaks if recognized within the 2 wk post-exposure period of effectiveness		
Food handlers: Other food handlers, but not patrons unless uncooked food was handled without gloves and patrons can be located within 2 wk of exposure		
Hospitals: Not recommended for hospital personnel		

8. **HEPATITIS B VACCINE**

MMWR 1987;36:353–366.; MMWR 1987;37:342–351.; MMWR 1991;40(RR-13).; *Guide for Adult Immunization*, American College of Physicians 3rd Edition, 1994:74–83.; NEJM 1997; 336:196.; Mayo Clin Proc 1997;74:377.; MMWR 1999;48:33.; MMWR 2001;50(RR-1).

Vaccine preparations

1. Recombivax HB (Merck & Co): Recombinant vaccine produced by *Saccharomyces cerevisiae* (baker's yeast) and available since July 1986; 10 or 40 µg HBsAg/m; usual adult dose is three 1-mL doses (10 µg) at 0, 1, and 6 mo; three 1-mL doses (40 µg) for dialysis patients
2. Engerix-B (Glaxo SmithKline): Recombinant vaccine available since 1989; 20 µg HBsAg/mL; usual adult dose regimen is three 1-mL doses (20 µg) at 0, 1, and 6 mo; alternative schedule is four 1-mL doses (20 µg) at 0, 1, 2, and 12 mo (for more rapid induction of immunity)
3. Twinrix (Glaxo SmithKline): bivalent vaccine with Havrix (HAV vaccine,

720 ELISA units/ml) + Energix-B (20 µg HBsAg/ml); usual adult regimen is 3 1 mL doses at 0, 1, and 6 mo.

Cost: Recombivax HB @ $57/dose (10 µg); Engerix-B @ $55/dose (20 µg); Twinrix @ $92/dose for HAV and HBV)

Adverse reactions: Injection site reactions in up to 20%. Systemic reactions are uncommon; anaphylaxis is rare, but epinephrine should be available for immediate use. Fever is reported in 1–6% of HBV vaccine recipients. Hypersensitivity to yeast and to thimerosal are contraindications to HBV vaccine. HBV vaccine appears to play no role in the etiology or relapses of multiple sclerosis (NEJM 2001;344:319.; NEJM 2001;344:327.)

Pre-exposure vaccination:

1. Regimen. Three IM doses (deltoid) at 0 time, 1 mo, and 6 mo; 0, 2 and 4 mo; or 0, 1, and 4 mo. There must be ≥4 wk between dose #1 and #2,≥8 wk between dose #2 and #3, and >4 mo between #1 and #3. If series is delayed, start where you left off. Usual adult dose is 1 mL (20 µg Engerix B or 10 µg Recombivax HB); hemodialysis patients and possibly other immunocompromised patients should receive 2–4 × the usual adult dose (usually 40 µg doses of either recombinant vaccine preparation). HBV deposited into fat rather than muscle results in lower seroconversion rates, so needle length is important. Needles for all men and for women 60–90 kg should be 2.5 cm, for women >90 kg should be 3.8 cm, and for women <60 kg should be 1.6 cm (JAMA 1997;277:1709.).

2. Response rate. >95% of young, healthy adults develop adequate antibody response (>10 mIU/mL). Non-response is greater with age over 40 yr, with certain HLA haplotypes, smoking history, obesity, HIV infection, hemodialysis, and accelerated schedule (JAMA 1993;270:2935.); response rates are 50–70% in persons with HIV infection; 60–70% with renal failure; 70–80% in diabetics; and 60–70% with chronic liver disease. Age-related response rates show >95% seroconversion rates in 20-yr-olds, 86% in 40-yr-olds, and 47% in persons >60 yr (Am J Prev Med 1998;15:73.). A meta-analysis of 24 studies with 11,037 vaccine recipients showed a continuous risk of non-response above 30 years. (CID 2002;35:1368.). This review also showed that a booster dose substantially improved the response rate. If the schedule is interrupted it may be resumed with good results providing the second and third doses are separated by ≥2 mo.

3. Post-vaccination serologic testing. Recommended for some persons whose subsequent clinical management depends on this knowledge (e.g., health care workers, dialysis patients, infants born to HBsAg-positive mothers) and for vaccine recipients who have decreased response rates: Age >30 yr, renal failure, HIV infection, diabetes, and chronic liver failure. When done, test at 1–6 mo after last dose. Studies in Taiwan show serologic titer decrease of about 10% per year, but efficacy persists (JID 2003;187:134.).

4. Revaccination. Revaccination based on measurements of serologic response is controversial. One point-of-view is that persons at risk, including health care workers, should have periodic antibody

measurements with boosters if levels are below 10mlU/mL (Arch Intern Med 1999;159:1481.). The contrary view from the ACIP is that antibody levels do not measure immunologic memory and that immunologic protection lasts more than 12 yr regardless of antibody levels (Clin Microbiol Rev 1999;12:351.; Arch Intern Med 2000;160:3170.). If done, revaccination of nonresponders will produce response in 15–25% with one additional dose and in 30–50% with three doses (Ann Intern Med 1982;97:362.). 13–60% of responders lose detectable antibody within 9 yr. New ACIP recommendations include routine postvaccination serologic testing for healthcare workers, patients with HIV infection and hemodialysis patients. Response is defined as HBsAb levels of >10 mIU/mL (MMWR 2001;50:RR-1.) Testing is done at ≥1 month after the 3rd dose.

5. Prevaccination serologic testing. Testing groups at highest risk is usually cost-effective if the prevalence of HBV markers is >20% (see table below). Routine testing usually consists of one antibody test: Either anti-HBc or anti-HBs. Anti-HBc fails to detect persons immune from prior vaccination and anti-HBs (only) will falsely identify HBsAg as susceptible. Average wholesale price of three-dose vaccine regimen is $165–$213; usual cost of serologic testing for anti-HBs or anti-HBc is $12–$20.

Prevalence of Hepatitis B Serologic Markers

Population group	*HBsAg (%)*	*Any marker (%)*
Immigrants/refugees from areas of high HBV endemicity	13	70–85
Alaska/Pacific Islands natives	5–15	40–70
Clients in institutions for the developmentally disabled	10–20	35–80
Users of illicit parenteral drugs	7	60–80
Sexually active homosexual men	6	35–80
Household contacts of HBV carriers	3–6	30–60
Patients of hemodialysis units	3–10	20–80
Health-care workers—frequent blood contact	1–2	15–30
Prisoners (male)	1–8	10–80
Staff of institutions for developmentally disabled	1	10–25
Heterosexuals with multiple partners	0.5	5–20
Health-care workers—no or infrequent blood contact	0.3	3–10
General population (NHANES II)		
Blacks	0.9	14
Whites	0.2	3

6. Side effects. Pain at injection site (3–29%) and fever >37.7°C (1–6%). Note: These side effects are no more frequent than

in placebo recipients in controlled studies. Experience in more than 4 million adults shows rare cases of Guillain-Barré syndrome with plasma-derived vaccine and no serious side effects with recombinant vaccines. Adverse reactions should be reported to 800-822-7967.

7. Vaccine efficacy. 80–95% for preventing HBV infection in gay men and virtually 100% if protective antibody response (≥10 mIU/mL) is achieved.

Candidates for pre-exposure vaccination:

All infants and children by the age of 18 yr

Persons with occupational risk

Now defined by the Occupational Safety and Health Administration, these include health care workers and many public service workers. For persons in health care fields, vaccination should be completed during training before students encounter blood

Persons with lifestyle risk

Heterosexual persons with multiple partners (more than one partner in the preceding 6 mo) or any sexually transmitted disease, homosexual and bisexual men, injecting drug users

Special patient groups

Hemophiliac persons

Hemodialysis patients

Environmental risk factors

Household and sexual contacts of HBV carriers, clients and staff of institutions for the developmentally disabled, prison inmates, immigrants and refugees from areas where HBV is highly endemic, international travelers to HBV endemic areas who are health care workers, who will reside there more than 6 mo, or who anticipate sexual contact with local persons

Pregnant women (MMWR 1991;40(RR-13)).: Risk of HBV transmission from HBsAg-positive pregnant woman to infant is 10–85% depending on HBeAg status. Perinatal infection has a 90% risk of chronic HBV infection and 25% mortality due to liver disease—cirrhosis or hepatocellular carcinoma. Children who do not acquire HBV perinatally are at increased risk for person-to-person spread during the first 5 yr. Over 90% of these infections can be prevented using active and passive immunizations. Recommendations follow.

1. All pregnant women should be tested for HBsAg during an early prenatal visit
2. Infants born to HBsAg-positive mothers should receive HBIG (0.5 mL) IM × 1 (preferably within 12 hr of delivery) and HB vaccine (0.5 mL) IM × 3 (5 µg Recombivax or 10 µg Engerix-B) at 0 time (concurrent with HBIG) at 1–2 mo, and at 6 mo. Test infants for HBsAg and antiHBs at 12–15 mo
3. Infants of HBsAg-negative mothers and children <11 yr should receive routine vaccination with three doses of Recombivax (2.5 µg) or Engerix-B (10 µg)

Postexposure vaccination: (MMWR 1991;40(RR-13).):

Acute exposure to blood: Occupational exposure

Definition of exposure is percutaneous (needlestick, laceration, or bite) or permucosal (ocular or mucous membrane) exposure to blood. Recommendations depend on HBsAg status of source and vaccination/vaccine response of exposed person.

Note: HBIG, when indicated, should be given as soon as possible, and value beyond 7 days post-exposure is unclear.

RECOMMENDATIONS FOR POSTEXPOSURE PROPHYLAXIS FOR PERCUTANEOUS OR PERMUCOSAL EXPOSURE TO HEPATITIS B, UNITED STATES

	Treatment when source is		
Exposed person	***Hepatitis B surface antigen positive***	***Hepatitis B surface antigen negative***	***Source not tested or unknown***
Unvaccinated	HBIG; × 1[a] and initiate HB' vaccine**	Initiate HB vaccine[b]	Initiate HB vaccine[b]
Previously vaccinated known responder	Test exposed for anti-HBs' 1. If adequate,[c] no treatment 2. If inadequate, HB vaccine booster dose	No treatment	No treatment
Known nonresponder	HBIG × 2 or HBIG × 1 *plus* 1 HB vaccine dose	No treatment	If known high-risk source, may treat as if source were HBsAg positive
Response unknown	Test exposed for anti-HBs 1. If inadequate,[c] HBIG × 1 + HB vaccine booster dose 2. If adequate, no treatment	No treatment	Test exposed for anti-HBs 1. If inadequate, HB vaccine booster dose 2. If adequate, no treatment

HBIG, hepatitis B immunoglobulin.

[a] HBIG dose 0.06 mL/kg IM.

[b] For HB vaccine dose, see p 114.

[c] Adequate antiHBs is 10 SRU by radioimmunoassay or positive by enzyme immunoassay (MMWR 1993;42:707).
[d] Antibody to hepatitis B surface antigen.

POST-EXPOSURE IMMUNOPROPHYLAXIS WITH OTHER TYPES OF EXPOSURES

(MMWR 40(RR-13):9, 1991)

Type of exposure	***Immunoprophylaxis***	***Comments***
Perinatal (HBsAg-positive mother)	HBIG + vaccination	HBIG + vaccine within 12 hr of birth
Sexual contact—acute HBV	HBIG (0.06 mL/kg IM) ± vaccination	HBIG efficacy 75%; all susceptible partners should receive HBIG and start vaccination within 14 days of last exposure; testing susceptibility with anti-HBc recommended if it does not delay prophylaxis >14 days. Vaccination is optimal if exposed person is not in a high-risk category and sex partner is HBsAg negative at 3 mo
Sexual contact—chronic carrier (HBsAg × 6 mo)	Vaccination[a]	
Household contact—acute HBV	None unless there is sexual contact or blood exposure (sharing toothbrushes, razors, etc)	With known exposure; HBIG plus vaccination
Household contact—chronic carrier (HBsAg × 6 mo)	Vaccination[a]	

[a] 1 mL IM × 3 at 0, 1, and 6 mo.

9. **SMALLPOX VACCINATION**

Recommendations for Using Smallpox Vaccine in a Pre-Event Vaccination Program: Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) [CDC MMWR 2003;52:RR-7.]:

Vaccination Method: The bifurcated needle is inserted into the vaccine vial to obtain a small droplet of vaccine which is delivered with 2–3 punctures (primary vaccination) or 15 punctures (revaccination) with sufficient force to allow a trace of blood after 15–20 seconds.

Normal Response: Most of the local reaction and significant complications occur at 5–15 days after vaccination, which corresponds with the time of viral replication and the immune response. Adverse events are much less frequent with revaccination and are most common in older perons who have not been vaccinated for decades or those with cellular immune deficiencies. With primary vaccination, the maximal inflammation and induration occurs at 6–8 days with a pustule, ulcer, or scab. Revaccination in a highly immune person may cause a lesion similar to that seen with a positive Tine test, and full resolution may occur at day three with nothing evident at 6–8 days. This may reflect good immunity or poor technique; it is called "equivocal response" and requires revaccination.

Contact vaccinia: Vaccinia virus can be recovered from the vaccination site from the time of the papule (2–5 days after vaccination) until the scab separates (14–21 days after vaccination); maximal shedding is at 4–14 days after vaccination and might be of shorter duration with revaccination.

Nosocomial transmission of vaccina: This has rarely been described and the majority of cases involve direct person-to-person transmission; the 2003 experience with 24,000 healthcare workers who received smallpox vaccination and continued to provide patient care showed no nosocomial transmission.

Contraindications: The vaccine is contraindicated in potential recipients with the following conditions or household contacts with these conditions: (1) history of eczema or atopic dermatitis; (2) other acute, chronic, or exfoliative skin conditions including burns, impetigo, varicella-

zoster, HSV, severe acne or psoriasis; (3) immunosuppression (HIV, leukemia, lymphoma, generalized malignancy, solid organ transplantation, cellular or humoral immunodeficiencies or therapy with alkylating agents, antimetabolites, radiation, or high dose steroids); (4) pregnancy; and (5) persons with coronary artery disease. The vaccine is contraindicated for potential recipients (but not household contacts) who are breast-feeding, are less than one year of age (not recommended for persons under 18 years), and those who are allergic to a vaccine component.

Pregnancy: The risk is small but fetal vaccinia is serious. During 1932–72, there were 20 affected pregnancies; 18 in vaccine recipients and 2 with contact vaccinia. Of the 20 pregnancies, 7 occurred during the first trimester and 13 occurred in the second trimester; only one of the 20 pregnancies was maintained to term and three survived. The vaccine is contraindicated in women who are pregnant or plan pregnancy within four weeks. A urine pregnancy test should be available on the day scheduled for vaccination. Inadvertent vaccination during pregnancy or pregnancy within four weeks should not be used as reason to terminate

pregnancy.

HIV infection: There has been one reported case of disseminated vaccinia in a patient with AIDS. There were also 732 recruits vaccinated between 1981 and 1985 who subsequently had positive serology in 1985–88 without known consequences. This gives a frequency of serious adverse events in this population of 0.14%. The 2003 military experience included inadvertent vaccination of 10 HIV-infected recruits with CD4 counts >300/mm^3; all had "takes" and none had complications. Vaccination is not recommended with HIV infection; mandatory HIV testing is not recommended, but the test should be available.

Major Adverse Events: (See Ann Intern Med 2003;138:488.)

1. Encephalitis: Develops at 5–15 days after primary vaccination. The mortality rate is about 25%, residual sequelae are noted in 25%, the virus is rarely detected in brain or CSF, natural history is completed in two weeks, it is not progressive and is managed with supportive care only. This is more common in children under one year of age and accounts for the delay in vaccination to the second year of life per a policy in the mid 1960s.
2. Progressive vaccinia: In the 1960s, this was most common in persons with leukemia or agammaglobulinemia. At present, the greatest concerns are for people with HIV, organ transplants, cancer chemotherapy, and other iatrogenic immunosuppressive disorders. The complication is characterized by continued viral replication with continuous enlargement and metastasis. Treatment is with VIG and possibly cidofovir.
3. Eczema vaccinatum: The condition is characterized by widespread vaccinal lesions in patients with eczema or history of eczema. This complication in the 1960s was more common with contact vaccinia than a complication in vaccine recipients due to exclusion of these patients for immunization. Treatment is with VIG, which reduces the

   mortality rate from 10% to about 1% with supportive care similiar to that given to burn victims.
4. Accidental implantation: This occurs when patients touch the vaccination site and then touch another anatomical site. The greatest concern is ocular involvement; about 6% with vaccinia in the eye develop vaccinal keratitis. VIG is controversial because of animal studies that suggest an antigen-antibody cause.
5. Fetal vaccinia: This complication is exceedingly rare. Pregnant women exposed to smallpox should be vaccinated because smallpox is associated with a mortality rate in pregnant women of up to 90% and fetal wastage nearly 100%.
6. Cardiac: Myocarditis at 1–3 weeks postvaccination. Most common with primary vaccination in white men in 20's; all military recruits with this complication in 2003 recovered without sequelae. Ischemic cardiac events (14 cases) and dilated cardiomyopathy (4 cases) were noted in the 2003 experience with about 500,000 vaccinations but were probably unrelated.

Treatment of Adverse Events: Clinical trials with VIG or any other antiviral agent have not been done with humans. Cidofovir may be used because of its in vitro activity against vaccinia.

EXPERIENCE WITH SMALLPOX VACCINATION IN 2003

The following table summarizes the adverse events encountered with vaccination of 450,293 military recruits in 2003 (JAMA 2003;289:3278.)

Reactions n = 450,293	***Rate/million***	**Historic Rate/million**

Mild/temporary			
Generalized vaccinia	36	80	45–212
Erythema multiforme	1	—	—
Inadvertent self inoculation	48	107	606
Contact vaccinia	21	47	8–27
Moderate-serious			
Encephalitis	1	2.2	2.6–8.7
Progressive vaccinia	0	0	1.5
Eczema vaccination	0	0	38
Myocarditis	37	82	100*

* Based on Finnish military recruit study. Acta Med Scand 1983;213:65.

10. **MENINGOCOCCAL VACCINE** (see p 133)

E. **IMMUNE GLOBULINS**

RECOMMENDED TREATMENT

Adapted from Guide for Adult Immunization, American College of Physicians, 3rd Edition, Philadelphia, 1994:86.; *and* MMWR 1994;43(RR-1)., *pp 5, 17*

Infection	***Indication***	***Preparation***	***Recommendation***

	Clinical tetanus	TIG*	3000–6000 units (therapy)
Vaccinia	Severe reaction to vaccinia vaccination	VIG*	CDC 404-639-3670
Varicella-zoster	Immunosuppressed or newborn contact	VZIG*	125 units/10 kg IM up to 625 units Available from state health departments

* Human antibodies.

F. **RECOMMENDATIONS FOR USE OF VACCINES IN IMMUNOCOMPROMISED HOST**

Recommendation of the Advisory Committee on Immunization Practices of the CDC (MMWR 1993;42(RR-4).; Clin Micro Rev 1998;11:1.)

Vaccine	Routine (not immuno-compromised)[a]	HIV infection/AIDS	HIV[a] response with CD_4 <200	Organ transplantation, chronic immuno-suppressive therapy, severely immuno-compromised[b]	Asplenia	Renal failure, alcoholism, alcoholic cirrhosis, and diabetes
Td	Recommended	Recommended	Reduced	Recommended	Recommended	Recommended
MMR(MR/M/R)[c]	Use if indicated	Contraindicated	Poor	Contraindicated	Use if indicated	Use if indicated
Hepatitis B	Use if indicated	Recommended[d]	Reduced	Use if indicated	Use if indicated	Use if indicated [c]
Hib	Not recommended	Not indicated	Reduced	Recommended	Recommended	Use if indicated

Pneumococcal	Recommended if ≥65 yr old	Recommended with CD4 > 200	Poor	Recommended	Recommended	Recommended
Meningococcal	Use if indicated	Use if indicated	No data	Use if indicated	Recommended	Use if indicated
Influenza	Recommended if ≥ 65 yr old	Recommended	Poor	Recommended	Recommended	Recommended
Varicella	Use if indicated	Contraindicated	No data	Contraindicated	Use if indicated	Use if indicated

[a] Non-routine vaccines:
Contraindicated vaccines for organ transplant recipients, chronic medication induced immunosuppression (alkalylating agents, radiation, chronic prednisone, anti-metabolites), severe immunosuppression (congenital immunodeficiency, AIDS, leukemia, lymphoma, aplastic anemia or generalized malignancy): BCG, OPV, smallpox, typhoid TY21a, and yellow fever.
Use if indicated in above population: elPV, cholera, plague, typhoid, inactivated rabies, anthrax
Patients with renal failure, alcoholism; cirrhosis or asplenia may receive the following vaccines if indicated: BCG, OPV, smallpox, typhoid TY21a, yellow fever, cholera, plague, rabies, anthrax

[b] Severe immunosuppression can be the result of congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids.

[c] See discussion of MMR.

[d] Patients with renal failure on dialysis or HIV infection should have their anti-HBs response tested after vaccination, and those found not to respond should be revaccinated with three doses.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Prophylactic Antibiotics in Surgery

Prophylaxis is recommended for procedures associated with high risk of infection, procedures involving implantation of prosthetic material, and some procedures when infections are especially serious. Cefazolin is usually preferred owing to the long half-life and established efficacy. Routine use of vancomycin is discouraged due to promotion of vancomycin-resistant enterococcus (Infect Control Hosp Epidemiol 1995;16:105.). A single dose given preoperatively 30 min before the skin incision is usually adequate; a second dose is often given if the procedure is long or is associated with large blood losses or if the drug has a short half-life. Postoperative doses are usually unnecessary (Med Lett 2001;43:93.).

Antimicrobial Agents in Surgery

Adapted from Med Lett 2001;43:93.; NEJM 1986;315:1129–1138.; Rev Infect Dis Suppl 1991;10, 13:S779.; Mayo Clin Proc 1992;67:288.; Clin Proc 1992;67:288.; CID 1992;15:S 313.; Arch Surg 1993;128:79.; *and Antibiotic Guidelines, Johns Hopkins Hospital 2003*

Type of surgery	***Preferred regimen****	***Alternative***	***Comment***
CARDIOTHORACIC			

Cardiovascular, coronary bypass, valve surgery	Cefazolin 1–2 g IV. pre-op ± q4h intraop*, or Cefuroxime 1.5 g IV pre-op ± q6h intraop	Vancomycin 1 g IV pre-op infused over 60 min** ± second dose when removed from by-pass	Likely pathogens: *S. epidermidis, S. aureus, Corynebacterium*, Gram-negative bacilli. Single doses appear to be as effective as multiple dosesprovided high serum concentrations are maintained throughout the procedure (Eur J Clin Microbiol Infect Dis 1994;13:1033). Main benefit is reduced rates of wound infections Some recommend a second dose at time of removal from bypass
Pacemaker insertion, defibrillator implant	Cefazolin 1–2 g IV pre-op*	Vancomycin 1 g IV pre-op infused over 60 min**	Likely pathogens: As above Meta-analysis of 7 controlled studies showed prophylaxis reduced infections associated with pacemaker implantation (Circulation 1998;97:1796)
Peripheral vascular surgery, abdominal aorta, and legs or any	Cefazolin 1–2 g IV pre-op	Vancomycin 1 g pre-op infused over 60 min**	Likely pathogens: *S. aureus, S. epidermidis*, Gram-negative bacilli, clostridia. Prophylaxis recommended for

procedure involving a prosthesis including coronary stents and grafts for hemodialysis			procedures on abdominal aorta and procedures on leg that include groin incision or amputation for ischemia and any vascular procedure involving a prosthesis (Scand J Infect Dis 1998;30:547) Many use prophylaxis with any vascular prosthetic material Prophylaxis is not indicated for carotid endarterectomy
Carotid or brachial artery	None		
Thoracic surgery: Lobectomy, pneumonectomy	Cefazolin 1–2 g IV pre-op or Cerfuroxime 1.5 g IV pre-op	Vancomycin 1 g IV pre-op infused over 60 min** or Clindamycin 600 mg IV pre-op	Efficacy of prophylaxis antibiotics for lung surgery is not established [RID 1991;13 (Suppl 10):S869]. Some studies show decreased rates of wound infection but no reduction in pneumonia or empyema One report showed efficacy of cephalosporin prophylaxis after chest tube insertion for chest trauma (Am Surg 1998;64:617)

GASTROINTESTINAL			
Esophageal dilatation or sclerotherapy	Cefazolin 1–2 g IV pre-op	Cefoxitin 1–2 g IV pre-op Clindamycin 600 mg IV pre-op	Likely pathogens: Gram-negative bacilli, Gram-positive cocci, anaerobes Antibiotic prophylaxis common practice, but proof of efficacy is lacking
Gastric surgery (high risk only)	Cefazolin 1–2 g IV pre-op	Clindamycin 600 mg IV + gentamicin 1.7 mg/kg	Likely pathogens: Enteric Gram-negative bacilli, Gram-positive cocci. Prophylaxis advocated for high risk that is usually due to reduced gastric acidity or motility—obstruction, treatment with H_2-blocker or proton pump inhibitor, hemorrhage, gastric cancer, and gastric bypass. Morbid obesity is also a high risk. Prophylaxis is usually given for percutaneous gastrostomy but efficacy not established (Gastroenterol 2000;95:3133) Prophylactic antibiotics are not indicated for uncomplicated duodenal ulcer surgery (Ann

			Intern Med 1987;107:824)
Biliary tract (high risk only) ERCP: See comment	Cefazolin 1–2 g IV pre-op	Gentamicin 1.7 mg/kg pre-op × 1 or q8h × 3	Likely pathogens: Enteric Gram-negative bacilli, enterococci, clostridia. Traditionally advocated only for high risk—acute cholecystitis, obstructive jaundice, nonfunctioning gallbladder, common duct stones, or age >70 yr. Meta-analysis of 42 studies showed benefit to high-risk and low-risk patients (Br J Surg 1990;77:283). ERCP—one study showed benefit of 1–3 pipericillin doses in patients with cholestasis (CID 1995;20:1236) Laparoscopic cholecystectomy: Prophylactic antibiotics are not indicated (Arch Surg 1999; 65:226; Arch Surg 1999;134:611)
Colorectal	Neomycin 1 g po and erythromycin 1 g po at 1	Cefoxitin 1–2 g IV or cefotetan 1 g IV or Metronidazole 0.5 g IV plus cefazolin 1–2 g IV	Likely pathogens: Enteric Gram-negative bacilli, anaerobes. Most U.S. surgeons use both an oral and a

	PM, 2 PM, and 11 PM the day before surgery (19,18, and 11 hr pre-op) ± cefoxitin 2 g IV or cefotetan 2 g IV	or metronidazole 0.5 g IV plus gentamicin 1.7 mg/kg IV	parenteral prep plus bowel cleansing (Dis Colon Rectum 1990;33:154). Some advocate three subsequent doses of parenteral agents at 8-hr intervals. Oral prep with metron idazole + neomycin or kanamycin is probably as effective as erythromycin + neomycin [RID 1991;13(Suppl 10):815)
Penetrating trauma abdomen	Cefoxitin 1–2 g IV immediately, then q6h or cefotetan 1–2 g IV q12h or clindamycin 900 mg IV + gentamicin 1.7 mg/kg immediately, then q8h	Ticarcillin-clavulanate or piperacillin-tazobactam or combination of an aminoglycoside + metronidazole	Likely pathogens: Enteric Gram-negative bacilli anaerobes. Patients with intestinal perforation should receive these agents for 2–5 days. Most studies use suboptimal doses of aminoglycosides [RID 1991 13(Suppl 10):S847]. If laparotomy shows no bowel injury, one dose is adequate
Appendectomy	Cefoxitin	Metronidazole 1 g IV	Likely pathogens: Enteric

	1–2 g IV pre-op or cefotetan 1–2 g IV	or clindamycin 600 mg IV ± gentamicin 1.7 mg/kg	Gram-negative bacilli, anaerobes. For perforated or gangrenous appendix continue regimen for 3–5 days. For nonperforated appendix 1–4 doses are adequate [RID 1991; 13(Suppl 10):S813]
Laparotomy, lysis of adhesions, splenectomy, etc without GI tract surgery	None		
GYNECOLOGY AND OBSTETRICS			
Vaginal and abdominal hysterectomy	Cefazolin 1–2 g IV pre-op or Cefotetan 1–2 g IV pre-op or Cefoxitin 1 g IV pre-op	Doxycycline 200 mg IV pre-op or clindamycin 600–900 mg IV pre-op or metronidazole 500 mg IV pre-op	Likely pathogens: Enteric Gram-negative bacilli anaerobes, group B streptococci, enterococcus. Efficacy of prophylaxis is established for vaginal and abdominal hysterectomy (Infect Dis Obstet Gynecol 2000;8:230) Single dose

			appears to be as effective as multiple doses. Recommendation for radical hysterectomy is cefazolin 1–2 g pre-op [RID 1991;(Suppl 10):S821; CID 1995;20:677]
Cesarean section (high risk only)	Cefazolin 1 g IV after clamping cord	Cefoxitin 2 g IV or cefotetan 2 g IV or clindamycin 900 mg IV or metronidazole 0.5 g IV after clamping cord	Likely pathogens as above. Prophylaxis advocated primarily for emergency procedures in high risk—active labor premature rupture of membranes, but low-risk patients may also benefit [RID 1991;13 (Suppl 10):S821; Drugs 1991;41:19] Antibiotics should be given after cord is clamped
Abortion (first trimester, high risk only)	First trimester: Doxycycline 100 mg po before and 200 mg po 30 min after or aqueous penicillin G 2	Metronidazole 500 mg po × 3 doses in perioperative period	Likely pathogens as above. Efficacy shown for first and second trimester abortions (Drugs 1991;41:19) and high-risk patients—prior PID, gonorrhea, or multiple sex partners. For patients with *N. gonorrhoeae* or *C. trachomatis*,

	mil units IV Second trimester: Cefazolin 1 g IV		treat STD with minimum delay in abortion (Am J Obstet Gynecol 1984;150:689) A meta-analysis showed benefit with prophylaxis for all therapeutic abortions (Obstet Gynecol 1996;87:884)
Dilation and curretage	Cefazolin 1 g IV pre-op (see comment)		Complicated procedures only
Cystocele or rectocele repair	None		
Tubal ligation	None		
HEAD AND NECK			
Tonsillectomy ± adenoidectomy	None		Controlled studies are limited
Rhinoplasty	None		

Major surgery with entry via oral cavity or pharynx	Clindamycin 600–900 mg IV ± gentamicin 1.7 mg/kg IV pre-op*	Cefazolin 1–2 g IV pre-op* Cefuroxime 1.5 g IV pre-op*	Likely pathogens: *S. aureus*, streptococci, oral anaerobes. Efficacy established but preferred agent is unclear (Head Neck 1997;19:188; Ear, Nose Throat J 1997;76:790) Controlled study showed cefazolin dose of 2 g superior to 0.5 g (Ann Surg 1988;207:108). Meta-analysis showed single dose of clindamycin alone was most effective (Plast Reconstr Surg 1991;87:429). Another study showed ampicillin-sulbactam (Unasyn) more effective than clindamycin (Arch Otolaryngol Head Neck Surg 1992;118:1159)
ORTHOPEDIC SURGERY			
Joint replacement	Cefazolin 1–2 g IV pre-op*	Vancomycin 1 g IV pre-op infused over 60 min**	Likely pathogens: *S. aureus, S. epidermidis*. Efficacy of prophylaxis is established (Lancet 1996; 347:1133; RID 1991;10:S42) Cefazolin dose should be 2 g

			for knee replacement with tourniquet (Orthop Rev 1989;18:694). Antibiotic-impregnated cement may be effective (Int Orthop 1987;11:241)
Open reduction of fracture/internal fixation	Cefazolin 1–2 g IV 1 g q8h × 1–3 days (closed hip fracture) or 10 days (open hip fracture)	Vancomycin 1 g IV pre-op infused over 60 min** repeat q12h × 1–3 days (closed hip fractures) or 10 days (open hip fracture)	Likely pathogens: *S. aureus; S. epidermidis* Efficacy established for compound or open fractures treated with screws, plates, or wires and surgical repair of closed fractures (Lancet 1996; 347:1133; Pharmacother 1991;11:157) Antibiotics are not indicated for arthroscopic surgery (Orthopedics 1997;20:133)
Compound fracture	Cefazolin 1–2 g IV q8h × 5–10 days or nafcillin 1–2 g q4h	Vancomycin 1 g IV q12h** or clindamycin 900 mg IV q8h	Start treatment immediately and continue 5–10 days
Amputation of	Cefazolin	Clindamycin 600 mg IV	Likely pathogens: *S. aureus*,

leg	1–2 g IV or cefoxitin 1–2 g or cefotetan 1–2 g IV pre-op*	+ gentamicin 1.7 mg/kg IV or Vancomycin 1 g IV pre-op infused over 60 min**	enteric Gram-negative bacilli, Clostridia Efficacy of prophylaxis is established (J Bone Joint Surg 1985;67:800)
NEUROSURGERY			
Cerebrospinal fluid shunt	Cefazolin 1–2 g IV pre-op ± second dose at 4 hr.	Clindamycin 600 mg IV pre-op ± second dose at 4 hr	Likely pathogens: *S. aureus, S. epidermidis*. Efficacy of antimicrobials supported with meta-analysis (CID 1993;17:98); agents used most were trimethoprim-sulfamethoxazole, cloxacillin, and cephalosporins for ≤48 hr. Some studies fail to show efficacy (Lancet 1994;344:1547)
Craniotomy	Cefazolin 1–2 g pre-op	Vancomycin 1 g IV over 60 min pre-op**	Likely pathogens: *S. aureus, S. epidermidis* Efficacy established (J Neurosurg 1990;13:383; Neurosurgery 1994;35:484), advocated even for low-risk

			procedures except where infection rates are <0.1% (Neurosurg 1989;24:401). Preferred drugs do not cross blood-brain barrier well presumably because most are soft tissue infections (Neurosurg Clin North Am 1992;3:355)
Spinal surgery	None		Rates of infection are too low for demonstrable benefit with lumbar discectomy; infection rates are higher and use of antibiotics more common with fusion, insertion of foreign material, or prolonged procedures, but benefit is not established (Spine 2000;25:2544)
OCULAR	Gentamicin, tobramycin, cipro-floxacin, olfloxacin or neomycin-gramicidin-polymyxin B as eye drops over 2–24 hr Cefazolin 100 mg subconjunctivally		Likely pathogens: *S. aureus, S. epidermidis*, streptococcus, enteric gram-negative bacilli, *Pseudomonas* Most use eye drops but some give subconjunctival injection of cefazolin, cefuroxime,

		ceftazidime, vancomycin, or ciprofloxacin (Mayo Clin Proc 1997;72:149) Post-operative: 5% povidone-iodine ophthalmic soln may be more effective than topical antibiotics (Am J Ophthalmol 1995;119:701) There is no consensus on best antibiotics or route of administration (Cornea 1999;18:383) There is no evidence of efficacy with procedures that do not invade the globe
UROLOGY		
Prostatectomy Sterile urine (high risk only)	Ciprofloxacin 500 mg po or 400 mg IV or gatifloxacin 400 mg po or IV	Likely pathogens: Enteric Gram-negative bacilli and enterococcus Prophylaxis is not usually recommended if pre-op urine is sterile Cefazolin sometimes advocated for open prostatectomy (Urol Clin North Am 1990;17:595)

Infected urine	Continue agent active in vitro or give single pre-operative dose		Sterilization of urine before surgery is preferred
Radical retropubic prostectomy or nephrectomy	Cefoxitin 1–2 g IV or cefotetan 1–2 g IV pre-op	Clindamycin 600 mg IV pre-op	
Prostatic biopsy	None		
Dilation of urethra	None		
MISCELLANEOUS			
Inguinal hernia repair	Cefazolin 1 g IV pre-op (see comment)		One study showed benefit of cefonicid, 1 g IV 30 min pre-op (NEJM 1990;322:153); sequel study showed diverse antibiotics (primarily cefazolin) in high-risk patients was beneficial (JID 1992;166:556) Prophylaxis is not generally recommended (Med Lett

		2001;43:91)
Mastectomy	Cefazolin 1 g IV pre-op (see comment)	One study showed benefit of cefonicid for breast surgery (NEJM 1990;322:153); Greatest risks were radical mastectomy and axillary node dissection: Most authorities do not recommend prophylaxis (Med Lett 2001;43:91)
Traumatic wound	Cefazolin 1–2 g IV q8h	Likely pathogens: *S. aureus*, group A strep, clostridia

* Pre-op usually indicates administration with induction of anesthesia. Intra-op dose often given with prolonged procedures. Optimal duration is usually unclear, but most studies show a single dose is adequate. Use of more than a single pre-operative dose is arbitrary and usually discouraged. When repeat dosing: cefazolin q4h, cefoxitin q4h, cefotetan q8h, clindamycin q8h, vancomycin q12h. With cefazolin, obese patients should receive 2 g (Surgery 1989;106:750).
** Vancomycin preferred for hospitals with a high rate of wound infections caused by methicillin-resistant *S. aureus* or *S. epidermidis* and for patients with allergy to penicillins or cephalosporins. Hypotension is a common complication with rapid infusion and may occur even if infused over 60 min. Treat with Benadryl and further slowing of infusion (J Thorac Cardiovasc Surg 1992;104:1423). Hospitals should reduce all unnecessary vancomycin use due to concern for possible promotion of vancomycin-resistant enterococci.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Antimicrobial Prophylaxis in Ambulatory Patients

(Mayo Clin Proc 2000;75:98.)

A. **Prevention of recurrent attacks of rheumatic fever** (Recommendation of AHA Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council of Cardiovascular Disease in the Young. JAMA 1992;268:2069.)

1. **Indications**

Rheumatic carditis: Long-term antibiotic prophylaxis well into adulthood and possibly for life. This includes continued prophylaxis after valve surgery

Rheumatic fever without carditis: Continue until age of early 20s and 5 yr past last rheumatic attack. Then reevaluate

2. **Regimens**

Preferred: Penicillin G benzathine 1.2 mil units IM every 4 wk

Alternatives: Penicillin V 250 mg po twice daily, sulfadiazine 1 g po once daily, or erythromycin 250 mg po twice daily (allergy to penicillins and sulfonamides)

B. **Meningococcal disease**

Prevention and Control of Meningococcal Disease (MMWR 2000;29:RR-7.): This document presents the CDC and the ACIP recommendations regarding control and prevention of infections caused by *N. meningitidis.* The two issues of keen importance are recommendations

for meningococcal vaccine and the recommendations for post-exposure prophylaxis.

Recommendations for the use of meningococcal vaccine:

1. Control of meningococcal outbreaks involving serogroup C.
2. Consideration for college freshman, particularly those living in dormitories and resident halls so that the student and parents can make "individualized, informed decisions" (MMWR 2000;49:RR-7.) (see below).
3. Routine use in high-risk patients including those with deficiencies in the terminal complement components, persons who are asplenic and those who are routinely exposed to *N. meningitidis* for research or laboratory work
4. Travelers to the "meningitidis belt" in sub-Saharan Africa extending from Senegal to Ethiopia. Updated information about risk to travelers is available at the CDC: 877-394-8747 and on the Internet at http://www.cdc.gov/travel/.
5. Efficacy is 90% for preventing meningococcal infection but does not appear to reduce mortality in those who get infected despite vaccination (CID 2002;35:1376.)

Antimicrobial prophylaxis for contacts of patients with meningococcal disease: The target population should include the following: household members, daycare center contacts, and anyone exposed to the patient's oral secretions (kissing, mouth-to-mouth resuscitation, or intubation). The drugs recommended for adults are:

rifampin (600 mg q12h × 4), ciprofloxacin (500 mg × 1), or ceftriaxone (250 mg IM × 1).

Recommendations for college students: The risk is small and the following recommendations are made:

1. Students and parents should be informed about meningococcal disease and the benefits of vaccination, but the ACIP does not recommend this as a routine vaccination strategy.
2. The risk for non-freshman students is about the same as for the general population.
3. The vaccine should be given to students at increased risk for meningococcal disease as defined above.

4. This policy has been criticized as being vague and inconsistent (JAMA 2001;286:720.)

C. **Pneumococcal infection in asplenic patients**(Recommendations of American Academy of Pediatrics Redbook, 22nd Edition, 1991, pp 52–53, 373–378; Sickle Cell Disease Guideline Panel, AHCPR Pub 93-0562, 1993, pp 39–42)

1. **Indications** Anatomically and functionally asplenic patients (including those with sickle cell disease), especially children and adolescents; indications in adult patients are unclear

2. **Regimens** Pneumococcal, meningococcal, and *H. influenzae* type B vaccines

   Preferred For adults and children >5 yr, penicillin V 250 mg po bid, usually for 2–4 yr in children

   Alternatives Penicillin G benzathine 1.2 mil units IM q4wk

D. **Persons with cochlear implants** (MMWR 2002;51:931.). This recommendation is based on reports of meningitis in 53 such patients including pneumococcal meningitis in 16 of the 23 patients with a microbial pathogen detected

E. **Prevention of recurrent bacterial UTIs in women** (See Fihn SD: NEJM 2003;349:3.)

1. **Indications** Young to middle-aged nonpregnant women with ≥2 recurrent infections within 6 mo or ≥3 recurrent infections in 12 mo

2. **Options**

   - Continuous prophylaxis: Indications are two or more symptomatic infections in one six month period or three or more in twelve months. Controlled trials show single daily doses of TMP-SMX, TMP, nitrofurantoin or a fluoroquinolone reduces recurrences by 95% (Int J Antimicrob Agents 2001;17:259.). This is usually given on a trial basis for six months but has been shown to be effective without resistance (Rev Infect Dis 1991;13:77.).
   - Postcoital prophylaxis may be used when there is a clear relationship with sex using a single postcoital dose (Ann Intern Med 2001;135:9.)

   - Self-treatment: Most women can accurately diagnose recurrent cystitis and can be given

a three day supply of antibiotics. They should be instructed to get medical attention if the symptoms persist for 48–72 hours.

3. **Regimens**

	Cost	Pregnancy category
Prophylaxis (6 months)		
TMP-SMX ½ SS tab qd or 3×/week	$11–28	C
Trimethoprim 100 mg hs × 6 mo	$103	C
Nitrofurantoin macrocrystals 50 or 100 mg hs × 6 mo	$166	B
Norfloxacin 200 mg hs	$353	C
Postcoital prophylaxis		
TMP-SMX ½ SS tab or whole tab	$0.30	C
Nitrofurantoin 50 or 100 mg	$1–2	B

Ciprofloxacin 250 mg × 1	$9	C
Levofloxacin 250 mg × 1	$7	C
Gatifloxacin 400 mg × 1	$7	C
Intermittent self-treatment		
TMP-SMX 1 DS bid × 3 d	$2	C
Trimethoprim 100 mg bid × 3 d	$23	C
Norfloxacin 400 mg bid × 3 d	$23	C
Ciprofloxacin 250 mg bid × 3 d	$53	C
Levofloxacin 250 mg qd × 3 d	$44	C
Gatifloxacin 400 mg qd × 3 d	$21	
or 400 mg × 1	$7	C

F. **Pertussis prevention** (Epidemiol Infect 1998;120:143.)

1. **Indications**

   All household and other close contacts regardless of age and immunization status

2. **Regimens**

   Preferred: Erythromycin 40–50 mg/kg/d (up to 2 g) in four doses × 14 days

   Note: Erythromycin estolate may be more effective than the ethylsuccinate or stearate in eliminating *B. pertussis* carriage

   Alternative: Trimethoprim/sulfamethoxazole 8 mg/40 mg/kg/d

3. **Prophylaxis vs infections in bone marrow and organ transplantation** Position paper from Eastern Cooperative Oncology Group (ECOG) (Ann Intern Med 1994;120:143.; NEJM 1998;338:141.)

   1. ***P. carinii* prophylaxis**: Trimethoprim-sulfamethoxazole (2 DS 2–3× wk) starting after engraftment when absolute neutrophil count is >1000/mm^3 × 4–12 mo or if chronic graft vs host disease and as long as immunosuppressive treatment given. If allergic to TMP-SMX: Aerosolized pentamidine (300 mg monthly)

   2. **Fungal prophylaxis/treatment**: Consider prophylaxis with fluconazole or low-dose amphotericin B. Patients with fever plus

      neutropenia × 3–5 days without response to broad-spectrum antibiotics should receive amphotericin B (0.5–1.0 mg/kg/d)

   3. **CMV prophylaxis**

      a. Allogenic transplant, CMV seronegative donor, and CMV seronegative recipient plus strict use of CMV negative blood products: No prophylaxis

      b. Allogenic transplant with CMV seropositive donor *or* CMV seropositive recipient: Ganciclovir 5 days/wk or valganciclovir for prophylaxis or for pre-emptive treatment (antigenemia or CMV VL) (Bone Marrow Transpl 2000;26:763.; Oncology 2000;14:1701.)

c. Autologous transplant and seronegative recipient: Use CMV negative blood products or leukocyte-filtered blood products. Valganciclovir prophylaxis (900 mg/d days 10–100) to prevent CMV disease approved for kidney and heart transplant D+R-

4. **Cirrhosis with ascites: Prevention of spontaneous bacterial peritonitis** Trimethoprim—sulfamethoxazole 1 DS 5 days/wk (Ann Intern Med 1995;122:595.) or norfloxacin 400 mg po qd (Hepatology 1990;12:716.) or ciprofloxacin 750 mg q wk (Hepatology 1995;22:1174.)

5. **Primary immune deficiency, such as X-linked agammaglobulinemia.** IV gamma-globulin 200 mg/kg monthly

6. **Preterm premature rupture of membranes.** Intravenous ampicillin (2 g q6h) plus erythromycin (250 mg IV q6h) × 48 hr followed by oral amoxicillin (250 mg q8h) plus erythromycin (333 mg po q8h) × 5 days (JAMA 1997;278:990.)

7. **Prevention of perinatal group B streptococcal (GBS) disease.** CDC recommends treatment of high-risk patients (MMWR 1996;45(RR-7):1.; MMWR 1998;47:665.)

   Risk factors

   - Risk based on *a*) history of prior infant who had GBS disease; *b*) GBS bacteruria during pregnancy, or *c*) delivery at <37 wk gestation (ruptured membranes at <37 wk without labor: Culture for GBS and treat positives or treat emperically until culture is negative)
   - Vaginal and rectal culture for GBS at 35–37 wk gestation
   - Culture not done: Intrapartum fever >100.4°F or ruptured membranes ≥18 hr

   Intrapartum prophylaxis IV penicillin G (5 mil units, then 2.5 mil units IV q4h until delivery). Alternatives: Ampicillin 2 g IV, then 1 g IV q4h or clindamycin 900 mg IV q8h until delivery *or* erythromycin 500 mg IV q6h until delivery

8. **Varicella** (Ann Intern Med 1999;130:922.)

PREVENTION OF VARICELLA IN ADULTS

Intervention	Efficacy	Cost	Candidate/comments
VZIG 625 units IM within 4 days	90%	$400	Immunocompromised persons; pregnant women; efficacy shown in children
Acyclovir* 40–80 mg/kg po within 7–9 days	80–85%	$120	Late presentation or vaccine contraindicated; 20% do not seroconvert
First vaccine dose within 3 days	70–90%	$40	Two dose regimen for any vaccine candidate; contraindicated for immunosuppressed patients and pregnant women

* Oral acyclovir has the benefit of demonstrated efficacy (Pediatrics 1993;92:219). Valacyclovir or famciclovir make more sense.

G. **High risk dog or cat bite** Amoxicillin-clavulanate (Augmentin) 500 mg po tid× 3–5 days; penicillin allergy—clindamycin 300 mg po qid or levofloxacin 500 mg po qd × 3–5 d

H. **Tuberculosis (see p 168)**

I. **Malaria (see p 142)**

J. **Influenza (see pp 196–197)**

K. **Endocarditis (see p 138)**

L. **Traveler's diarrhea (see p 141)**

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Prevention of Bacterial Endocardits

Recommendations of the American Heart Association, Infectious Diseases Society of America, American Dental Association, American Academy of Pediatrics, and American Society for Gastrointestinal Endoscopy (JAMA 1997;277:1794.; CID 1997;25:1448.; Med Lett 2001;43:98.)

A. **CARDIAC CONDITIONS**

Cardiac conditions considered at risk (not all inclusive)

a. High Risk

Prosthetic cardiac valve, including bioprosthetic and homograph valves

Prior endocarditis

Complex cyanotic congenital heart disease

Surgically constructed systemic pulmonary shunts

b. Moderate Risk

Rheumatic and other acquired valvular dysfunction (even after valve surgery)

Hypertrophic cardiomyopathy (IHSS)

Mitral valve prolapse with valve regurgitation (patients with mitral valve prolapse associated with thickening and/or redundancy of the valve may be at increased risk, especially men age $ 45 yr)

Prophylaxis not recommended

Isolated secundum atrial septal defect

Surgical repair without residual >6 mo of secundum atrial defect, ventricular septal defect, or patent ductus or arteriosus (without residual beyond 6 mo)

Prior coronary bypass surgery

Mitral valve defect without regurgitation (see above)

Physiologic or functional heart murmurs

Prior rheumatic fever without valve disease

Cardiac pacemakers and implanted defibrillators

Prior Kawasaki's disease without valve dysfunction

B. **Procedures**

Endocarditis prophylaxis recommended

Dental procedures: Extractions; periodontal procedures—surgery, scaling, root planing, probing; dental implant, root canal, subgingival placement of antibiotic strips; initial placement of orthodontic bands; intraligamentary local anesthetic injections, and tooth cleaning if bleeding is anticipated

Note: Three major studies have challenged the benefit of prophylactic antibiotics before dental procedures to prevent endoarditis (Arch Intern Med 1992;152:1869.; Lancet 1992;339:135.; and Ann Intern Med 1998;129:761.). Some authorities recommend prophylaxis only with extractions and gingival surgery and only when the risk is a prosthetic valve or previous endocarditis (Ann Intern Med 1998;129:829.).

Tonsillectomy and adenoidectomy

Surgical procedures that involve intestinal or respiratory mucosa

Bronchoscopy with a rigid bronchoscope

Sclerotherapy for esophageal varices*

Esophageal dilation*

Endoscopic retrograde cholangiography with biliary obstruction*

Surgical procedures that involve intestinal mucosa*

Gallbladder surgery*

Cystoscopy

Urethral dilation

Endocarditis prophylaxis not recommended**

Dental procedures: Restorative dentistry, local anesthesia, intracanal endodontic treatment, placement of rubber dams, suture removal, placement of removable prosthodontic or orthopedic appliances, fluoride treatments, impressions, orthodontic appliance adjustment, shedding of primary teeth

Endotracheal intubation

Tympanostomy tube insertion

Bronchoscopy with flexible bronchoscopy with or without biopsy**

Transesophageal echocardiography

Endoscopy of GI tract with or without biopsy**

Cardiac catheterization including balloon angiopathy

Transesophageal echocardiography**

Implanted cardiac pacemakers, defibrillators, and coronary stents

Incision and drainage of prepped sites

Circumcision

Vaginal hysterectomy**

Vaginal delivery**

Cesarean section

Genitourinary surgery in uninfected tissue: urethral catheterization, uterine dilation and curettage, therapeutic abortion, sterilization procedures, or insertion or removal of intrauterine device

Recommended Regimens Based on recommendations of the American Heart Association (JAMA 1997;227:1794.; CID 1997;25:1454.; Med Letter 2001;43:98.)

C. **Dental, oral and upper respiratory procedures**

Standard

Amoxicillin: 2.0 g po 1 hr before procedure

Alternatives: Penicillin V, 2 g po 1 hr pre-procedure; then 1 g 6 hr after first dose

Amoxicillin or penicillin allergy

Clindamycin 600 mg po 1 hr pre-procedure or

Cephalexin or cefadroxil, 2 g po 1 hr pre-procedure or

Azithromycin or clarithromycin, 500 mg po 1 hr pre-procedure

Cannot take oral medications

Ampicillin 2.0 g IM or IV 30 min pre-procedure

Amoxicillin or penicillin allergy and unable to take oral medicines

Clindamycin 600 mg IV within 30 min pre-procedure or

Cefazolin 1 g IM or IV within 30 min pre-procedure

D. **Genitourinary or gastrointestinal procedures**

High risk*: Ampicillin, 2 g IM or IV plus gentamicin 1.5 mg/kg IM or IV × 30 min of start-ing procedure; 6 hr later ampicillin 1 g IV or amoxicillin 1 g po

High risk plus penicillin allergy: Vancomycin 1 g IV over 1–2 hr plus gentamicin 1.5 mg// kg IV or IM (≤ 120 mg) complete infusion within 30 min of starting procedure

Moderate risk: Amoxicillin, 2 g po 1 hr pre-procedure or ampicillin 2.0 g IM or IV within 30 min of starting procedure

Moderate risk plus penicillin allergy: Vancomycin 1 g IV over 1–2 hr; complete infusion within 30 min of starting the procedure

E. **Miscellaneous issues** (CID 1997;25:1454.)

Target organisms: Upper respiratory tract procedures—*S. viridans*; GI and GU procedures—*E. faecalis*

Patients already receiving an antibiotic: Pick from a different class. Thus, if receiving a beta-lactam, use clindamycin, clarithromycin, or axithromycin

Anticoagulated patients: Avoid IM injections of antibiotics

Procedures involving infected tissue: Treat cause of infection

Cardiac surgery candidates: Antibiotic prophylaxis advocated, usually a first generation cephalosporin or vancomycin

Cardiac transplant recipients: Experience is very limited, but most treat as the moderate-risk category

Endocarditis experience: Most cases of strep viridans endocarditis have not followed dental procedures; most procedure related endocarditis occurs within 2 wk of the procedure

Effectiveness of prophylaxis: Efficacy of prophylaxis has never been shown (CID 1999;29:1.). Nevertheless, most infectious disease-trained physi-cians follow these guidelines, mainly because of the liability risk rather than the supporting science (CID 2002;34:1621.).

F. **GProphylaxis for Dental, Gastrointestinal, or Genitourinary Procedures in Patients with Prosthetic Joints**

1. Analysis by Gillespie showed no evidence of benefit (Infect Dis Clin North Am 1990;4:465.).
2. Review in CID 1995;20:1420.: Patients with prosthetic joints do not require prophylaxis for dental, gastrointestinal, or genitourinary procedures; possible exceptions are long procedures, surgery in infected area (e.g., periodontal disease), and other procedures with a high risk of bacteremia (Med Lett 1995;37:79.; J Bone Joint Surg 1996;78-A:1755.).
3. Updated statement of American Academy of Orthopedic Surgeons and American Dental Association (J Am Dent Assoc 1997;128:1004.): Prophylaxis is not indicated for dental patients with pins, plates, and screws, and it is not routinely indicated for most dental patients with total joint replacements. However, it is advisable to consider prophylaxis in a small number of patients who may be at potential increased risk of hematogenous total joint infection.

Footnotes

*Prophylaxis is recommended for high-risk patients and is considered optional for medium-risk patients.

**Prophylaxis is optional for high-risk patients.

*High risk: Prosthetic valve, history of endocarditis or surgically constructed systemic shunts or conduits or complex cyanotic congenital heart disease.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Prevention of Diseases Associated with Travel

A. **International Travel Directory: CDC Travel Hotline and Fax Information Service**

Travel advise	877-394-8747	24 hr/d voice mail
Traveler's Health FAX service	888-232-3299	24 hr/d automated FAX service (patients and providers)
Travel information	http://www.cdc.gov/	Select "Traveler's Health"
Malaria—Prevention and management	770-488-7100	
Travel—Emergency consultation	770-488-7100	24 hr/d service

CDC Parasitic Diseases Drug Service	404-639-3670	Drugs for special use

B. **TRAVELER'S DIARRHEA** (*Adapted from* Med Lett 2002;44:33.; NEJM 1993;328:1821.; CID 1993;16:616.; Infect Dis Clin North Am 1998;12:301.)

1. Risk

   High-risk areas (incidence 20–50%): Developing countries of Latin America, Africa, Middle East, and Asia

   Intermediate risk: Southern Europe and some Caribbean islands

   Low risk: Canada, Northern Europe, Australia, New Zealand, United States

2. Agents

   E. coli (enterotoxigenic—most common, enteroinvasive, enteroadherent)

   Shigella

   Campylobacter jejuni

   Aeromonas (especially Thailand)

   Plesiomonas shigelloides

   Salmonella sp

   Non-cholera *vibrios* (coastal Asia)

   Rotavirus (Mexico)

   Norovirus (cruise ships)

   Giardia (North America and Russia)

   Cryptosporidium (Russia)

E. histolytica (Rare)

3. Prevention

   Safe foods: Food served fresh and steaming hot; dry food (e.g., bread); hyperosmolar food (e.g., jellies, acidic fruits); fruit that is self-peeled; alcoholic beverages; carbonated beverages; water that is filtered and iodinized

   Avoid: Salads, cold foods, sauces, cream-filled desserts, raw seafood, raw meat, soft cheeses, tapwater, ice

4. *Antimicrobial prophylaxis* (CID 2000;31:1079.)

   a. Candidates for prophylaxis Travelers with important underlying health problem (active IBD, type I diabetes, elderly person with heart disease, AIDS) Trip will be ruined if traveler has brief illness Traveler requests chemoprophylaxis and/or is unwilling to follow dietary instructions (consider bismuth subsalicylate)

   b. Recommended regimens for selected patients (see a)

Regimen	Cost/d	Comment
Bismuth subsalicylate 2–262 mg tabs qid*	$3.40	Less effective than antimicrobials; few side effects*
Fluoroquinolones (once daily)		
Norfloxacin 400 mg/d Ciprofloxacin 500 mg/d Ofloxacin 300 mg/d Levofloxacin 500 mg/d	$3.80 $4.51 $4.92 $8.52	Fluoroquinolones are most predictably effective drugs; concern is abuse, resistance, cost, and side effects

* Pepto-Bismol turns tongue and stools black, sometimes causes tinnitis, may reduce absorption of doxycycline (sometimes given for malaria prophylaxis), and should not be taken with salicylates or anticoagulants and should not be taken >3 wk.

5. **Treatment of traveler's diarrhea** (CID 2000;31:1079.)[a] and CDC (http://www.cdc.gov/travel *accessed 8/1/03*)

Clinical feature	Treatment options
Mild (or moderate diarrhea: ≥3 loose stools/8 hrs with no loose stools/d) Fever or blood	No treatment *or* loperamide 4 mg, then 2 with each loose stool up to 16 mg/d *or* bismuth subsalicylate 2–262 mg tabs qid
Severe: Diarrhea is severe (≥ 3 stools/8 hrs), associated with fever or bloody stools	Loperamide × fluoroquinolone[b] 1. Norfloxacin 400 mg po bid × 3 d 2. Ciprofloxacin 500 mg po bid × 3 d 3. Levofloxacin 500 mg qd × 3 d Pregnancy: Loperamide + azithromycin 1000 mg × 1 or 500 mg qd × 3 d

[a] The 3-day course of treatment appears superior to single dose treatment for salmonellosis (AAC 1989;33:1101; JID 1992;165:1557) and for shigellosis due to *S. dysenteriae* type 1 (Ann Intern Med 1992;117:727). A study of shigellosis in Thailand

failed to show loperamide is contraindicated when given with a quinolone (Ann Intern Med 1985;102:582).

[b] Rates of C. jejuni fluoroquinolone resistance are 20–25% in U.S., 60–80% in Taiwan, Thailand, and Spain (Emerg Infect Dis 2001;7:24).

6. **Oral rehydration**: Potable fruit juice, caffeine-free soft drinks, salted crackers. Severe symptoms: WHO Oral Rehydration Salts. Ingredients/L water: NaCl 3.5 g (3/4 tsp), trisodium citrate 2.9 g (could use 1 tsp baking soda) and glucose 20 g, KCl 1.5 g (1 cup orange juice *or* bananas). Packets of oral rehydration salts are available from Cera Products, Jessup, MD (888-237-2598) and Jianas Bros, Kansas City, MO (816-421-2880)

7. **Antibiotic resistance**: Rate of resistance by *Shigella, Salmonella*, and *E. coli* is 50–90% for tetracycline and 35–76% for TMP-SMX (Infect Dis Clin North Am 6:333, 1992). Quinolone resistance is increasing. About 50% of *campylobacter* strains in Thailand are resistant to ciprofloxacin (J Trav Med 1994;1:119.)

C. **MALARIA PROPHYLAXIS** (*CDC Health Information for International Travel 1996–97, U.S. Department of Health and Human Services, pp 128–139*; Med Lett 2002;44:33.; MMWR 1997;46:55.)

CDC Malaria Hotline: Recommendations for prevention and case management—770-488-7788 (8 AM–4:30 PM EST) Emergency hotline for treatment guidance after hours—770-488-7100; http://www.cdc.gov/

Risk areas: Most areas of Central and South America, Hispaniola, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. During 1998 there were 1,227 reported cases of malaria in the U.S. including 43% *P. falciparum*, 38% *P. vivax*, 3.5% *P. malariae*, and 2.1% *P. ovale* (MMWR 2001;50:55–5.). Areas of acquisition included Africa (60%), Asia (20%), Central America and Caribbean (19%). Of the 1,227 cases at least 73% were U.S. citizens who did not receive malaria prophylaxis. There were 4 deaths attributed to

malaria for a mortality rate of 0.3%.

Drug resistance of *P. falciparum* to chloroquine (CRPF) is probable or confirmed in all countries with *P. falciparum* except Central America west of the Panama Canal Zone, Haiti, the Dominican Republic, Egypt, and most of the Middle East. Resistance to both Fansidar and chloroquine is widespread in Thailand, Myanmar (formerly Burma), Cambodia, and the Amazon basin of South America and has been reported in sub-Saharan Africa. Resistance to mefloquine has been reported primarily in Thailand. There is no documented resistance to tetracycline.

Advice to travelers (Med Lett 2002;44:33.)

1. Personal protection:
    a. Transmission is most common between dusk and dawn.
    b. Precautions include remaining in well-screened areas and using mosquito nets, clothing that covers most of the body, insect repellent containing DEET on exposed areas, and pyrethroid containing insect spray for environs and clothing. Permethrin may also be sprayed on clothing.

Drug	*Regimen*
Mefloquine[a]	250 mg q wk beginning 2 wk before travel, during travel and 4 wk after leaving
Doxycycline[b]	100 mg daily beginning 1–2 days before travel, during travel, and 4 wk after leaving
Atovaquone/proguanil[c] (Malarone)	250/100 mg (1 tab) daily beginning 1–2 days before travel, during travel, and 1 wk after returning
Alternatives:	
Primaquin	30 mg base qd — 2 wk before, during and 4 wk after
+ chloroquine[d]	500 mg (300 mg base) q wk — 2 wk before, during and 4 wk after
+ Fansidar	3 tabs for presumptive treament — 2 wk before, during and 4 wk after
or plus proguanil	200 mg daily — 2 wk before, during and 4 wk after
Chloroquine sensitive[e] Chloroquine	500 mg (300 mg base) 1–2 wk before travel, during travel and 4 wk after travel

[a]Mefloquine: Side effects include seizures and psychosis although both are rare (Lancet 1996;347:326). They are usually associated with high blood levels (Am J Trop Med Hyg 2001;65:189) Contraindications include pregnancy and travelers with history of epilepsy or psychiatric disorders. This drug is safe during the second and third trimesters of pregnancy (JID 1994;169:595); experience in first trimester is limited. Mefloquine resistance is reported in Thai-Cambodian and Thai-Myanmar border and western Cambodia.

[b]Doxyclycline: Efficacy is similar to mefloquine (Ann Intern Med 1997;126:963). Patients must be warned of photosensitivity and GI intolerance.

[c]Malarone is now available in the U.S. (Failure rate reported at 3/1374 (0.2%) (AAC 2002;46:1163)

[d]Use of chloroquine in areas with chloroquine-resistant *P. falciparum* should be accompanied by Fansidar to promptly treat febrile illness. Chloroquine and proguanil may be used in pregnancy.

[e]Haiti, Dominican Republic, Central America west of the Panama Canal, and Middle East.

Drugs to Prevent Malaria in Areas of Chloroquine-resistant *P. falciparum* (adapted from *Med Lett 2000;42:9*)

Countries with a Risk of Malaria* *(Reprinted from Med Lett 2002;44:33)*

AFRICA

- Angola
- Benin
- Botswana
- Burkina Faso
- Burundi
- Cameroon
- Central African Republic
- Chad
- Comoros
- Congo
- Côte d'lvoire
- Democratic Republic of the Congo (formerly Zaire)
- Djiubouti
- Equitorial Guinea
- Eritrea
- Ethiopia
- Gabon
- Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Kenya
- Liberia
- Madagascar
- Malawi

Mali
Mauritania
**Mauritius
Mayotte (French territorial collectivity)
Mozambique
Namibia
Niger
Nigeria
Rwanda
São Tomé and Principe
Senegal
Sierra Leone
Somalia
**South Africa
Sudan
Swaziland
Tanzania
Togo
Uganda
Zambia
Zimbabwe

AMERICAS

**Argentina
**Belize
**Bolivia
Brazil
**Colombia
**Costa Rica
**Dominican Republic

Ecuador
**El Salvador
French Guiana
**Guatemala
**Guyana
Haiti
**Honduras
**Mexico
Nicaragua
**Panama
**Paraguay
**Peru
**Suriname
**Venezuela

ASIA

Afghanistan
Armenia
**Azerbaijan
Bangladesh
**Bhutan
Cambodia
**China, People's Republic
Georgia
India
Indonesia
**Iran
Iraq
**Korea
Laos

Malaysia
**Myanmar
**Nepal
**Oman
Pakistan
**Philippines
**Saudi Arabia
Sri Lanka
**Syria
Tajikistan
**Thailand
Turkey
**Turkmenistan
**United Arab Emirates
**Viet Nam
Yemen

OCEANIA

Papua New Guinea
Solomon Islands
Vanuatu

*Only includes countries for which prophylaxis is recommended. For more information: The Medical Letter's Advice for Travelers CD-ROM or CDC at 1-888-232-3228.

**No malaria in urban areas.

Distribution of Malaria and Chloroquine-resistant *Plasmodium falciparum,* 1997

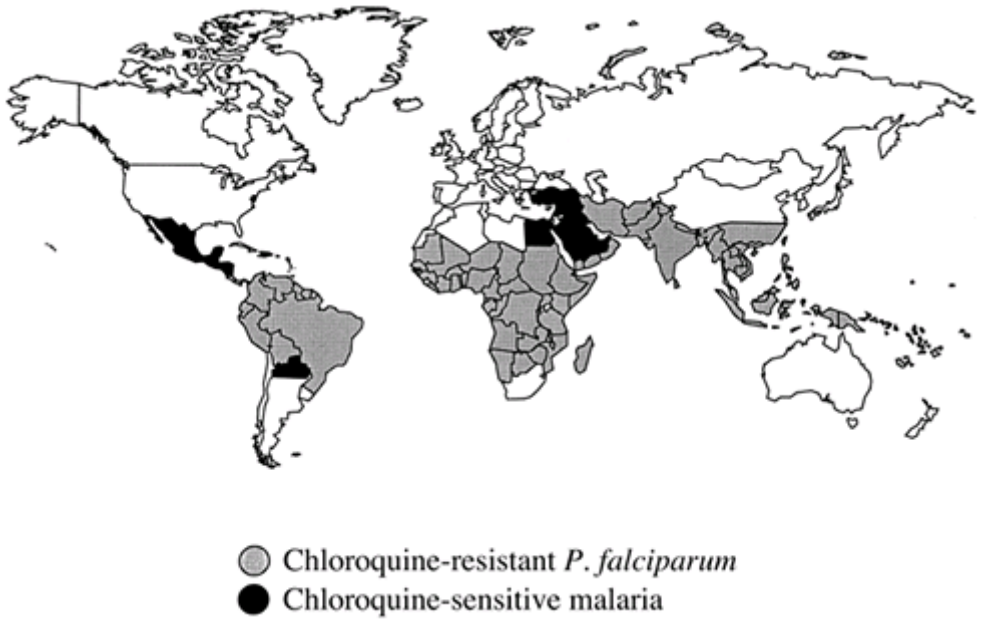

Figure. No caption available

CDC Health Information for International Travel 1999-2000. Washington DC: Government Printing Office, 2001:104

DRUGS USED IN PRESUMPTIVE TREATMENT OF MALARIA

Drug	Adult dose
Pyrimethamine-sulfadoxine (Fansidar)	3 tabs po, single dose

Atovaquone + proguanil (Malarone)	4 tabs as single daily dose × 3

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D. **VACCINES** (*See* pp 93–96 *for complete listing*)

1. **Hepatitis A**:

   Prevalence of antibody: Age related <10% in preadolescent and 75% in elderly

   Indication: Susceptibility (anti-HAV negative) and travel to area where HAV endemicity is high or moderate

2. **Hepatitis B**:

   Prevalence of antibody: Risk related general U.S. adult population 3% in caucasians, 14% in African Americans, and 35–80% in gay men. See p 264–266.

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   Indication: Susceptibility (anti-HBcAg negative) and travel to area where HBV endemicity is high or moderate plus: visits frequent, long stays, medical or dental care, or unprotected sex with residents

   Prevalence of HAV and HBV (Med Letter 2001;43:67.)

	HAV prevalence	**HBV prevalence**

U.S., Canada, Australia, Japan, northern and western Europe	Low	Low
Caribbean	Moderate	Moderate; high in Haiti and Dominican Republic
Central America	High	
South America	High	High in Amazon River basin
Eastern and southern Europe and Russia	Moderate	Moderate
Middle East	High	Moderate
Africa	High	Moderate–high
Asia (except Japan)	High	Moderate–high

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Treatment of Fungal Infections

Adapted from IDSA Recommendation 1999; CID 2000;30:652.; *nonbacterial infections consultantsof the Medical Letter (1997;39:86), and other sources* (CID 1998;26:1383.; AAC 1998;42:606.)

Fungus	*Form*	*Preferred treatment*	*Alternative agent(s), comment*
Aspergillus	Aspergilloma (fungus ball)		Massive hemoptysis—surgical resection with perioperative amphotericin; progressive invasive disease—amphotericin B IV, total dose 30–40 mg/kg; intracavitary amphotericin B (Thorax 1993;48:928). Surgical resection: High rates of complications (Ann Thorac Surg 1992;54:1159)
	Bronchopulmonary	Corticosteroids	Short courses for exacerbations
	Indolent, nonmeningeal	Itraconazole*** 400 mg/d po	Itraconazole*** is less effective with sinus or CNS involvement, or disseminated disease (Arch Intern Med 1997;157:1857)
	Sinusitis: Acute invasive	Surgery	Immunocompetent: Surgery alone often successful (RID 1990;12:1147)
	Sinusitis: Allergic	Surgical drainage (Medicine 1988;67:231)	
	CNS	Surgery ± amphotericin B + 5-FC	Case reports of success with amphotercin B lipid complex, itraconazole, and voriconazole (CID 1995;21:1485)
	Invasive pulmonary or extrapulmonary	Voriconazole 6 mg/kg IV × 2 doses day 1, then 4 mg/kg IV bid for ≥ 7 days, then 200 mg po bid (see comment) (NEJM 2002;347:408)	Caspofungin 70 mg IV, then 50 mg/d IV Experimental: Voriconazole Surgery successful in some cases (J Clin Oncol 1997;15:139) **Alternatives:** Amphotericin B 1.0–1.5 mg/kg/d IV or a lipid formulation. Note: The IDSA guidelines rank amphotericin B as preferred for invasive asper- gillosis, but a more recent clinical trial of amphotericin B (1–1.5 mg/kg/d) versus voriconazole showed voriconazole was significantly better in clinical outcome, survival, and adverse events (NEJM 2002;347:408) Itraconazole*** 600 mg/d po × 4 days, then 200 mg bid; failure rate highest in extrapulmonary disease and relapse rate high in immunosuppressed patients (Am J Med 1994;97:135; Arch Intern Med 1997;157:1857) Flucytosine (100 mg/kg/d po) or rifampin (600 mg/d po) or

			azoles sometimes added, but efficacy is not established and antagonism is seen in animal models
Blastomyces	Severe pulmonary	Amphotericin B when > 500 mg 0.7–1 mg/kg/d	Total amphotericin B dose: 1.5–2.5 g or switch to itraconazole amphotericin B and stable
	Mild to moderate pulmonary	Itraconazole*** 200–400 mg/d po for ≥6 mo	**Alternative:** Ketoconazole 400–800 mg/d, fluconazole 400–800 mg/d, amphotericin B 0.5–0.7 mg/kg IV*, total dose 20–40 mg/kg
	Disseminated (immunocompetent without CNS involvement)	Itraconazole*** 200–400 mg/d × ≥6 mo po or amphotericin B 0.7–1 mg/kg/d	**Alternative:** Ketoconazole 400–800 mg/d or fluconazole 400–800 mg/d Osteomyelitis: Treat ≥ 1 yr Progression on azoles or seriously ill: Amphotericin B to total dose 1.5–2.5 g
	Disseminated (immunocompromised or CNS involvement)	Amphotericin B 0.7–1.0 mg/kg/d for total dose 2 g	Some patients may be switched to fluconazole (800 mg/d) when clinically stable
Candida	Localized-mucocutaneous Oral (thrush)	Clotrimazole troche 10 mg troches 5×/days × 7–14 days Fluconazole	Fluconazole is **preferred** by Medical Letter consultants (1997;39:86); AIDS: Continue any of above regimens

Onychomycosis	Itraconazole 200 mg bid × 1 wk repeated monthly × 3–4 mo	**Alternative:** Terbinafine is alternative, but experience is inconsistent (AAC 1998;42:1057; AAC 1987;31:1558)
Esophageal	Fluconazole 100 mg po qd (up to 400 mg/d) × 14–21 days	Patients with AIDS may require continuous suppression with 100–200 mg/d **Alternatives:** Ketoconazole 200 mg po bid × 2–3 wk, itraconazole*** 200 mg po qd × 2–3 wk, or amphotericin B 0.3–0.7 mg/kg/d
Biliary	Amphotericin B or fluconazole	Must establish functional drainage Local installation of antifungals is unnecessary
Peritonitis Urinary	Amphotericin B or fluconazole; usually 2–3 wk Fluconazole 200 mg po qd × 7–14 days	Catheter-associated: Must remove catheter. Catheter instillations of ampho-tericin B are painful and should be avoided Non-catheter associated: Treat 2–3 wk Asymptomatic candiduria rarely requires therapy Main indications to treat: Possible disseminated candidiasis, symptomatic UTI, neutropenia, renal transplant, or candidate for urologic manipulation Bladder installations of amphotericin B (50 mg/mL) via closed triple lumen catheter × 5 days(rarely indicated because of high frequency of relapse) **Alternative:** Amphotericin B 0.7–1.0 mg/kg/d × 1–7 days or flucytosine 25 mg/kg qid (must have normal renal function)
Bloodstream (septicemia)	Fluconazole 400 mg/d po or IV (see comment: voriconazole is the preferred azole for fluconazole–resistant Candida) Amphotericin B IV ≥ 0.7–mg/kg/d*; total dose: 3–10 mg/kg Caspofungin (see comment)	Remove or change IV lines. Line sepsis: Remove line and treat with fluconazole 400 mg/d IV (NEJM 1994;331:1325) Voriconazole is active in vitro vs 99% of *C. albicans*, *C. parapsilosis, C. tropicalis*, and *C. krusei* (Antimicrob Ag Chemother 2002;46:1647) Amphotericin B is more predictably active versus non-albicans *Candida* sp, especially *C. krusei* Caspofungin 70 mg IV, then 50 mg/d IV appears equal to amphotericin and is less toxic (NEJM 2002;347:2020) Treat until negative blood cultures × 2 wk and resolution of signs and symptoms
Disseminated or metastatic (deep organ infection)	Amphotericin B 0.7–1.0 mg/kg/d*; total dose 20–40 mg/kg IV	**Indications for flucytosine:** Normal marrow and renal function or clinical deterioration with amphotericin B **Alternative:** Fluconazole 400 mg/day po or IV (best results with peritonitis, UTI, and hepatosplenic abscesses); may give up to 800 mg/d; caspofungin IV 70 mg, then 50 mg/d Voriconazole 6 mg/kg IV ×2 on day 1, then 4 mg/kg IV bid (especially for fluconazole-resistant strains
Hepatosplenic candidiasis	Fluconazole 6 mg/kg/d (stable patient)	Treat until there is resolution of lesions Amphotericin preferred for acutely ill patients and those with

	Pulmonary—severe or progressive infiltrate	Fluconazole 400–800 mg/d po Amphotericin B 0.5–0.7 mg/kg/d IV*; total dose: 7–20 mg/kg IV	**Alternatives:** ketoconazole 400–600 mg/d × 6–18 mo po Itraconazole*** 400 mg/d × 6–18 mo po
	Diffuse pneumonia	Amphotericin B 0.5–0.7 mg/kg/d	Amphotericin several weeks followed by azole for ≥ 1 yr Evaluate for extrapulmonary disease; presume immunodeficiency
	Nodule—asymptomatic	No therapy	If resected, no antifungal treatment is indicated unless immunosuppressed
	Cavity—asymptomatic	Observation	Consider resection if cavity persists ≥ 1–2 yr, progresses in size, or is near the pleura
	Cavity—symptomatic	Azole therapy or resection	Fluconazole 400 mg/d, ketoconazole 400 mg/d, or itraconazole*** 400 mg/d
	Cavity—rupture into pleura	Lobectomy or decortication + amphotericin B or azole	May give amphotericin B or azole 1 wk before surgery Chest tube drainage without surgery may be adequate
	Cavity—chronic fibrocavitary	Azole ≥ 1 yr	Azoles—above doses Failure to respond—switch azoles, increase dose of fluconazole, use amphotericin B or resect
	Disseminated (nonmeningeal)	Itraconazole 200 mg bid	**Alternatives:** Fluconazole 400–600 mg/d or ketoconazole 400 mg/d × 6–18 mo or longer or amophotericin B Itraconazole appears superior to fluconazole in response rates and relapse rates (Ann Intern Med 2001;133:676) May require surgical debridement Patients with fulminant disease should receive amphotericin B; indolent lesions may be treated with azoles. AIDS patients need lifelong treatment with azoles
	Meningitis	Fluconazole 400–800 mg/d po lifelong	**Alternative:** Fluconazole 800 mg/d + intrathecal amphotericin B 0.01–1.5 mg 1–7 ×/wk, itraconazole 400–600 mg/d or intrathecal amphotericin usually used for fluconazole failures Hydrocephalitis requires a shunt for decompression and does not indicate treatment failure
Cryptococcus	Pulmonary—stable and immunocompetent	Usually none	Exclude extrapulmonary disease: Culture blood, urine, and CSF; follow-up x-rays q 1–2 mo × 1 yr
	Pulmonary (mild moderate)	Fluconazole 200–400 mg/d × 6–12 mo Itraconazole 200–400 mg/d × 6–12 mo Amphotericin B 0.5–1.0 mg/kg/d,	Must do LP to exclude meningitis Fluconazole usually preferred

		1–2 g	
	Pulmonary—progressive and/or immuno-suppressed host	Amphotericin B 0.5–1.0 mg/kg/d IV*; total dose 1–2 g	**Alternative** for pulmonary or extrapulmonary nonmeningeal disease that is mild to moderate: Fluconazole 200–400 mg/d or itraconazole 200–400 mg/d × 6–12 mo in immunocompetent patients. AIDS patients—treatment is lifelong unless CD4 count increases to > 200/mm^3
	Extrapulmonary non-meningeal, non-HIV associated	Fluconazole 200–400 mg/d × 3–12 mo	**Duration fluconazole:** Asymptomatic 3–6 mo mild–moderate disease 6–12 mo **Alternative:** Itraconazole 200–400 mg/d × 6–12 mo or amphotericin B 0.4–0.7 mg/kg/d, total dose 1–2 g
	Cryptococcemia (positive Crypt Ag assay) or positive urine cult Meningitis—immunocompetent	Azole therapy Amphotericin B 0.7–1.0 mg/kg/d + flucytosine 100 mg/kg/d × 2 wk, then fluconazole 400 mg/d × ≥ 10wk	Must do LP to exclude meningitis Amphotericin B 0.7–1.0 mg/kg/d ± flucytosine 100 mg/kg/d × 6–10 wk
	Meningitis—AIDS patients	Amphotericin B 0.7–1 mg/kg/d + flucytosine 100 mg/kg/d × 14 days then fluconazole 400 mg/id × 8 wk, then 200 mg/d	**Alternative:** Fluconazole 400–800 mg ± flucytosine 100–150 mg/kg/d × 6 wk then fluconazole 200 mg/d (considered safe for initial treatment only if mental status is normal) Maintenance treatment for life with fluconazole (200 mg/d) required for all AIDS patients unless CD4 count increases > 200 Fluconazole may be used in dose up to 800 mg/d (JID 1994;170:238)
Histoplasma	Pulmonary—acute ± erythema nodosum	Usually none	Focal infiltrates: Consider itraconazole 200 mg/d × 6–12 wk in patients who fail to improve after 1 mo Severe disease: Amphotericin B 0.7 mg/kg/d for total course of up to 35 mg/kg × prednisone 60 mg/d × 12 wk posthospital discharge—itraconazole 200–400 mg/d to complete 12 wk of therapy
	Pulmonary—chronic	Amphotericin B, then itraconazole*** po 200–400 mg/d × 12–24 mo (severe disease) Itraconazole × 12–24 mo (mild–moderate disease)	**Alternatives:** Ketoconazole, 200–800 mg/d × 12–24 mo or amphotericin B 0.7 mg/kg/d IV*; total dose: 30–40 mg/kg; amphotericin B is preferred for patients who are seriously ill, immunosuppressed, or fail oral treatment Treat until clinical symptoms and lab tests are negative including ESR and histoplasma antigen assay, usually >12 mo amphotericin B 0.5–0.6 mg/kg/d IV*; total dose: 30–40 mg/kg Surgery for intractable hemoptysis despite medical treatment
	Disseminated—immuno-competent, without CNS involvement	Amphotericin B until stable, then itraconazole*** 200–400 mg/d × 6–18 mo	**Alternatives:** Amphotericin 0.7–1.0 mg/kg/d IV* or ketoconazole 200–400 mg/d × 6–12 mo or fluconazole 200–400 mg/d × 6–18 mo

		(severe disease) Itraconazole 200–400 mg/d × 6–18 mo (mild–mod disease)	Treat until histoplasma antigen assays in blood and urine are > 4 units, usually > 1 yr Intraconazole is preferred for patients with mild or moderately severe disease and for patients who have responded to amphotericin B (CID 1996;23:996; Am J Med 1992;93:489)
	Disseminated—AIDS	Amphotericin B 0.7–1.0 mg/kg/d IV*; then itraconazole 400 mg/d Itraconazole*** 600 mg/d × 3 days, then 200 mg po bid × 12 wk	Patients with severe illness should receive amphotericin B; AIDS patients should receive lifelong maintenance with itraconazole***, 200–400 mg po qd (Ann Intern Med 1993;118:610; Am J Med 1995;98:336) Fluconazole (800 mg/d) is less effective, and ketoconazole should not be used (Am J Med 1997;103:223; Medicine 1990;69:361) Maintenance therapy: Itraconazole 200–400 mg/d for life or amphotericin B, 50 mg/wk. Immune reconstitution may alter this recommendation
	Meningitis	Amphotericin B 0.7–1 mg/kg/d to complete 35 mg/kg then fluconazole 800 mg/d for additional 12 mo	Relapse on amphotericin B: Intrathecal or intraventricular amphotericin B Itraconazole is more active in vitro but fails to penetrate CNS
	Pericarditis	Non-steroidal anti-inflammatory agents × 2–12 wk or corticosteriods × 1–2 wk if hemodynamic compromise Percutaneous or surgical drainage for severe hemo-dynamic compromise	Usually no azole therapy except with corticosteroid treatment: Itraconazole 200–400 mg/d × 12 wk
	Fibrosing mediastinitis	Trial with itraconazole 200–400 mg/d Intravascular stents for vascular obstruction	Progressive obstruction vena cava, airways, heart, esophagus: Surgical mortality is 20% (Medicine 1990;69:361) Corticosteroids are not helpful (Medicine 1988;67:295) Itraconazole is advocated only if work-up fails to distinguish granulomatous and fibrosing mediastinitis, ESR increased, or CF titer > 1:32
	Granulomatous mediastinitis	Amphotericin B, then itraconazole 200–400 mg/d × 6–12 mo ± prednisone 40–80 mg/d × 2 wk	Less severe cases can be treated with itraconazole alone × 6–12 mo Use steroids for airway obstruction Surgery recommended if symptoms of obstruction persist despite antifungal therapy
	Ocular	Laser photocoagulation Intraocular steroids Retinal irradiation	Appears to be immune-mediated disease
Malassezia furfur	Fungemia	Amphotericin B 1 mg/kg/d	May require removal of IV line

Paracoccidioides	Pulmonary or mucocutaneous	Itraconazole*** po 100 mg/d × 6 mo	**Alternatives:** Amphotericin B 0.4–0.5 mg/kg/d IV*; total dose: 30–35 mg/kg (preferred for severe disease); sulfonamides (such as sulfadiazine, 4–6 g/d po × 6–12 mo) or ketoconazole 200–400 mg/d po × 6–12 mo
Phycomycetes *Absidia* *Mucor* *(Mucormycosis)* *Rhizopus*	Pulmonary and extra-pulmonary	Amphotericin B IV 1.0–1.5 mg/kg/d IV*; total dose: 30–40 mg/kg	Rhinocerebral: Surgical debridement required.
Penicillium marneffei	Disseminated disease involving skin, marrow, nodes, lung, ± liver	Amphotericin B, then itraconazole	Endemic in Thailand, China, Vietnam, Hong Kong, Indonesia
Pseudoallescheria boydii	Sinusitis, endophthalmitis	Ketoconazole 400–800 mg/d po × 1–12 mo Itraconazole*** 200 mg bid po × 1–12 mo Voriconazole 6 mg/kg bid × 1 day, then 4 mg/kg bid IV bid, then 200 mg po/d	**Alternative:** Miconazole 600 mg IV q8h
Sporothrix	Lymphocutaneous	Itraconazole*** 100–200 mg/d po × 3–6 mo	**Alternatives:** Potassium iodide (1 g/mL) 5 drops tid increasing to 40–50 gtts tid × 3–6 mo Itraconazole is preferred; fluconazole (400 mg/d × 6 mo) should be used only with intolerance to itraconazole. SSKI has side effects and is inconvenient but is less expensive Local hyperthermia × 2–3 mo
	Disseminated	Amphotericin B 0.5 mg/kg/d IV*	**Alternative:** Itraconazole 200 mg po bid Amphotericin is preferred for CNS, severe disseminated disease, and itraconazole failures
	Pulmonary	Amphotericin B until clinically stable, then itraconazole*** 200 mg bid po	Focal disease with cavity; cure rates with antifungal agents are <50%; surgical resection often required
	Meningeal	Amphotericin B, 1–2 g	Life-long maintenance with itraconazole 200 mg bid or fluconazole ≥800 mg qd
	Osteoarticular	Itraconazole 200 mg bid × 12 mo	**Alternative:** Amphotericin B, 1–2 g or fluconazole 800 mg/d × 12 mo
	Pregnancy	Amphotericin B	Exception is local hyperthermia for lymphadenitis

(Sporotrichosis)			
	AIDS	Amphotericin B 1–2 g, then itraconazole	Itraconazole may be used for less serious disease and for life-long maintenance after treatment with amphotericin B

* Amphotericin B: Lipid formulations compared with amphotericin B appear to be equally effective, have the disadvantage of high cost (10- to 20-fold greater), and the advantage of reduced nephrotoxicity and reduced frequency and severity of infusion-related adverse effects. See summary on p 159.
** Flucytosine levels should be 25–50 µg/mL; some advocate maximum daily dose of 100 mg/kg/d and reduced dose (50–75 mg/kg/d) if levels are unavailable. Follow platelet count and WBC daily (CID 1993;16:1).
*** Itraconazole: Usual dose regimen is 200 mg tid (loading dose) × 3 days, then 200 mg bid for severe infections. Itraconazole SHOULD be given with food, and Coca-Cola or other acid drink may be given to improve absorption. Bioavailability may be improved with liquid formulation which should be given on an empty stomach. Blood levels should be monitored in any recipient of itraconazole given for a serious infection for a prolonged period, especially if there is concern about absorption or compliance. Levels measured after 1 wk should be ≥ 1 µg/mL; usual therapeutic levels are 1–10 µg/mL. Fluconazole has advantages of more predictable absorption, reduced drug interactions, and good CNS penetration.

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COMPARISON OF ANTIFUNGAL AGENTS

Antifungal agents	*Amphotericin (Fungizone)*	*Flucytosine (Ancobon)*	*Ketoconazole (Nizoral)*	*Fluconazole (Diflucan)*	*Itraconazole (Sporanox)*	*Caspofungin (Cancidas)*
Oral bioavail-ability	Nil	>80%	75%	>80%	>70%	Nil
Effect of gastric achlorhydria	—	—	Reduced absorption	—	Reduced absorption	—
Serum half-life	15 days	3–6 hr	6–10 hr	24–30 hr	30–45 hr	9–11 hr
Half-life—anuria	15 days	70 hr	6–10 hr	100 hr	30–45 hr	9–11 hr
Urine level (active agent)	3%	80%	<2–4%	80%	<1%	1%
CSF levels (% serum)	3%	75%	<10%	70–90%	<1%	?

Usual dose/d	25–50 mg IV/day	1500–2500 mg po q6h	200–400 mg po/day	100–200 mg IV or po/day	200–400 mg IV or po/day	70 mg IV, then 50 mg/d IV $360/50mg
Cost (average wholesale)/d	$11/50 mg Ampho $480–1200/3 g lipid preps.	$100/7 g po	$4/200 mg po	$13/200 mg po $133/400 mg IV	$8/200 mg po $177/250 mg IV	$360/50 mg

COMPARISON OF AMPHOTERICIN PREPARATIONS LIPID FORMULATIONS OF AMPHOTERICIN B: IDSA GUIDELINES

(CID 2000;30:653.; CID 2003;37:415.)

Potential advantages compared with conventional amphotericin B: Increased daily dose (up to 10-fold); high tissue concentration, especially in RE system (lungs, spleen, liver), reduced infusion related reactions (especially AmBisome), substantial decrease in nephrotoxicity

Disadvantages compared with conventional amphotericin B: the lipid-based formulations are **much** more expensive: Amphotericin B: $11/d; AmBisome: $800–$1500/d; Abelcet: $640/d; Amphotec: $480–640/d (average wholesale price, 2003)

Indications (See IDSA Guidelines, CID 2000;30:653.)

1. Patients receiving amphotericin B who develop renal dysfunction (creatinine>2.5 mg/mL), severe infusion related adverse events or disease progression despite>500 mg total dose of amphotericin
2. Patients who require amphotericin therapy with baseline creatinine>2.5 mg/mL
3. Some immunocompromised patients with life-threatening mold disease (aspergillosis or zygomycosis)

Update: Some argue it is time to embrace the lipid preparations as the new standard since experience shows that these preparations are as active or more active than amphotericin B desoxycholate, they are superior for some and are clearly less toxic (CID 2003;37:415.)

COMPARISON OF LIPID-BASED AMPHOTERICIN PREPARATIONS

(CID 2003;37:415.)

Preparation	***Amphotec (ABCD)***	***Abelset (ABLC)***	***AmBisome (LAmB)***
FDA approval	Invasive aspergillosis plus contraindication or failure with Ampho B	Invasive fungal infections plus contraindications or failure with Ampho B	Empiric RX in neutropenic patients Cryptococcal meningitis with AIDS Candida, Crypto, and As-pergillis infection plus failure or contraindication with Ampho B
Dose—FDA approved	3–4 mg/kg/day		3 mg/kg/d—empiric therapy 3–5 mg/kg systemic fungal disease 6 mg/kg cryptococcal meningitis
Efficacy*			
Aspergillis	34%	46%	61%
Candidiasis	59%	75%	80%

Cryptococcosis	45%	67%	100%
Tissue penetration**			
Liver	2×	2×	0.5–1×
Kidney	0.1×	0.2×	0.2×
Lung	—	2×	0.2×
Brain	0.1	0.1	1.2×
C_{max}	3.1 µg/mL	1.7 µg/mL	83 µg/mL
Usual AWP (/day)	$400–500	$800–850	$950–1300
* Efficacy based on non-comparative clinical trials			
** Tissue concentrations relative to amphotericin B			

SPECTRUM OF ACTIVITY OF ANTIFUNGAL AGENTS

(Based on in vitro sensitivity tests and animal models)

	Asper-gillus	***Blasto-myces***	***Candida albicans***	***Candida krusei***	***Chromo-mycosis agents***	***Crypto-coccus***	***Coccidi-oides***	***Histo-plasma***	***Paracoccidi-oides***	***Phyco-myces (mucor-mycosis)***
Amphotericin B	+*	+*	+*	+*		+*	+*	+*	+	+*
Flucytosine	+		+	—	+*	+	—	—	—	—
Ketoconazole	—	+	+	—	+	+	+	+	+	—
Fluconazole	—	+	+*	—	—	+*	+*	+	+	—
Itraconazole	+	+*	+	—	+	+	+	+*	+*	—
Voriconazole	+	+	+	+	+	+	+	+	?	—
Caspofungin	+	—	+	+	—	—	—	—	—	—

* Preferred agent(s) for most clinical infections.

COMPARISON OF AZOLES

	Ketoconazole	*Itraconazole*	*Fluconazole*	*Voriconazole*
Bioavailability	75%	>70%	>80%	95%
Half live (hrs)	8	30	28	8
CSF/plasma	<10	<1	>80	>50
Urine levels	<5	<1	80	<2
Side effects*	Reduced libido Menstrual changes	Cardiomyopathy Hypokalemia	Alopecia	Vision changes
Drug interactions**	Steroids, ritonavir saquinavir, carbamazepine, phenytoin, INH	Statins, pimozide, protease inhibitors, verapamil, INH, carbamazepine, phenoparbital	Theophyllin	Statins, omeprazole, phenytoin

* All may cause hepatitis, GI intolerance, and rash
** All have decreased AUC with rifampin and increased AUC with warfarin, sulfonaureas, phenytoin, midzolium, tirzolam, alprazolam, cyclosporin, and tacrolimus.

TREATMENT OF DERMATOPHYTIC FUNGAL INFECTIONS

Condition	*Agents*	*Location*	*Treatment*
Tinea corporis (ringworm)	*T. rubrum* *T. mentagrophytes* *M. canis* *E. floccosum*	Circular, erythema well demarcated with scaly, vesicular, or pustular border Non-hairy skin Pruritic	Topical agents: Miconazole, clotrimazole, econazole, naftifine, ciclopirox, or terbinafine bid or ketoconazole, oxiconazole, sul-conazole qd for ≥4 wk. If no response then griseofulvin × 2–4 wk (see below)
Tinea cruris (Jock itch)	*E. floccosum* *T. rubrum* *T. mentagrophytes*	Erythema and scaly groin and upper thighs Pruritic	Topical agents as above. Loose fitting clothes Absorbent powder. Unresponsive cases: Griseofulvin × 2–4 wk
Tinea pedis (athlete's foot)	*T. rubrum T. mentagrophytes* *E. floccosum*	Foot, especially fissures between toes; scaly, vesicles, pustules ± nail involvement	Topical agents as above. Keep feet dry and cool Unresponsive cases: griseofulvin 4–8 wk

Tinea unguium (nail involvement)	*T. rubrum* *T. mentagrophytes* *Candida* *T. soudanense*	Nails, usually distal and lateral nail thick-ening with adjacent skin involved	Oral griseofulvin or ketoconazole 6–24 mo (until new nail) or itraconazole 200 mg bid × 1 wk × 2 (fingernails) separated by 3 wk; 200 mg/d × 12 wk or 200 mg bid × 1 wk/mo × 3–4 mo (toenails) (Med Lett 1996;38:5), terbinafine (Lamisil) 250 mg/d × 6 wk (fingernails) or 12 wk (toenails) (Med Lett 38:76, 1996) or butenafine (Mentax) (1%) topical qd × 4 wk (Med Lett 39:63, 1997)
Tinea capitis (ringworm—scalp)	*T. tonsurans* *T. mentagrophytes* *T. verrucosum* *M. canis*	Scaling and erythematous area of scalp with broken hairs and localized alopecia	Griseofulvin × 4–8 wk + 2.5% selenium sulfide shampoo 2×/wk. Alternative to griseofulvin is ketoconazole
Tinea versicolor	*Malassezia furfur*	Scaling oval macular and patchy lesions on upper trunk and arms; dark or light, fail to tan	Topical 2.5% selenium sulfide applied as thin layer over entire body × 1–2 hr or overnight for 1–2 wk, then monthly × 3; wash off. Alternatives: Topical clotrimazole, econazole, ketoconazole, naftifine, haloprogin, or oral ketoconazole

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Treatment of Mycobacterial Infections

I. **Tuberculosis**

Guidelines of CDC, American Thoracic Society, and Infectious Diseases Society of America (Am J Respir Crit Care Med 2003;167:603.; MMWR 2003;52:RR-11.; NEJM 2001;345:189.)

A. **Treatment**

1. Four drug treatments preferred for initial empiric treatment: Isoniazid (INH), rifampin (Rif), pyrazinamide (PZA), and ethambutol (EMB).
2. Directly observed therapy (DOT) is preferred for all patients. Priorities for DOT: Pulmonary TB with positive smear, treatment failure, relapse, drug resistance, HIV co-infection, current or prior drug abuse, psychiatric illness, memory impairment, or prior non-adherence.
3. Susceptibility tests should be performed on the initial isolate and on any isolate obtained at 3 mo post-treatment (failure to convert).
4. Future therapy: Fluoroquinolones are the most promising new agents (BMJ 2002;325:1282.).
5. Monitoring: Some recommend routine baseline LFTs and periodic monitoring due to hepatotoxicity of INH, PZA, and rifampin. Increases in ALT in up to 20%, but major liver disease in <1% (BMJ 2002;325:1282.)
6. Relapse: Probability of relapse is <5%; most occur within 6 months and involve drug sensitive strains.
7. Resistant strains: Give 4 active drugs, usually 3 oral and one parenteral aminoglycoside.

Regimen Options for Initial Treatmentof TB Among Adults

Drugs	***Phase 1 (8 weeks)***	***Phase 2*: Regimen, doses, minimal duration***

INH RIF RZA EMB	8 weeks 7 d/wk, 56 doses, 8 wks 5 d/wk, 40 doses, 8 wks	INH/RIF 7 d/wk, 126 doses or 5 d/wk, 90 doses, 18 wks INH/RIF 2×/wk, 36 doses, 18 wks INH/RPT, 1×/wk, 18 doses, 18 wks**
INH RIF RZA EMB	2 wk/6 week 7 d/wk, 14 doses, 2 wks, then 2×/week, 12 doses, 6wks	INH/RIF 2×/wk, 36 doses, 18 wks INH/RPT 1×/wk, 18 doses, 18 wks**
INH RIF RZA EMB	8 weeks 3×/wk, 24 doses, 8 wks	INH/RIF 3×/wk, 54 doses, 18 wks
INH RIF EMB	8 weeks 7 d/wk, 56 doses or 5 d/wk, 40 doses, 8 wks	INH/RIF 7 d/wk, 217 doses or 5 d/wk, 155 doses, 31 wks INH/RIF 2×/wk, 62 doses, 31 wks

INH = Isoniazide, RIF = Rifampin, RPT = rifapentine, PZA = Pyrazinamide, EMB = Ethambutol
* Patients with cavitation at baseline and positive cultures at 2 months should receive 31 week continuation phase for total of 9 months.
** Not recommended for HIV infected patients.

Recommended First Line Drugs

(Am Rev Respir Crit Care 2003;167:603.)

Agent	*Forms*	*Daily dose*	*Twice/thrice weekly dose*	*Cost/mo daily regimen*	*Adverse reactions*	*Comment*

Isoniazid (INH)	Tabs: 50 mg, 100 mg, 300 mg Syrup: 50 mg/5 mL Vials: 1g (IM)	5 mg/kg po or IM Max—300 mg, po or IV	15 mg/kg Max—900 mg	$1.50	Elevated ALT 10–20% clinical hepatitis* 0.6%, peripheral neuropathy 0.2%	Liver injury increased with RIF and/or PZA, EtOH, age Peripheral neuropathy is prevented with pyridoxine (50 mg/d) suggested for diabetes, HIV, uremia, alcoholism, malnutrition, pregnancy, or seizure disorder
Rifampin (RIF)	Caps: 150 mg, 300 mg Vials: 600 mg (IV)	10 mg/kg Max—600 mg po or IV	10 mg/kg Max—600 mg	$123	Orange discoloration of secretions and urine, purpura (rare) Hepatitis*, cholestatic Pruritis ± rash 6% Flu sx with 2×/wk	Multiple drug interactions: accelerates clearance of methadone, warfarin, corticosteroids, estrogens, ketoconazole, cyclosporine, phenytoin, oral hypoglycemics, protease inhibitors
		wt (kg)	*Daily*	*2×/wk*	*3×/wk*	

Pyrazinamide (PZA)	Tabs: 500 mg	40–55 56–75 76–90	1.0 g 1.5 g 2.0 g	2.0 g 3.0 g 4.0 g	1.5 g 2.5 g 3.0 g	$127	Hepatitis*—frequent with RIF + PZA Nongouty polyarthralgias Hyperuricemia (gout rare)	Severe liver injury in 6% given PZA + RIF Hyperuricemia is usually inconsequential
Ethambutol (EMB)	Tabs: 100 mg, 400 mg	40–55 56–75 76–90	0.8 g 1.2 g 1.6 g	2.0 g 2.8 g 4.0 g	1.2 g 2.0 g 2.4 g	$168	Optic neuritis, dose-related	Decreased acuity or red–green discrim-ination; dose-related

* All patients receiving INH, rifampin, and/or pyrazinamide should be instructed to report immediately any symptoms of hepatitis: anorexia, nausea, vomiting, jaundice, malaise, fever >3 days, or abdominal tenderness. Risk of hepatitis is greater with age >35 yr and daily alcohol use.

Second Line Antituberculous Drugs

Agent	***Forms***	***Daily dose* (maximum)***	***Adverse reactions***	***Monitoring/comments***
Streptomycin	Vials	15 mg/kg/d* 1 g/d Age >50 yrs 10 mg/kg/d 750 mg/d	Auditory, vestibular, and renal toxicity	Audiometry and vestibular tests at baseline and periodically; renal function tests
Capreomycin	Vials:	15 mg/kg IM	Auditory, vestibular,	Audiometry and vestibular tests at

(Capastat)	1 g	(1 g)	and renal toxicity	baseline and periodically; renal function; high frequency hearing loss in 3–10%
Kanamycin (Kantrex)	Vials: 75 and 500 mg 1 g	15 mg/kg IV or IM 1 g	Auditory, vestibular, (rare), and renal toxicity	Audiometry and vestibular tests at baseline and periodically;
Amikacin (Amikin)	Vials: 0.1, 0.5 and 1 g	15 mg/kg IV or IM	Auditory, vestibular, and renal toxicity	Audiometry and vestibular tests at baseline and periodically; renal function
Ethionamide (Trecator)	Tabs: 250 mg	500–750 mg qd; 15–20 mg/kg/d	GI intolerance, hepatotoxicity, photosensitivity, arthralgias, impotence, metallic taste	Hepatic enzymes monthly and D/C if transaminase ≥5 × upper limits normal. GI intolerance—may need to gradually increase dose and/or give hs and 30 min after antiemetic
Gatifloxacin	Caps: 400 mg	400 mg/d	Nil	No monitoring for ADR
Moxifloxacin	Caps: 400 mg	400 mg/d	Nil	No monitoring for ADR
Levofloxacin	Caps: 500 and 750 mg	500 mg bid	Nil	No monitoring for ADR

PAS	Tabs: 500 mg, 1 g	4–6 g po bid; 150 mg/kg/d	GI intolerance, hepatotoxicity, sodium load, hypersensitivity	Delayed release granules should be given with acidic food or drink
Cycloserine (Seromycin)	Caps: 250 mg	500–750 mg po bid; 10–15 mg/kg/d	Psychosis, rash, convulsions	Assess mental status; some give pyridoxine (50 mg/250 mg cycloserine) to decrease psychiatric effects, seizures, and neuropathy
* Give IM or IV 5–7 days/wk × 2–4 months, then 2–3×/wk after culture conversion				

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B. **Diagnostic Tests**

1. **AFB smear**: Sensitivity of AFB stain with expectorated sputum, induced sputum and bronchoscopy aspirates are similar at 40–60% in culture positive cases (Am J Respir Crit Care Med 2000;162:2238.). Specificity depends on the prevalence of TB and MOTT, but may be as low as 50% (J Clin Micro 1998;36:1046.)

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2. **Nucleic acid amplification** (NAA assays) (Am J Respir Crit Care Med 2001;164:2020.): Commercially available as MTB (Gen Probe) and Amplicor (Roche) at $50–100/assay. Sensitivity of NAA assays is 80–84% including virtually all smear-positive cases and about half of smear-negative/culture-positive cases. CDC recommendations (MMWR 2000;49:593.):
   - AFB smear and NAA on the first sputum collected. If the smear is positive and the NAA is positive, TB is diagnosed with near 100% certainty.
   - If the smear is positive and the NAA is negative, the sputum should be tested for inhibitors by spiking the sample with lysed *M. tuberculosis* and repeat the assay. If inhibitors are not present, the patient is assumed to have MOTT.
   - If the smear is negative and the NAA is positive, additional sputum samples are recommended. If positive, the patient is presumed to have TB.
   - If both the smear and the NAA are negative, additional specimens should be tested by NAA and, if negative, TB is assumed to be excluded.

3. **AFB culture**: Frequency of false positive results in a review of 14 studies with >100 patients show a mean of 3.1% false positives (CID 2000;31:1390.). The presumed mechanism is laboratory cross-contamination. The major clue is a single positive culture, especially if not supported by clinical observations.
4. **Broth-based cultures**: When combined with DNA probes, broth-based cultures are capable of detecting *M. tuberculosis* within two weeks with smear-positive cases and within three weeks with smear-negative cases (Am J Clin Path 2000;113:770.; Diag Microbiol Infect Dis 2000;37:31.)

C. **Monitoring Drug Therapy**

1. **Monitoring for adverse drug reactions (ADRs)**
   a. Most frequent reactions with standard 4 drug therapy are rash ± fever, hepatitis, and GI intolerance. The main cause of hepatotoxicity appears to be PZA (Am J Resp Crit Care Med 2003;167:1472.). Ethambutol is a rare cause of toxicity except for occasional cases of dose-related vision changes.
   b. Recommendations
      - INH: Baseline and monthly LFTs if pre-existing liver disease, or development of abnormal LFTs that do not require discontinuing INH Monthly inquiries about symptoms that suggest hepatitis
      - RIF: No monitoring for ADRs
      - PZA: LFTs as for INH; uric acid is usually elevated, but usually is not consequential and monitoring is not recommended
      - EMB: Baseline visual acuity and Ishihara test of color discrimination. Inquire about vision changes at each monthly visit and warn to contact clinic immediately if vision changes. Monthly tests of acuity and color discrimination with doses >15–20 mg/kg for >2 months or with renal failure
2. **Duration of therapy with drug-sensitive strains**

   Initial 8 week course: Identical for all patients

   Continuation phase:

   - Cavitation or positive culture at 2 months

Cavitation	*Positive culture at 8 wks*	*Duration continuation phase*
+	-	4 mo.

-	+	4 mo.
+	+	7 mo.

- No cavitation, negative culture at 2 months, negative HIV and no extrapulmonary TB: RIF/INH or RPT/INH × 4 mo.
- HIV or extrapulmonary TB: INH/RIF (only)

- Rationale: Risk for relapse with cavitation and/or positive sputum at 2 months using standard initial 4 drug initial phase and INH/RIF 2×/week × 16 weeks USPH study 22 (Lancet 2002;360:528.).

Cavity	***Sputum positive at 2 mo***	***Sputum negative at 2 mo***
Yes	21% (n = 48)	5% (n = 150)
No	6% (n = 17)	2% (n = 181)

3. **Treatment interruptions**

Initial phase

Duration of interruption <14 days: Continue therapy, if not completed in 3 months—restart

Duration ≥14 days: Restart

Continuation phase:

≥80 doses: No additional therapy

<80% doses

Duration of interruption <3 months: Continue, if not completed in 6 months—restart

Duration of interruption ≥3 months: Restart 4 drug initial phase

4. **Evaluation of response**: Symptoms usually improve within 4 wk, and 85% of patients treated with INH-rifampin containing regimen convert sputum culturees to negative by the end of 2 mo. Sputum smear and culture should be performed at least monthly until conversion is documented. Weekly sputum smears with quantitation are encouraged. Patients with positive sputum cultures after 2 mo of treatment need reevaluation, drug susceptibility test, and directly observed treatment. If resistance noted, give at least two active drugs under DOT. Patients with negative cultures ≤2 mo should have one additional smear and culture at completion of treatment. Some recommend x-ray at 2–3 mo and at completion of treatment.

5. **Relapse**: Most relapses occur within 6 months and involve drug sensitive strains. Major risks are: (1) extent and severity of the lung disease as indicated by cavitation and bilateral infiltrates, and (2) positive cultures at two months (Lancet 2002;360:528.)

D. **Special Considerations With Treatment**

1. **HIV Infection**

Identical for general population except:

- CD4 <100/mm^3: Continuation phase should be daily or 3×/week
- Once weekly rifapentine regimen should not be used.
- Positive cultures at 2 months: Strongly consider 7 month continuation phase (total 9 mo.)
- In absence of prior HIV therapy and CD4 <350/mm^3: Delay antiretroviral drugs for 4–8 weeks.
- RIF may be used with 2 NRTIs + EFV, RTV + SQV (Invirase or Fortovase) or AZT/3TC/ABC.
- Rifabutin combined with other PIs and NNRTI requires a dose adjustment of both. See: http://www.cdc.gov/nchstp/tb/ or http://www.medscape.com/updates/quickguide
- When starting NNRTI or PI in patient receiving RIF, substitute rifabutin 2 weeks prior to NNRTI or PI to give a 2 week washout period for RIF
- Paradoxical reaction: Frequency in 7–36%; clinical features—high fever; increased adenopathy, CNS lesions, pulmonary infiltrates and pleural effusions. Treatment is symptomatic; if severe, give prednisone 1 mg/kg and reduce dose at 1–2 weeks.

2. **Extrapulmonary TB**

Standard 4 drug initial phase followed by INH/RIF for 4–7 months except for CNS. TB which is treated 9–12 months.

Site	*Duration*	*Steroids*
Lymph nodes	6 months	No
Bone or joint	6–9 months	No
Pleural disease	6 months	No
Pericarditis	6 months	Recommended
CNS TB	9–12 months	Recommended
Disseminated	6 months	No
GU TB	6 months	No
Peritoneal	6 months	No

3. **Culture negative suspected active TB**

   Low probability: No initial treatment

   Culture negative at 2 mo and x-ray unchanged

   - RIF ± INH × 4 mo.
   - INH × 9 mo
   - RIF/PZA × 2 mo

   High probability

   INH/RIF/EMB/PZA × 2 mo

   - Culture negative at 2 mo. and x-ray improved: INH/RIF × 2 mo
   - Culture negative and x-ray unchanged: D/C therapy

4. **Pregnancy and breast feeding**

   Regimen: INH/RIF/EMB × 9 mo or standard treatment wit INH/RIF/EMB/PZA × 2 mo, then INH/RIF × 4 mo. The issue is the safety of PZA, which has no evidence of adverse effects in pregnancy, but inadequete experience to assure safety.

   Streptomycin: Only anti-TB drug with documented harm to human fetuses.

5. **Renal insufficiency**

Drug	*Dose with CrCl <30 cc/min*
INH	Standard
RIF	Standard
RZA	25–35 mg/kg 3×/wk
EMB	15–25 mg/kg 3×/wk
Levofloxacin	750–1000 mg 3×/week
Cycloserine	250 mg qd or 500 mg 3×/wk
Ethionamide	Standard
PAS	Standard
Aminoglycosides	12–15 mg/kg 2–3×/wk

6. **Hepatic disease**

   Regimen excluding INH: RIF/PZA/EMB × 6 months

   Regimen excluding PZA: INH/RIF/EMB × 2 months, then INH/RIF × 7 months

Regimen for severe liver disease:

- RIF/fluoroquinolone/cycloserine/aminoglycoside × 18 months or
- Streptomycin/EMB, fluoroquinolone/another second line drug × 18–24 months

7. **Drug-resistant TB**

Drug Resistance	*Regimen*
INH	RIF/PZA/EMB ± fluoroquinolone 6 mo
INH/RIF	Fluoroquinolone/PZA EMB aminoglycoside ± alternative agent ± 18–24 mo
RIF	INH/PZA/EMB ± fluoroquinolone 9–12 mo
INH/RIF and EMB or PZA	Fluoroquinolone/aminoglycoside/2 alternative agents and PZA or EMP (if active)

II. **Preventive Treatment for Tuberculosis Infection in the U.S.**

ATS/CDC Statement Committee on Latent Tuberculosis Infection [MMWR 2000;49(RR-6).; Am J Resp Crit Care Med 2000;161:S221.; MMWR 2003;52:735.)

A. **Testing** (NEJM 2002;347:1860.)

1. Testing methods: The traditional method is the PPD skin test which has been used for more than 100 years. A new test has been approved by the FDA which mesures the release of interferon-gamma in blood following stimulation by PPD (JAMA 2001;286:1740.). At present, the usual test is the traditional PPD skin test with the following characteristics:
   - Standard test: 5 tuberculin units given intracutaneously and read at 48–72 hours, although reading up to one week is considered accurate (ARRD 1986;134:1043.).
   - BCG: In one study, only 8% of those given BCG vaccine at birth had a positive PPD skin test at 15 years (ARRD 1992;145:621.). BCG is given in countries that have the highest incidence of tuberculosis making it difficult to discount a positive PPD. The current recommendation is to ignore BCG vaccination when interpreting PPD skin tests.

- Sensitivity: 10–20% of persons with tuberculosis have negative skin tests (NEJM 1971;285:1506.; Chest 1980;77:32.).
- Anergy testing: Most authorities no longer recommend it.
- Boosting: The concern is that a negative test may boost the size of the reaction with a second test. The recommendation is that persons who undergo annual PPD skin tests such as health care workers should undergo two-step testing on initial evaluation with the second PPD given one week after a negative test.

2. **Indications for PPD**

Risk	***Example***
Recent TB exposure	Recent close (>12 hours) contact with active case
	Health care workers with TB cases
Risk of TB infection	Prior residence in countries with high TB rates
	Homeless
	Residents of long-term care facilities
Risk of activation of latent infection	HIV infection Recent TB infection: children <4 years, PPD conversion (>10 mm induration) in ≤2 years, injection drug use, silicosis, renal failure, diabetes, immunosuppressive therapy, hematologic cancers, prior gastrectomy or jejunoileal bypass Malnourished or recent weight loss > 10% ideal weight

B. **Candidates for treatment of latent tuberculosis**

Induration caterogy of PPD

≥5 mm	HIV infection Recent contacts of active TB Fibrotic changes on x-ray consistent with TB Immunosuppressed: Organ transplants and others with immuno-suppression including chronic prednisone (equivalent to 15 mg/d for≥1 mo)
≥10 mm	Recent immigrants (<5 yr) from high prevalence area Injection drug users Residents and employees of prisons, jails, nursing homes, long term care facilities for elderly, hospitals, homeless shelters Mycobacteria lab personnel Patients with silicosis, diabetes, renal failure, leukemia, lymphoma, ca head or neck, weight loss>10%, gastrectomy and jejuroleal by-pass
≥15 mm	Persons with no risk factors (Note that targeted PPD skin testing should be done only in people with defined risks. It is often unclear why these people are tested and treatment is optional)

C. **Antimicrobial regimens** (MMWR 2003;52:735.)

1. Recommended regimens

INH 300 mg/d × 9 mo

INH 300 mg/d × 6 mo (not for HIV co-infection or patients with fibrotic lesions on chest x-ray)

INH 900 mg 2 ×/wk (DOT) × 9 mo

INH 900 mg 2 ×/wk (DOT) × 6 mo (not for HIV co-infection or patients with fibrotic lesions on chest x-ray)

Rifampin 600 mg/d × 4 mo (contacts of patients with INH resistant, rifampin susceptible strains)

Note: The 2 month course of RIF + PZA is no longer recommended due to high rates of hepatotoxicity (MMWR 2003;52:735.)

INH regimen

- Efficacy: Studies of more than 70,000 participants show efficacy of about 60% in reducing active tuberculosis (Bibl Tuberc 1970;26:28.). Most studies were done with one year of therapy; a study of INH for six months showed 65% efficacy (Bull WHO 1982;60:555.).

- Hepatitis: Increases in serum transaminase levels occur in 10–20%, but symptomatic hepatitis is uncommon with about one case per 1,000 (JAMA 1992;281:1014.). The risk increases with alcohol consumptoin and with increasing age, but age is no longer considered in the recommendations for treatment.
- Peripheral neuropathy: Allegedly occurs in up to 2% (Am Rev Tuberc 1954;70:504.) and may be prevented with pyridoxine (Tubercle 1980;61:191.).
- Current recommendations: INH for 6–9 months in the usual dose of 300 mg/day, monthly clinical monitoring, baseline transaminase levels only in persons with risk factors for hepatitis, abstinence from alcohol during the INH course and suspension of treatment if transaminase levels exceed the upper limit of normal by five-fold. The alternative regimen is 900 mg twice weekly by directly observed therapy.

Rifampin regimen

- Efficacy: Thought to be equivalent to INH (ARRD 1992;145:36.).

- Adverse reactions: Uncommon.
- Drug interactions: Common and often important.
- Current recommendations: 600 mg/day for four months with clinical monitoring at monthly intervals, baseline transaminase measurements only for persons at risk for hepatitis, and concern for drug interactions such as protease inhibitors, warfarin, contraceptive pills, and methadone.

D. **Monitoring**

Laboratory monitoring: INH

- No lab tests at baseline unless the following:HIV infection, pregnancy, or<3 mo postpartum, history of liver disease (HCV, HBV, alcoholic hepatitis, cirrhosis), persons who use EtOH daily
- Baseline lab tests: AST, ALT, and bilirubin
- Active hepatitis and end-stage liver disease are relative contraindications to INH and PZA
- Follow-up lab tests: symptoms of hepatotoxicity—D/C INH if AST/ALT ≥3×ULN + symptoms or AST/ALT>5 × ULN without symptoms

Clinical monitoring: Monitor for symptoms of hepatotoxicity at baseline and every mo for INH regimen.

III. **Atypical Mycobacteria Treatment** *(Recommendations of American Thoracic Society:* Am Rev Respir Dis 1997;156:S1.) *and M. Iseman (personnel communication 2003)*

Agent	*Condition*	*Treatment and comment*
M. kansasii	Pulmonary and extrapulmonary	RIF + EMB + INH ± AK 15–18 mo (AK for extensive disease) RIF + EMB × 9 mo RIF + EMB + clarithromycin or azithromycin × 9 mo RIF + EMB + AK × 9 mo Contraindication or resistance to RIF: EMB + CIP + clarithromycin
M. avium	Pulmonary and extrapulmonary	Clarithromycin or azithromycin + EMB + RIF ± AK × 18–24 mo Clarithromycin + EMB + CFZ ± AK × 18–24 mo RIF + EMB + CFZ ± AK ± ciprofloxacin × 18–24 mo Use for macrolide resistance or intolerance Clarithromycin + EMB ± CFZ × 18–24 mo Use for elderly patients with less extensive disease Note: Can substitute azithromycin for clarithromycin if intolerant of clarithromycin or to avoid interaction between clarithromycin and RIF Note: Twice weekly therapy is probably as effective as daily therapy—advantages include reduced cost and toxicity
M. fortuitum	Cutaneous and bone	In vitro tests required Standard: Amikacin (10–15 mg/kg/d) + cefoxitin (12 g/d) or imipenem ≥ 2 wk, then oral regimen based on vitro activity—usually clarithromycin (500 mg bid), doxycycline (100 mg bid), sulfamethoxazole (1 g tid) ± ciprofloxacin (500 mg bid) × ≥ 4 mo (cutaneous) or ≥ 6 mo (bone)* Surgery: Usually indicated for extensive disease and with foreign bodies
	Pulmonary	Most lung disease caused by rapid growers i.e. *M. abscessus* *M. fortuitum*: Two oral agents based on in vitro activity × 6–12 mo
M. abscessus	Cutaneous	Standard: Amikacin + cefoxitin or imipenem as above, then oral agent if any are active in vitro—usually clarithromycin ± clofazimine × ≥4 mo

	Pulmonary	Standard: Amikacin + cefoxitin (as above) × 2–4 wk, then periodic parenteral treatment or clarithromycin for suppressive therapy* Surgery: May be curative for local disease (Am Rev Respir Dis 1993;148:1271)*
M. chelonae	Cutaneous	Standard: Tobramycin + cefoxitin (12 g/d) or imipenem × ≥ 2 wk, then oral agents based on in vitro activity especially clarithromycin (500 mg bid) monotherapy × 6 mo* (Am Intern Med 1993;119:482)
M. marinum	Cutaneous	Standard: Multiple regimens—clarithromycin (500 mg bid); doxycycline (100 mg bid); TMP-SMX (DS bid); rifampin (600 mg bid) + ethambutol (15 mg/kg/d)—all ≥ 3 mo* Surgery: Infections in closed space of hand and refractory infections
M. scrofulaceum	Lymphadenitis	Surgical excision; very resistant to drugs—INH, rifampin, streptomycin + cycloserine (rare in U.S.)
M. ulcerans	Buruli ulcer	Rifampin + amikacin (7.5 mg/kg IV bid) or ethambutol + TMP-SMX (1 DS tid) × 4–6 wk; surgical excision
M. haemophilum	Skin, soft tissue, osteomyelitis	Sensitive to ciprofloxacin, cycloserine, kanamycin, rifabutin; experience with treatment limited (Ann Intern Med 1994;120:118)
M. bovis	Pulmonary	As with *M. tuberculosis* but resistant to pyrazinamide
M. szulgae	Pulmonary, extrapulmonary	Same as *M. kansasii* (Thorax 1987;42:838)
M. malmoense	Pulmonary, disseminated	Clarithromycin + ethambutol + rifabutin ± streptomycin × 18–24 mo (Tubercle 1985;66:197; CID 1994;18:596)

M. xenopi	Pulmonary	Rifampin or rifabutin + clarithromycin ± streptomycin; surgery for relapses (Am Rev Respir Dis 1981;123:104; Tubercle 1988;69:47)
M. simiae	Pulmonary	Clarithromycin, ethambutol, rifabutin + streptomycin (need in vitro susceptibility tests)
M. smegmatis	Soft tissue, bone, etc	Ethambutol, amikacin, ciprofloxacin, sulfonamides, clofazimine, imipenem, doxycycline
M. gordonae	Pulmonary, disseminated	Combinations of rifampin, ethambutol, streptomycin ± INH, clofazimine, clarithromycin (AAC 1992;36:1987; Dermatology 1993;187:301)
M. genavense	Disseminated	Clarithromycin + other agents—INH, ethambutol, rifampin, ciprofloxacin, pyrazinamide (AIDS 1993;7:1357)

* Efficacy is established.

A. Doses

Amikacin: 12–15 mg/kg/day IV or IM or 15–22 mg/kg tiw

Azithromycin: 250–500 mg/day or 500 mg tiw

Cefoxitin: 2 g IV q8–12h

Ciprofloxacin: 500–750 mg bid, 750 mg qd or 750 mg tiw

Clarithromycin: 500–750 mg/d, 500 mg bid or 750 mg tiw

Doxycycline: 100 mg bid

Ethambutol: 25 mg/kg/d × 2 mo, then 15 mg/kg or 25–30 mg/kg tiw

Imipenem: 1 g IV q12h

Isonazid: 300–600 mg/d or 600 mg tiw

Levofloxacin: 500–750 mg/day or 750 mg tiw

Linezolid: 600 mg IV or po bid

Rifabutin: 150–300 mg/d or 300 mg tiw

Rifampin: 600 mg qd or 600 mg tiw

Streptomycin regimens

Wt/age	*Initial 6–12 wks*	*Maintenance*
>50 kg <50 yr	1 g 5×/wk	1 g 3×/wk
<50 kg <70 yr	500 mg 5×/wk	750 mg 2×/wk
>70 yr	750 mg 2×/wk	750 mg 2×/wk

B. **Classification of atypical mycobacteria** *(adapted from* Am Rev Respir Crit Care Dis 1997;156:59.)

	M. kansasii	U.S., Europe coal mining	Pigmented	
	M. abscessus	Mostly U.S.	Nonpigmented Rapid growth	
	M. xenopi	Europe canada	Pigmented slow growth	
Lymphadenitis	*M. avium*	Worldwide	Nonpigmented	*M. fortuitum, M. chelonae, M. ab-scessus, M. kansasii, M. haemophilum*
	M. scrofulaceum	Worldwide	Pigmented	
	M. malmoense	U.K. Scand	Slow growth	
Skin	*M. marium*	Worldwide	Growth at 28–30°C	*M. aviam, M. kansasii, M. nonchromo-genicum, M.*

	M. ulcerans	Australia SE Asia, Africa	Pigmented Slow growth	
Disseminated	*M. avium*	Worlwide	AIDS patients—80% pigmented	*M. xenopi, M. abscessus, M. malmoense, M. simiae, M. genovense, M. marium, M. fortuitum, M. canspicum*
	M. kansasii	U.S.	Photochromogen	
	M. chelonae	U.S.	Nonpigmented	
	M. haemophilum	U.S. Australia	Nonpigmented Needs hemin, low temperature, and CO_2	

Runyon classification

		M. marium	7–14	Optimal growth at 32°C. Rare contam-inant. Skin and soft tissue
		M. simiae	7–14	Rare human pathogen. Lung
		M. asiaticum	7–14	Rarely pathogenic
Scotochromogens (slow	II	*M. scrofula-ceum*	10–28	Nearly disappeared from U.S. Lymphadenitis
		M. szulgae	12–28	Infrequent human pathogen. Lung
		M. gordonae	10–28	Rarely pathogenic. Environmental contaminant
		M. flavescens	7–10	Rarely pathogenic. Environmental contaminant
Nonphotochromogens	III	*M. avium*	10–21	*M. avium* and *M. intracellulare* sometimes referred to as *M. avium*

(slow growing)				
		M. malmoense	18–84	Infrequent human pathogen. Lung. Optimal growth at 20–32°C. Skin and soft tissue in immunosuppressed
		M. haemophilum		
		M. terrae complex	10–21	Rarely pathogenic. Environmental contaminant
		M. gastri	10–21	Rarely pathogenic. Environmental contaminant
		M. flavescens		Rarely pathogenic
		M. triviale	10–21	Environmental contaminant
Rapid growers	IV	*M. fortuitum*	3–7	Environmental contaminant. Ulcers
		M. chelonae	3–7	Environmental contaminant. Ulcers
		M. smegmatis	3–7	Rarely pathogenic
		M. phlei	3–7	Rarely pathogenic

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Drugs for Treatment of Parasitic Infections

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Infection	*Drug*	*Adult dosage*
Acanthamoeba keratitis		
Drug of choice:	See footnote [1]	
AMEBIASIS (*Entamoeba histolytica*)		
asymptomatic		
Drug of choice:	Iodoquinol	650 mg tid × 20 d
or	Paromomycin	25–35 mg/kg/d in 3 doses

		× 7 d
Alternative:	Diloxanide furoate[2]	500 mg tid × 10 d
mild to moderate intestinal disease[3]		
Drug of choice:[4]	Metronidazole	500–750 mg tid × 7–10 d
or	Tinidazole[5]	2 g/d divided tid × 3 d
severe intestinal and extraintestinal disease[3]		
Drug of choice:	Metronidazole	750 mg tid × 7–10 d
or	Tinidazole[5]	800 mg tid × 5 d
AMEBIC MENINGOENCEPHALITIS, PRIMARY		
Naegleria		
Drug of choice:	Amphotericin B[6,7]	1 mg/kg/d IV, uncertain duration

Acanthamoeba		
Drug of choice:	See footnote [8]	
Balamuthia mandrillaris		
Drug of choice:	See footnote [9]	
Sappinia diploidea		
Drug of choice:	See footnote [10]	
ANCYLOSTOMA caninum (Eosinophilic enterocolitis)		
Drug of choice:	Albendazole[7]	400 mg once
or	Mebendazole	100 mg bid × 3 d
or	Pyrantel pamoate7	11 mg/kg (max. 1 g) × 3 d
or	Endoscopic removal	
Ancylostoma duodenale, see HOOKWORM		

ANGIOSTRONGYLIASIS		
Angiostrongylus cantonensis		
Drug of choice:	See footnote [11]	
Angiostrongylus costaricensis		
Drug of choice:	See footnote [12]	
ANISAKIASIS(*Anisakis*)		
Treatment of choice:	Surgical or endoscopic removal	
ASCARIASIS (*Ascaris lumbricoides*, roundworm)		
Drug of choice:	Albendazole[7]	400 mg once
or	Mebendazole	100 mg bid × 3 d or 500 mg once
or	Pyrantel pamoate[7]	11 mg/kg once (max. 1 g)

BABESIOSIS (*Babesia microti*)		
Drugs of choice:[13]	Clindamycin[7]	1.2 g bid IV or 600 mg tid po × 7–10 d
	plus quinine	650 mg tid po × 7 d
or	Atovaquone[7]	750 mg bid × 7–10 d
	plus azithromycin[7]	600 mg po daily × 7–10 d
Balamuthia mandrillaris, see AMEBIC MENINGOENCEPHALITIS, PRIMARY		
BALANTIDIASIS (*Balantidium coli*)		
Drug of choice:	Tetracycline[7,14]	500 mg qid × 10 d
Alternatives:	Metronidazole[7]	750 mg tid × 5 d
	Iodoquinol[7]	650 mg tid × 20 d
BAYLISASCARIASIS (*Baylisascaris procyonis*)		

Drug of choice:	See footnote [15]	
BLASTOCYSTIS *hominis* infection		
Drug of choice:	See footnote [16]	
CAPILLARIASIS (*Capillaria philippinensis*)		
Drug of choice:	Mebendazole[7]	200 mg bid × 20 d
Alternative:	Albendazole[7]	400 mg daily × 10 d
Chagas' disease, see TRYPANOSOMIASIS		
Clonorchis sinensis, see FLUKE infection		
CRYPTOSPORIDIOSIS (*Cryptosporidium*)		
Drug of choice:	See footnote [17]	
CUTANEOUS LARVA MIGRANS (creeping eruption, dog and cat hookworm)		
Drug of choice:[18]	Albendazole[7]	400 mg daily × 3 d
or	Ivermectin[7]	200 µg/kg daily × 1–2 d

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MANUFACTURERS OF SOME ANTIPARASITIC DRUGS

ALBENDAZOLE—*Albenza* (GlaxoSmithKline)

§**ARTEMETHER**—*Artenam* (Arenco, Belgium)

§**ARTESUNATE**—(Guilin No. 1 Factory, People's Republic of China)

ATOVAQUONE—*Mepron* (GlaxoSmithKline)

ATOVAQUONE/PROGUANIL—*Malarone* (GlaxoSmithKline)

BACITRACIN—many manufacturers

§**BACITRACIN-ZINC**—(Apothekernes Laboratorium A.S., Oslo, Norway)

§**BENZNIDAZOLE**—*Rochagan* (Roche, Brazil)

†**BITHIONOL**—*Bitin* (Tanabe, Japan)

CHLOROQUINE HCl and CHLOROQUINE PHOSPHATE—*Aralen* (Sanofi), others

CROTAMITON—*Eurax* (Westwood-Squibb)

DAPSONE—(Jacobus)

†**DIETHYLCARBAMAZINE CITRATE USP**—(University of Iowa School of Pharmacy)

§**DILOXANIDE FUROATE**—*Furamide* (Boots, United Kingdom)

§**EFLORNITHINE** (Difluoromethylornithine, DFMO)—*Ornidyl* (Aventis)

FURAZOLIDONE—*Furoxone* (Roberts)

§**HALOFANTRINE**—*Halfan* (GlaxoSmithKline)

IODOQUINOL—*Yodoxin* (Glenwood), others

IVERMECTIN—*Stromectol* (Merck)

MALATHION—*Ovide* (Medicus)

MEBENDAZOLE—*Vermox* (McNeil)

MEFLOQUINE—*Lariam* (Roche)

§**MEGLUMINE ANTIMONATE**—*Glucantime* (Aventis, France)

†**MELARSOPROL**—*Mel-B* (Specia)

METRONIDAZOLE—*Flagyl* (Searle), others

§**MILTEFOSINE**—(Zentaris)

†**NIFURTIMOX**—*Lampit* (Bayer, Germany)

*__NITAZOXANIDE__—*Cryptaz* (Romark)

§**ORNIDAZOLE**—*Tiberal* (Roche, France)

OXAMNIQUINE—*Vansil* (Pfizer)

PAROMOMYCIN—*Humatin* (Monarch); *Leshcutan* (Teva Pharmaceutical Industries, Ltd., Israel; (topical formulation not available in U.S.)

PENTAMIDINE ISETHIONATE—*Pentam 300*, *NebuPent* (Fujisawa)

PERMETHRIN—*Nix* (GlaxoSmithKline), *Elimite* (Allergan)

PRAZIQUANTEL—*Biltricide* (Bayer)

PRIMAQUINE PHOSPHATE USP

§**PROGUANIL**—*Paludrine* (Wyeth Ayerst, Canada; AstraZeneca, United Kingdom); in combination with atovaquone as *Malarone* (GlaxoSmithKline)

§**PROPAMIDINE ISETHIONATE—***Brolene* (Aventis, Canada)

PYRANTEL PAMOATE—*Antiminth* (Pfizer)

PYRETHRINS and PIPERONYL BUTOXIDE—*RID* (Pfizer), others

PYRIMETHAMINE USP—Daraprim (GlaxoSmithKline)

§**QUININE DIHYDROCHLORIDE**

QUININE SULFATE—many manufacturers

†**SODIUM STIBOGLUCONATE**—*Pentostam* (GlaxoSmithKline, United Kingdom)

*__SPIRAMYCIN__—*Rovamycine* (Aventis)

†**SURAMIN SODIUM**—(Bayer, Germany)

THIABENDAZOLE—Mintezol (Merck)

§**TINIDAZOLE**—Fasigyn (Pfizer)

*__TRICLABENDAZOLE__—*Egaten* (Novartis, Switzerland)

TRIMETREXATE—*Neutrexin* (US Bioscience)

Footnotes

**Available in the U.S. only from the manufacturer.*

§*Not available in the U.S.*

†*Available under an Investigational New Drug (IND) protocol from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; 404-639-3670 (evenings, weekends, or holidays: 404-639-2888).*

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Treatment of Viral Infections

A. **HERPESVIRUS GROUP** (Med Lett 2002;44:9.; NEJM 1999;340:1255.; Lancet 2001;357:1513.; Med Lett 2002;44:95.)

Virus	*Regimen**	*Comment*
HERPES SIMPLEX		
Genital—primary	Acyclovir: 400 mg po tid × 7–10 days, ($14) Severe: 5 mg/kg IV q8h × 5–7 days	Shortens duration of pain, reduces viral shed-ding and reduces duration of systemic symptoms (Med Lett 1995;37:117). Avoid sex until no visible lesions; effect of treatment on transmission is unknown
	Valacyclovir: 1 g po bid 7–10	Valacyclovir and acyclovir

	days ($79)	are equally effective (AAC 1995;35:181)
	Famciclovir: 250 mg po tid × 5–10 days ($55)	
Genital—recurrent	Acyclovir: 400 mg po tid × 5 days ($11)	Slight benefit, but only if started early (MMWR 1993;RR-14:23) preferably within 24 hr (Arch Intern Med 1996;156:1729)
	Valacyclovir: 500 mg po qd × 3 days ($11)	Higher doses may be required in HIV-infected patients
	Famciclovir: 125 mg po bid × 5 days ($33)	
Genital—prophylaxis	Acyclovir: 400 mg po bid ($43/mo) Valacyclovir: 500–1000 mg qd ($108/mo) Famciclovir: 250 mg po bid ($220/mo) Immunocompromised: acyclovir 200–400 mg po 3–5×/d ($80/mo)	Indicated with ≥6 recurrences/yr. Good efficacy and good safety profile with acyclovir prophylaxis up to 7 yr (JAMA 1991;265:747; Arch Dermatol 1993; 129:582; JID 1994;169:1338). Decreases HSV shedding

	Docosanol 10% cream, topical 5×/d (Med Lett 2000;42:108) ($14)	
Encephalitis	Acyclovir: IV-10–15 mg/kg q8h × 14–21 days	High rates of long-term morbidity in survivors (NEJM 1986;314:144)
Mucocuteaneous in immuno-competent host	Acyclovir: 5 mg/kg IV q8h × 5 days	Alternatives: Acyclovir 400 mg po 5×/d × 10 days Valacyclovir 1 g po tid × 10 days Famciclovir 500 mg po bid × 7 days
Mucocutaneous progressive/compromised host	Acyclovir: IV—5 mg/kg q8h × 7–14 days; po—400 mg po 5×/d × 7–14 days Famciclovir: 250 mg po tid Valacyclovir: 500 mg po bid	AIDS patients often require preventative therapy with acyclovir 200–400 mg po 3–5×/d indefinitely
Burn wound	Acyclovir: IV—5 mg/kg q8h × 7 days; po—200 mg 5×/d × 7–14 days	
Prophylaxis—high- risk	Acyclovir: IV—5 mg/kg q8h;	Organ and bone marrow

pateients	po—200–400 mg 3–5×/d	transplant recipients; treat seropositive patients for 1–3 mo post-transplant (NEJM 1989;320:1381)
Keratitis	Trifluridine: Topical (1%) 1 drop q2h up to 9 drops day × 10 days	Ophthalmologist should supervise treatment. Alternative is vidarabine 3% ointment, 1/2 inch ribbon 5×/d.
Acyclovir-resistant	Foscarnet: IV—40 mg/kg/q8h × 14–21 days Topical trifluridine for accessible lesions using 1% ophthalmic solution tid (Lancet 1992;340:1040)	Thymidine kinase deficient strains are most common cause of resistance and are almost always from immunosuppressed patients unresponsive to acyclovir (NEJM 1991; 325:551; NEJM 1989;320:293; J Infect Dis 1990;161:1078). Most acyclovir-resistant strains are also resistant to famciclovir, penciclovir, and ganciclovir, but respond to foscarnet (CID 1998;27:1525) Foscarnet-resistant HSV may become acyclovir

		susceptible (JID 1994;109:193); most acyclovir-resistant HSV are resistant to penciclovir (Famciclovir) and ganciclovir
VARICELLA-ZOSTER (see Ann Intern Med 130:922, 1999)		
Chickenpox, adult immunocompetent	Valacyclovir: 1 g po tid × 5 days	Must treat within 24 hr of exantham; efficacy established (Ann Intern Med 1992;117:358)
Chickenpox, adult immunosuppressed	Acyclovir: 10 mg/kg IV q8h × 7 days ($1058)	Treat as quickly as possible
Pneumonia	Acyclovir: IV 10–12 mg/kg q8h × 7 days ($1058) Valacyclovir: 1 g po tid × 10 days ($267)	Efficacy not clearly established but appears best if treatment is initiated within 36 hr of admissions (RID 1990;12:788)
Dermatomal or disseminated zoster; immunosup-pressed	Acyclovir: IV 10 mg/kg q8h × 7 days ($1075)	Indications to treat are greater for severe disease, early disease, or zoster in immuno-suppressed host

		(NEJM 1983;308:1448; AmJ Med 1988;85 Suppl 2A:84; Infect Dis Clin Pract 1993;2:100) Treatment can be started as long as new lesions are forming Foscarnet for acyclovir-resistant strains, 60 mg/kg IV 2–3 ×/day for 7–14 days (NEJM 1993;308:1448)
Normal host	Valacyclovir: 1 g po tid × 7 days ($119) Acyclovir: 800 mg po 5×/d × 7–10 days ($43) Famciclovir: 500 mg po tid × 7 days ($155) Any of the above with or without prednisone: 60 mg/d po × 7 days, 30 mg/d days 8–14, 15 mg/d days 15–21 (Ann Intern Med 1996;125:376) Pain control: Tricyclics; other options—gabapentin, carbamazepine, lidocaine	Antiviral drugs hasten healing of cutaneous lesions and reduce pain including acyclovir (Am J Med 1988;85:84; NZ Med J 1991; 10 Suppl 102:93); valacyclovir (AAC 1996; 39:1546); and famciclovir (Ann Intern Med 1995;123:89) Patient > 50 yr and those with ophthalmic zoster are most likely to benefit Ophthalmic zoster: Consult ophthalmologist

		patch, topical capsaicin, regional nerve block, acupuncture. Narcotics are effective and under-used	(Ophthalmology 1986;793:63) Antiviral treatment should be started within 72 hr of rash onset or while lesions are still forming Meta-analysis of reports of oral acyclovir in 691 patients with zoster showed a 2-fold reduc-tion in duration of pain (CID 1996;22:341) Comparative trial of acyclovir vs. valacyclovir showed slight advantage with valacyclovir (AAC 1995;39:1546) Controlled trial showed prednisone added to acyclovir was associated with more rapid healing, more rapid return to normal sleep, and more rapid return to normal activity (Ann Intern Med 1996;125:376). Others have shown less impressive results (NEJM 1994;330:896) Valacyclovir is superior to

		acyclovir for re-ducing duration of pain (AAC 1995;39:1546) Post-herpetic neuralgia: Amitriptyline
Acyclovir resistant strains	Foscarnet: 40 mg/kg q8h IV × 10 days ($1061)	Most VZV strains resistant to acyclovir are resistant to ganciclovir and famciclovir
Exposure (zoster or chickenpox); immunosup-pressed Susceptible health care workers	Varicella-zoster immune globin, 625 units IM within 96 hr of exposure None	Patient susceptible and has substantial exposure (Ann Intern Med 1988;108:221); alternative is to treat chickenpox promptly with acyclovir if it occurs Must refrain from patient contact during days 8–21 postexposure
Prophylaxis in organ transplant recipients	Acyclovir: 5 mg/kg IV q8h or 200 mg po q6h to 1yr	Lancet 1983;2:706; NEJM 1989;320:1381 Acyclovir if CMV serology D–R–(Otherwise ganciclovir/valganciclovir × 3–6 mo)

CYTOMEGALOVIRUS		
Immunocompetent	None	
Immunosup-pressed pneumonitis, esophagitis, colitis, and CNS infection	Ganciclovir: Induction, 5 mg/kg IV bid × 14–21 days, Maintenance, 6 mg/kg IV 5 days/wk or oral ($630–779/mo) or valganciclovir (see below) Foscarnet: Induction, 60 mg/kg IV q8h or 90 mg/kg q12h × 14–21 days, Maintenance, 90 mg/kg IV qd ($2425/mo) Valganciclovir 900 mg po bid × 21 days, then 900 mg qd (maintenance—$1726/month) Cidofovir (Vistide) 5 mg/kg IV q wk × 2, then 5 mg/kg IV q 2 wk + probenecid	Valganciclovir gives serum levels comparable to those achieved with IV ganciclovir (AAC 2000;44:2811) Efficacy of treatment is established for CMV pneumonitis, esophagitis and radiculopathy; response is less impressive with enteritis and colitis (CID 1993;17:644; JID 1993; 167:278; JID 1993;167:1184; JID 1995; 172;622) Foscarnet is therapeutically comparable with ganciclovir for CMV colitis in AIDS patients (Am J Gastroenterol 1993;88:542). Main problem is poor quality of life because of long hours of infusions

Marrow transplant recipients	Ganciclovir: 7.5–10 mg/kg/d IV × 20 days ± maintenance: 5 mg/kg 3–5×/wk for 8–20 doses or valganciclovir CytoGam (Hyperimmune) in dose of 100–150 mg/kg good for seven doses	Ganciclovir plus hyperimmune globulin: Efficacy best supported for marrow recipients (Ann Intern 1988;109:777; Ann Intern Med 1988;109:783; Transplant 1993;55:1339; JID 1988;158:488; CID 1993;7:S392) Ganciclovir monotherapy: Response rates 22–50% (Pharmacotherapy 1992;12:300) CMV hyperimmune globulin (CytoGam) added by some if severe CMV disease, infection of allograft, recurrent disease, or hypogammaglobulinemia
Solid organ transplants	Ganciclovir, valganciclovir, and CytoGam (as above)	Response rates to ganciclovir in heart, liver, and renal transplant recipients in 14 reports: 67/85 (79%) (Pharmacotherapy 1992;12:300). Maintenance therapy used in 2 of 14

		reports
Prophylaxis Marrow transplant	Allogenic transplant: D–R+: No prophylaxis D+ or R+ Ganciclovir, 5–6 mg/kg IV 5–7 days/wk × 3 mo or Acyclovir 10 mg/kg IV q8h × 1 mo, then 800 mg po qid × ≥ 3 mo IVIG 500 mg/kg q2wk × 3 mo + cultures for CMV × 120 days, positive culture: Ganciclovir + IVIG to day 100 or until 2–3 wk after last culture D–R–: No prophylaxis autologous transplant: R–: CMV neg-ative blood products or leukocyte–filtered products	Recommendations of ECOG (Ann Intern Med 120:143, 1994); **D, donor; R, recipient; CMV seropositive** Optimal results are with ganciclovir for 3–4 mo (Ann Intern Med 1993;118:173; Lancet 1994;343:749; Lancet 1995;341:1380) Oral ganciclovir is superior to oral acyclovir for CMV prophylaxis in renal transplants (Transplantation 1998;66:1682)
Organ transplant recipients		
Renal	Acyclovir 800 mg po qid × 3 mo or Valacyclovir 1 g bid × 3 mo	Supporting data

		○ Oral acyclovir in renal transplants—NEJM 1989;320:1381 ○ IV ganciclovir in marrow, liver, and heart transplants—NEJM 1996;335:721 ○ Oral ganciclovir in liver transplants—Lancet 1997;350:1729 ○ Meta-analysis of oral agents—Transplantation 1998;65:641 ○ Oral valacyclovir—NEJM 1999;340:1462
Liver	Ganciclovir 1 g po tid × 2–3 mo or Ganciclovir 5–6 mg/kg IV 5–7 days/wk × 3 mo	
Heart	Ganciclovir 5 mg/kg IV q12h × 2 wk, then 5–6 mg/kg IV 5 d/wk to complete 3 mo	
EPSTEIN-BARR VIRUS		
Oral hairy leukoplakia	Acyclovir 800 mg po 5×/d or valacyclovir	Efficacy established. Relapse rates high; ganciclovir is also effective
EBV-associated lymphomas	No antiviral agent	Acyclovir confers no benefit (NEJM 1984;311:1163)
Infectious mononucleosis	No antiviral agent	Prednisone (80 mg/d × 2–3

		days, then taper over 2 wk) in selected cases
HEPATITIS B		
Chronic HBV (see p 199)	Lamivudine: 100 mg/d po indefinitely Adofovir: 10 mg/d po indefinitely Interferon alfa-2b 5 mil units/d or 10 mil units 3×/wk SC or IM 4 mo ($6820)	High rates of resistance with prolonged treatment with lamivudine Adofovir is active vs lamivudine-resistant strains and resistance rates are low Tenofovir is probably as effective as adofovir, but not FDA-approved for HBV
HEPATITIS C		
Chronic HCV (see p 197)	Pegylated interferon 1 µg/kg SC × 48 wks ($12,493) plus ribavirin 1000–1200 mg po/d × 48 wks ($16,531) Interferon alfa 2b + ribavirin 1000–1200 mg po/d × 48 wks ($19,304)	
INFLUENZA		

Influenza A & B treatment Influenza A treatment	Zanamivir 10 mg bid × 5d by inhaler ($48) Oseltamivir 75 mg po bid × 5 days ($63) Rimantadine 200 mg po qd or 100 mg po bid × 5 days ($20) Amantadine 100 mg po bid × 5 days or 100 mg/day if > 65 yrs or renal failure ($1)	Efficacy of all four antivirals required initiation within 48 hrs of onset of symptoms Efficacy in reducing flu-related complications including pneumonia is unknown There is cross-resistance between amantadine and ramantadine
Influenza A & B prevention (see below)	Oseltamivir: 75 mg/d ($265/6 wks) Ramantadine 100 mg po bid or 200 mg qd ($171) Amantadine 100 mg po bid or 200 mg qd ($13)	Efficacy of amantadine or ramantadine pro-phylaxis is 70–90% (NEJM 2000;343:1778) Oseltamivir is FDA-approved for prophylaxis, is effective vs both influenza A and B, and is less frequently associated with resistance; however, it is more expensive
* Prices are AWP 2002 for lowest dose for designated duration		

B. **INFLUENZA** (MMWR 2000;49(RR-3).)

1. **PREVENTION**

Vaccination: Preferred method to prevent influenza. Vaccine efficacy in healthy persons shows 70–90% efficacy when there is a good match between vaccine strain and epidemic strain. This has occurred in 13 of the last 14 seasons; the exception was the 1997–98 season when the epidemic was H_3N_2-Sydney. Vaccination "spin off" includes protection of vulnerable elderly residents of nursing homes when the health care workers who serve them have flu vaccine (JID 1997;75:.; Lancet 2000;355:93.). The optimal time to vaccinate is Oct—mid November (see p 104 for vaccination guidelines)

Antiviral agents

Agent	*Dose (prophylaxis)*	*Activity*	*Cost (/wk)*	*Comment*
Amantadine	200 mg/d × 6 wk	Flu A	$5	13% had CNS toxicity[a]
Rimantadine	200 mg/d × 6 wk	Flu A	$28	6% had CNS toxicity[a]
Oseltamivir	75 mg/d × 6 wk	Flu A & B	$39	GI side effects in 10–20%[b]

[a] NEJM 1982;307:580.

[b] JAMA 1999;282:1240; NEJM 1999;341:1336.

2. **DIAGNOSIS**

   a. **Clinical**: Physician diagnosed flu is about 70% specific, about the same as the rapid tests. Key clues are fever, epidemic of influenza, and typical respiratory tract symptoms (Arch Intern Med 2000;160;3082.).

   b. **Rapid tests for office use**: Flu O1A (Biostar), QuickView (Quidel), and Zstatflu (ZymaTx). These cost $15–20/test, results available in 10–20 min, and sensitivity of 57–77%. All three will distinguish influenza A and B. Medical Letter consultants considered QuickVue to be "the easiest and fastest" (Med Lett 1999;41:121.)

3. **TREATMENT** MMWR 2000;49(RR-3).; JAMA 1999;282:1240.; Lancet 2000;355:1845.; BMJ 2003;326:1235..

   Meta-analysis of published reports showed neuraminidase inhibitors for treatment had an average 1–2 day reduction in symptoms and a 30% reduction in antibiotic use; for prevention there was 69–92% efficacy for prevention (BMJ 2003;326:1235.)

Comparison of drugs for influenza treament

	Amantadine	***Rimantadine***	***Zanamivir***	***Oseltamivir***
FDA approval	1966	1993	1999	1999
Activity:	A	A	A & B	A & B

influenza				
FDA approval				
Prophylaxis	+	+	-	+
Therapy	+	+	+	+
In vivo efficacy				
Healthy persons	+	+	+	+
High-risk persons	-	-	-	+
Prophylaxis				
efficacy	70–90%	70–90%	92%	82%
Treatment				
duration	3–5 d	3–5 d	5 d	5 d

Need to treat				
within 48 hr	+	+	+	+
Response–decrease				
duration by	1–1.5 d	1–1.5 d	1–1.5 d	1–1.5 d
Treatment regimen				
Age 14–64	100 mg bid	100 mg bid	10 mg bid	75 mg bid
>65 yr	100 mg/d	100 mg/d	Same	Same
Renal failure	Dose change	100 mg/d	Same	75 mg/d
Liver failure	Standard	100 mg/d	ND	ND
Prophylaxis regimen	Same	Same	10 mg/d	75 mg/d
Side effects	CNS-moderate	CNS-modest	Bronchospasm	GI

Cost/5 days				
treatment (AWP)	$2	$20	$48	$63
Cost/6 wks prevention	$13	$171	—	$265

C. **HEPATITIS VIRUSES**

1. **Hepatitis C**: Current recommendations for management NIH Consensus Conference: Managment of Hepatitis C, 2002 (http://consensus.nih.gov/cons/116/116cdc_statement.htm)

    a. Natural history: 85% develop chronic infection (viral persistence > 6 mo usually with elevated ALT). About 10–20% develop cirrhosis within 20 yr, and 1–5% develop hepatocellular carcinoma within 20 yr (NEJM 1992;327:1906.; NEJM 1995;332:1463.). Extrahepatic manifestations include arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryogobulinemia.

    b. Laboratory tests (see J Clin Micro 2002;40:4407.)

        1. EIA: Standard screening test: Reliable, inexpensive, and FDA arproved; 3rd generation tests show sensitivity and specificity > 99% in immunocompetent patients

            - False negatives: Rare, but seen with hemodialysis and HIV
            - False positives: Autoimmune disorders

            Confirmatory tests: May be unnecessary with liver disease and risk.

            Others—qualitative HCV RNA

        2. Qualitative HCV RNA with threshold of detection of 50 IU/mL (100 viral

genes/mL)—Confirmatory test

Specificity: >98%, positive confirms EIA; negative may reflect transient decline and should be repeated

Use: Confirmation of EIA and determination if acute infection cleared

3. Quantitative HCV RNA: Monitor response

   Techniques: PCR (qPCR) or branched DNA (bDNA)

   Units: IU is not actual viral particles

   Use: Monitor response to therapy

   Not useful for prognosis

4. ALT: Weak association with severity of liver disease; useful to monitor response to treatment but pegylate interferon can cause elevated ALT. 30% with chronic HCV have normal ALT levels, some progress to cirrhosis

5. Liver biopsy: Used to:

   - Detect other causes of liver disease; iron, steatosis, alcoholic liver disease, etc.
   - Baseline for subsequent evaluation
   - Basis for therapy (although the 80% response rate with genotype 2 or 3 may preclude need for liver biopsy)

6. Hepatocellular carcinoma

   - Incidence: 0–3% per year with HCV—associated cirrhosis
   - Screening: alpha-fetoprotein or ultrasound; some screen with one or both q6 mo but no standard based on adequate study and no need in absence of cirrhosis

c. Results with treatment using pegylated interferon + ribavirin (NEJM 2002;347:975.;

Lancet 2001;258:958.)

Clinical trials	Genotype 1	Genotype 2,3
Pegylated interferon + ribavirin vs. interferon + ribavirin	Pegylated interferon superior to interferon	Interferon and pegylated interferon are equivalent
Sustained viral response (SVR)	42–46% w/Rx 48 wks	76–82% w/Rx 24 wks

d. Indications to treat

1. HCV RNA levels >50 IU/mL and
2. Liver biopsy showing portal or bridging fibrosis and at least moderate inflammation and necrosis (most have persistently elevated ALT) and
3. No contraindications (especially active IDU, alcoholism, neuropsychiatric disorder and other co-morbidities)
4. Decompensated liver disease—transplant is treatment choice
5. Acute HVC: Treat, but timing is unclear
6. Co-morbidities
    - Active IDU: Case-by-case decision
    - HIV: Case-by-case decison (Response is reduced and methods to sequence treatment of HIV and HCV are unclear)
    - EtOH: Heavy consumption (>80 g/d compromises HCV Rx)

e. Treatment

1. Genotype 1: Pegylated interferon + ribavirin × 48 weeks*
2. Genotype 2 or 3: Pegylated interferon + ribavirin or interferon + ribavirin × 24 weeks*
3. Retreatment

   Nonresponders: May have improved histology 15–20% of nonresponders to interferon-ribavirin respond to pegylated interferon-ribavirin

   Relapse: Most relapse again if given same regimen
4. Side effects of interferon: Dose related. Dose reduction is required in 10–40%; treatment is discontinued because of side effects in 10–20%. The major side effects follow.

Flu-like symptoms—fever, chills, headache, arthralgias, myalgia, tachycardia; most patients experience these effects early in therapy, but they improve with continued treatment and acetaminophen therapy.

Hematologic—reduced neutrophil and platelet counts may occur and require dose reduction or supportive therapy.

Late side effects—fatigue, myalgias, bone marrow suppression, rash, autoimmune thyroid disorders, alopecia, irritability, and neuropsychiatric effects (especially depression).

Rare side effects—autoimmune disease, suicide risk, cardiac failure, renal failure, hearing loss, pulmonary fibrosis, retinopathy.

Ribavirin—most patients develop hemolytic anemia that may require dose reduction. Ribavirin may cause gout and is teratogenic.

2. **Hepatitis B**

Indications to treat: (1) detectable HBsAg±HBeAg; HBV DNA (usually >100,000 c/mL), and

(2) liver histology showing necroinflammation (Hepatology 2001;34:1225.). FDA approved agents include interferon and nucleosides/nucleotides.

a. Interferon-alfa: Meta-analysis of 15 trials involving 837 patients with doses of 7–30 MU/m^2/wk showed trends favoring treatment in all studies, improvement in all disease markers with treatment, and superior results with high doses (>5 MU/m^2/wk) (Ann Intern Med 1993;119:312.). About 33% showed disappearance of HBeAg with interferon versus 12% in controls (NEJM 1997;336:347.). Current recommendations are:

   - 5 million units/d or 10 million units SC 3 ×/wk × 4 mo (30–35 million units/wk). Lower doses are less effective, and higher doses are usually too toxic. Drug costs about $5,400 (AWP).
   - Monitor ALT levels at 2- to 4-wk intervals; HBsAg, HBeAg, and HBV DNA at baseline; at end of treatment and 6 mo later. Increase in aminotransferase levels should not lead to discontinuation.
   - Best response is with high baseline aminotransferase, low HBV DNA, active histologic changes indicating inflammation and necrosis, fibrosis, short duration before therapy, and absence of complicating disease (NEJM 1990;323:295.; Am J Gastroenterol 1993;88:1887.; Ann Intern Med 1993:119:312.).

b. Nucleoside analogs:

   1. Lamivudine (NEJM 1998;339:61.): Administration of 100 mg lamivudine (3TC) po for 1 yr was associated with ALT normalization in 72% of patients, HBeAg seroconversion in 16%, improvement in hepatic necroinflammation in 56% of patients and a sustained virologic response in about 50% at one year (NEJM 1998;339:61.; NEJM 1998;341:1256.). Low frequency of side effects make lamivudine a first line therapy for chronic hepatitis B. However, drug resistance with the YMDD mutation occurs at a rate of about 15% per yr (NEJM 2003;348:800.). One recommendation is to treat patients with HBeAg until they are negative for e antigen of there is drug resistance (BMJ 2003;323:1164.).
   2. Adefovr (NEJM 2003;348:800.): Administration of 10 mg/d po × 48 wks showed statistically significant improvement in HBV DNA quantitative counts and in

histologic changes. The optimal duration of treatment is unclear but may be lifelong. Resistance in vitro is only about 2% with treatment × 1 year and the drug appears to be well tolerated (NEJM 2003;348:800.; NEJM 2003;348:808.).

3. Tenofovir: Highly active against HBV but not FDA approved for this indication. Like adofovir it is well tolerated and does not seem to induce resistance.

4. Combination: Despite the theoretical rationale for combination therapy, there are few data to support the use of interferon and nucleoside analoges at present.

3. **Chronic hepatitis D**: Efficacy demonstrated for interferon-alfa in patients with the following criteria: positive HBsAg, anti-HDV IgG and IgM, positive HDV RNA × 3, alanine aminotransferase ≥ 2 × upper limit of normal × 6 mo, histologic evidence of chronic hepatitis and positive intrahepatic HDV antigen. Patients with advanced cirrhosis were excluded. Optimal regimen was 9 million units IM 3 ×/wk for 48 wk. Response, which was generally transient, was shown by normal alanine transferase and elimination of serum HDV RNA in 7 of 14 patients vs 0 of 13 placebo recipients (NEJM 1994; 330:88.; JAMA 1999;282:511.).

D. HANTAVIRUS PULMONARY SYNDROME

1. **Definition** (MMWR 2002;51 RR-9.; CID 2002;34:1224.)

   Clinical features: HPS due to Sin Nombre virus has a median incubation period of 14–17 days, a prodrome of 3–5 days, and clinical features consisting initially of myalgias, GI symptoms (nausea, vomiting, diarrhea), and fever. A clue to the diagnosis in the prodrome stage is thrombocytopenia. The second stage is characterized by cardiopulmonary involvement with tachypnea, tachycardia, cough, and postural hypotension. The complete blood count is highly characteristic with hemoconcentration, leukocytosis with a left shift, thrombocytopenia and circulating immunoblasts that may resemble atypical lymphocytes. By 48 hours postadmission most patients have DIC with typical x-ray changes. The mortality rate is 38% in 344 cases in the U.S.

   Diagnosis: The diagnosis is established with serology (EIA IgM) or RT-PCR for Hantavirus during the first 10 days of illness.

Epidemiology: Rats and mice are hosts for Sin Nombre virus and transmit it by droppings, saliva, and urine. In the U.S. there were 344 cases reported from 1992 to June 2003 from 31 states, primarily in June and July in the Four Corners area (Arizona, Colorado, New Mexico, and Utah) (http://www.cdc.gov/ncidod/diseases/hanta.hantavirus.htm). Other areas with HPS are Argentina, Boliva, Brazil, Canada, Chile, Panama, Paraguay, and Uruguay. The average age was 37 years. Person-to-person with nosocomical spread was reported in Argentina (Emerg Infect Dis 1997;3:171.).

Treatment: Supportive care. A trial with ribavirin was unsuccessful (CID 2002;34:304.).

E. **SEVERE ACUTE RESPIRATORY SYNDROME (SARS)**

1. **Case definition**: CDC 7/11/03 (http://www.cdc.gov/ncidod/sars/casedefinition)

   a. **Clinical Criteria**

      1. Asymptomatic or mild respiratory illness
      2. Moderate respiratory illness
         - Temperature of >100.4°F (>38°C)*, and
         - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia).
      3. Severe respiratory illness
         - Temperature of >100.4°F (>38°C)*, and
         - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), radiographic evidence of pneumonia, respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

   b. **Epidemiologic Criteria**

      1. Travel (including transit in an airport) within 10 days of onset of symptoms

         to an area with current or previously documented or suspected community

transmission of SARS, or

2. Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS. The last date for illness onset is 10 days (i.e., one incubation period) after removal of a CDC travel alert. The case patient's travel should have occurred on or before the last date the travel alert was in place.

c. **Laboratory Criteria**

1. Confirmed
    - Detection of antibody to SARS-CoV in specimens obtained during acute illness or >28 days after illness onset, or
    - Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or
    - Isolation of SARS-CoV.
2. Negative
    - Absence of antibody to SARS-CoV in convalescent serum obtained >28 days after symptom onset.
3. Undetermined
    - Labatory testing either not performed or incomplete.

d. **Case Classification**

1. Probable case: Meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed, negative, or undetermined.
2. Suspect case: Meets the clinical criteria for moderate respiratory illness of unknown etiology, and epidemiologic criteria for exposure; laboratory criteria confirmed, negative, or undetermined.

2. **Diagnostic Evaluation**

a. Chest x-ray

b. Pulse oximetry

c. Blood cultures

d. Sputum gram stain and culture

e. Tests for influenza and RSV

f. "Consider" urinary antigen test for *S. pneumoniae* and *Legionella*

g. Acute and convalescent sera separated by >21 days for patients who meet definition of SARS case sent to state or local health departments for testing at CDC

3. **Prevention**: Transmission occurs primarily by direct contact with infectious material including large respiratory droplets; unlike TB, spread may also occur by direct contact with respiratory secretions. The following recommendations are designed to prevent spread to health care workers and to close contacts.

   a. Precautions for hospitalized patients: This includes standard precautions (hand hygiene), airborne precautions (N95 respirators), and contact precautions (gown and gloves).

   b. Advice to close contacts: Be alert to detect fever or respiratory symtpoms. If symptoms develop, avoid contact with others and seek medical attention.

   c. Advice to travelers: Elective travel to epidemic areas should be avoided. If travel to these areas is required, the traveler should carry a thermometer, household disinfectant, surgical mask, and disposable alcohol-based hand rubs. It is also advised to check with health insurance plans about medical care coverage.

   d. Ambulatory care and emergency rooms: Screening should be done for possible cases identified as the presence of fever, respiratory symptoms,

   recent travel to endemic areas, and close contact with a suspected SARS patient.

   e. Suspected cases should be evaluated in a separate area.

   f. The suspected person with SARS should wear a surgical mask. Health care personnel

should wear an N95 respirator; if not available, a surgical mask should be worn.

F. **WEST NILE VIRUS**

West Nile Virus (WNV) Infection: Information for Clinicians [CDC http://www.cdc.gov/ncidod/dvbid/westnile/resources/fact_sheet_clinicians.htm; accessed 7/26/03]: The following is a summary of WNV from the CDC website and other sources:

1. **Clinical Features**

   a. **Mild infection**

      1. About 80% are asymptomatic and 20% develop mild illness.
      2. Incubation period is 3–14 days for those with clinical symptoms.
      3. Symptoms usually last 3–6 days.
      4. Clinical features are sudden onset of afebrile illness accompanied by malaise, anorexia, nausea, vomiting, eye pain, headache, myalgias, rash and/or lymphadenopathy.

   b. **Severe infection**

      1. About 1 in 150 cases will cause severe neurologic disease, most commonly encephalitis and less commonly, meningitis
      2. The major factor for severe neurologic disease is advanced age.
      3. Features of severe disease are fever, weakness, GI symptoms, and a change in mental status; a minority develop a maculopapular or morbilliform rash involving the neck, trunk, arms, or legs.
      4. A small number of patients have developed severe muscle weakness and flaccid paralysis or Parkinson's syndrome
      5. Neurologic presentations include ataxia, cranial nerve abnormalities, myelitis, optic neuritis, polyradiculitis, and seizures.

   c. **Clinical suspicion**

This diagnosis should be suspected in adults over 50 years who develop unexplained encephalitis or meningitis in summer or early fall, especially if there are local cases or travel to an implicated area.

d. **Neurologic complications**

1. Viral encephalitis, characterized by:
    - Fever = 38°C or 100°F, and
    - CNS involvement, including altered mental status (altered level of consciousness, confusion, agitation, or lethargy) or other cortical signs (cranial nerve palsies, paresis or paralysis, or convulsions), and
    - An abnormal CSF profile suggesting a viral etiology (a negative bacterial stain and culture with a mononuclear pleocytosis [WBC 5–1500 cells/mm^3] and/or elevated protein level [>40 mg/dl]).
2. Aseptic meningitis (among persons aged 17 years and up), characterized by:
    - Fever = 38°C or 100°F, and
    - Headache, stiff neck and/or other meningeal signs, and
    - An abnormal CSF profile suggesting a viral etiology (a negative bacterial stain and culture with a pleocytosis [WBC between 5 and 1500 cells/mm^3] and/or elevated protein level [=40 mg/dl]).
3. Poliomyelitis-like syndromes: acute flaccid paralysis or paresis, (which may resemble Guillain-Barré syndrome), or other unexplained movement disorders such as tremor, myoclonus or Parkinson's-like symptoms,

especially if associated with atypical features, such as fever, altered mental status, and/or a pleocytosis. Afebrile patients with asymmetric weakness, with or without areflexia, have also been reported in association with West Nile virus.

2. **Diagnosis**

1. The most efficient method is detection of IgM in serum which is usually positive at the time of viral clearance and at the onset of neurologic disease.
2. False positive test may be a problem in patients recently vaccinated against or recently infected with related flaviviruses including yellow fever, Japanese encephalitis, or dengue.
    a. **Laboratory findings**
        - Total leukocyte counts are normal or elevated with lymphopenia and anemia.
        - Some have hyponatremia.
        - CSF shows pleocytosis with predominance of lymphocytes, protein is universally elevated and glucose is normal.
        - CT scans of the brain are usually normal, but about one third have MRI demonstrated enhancement of the leptomeninges, the periventricular areas of both.
3. **Treatment**: The usual treatment is supportive. There is an NIH-sponsored trial with hyperimmune globulin, which should be started early.

G. **Activity of Antivirals** (adapted and updated from NEJM 1999;340:1255.)*

Agent	***Proven efficacy***	***Possible efficacy***
Acyclovir	HSV, VZV, CMV	EBV, herpes B
Adefovir	HBV	HIV
Amantadine	Influenza A	—

Cidofovir	HSV, VZV, CMV, Molluscum	Small pox virus, monkey pox
Famciclovir	HSV, VZV	Hepatitis B
Foscarnet	CMV, HSV, VZV	HHV-8, HIV
Ganciclovir	CMV, HSV	HSV, VZV, EBV, HHV-8, HBV
Interferon-alfa	HBV, HCV, HHV-8, HPV	Hepatitis D, SARS-CoA
Lamivudine	HBV, HIV	—
Oseltamivir	Influenza A & B	
Penciclovir	HSV	
Ribavirin	Lassa fever, HCV	RSV, paraflu, influenza A & B, measles, Hantavirus, vaccinia
Rimantadine	Influenza A	

Valacyclovir	HSV, VZV, CMV	EBV
Valganciclovir	CMV, HSV	
Zanamivir	Influenza A & B	
* Antiretroviral agents for HIV are not included		

Footnotes

*Failure to achieve early viral response (≥2 log decrease in HCV RNA) at 12–24 weeks: stop therapy

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Sepsis and Sepsis Syndrome

A. **CONSENSUS CONFERENCE DEFINITIONS** (Crit Care Med 1992;20:864.; Chest 1992;161:1644.; NEJM 2001;344:707.)

Systemic inflammatory response syndrome (SIRS). Two or more:

1. Temperature >38°C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min
4. White blood cell count >12,000/mm^3, <4,000/mm^3, or >10% immature (bands) forms

Sepsis. SIRS plus a documented infection (positive culture for organism).

Severe sepsis. Sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock. Sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities.

Culture negative populations.

Culture negative sepsis. SIRS plus empirical antibiotic treatment for a clinically suspected infection but in whom all cultures were negative.

Culture negative severe sepsis. SIRS associated with organ dysfunction, hypoperfusion, or hypotension. However, all cultures were negative.

Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Culture negative septic shock. SIRS associated with hypotension despite fluid resuscitation plus hypoperfusion abnormalities. However, all cultures were negative.

B. **EMPIRIC ANTIBIOTIC SELECTION FOR SEPSIS** (Med Lett 2001;43:69.)

1. **Life-threatening sepsis**: Aminoglycoside (gentamicin, tobramycin, or amikacin)plus one of the following:
    - Third-generation cephalosporin (cefotaxime, cefepime, or ceftriaxone)
    - Ticarcillin-clavulanic acid or piperacillin-tazobactam
    - Imipenem or meropenem

    Suspected methicillin-resistant*S. aureus*: Add vancomycin ± rifampin
2. **Intra-abdominal or pelvic infection**:
    - Any of the following with or without an aminoglycoside: Ticarcillin-clavulanic acid, piperacillin-tazobactam, ampicillin-sulbactam, imipenem, cefoxitin, or cefotetan
3. **Biliary tract source**:
    - Piperacillin + metronidazole ± aminoglycoside
    - Piperacillin-tazobactam or ampicillin-sulbactam ± aminoglycoside
4. **Urinary tract infection** (Nosocomial):
    - Third-generation cephalosporin ± aminoglycoside
    - Fluoroquinolone ± aminoglycoside
    - Ticarcillin/clavulanate or piperacillin/tazobactam ± aminoglycoside
    - Imipenem or meropenem ± aminoglycoside
5. **Meningitis**
    - Community-acquired: Ceftriaxone or cefotaxime + vancomycin 2–4 g/d, ± rifampin
    - Nosocomial: Ceftazidime + vancomycin 2–4 g/d
6. **Nosocomial pneumonia**: Aminoglycoside + cefepime, imipenem, or meropenem ± vancomycin if MRSA suspected

7. **Community-acquired pneumonia**:

   - Ceftriaxone or cefotaxime + macrolide (azithromycin, clarithromycin, or erythromycin)
   - Fluoroquinolone (levofloxacin, gatifloxacin, or moxifloxacin)
   - Aspiration pneumonia suspected: Add clindamycin or metronidazole

8. **Neutropenia + sepsis**
   - Ceftazidime ± aminoglycoside
   - Imipenem, meropenem, or cefepime ± aminoglycoside
   - Piperacillin/tazobactam or ticarcillin/clavulanate, each with amikacin
   - All of above: Add vancomycin if MRSA are suspected

9. **Endocarditis**: Vancomycin + gentamicin

C. **DROTRECOGIN (XIGRIS)**

Product: Activated protein C exerts antithrombotic effect by inhibition of Factor Va and VIIIa, increases fibrinolysis and inhibits TNF.

Indication: Severe sepsis with:

1. APACHE II score >25,
2. suspected or proven source of infection, and
3. ≥3 signs of systemic inflammation and ≥ one spesis-induced organ dysfunction.

Dose: 24 mcg/kg/hr by continuous infusion × 96 hr (No dose modification for renal or hepatic failure)

Efficacy: In the major clinical trial the 28 day mortality was 25% in drotrecogen recipients compared to 31% in the placebo group ($p<0.05$) (NEJM 1999;340:207.).

Side effects: Major toxicity causes bleeding; in the large clinical trial the frequency of serious bleeding events was 3.5% in drotrecogen recipients compared to 2% with placebo recipients.

Contraindication: Active, recent, or high risk of bleeding include trauma, epidural catheter, or intracranial lesion. Drug should be stopped 2 hours before invasive procedures and can be

started 12 hrs after major surgery if hemostatis is adequate.

D. **INTRAVASCULAR CATHETER-RELATED INFECTION**: Recommendation of IDSA (CID 2001;32:1249.)

Nontunneled central venous catheters

1. Blood culture × 2, remove catheter, culture catheter tip and insert new catheter over guidewire
2. Empiric antibiotics if seriously ill
3. Serious or complicated infection including septic thrombophlebitis, endocarditis or osteomyelitis: Remove CVC and treat 4–6 wks (6–8 wks for osteomyelitis)
4. Uncomplicated infection:
    - Coag-neg staph: Remove CVC and treat 5–7 days or retain catheter and treat 10–14 days ± lock therapy
    - *S. aureus*: Remove CVC and treat 14 days; if TEE is positive: treat for endocaraditis
    - GNB: Remove CVC and treat 10–14 days
    - *Candida*: Remove CVC and treat with antifungal × 14 days

Tunneled central catheters

1. Complicated infections such as port abscesses: Remove CVC and treat with antibiotics 10–14 days
2. Other major complications such as septic thrombophlebitis, endocarditis, or osteomyelitis: Remove CVC and treat with antibiotics 4–6 wks or 6–8 wks for osteomyelitis
3. Uncomplicated infections:
    - Coag-neg staph: Retain CVC and treat with antibiotics for 7 days + antibioitic lock therapy for 10–14 days. If there is persistence or deterioration: Remove CVC.

    - *S. aureus*: Remove CVC and treat 14 days or keep CVC and remove if there is clinical progression
    - GNB: Remove CVC and treat 14 days or retain CVC and give systemic antibiotics + lock therapy. Failure to respond: Remove CVC and treat 10–14 days
    - *Candida*: Remove CVC and treat with antifungal therapy

10–14 days

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Compromised Host

PATHOGENS ASSOCIATED WITH IMMUNODEFICIENCY

Condition	*Usual conditions*	*Pathogens*
Neutropenia (<500/mL)	Cancer chemotherapy; adverse drug reaction; leukemia	**Bacteria:** Aerobic GNB (coliforms and pseudomonads); *S. aureus, Strep viridans*, *S. epidermidis* **Fungi:** *Aspergillus, Candida* sp
Cell-mediated immunity	Organ transplantation; HIV infection; lymphoma (especially Hodgkin's disease); corticosteroid therapy	**Bacteria:** *Listeria, Salmonella*, *Nocardia*, mycobacteria (*M. tuberculosis* and *M. avium*),*Legionella* **Viruses:** CMV, *H. simplex*, varicella-zoster, JC virus **Parasites:** *Pneumocystis*

		carinii; Toxoplasma; Strongyloides stercoralis; cryptosporidia **Fungi:** *Candida, Cryptococcus*, *Histoplasma, Coccidioides*
Hypogamma-globulinemia or dysgamma-globulinemia*	Multiple myeloma; congenital or acquired deficiency; chronic lymphocytic leukemia	**Bacteria:** *S. pneumoniae, H. influenzae* (type B) **Parasites:** *Giardia* **Viruses:** Enteroviruses
Complement deficiencies C2, 3 C5 C6–8 Alternative pathway	Congenital	**Bacteria:** *S. pneumoniae, H. influenzae* *S. pneumoniae, S. aureus*, *Enterobacteriaceae* *Neisseria meningitidis* *S. pneumoniae, H. influenzae, Salmonella*
Hyposplenism	Splenectomy; hemolytic anemia	*S. pneumoniae, H. influenzae*, DF-2
Defective chemotaxis	Diabetes, alcoholism, renal failure,	*S. aureus*, streptococci, *Candida*

	lazy leukocyte syndrome, trauma, SLE	
Defective neutrophilic killing	Chronic granulomatous disease, myeloperoxidase deficiency	Catalase-positive bacteria:*S. aureus, E. coli; Candida* sp

* Patients with primary immune deficiency disorders should receive IV immunoglobulin (200 mg/kg monthly) (Med Lett 1992;34:116).

GUIDELINES FOR USE OF ANTIMICROBIAL AGENTS IN NEUTROPENIC PATIENTS WITH UNEXPLAINED FEVER

(Infectious Disease Society of America, CID 2002;34:730.; reprinted with permission)

Definition: Fever is defined as a single oral temp of 38.3°C × 1 or 38.0°C for over one hour. Neutropenia is defined as an ANC $<500/mm^3$ or $<1000/mm^3$ with a predicted decrease to $<500/mm^3$.

Evaluation for vancomycin need:

1. suspected catheter-related infection,
2. known colonization with beta-lactam resistant *S. pneumoniae* or MRSA,
3. positive blood cultures for GP bacteria prior to identification, or
4. hypotension.

Assessment for possible oral antibiotic treatment: Patients at low risk for complications may often be treated with oral antibiotics if there is no focus of infection and lack of findings for systemic infection such as rigors or hypotension. If outpatient treatment is to be used, there must be access to medical care 24/7.

Risk assessment: Factors supporting low risk are an ANC exceeding 100/mm^3, absolute monocyte count exceeding 100/mm^3, normal chest x-ray, nearly normal renal and hepatic tests, neutropenia less than 7 days, malignancy in remission, temperature peak less than 39°C, early evidence of marrow recovery, and none of the following: IV catheter site infection, neurologic or mental status changes, appearance of illness, abdominal pain or cormorbidity/complications.

Antibiotic selection (Figure 1)

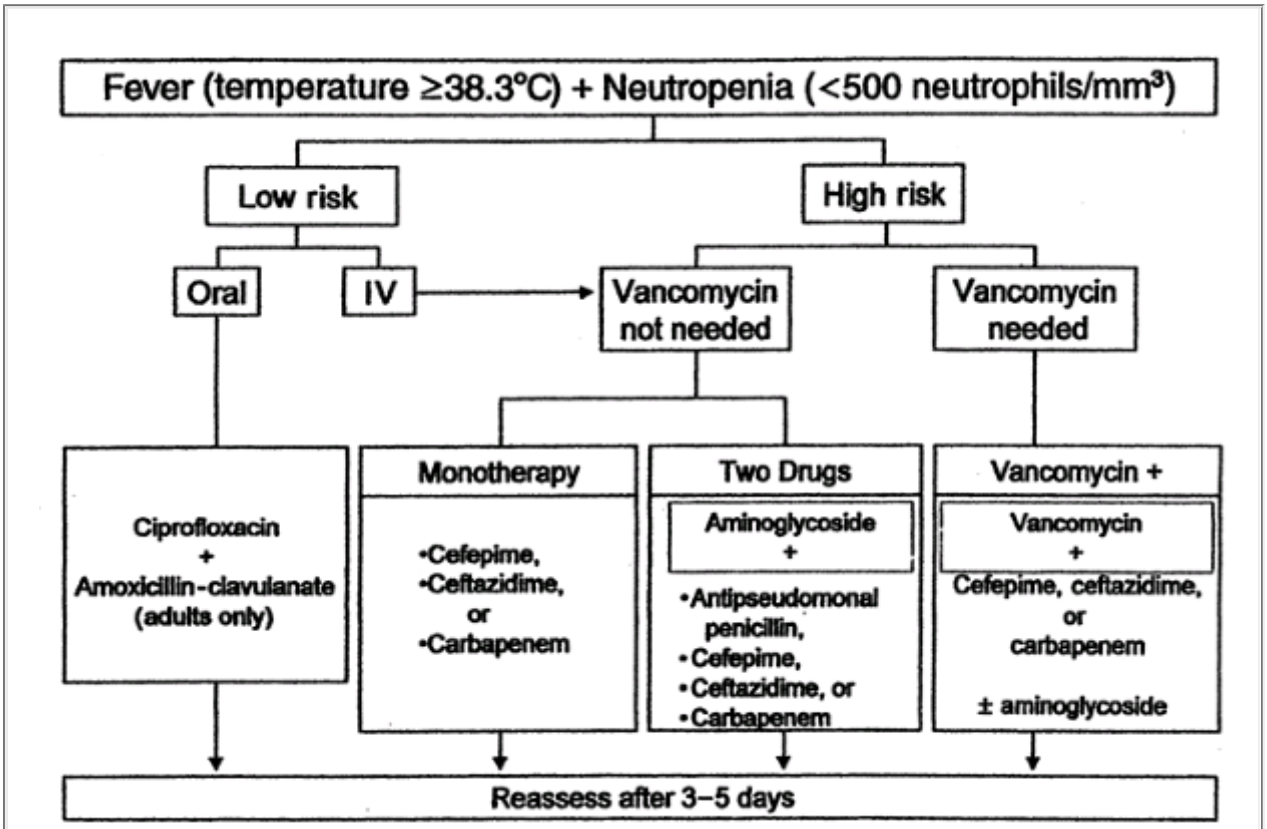

FIGURE 1: GUIDE TO INITIAL MANAGEMENT

1. Low risk, oral treatment: Ciprofloxacin plus amoxicillin-clavulanate.
2. Low risk, IV therapy: Cefepime, ceftazidime, or carbapenem
3. High risk with no need for vancomycin: Monotherapy (see Figure 1) or dual therapy: aminoglycoside plus either an antipseudomonal penicillin, cefepime, ceftazidime, or carbapenem.
4. High risk and vancomycin needed: Vancomycin plus cefepime,

ceftazidime, or carbapenem plus/minus aminoglycoside.

Modifications of therapy based on response at 3–5 days (Figures 2 and 3)

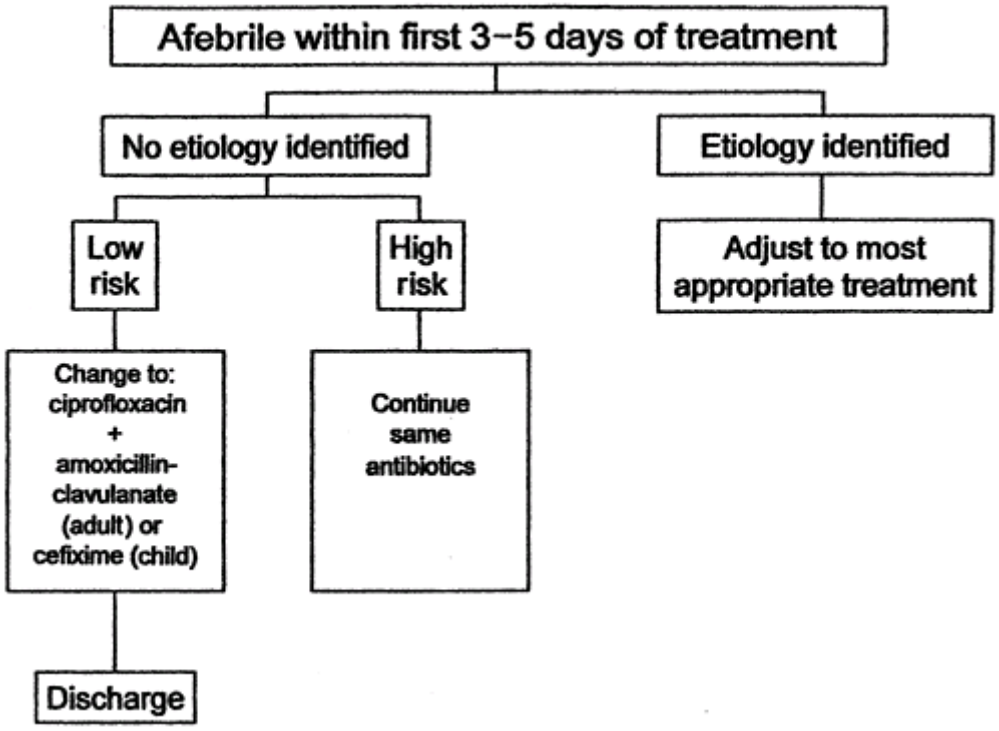

Figure 2: Management of patients who become afebrile in first 3–5 days of initial antibiotic therapy.

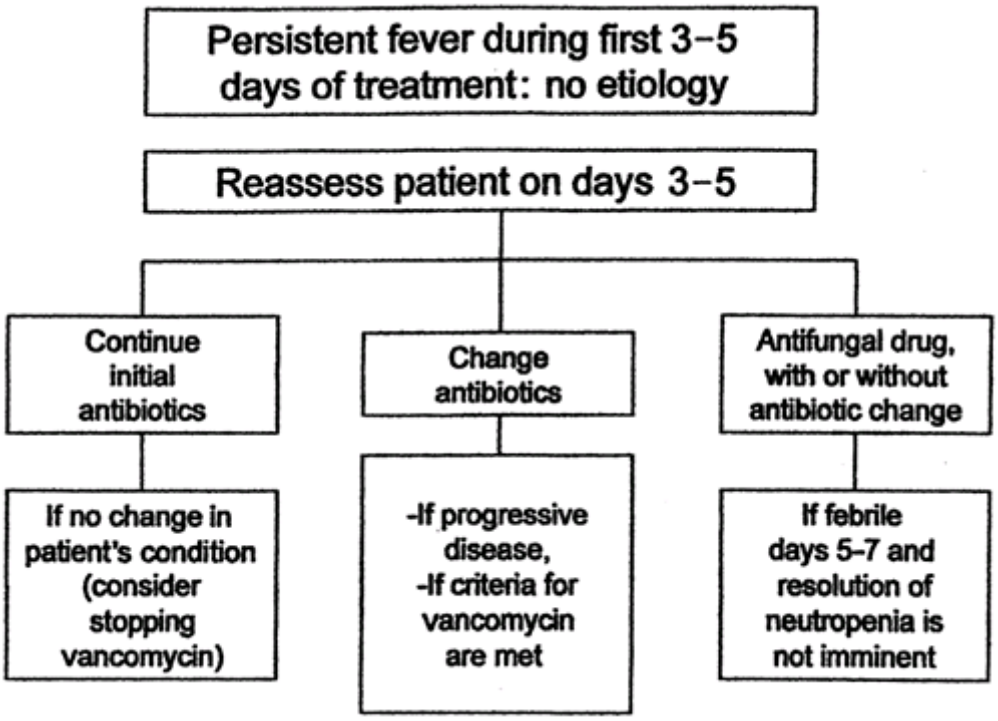

Figure 3: Treatment of patients who have persistent fever after 3–5 days of treatment and for whom the etiology of the fever is not found.

1. Response and pathogen defined: Adjust therapy based on pathogen.
2. Response and no pathogen identified: Oral therapy should be continued. IV therapy may be changed to oral ciprofloxacin plus amoxicillin-clavulanate after 48 hours
3. Persistent fever at 3 days and no change in patient condition: Continue same antibiotics, but consider discontinuing vancomycin if there is no clear need for it.
4. Persistent fever at 3–5 days and progressive disease: Change antibiotic regimen depending on the initial regimen. This includes the addition of vancomycin if it was not initially used and there are criteria for it, or consideration of discontinuing vancomycin if it was included in the initial regimen.
5. Persistent fever at days 5–7: Consider antifungal agent such as amphotericin B, lipid amphotericin B (no more effective, but reduced toxicity), or fluconazole. Fluconazole is acceptable at an

institution where *Aspergillus* and azole-resistant *Candida* infections are uncommon, where fluconazole was not used as prophylaxis, and when there is no evidence of pulmonary disease or sinusitis. Recent reviews have not shown clear advantages in efficacy for empiric use of amphotericin B, lipid amphotericin, itraconazole, or fluconazole.

Antibiotic discontinuation (Figure 4): Low risk patients may have antibiotics discontinued when they are afebrile 5–7 days. If the ANC increases above 500/mL, stop antibiotics at 4–5 days. If there is persistent fever at day 3 and persistent ANC <500/mm^3, continue antibiotics for 2 weeks and reasses.

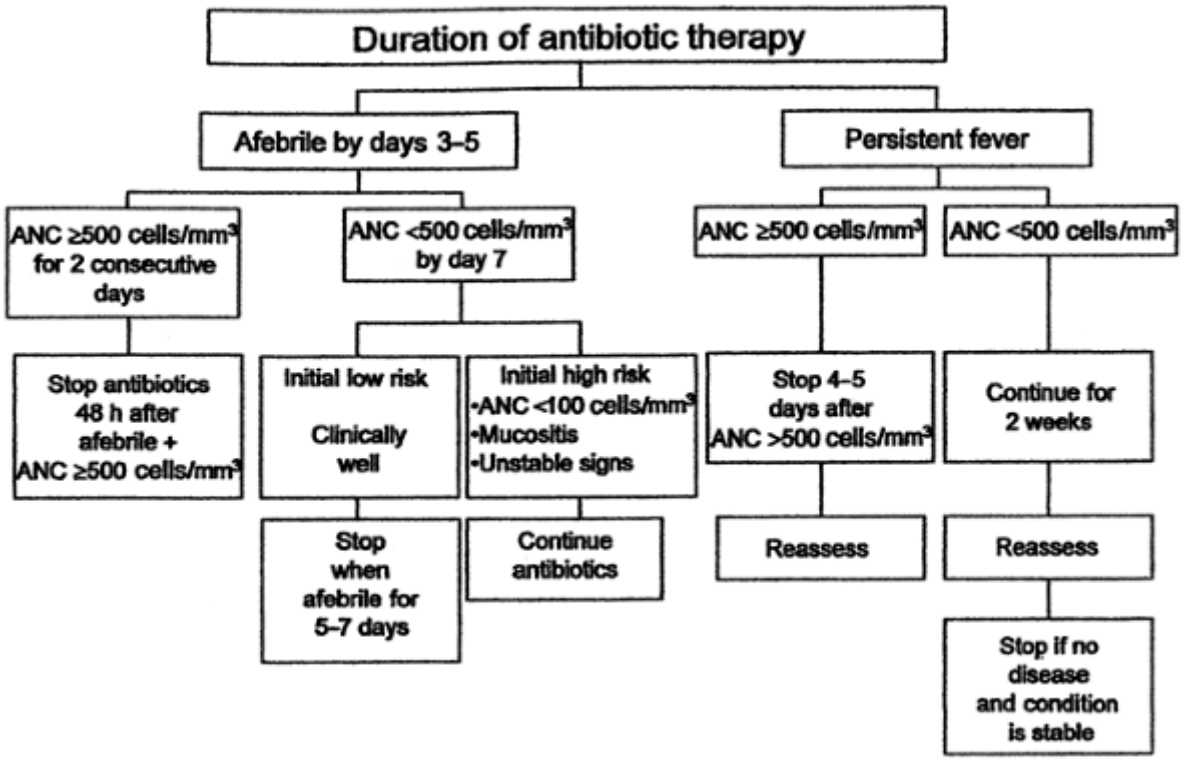

FIGURE 4: DURATION OF ANTIBIOTIC THERAPY

Miscellaneous issues

Antiviral drugs: Not recommended unless there is laboratory or clinical support for use.

Granulocyte transfusions: Not recommended.

G-CSF or GM-CSF: Not recommended for routine use, but may be considered if there is an expected long delay in marrow recovery and those with documented infections who do not respond to antibiotics.

Prophylaxis in neutropenic patients without fever: TMP-SMX is sometimes recommended for PCP regardless of neutropenia. There are good data supporting efficacy of prophylaxis with TMP-SMX, quinolones, fluconazole, and itraconazole for reducing the number of infectious complications of neutropenia, but the Panel recommends against this prophylaxis due to the concerns for antibiotic resistance and the failure of these studies to show reduction in mortality.

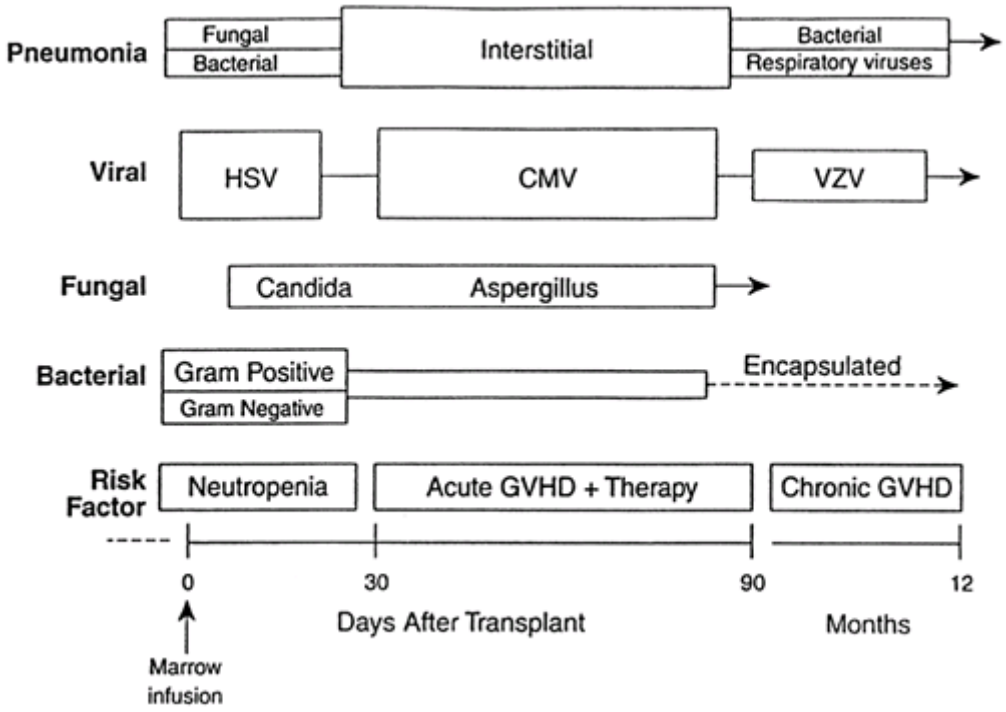

FIGURE 5: COMMON INFECTIONS BY TIME AFTER MARROW TRANSPLANTATION*

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Toxic Shock Syndrome: Case Definition of Cdc (MMWR 29:229, 1980)

1. Fever: Temperature ≥38.9°C (102°F).
2. Rash: Diffuse macular erythroderma.
3. Desquamation: 1–2 wk after onset, especially palms and soles.
4. Hypotension: Systolic <90 mm Hg for adults or <5th percentile by age for children or orthostatic syncope.
5. Involvement of three or more of the following organs.

    GI: Vomiting or diarrhea at onset

    Muscular: Severe myalgia or creatine phosphokinase >2× normal

    Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia

    Renal: BUN or creatinine ≥2× normal or ≥5 WBC/HPF in absence of UTI

    Hepatic: Bilirubin or transaminase levels ≥ 2× normal

    Hematological: Platelets <100,000/mm^3

    CNS: Disoriented or altered consciousness without focal neurologic signs when fever and neurologic signs are absent
6. Negative results for the following (if obtained): Cultures of blood, throat, and cerebrospinal fluid; negative serology for Rocky Mountain spotted fever, leptospirosis, or measles.

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Group A Streptococcal Infections

Classification and Definition of Group A Streptococcal Toxic Shock Syndrome: Working Group on Severe Streptococcal Infections (CDC) (Reprinted with permission from JAMA 269:390, 1993)

Proposed Case Definition for the Streptococcal Toxic Shock Syndrome*

I. Isolation of group A streptococci (*Streptococcus pyogenes*)
   A. From a normally sterile site (e.g., blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound)
   B. From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion)

II. Clinical signs of severity
   A. Hypotension: Systolic blood pressure ≤ 90 mmHg in adults or <5th percentile for age in children and
   B. ≥2 of the following signs
      1. Renal impairment: creatinine ≥177 µmol/L (≥2 mg/dL) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a ≥2-fold elevation over the baseline level
      2. Coagulopathy: platelets ≤100 × 10°/L (≤100,000/mm^3) or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
      3. Liver involvement: alanine amino-transferase

(SGOT), asparate amino-transferase (SGPT), or total bilirubin levels greater than or equal to twice the upper limit of normal for age. In patients with preexisting liver disease a ≥2-fold elevation over the baseline level
4. Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
5. A generalized erythematous macular rash that may desquamate
6. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

* An illness fulfilling criteria IA and IIA and IIB can be defined as a definite case. An illness fulfilling criteria IB and IIA and IIB can be defined as a probable case if no other etiology for the illness is identified.

Therapy of Streptococcal Infections of Skin and Soft Tissue

(NEJM 1996;334:240.; AAC 2003;423:104.)

1. Antibiotic: *S. pyogenes* is exquisitely sensitive to beta-lactams; penicillin is preferred for pharyngitis, erysipelas, impetigo, and cellulitis. Experimental models of fulminant infections show clindamycin is superior, presumably because it inhibits protein synthesis and activity is independent of inoculum size. Clindamycin or clindamycin plus penicillin is preferred for necrotizing fasciitis, myositis, empyema, and streptococcal toxic shock syndrome. Studies in the mouse myositis model show clindaymcin is superior to penicillin for inhibiting streptococcal toxin production in vivo; penicillin combined with clindamycin showed no antagonism

(AAC 1987;31:213; AAC 2003;423;104)

2. IVIG: Anecdotal studies support use for streptococcal toxic shock syndrome at suggested dose of 1g/kg day 1 then 0.5g/kg on days 2 and 3 (CID 2003;37:333)
3. Surgery: Prompt and aggressive exploration and debridement of deep-seated infections are important

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Anaerobic Infections

1. Susceptibility in vitroa

Susceptibility	*B. fragilis group*	*Bacteroides (other), Prevotella*	*Fusobacteria*	*Peptostrep*	*Clostridia*
>95%	Beta-lactam-BL inhibitors Chloramphenicol Imipenem Metronidazole	Same as *B. fragilis* Cefoxitin Cefoperazone Cefotaxime Clindamycin Trovafloxacin Moxifloxacin Gatifloxacin	Same as *B. fragilis* Penicillin G Piperacillin Trovafloxacin Moxifloxacin Cefotetan Cefoxitin	Same as *B. fragilis* Penicillin G Piperacillin Ceftazidime Cefotetan Cefoperazone Ceftriaxone Trovafloxacin Gatifloxacin Moxifloxacin Clindamycin	Ampicillin-sulbactam Chloramphenicol Imipenem Penicillin G Piperacillin Cefotaxime Piperacillin
85–95%	Cefoxitin Gatifloxacin Moxifloxacin	Cefotetan Ceftazidime Ceftriaxone	Cefoperazone Cefotaxime Moxifloxacin Gatifloxacin Clindamycin	Metronidazole Ciprofloxacin Levofloxacin	Cefotetan Cefoxitin Ceftriaxone
70–84%	Piperacillin Ceftizoxime Clindamycin	Penicillin G	Ceftazidime Ciprofloxacin		Cefoxitin Clindamycin
50–69%	Cefotetan Cefoperazone Cefotaxime Ceftazidime Ceftriaxone	Levofloxacin	—	—	Metronidazole Fluoroquinolones
<50%	Levofloxacin Ciprofloxacin Penicillin G	Ciprofloxacin			Ceftazidime

2. **Outcome of *Bacteroides* bacteremia in 128 patients**(CID 30:870, 2000)

	Active drug	*Inactive drug*	*P value for difference*
Mortality	16%	45%	0.04
Clinical failure	22%	82%	0.002

Microbiological persistence	12%	42%	0.06

3. **Susceptibility of anaerobic bacteria**. Modified from National Committee for Clinical Laboratory Standards, Working Group on Anaerobic Susceptibility Testing (J Clin Microbiol 26:1253, 1988.; updated Antimicrob Ag Chemother 2001;45:1238.)

ESSENTIALLY ALWAYS ACTIVE

- Metronidazole (except some nonsporulating GPB)
- Chloramphenicol
- Imipenem/meropenem
- Beta-lactam-beta-lactamase inhibitor combinations (especially piperacillin-tazobactam)

USUALLY ACTIVE

- Clindamycin (increasing in vitro resistance—AAC 2001;45:1238.; AAC 2003;47:148.)
- Cefoxitin
- Antipseudomonad penicillins
- Trovafloxacin/moxifloxacin/gatifloxacin

UNPREDICTABLE ACTIVITY

- Cephalosporins (other)
- Penicillins (other—especially antistaphylococcal agents)
- Vancomycin (Gram-positive anaerobes only)
- Erythromycin (Fusobacteria often resistant)
- Tetracyclines

VIRTUALLY NEVER ACTIVE

- Aztreonam
- Aminoglycosides
- Trimethoprim-sulfamethoxazole

Footnote

[a]Adapted from: Principles and Practice of Infectious Diseases, AAC 1999;43:2231; AAC 1999;43:2320; CID 2000;30:870; AAC 2001;45:1238; Anaerobe 2001;7:285; CID 2002;35:S126; AAC 2003;47:148.

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Fever of Unknown Origin

A. **Definition**

Classic (Medicine 1961;40:1.):

1. Illness × ≤ 3 wks,
2. Documented fever ≥ 101°F (38.3°C), and
3. Negative diagnostic evaluation with one week in hospital

Contemporary: 2 modifications

1. Emphasis on diagnostic evaluation in outpatient clinic
2. Emphasis on subtypes
   - Nosocomial: Posteroperative complications, drug fever, *C, difficile*, phlebitis pulmonary emboli, ICU sinusitis (Brit J Hosp Med 1996;56:21.)
   - Immunodeficient (chemotherapy etc): Infection (JID 1990;161:381.)
   - HIV-associated (pre-HAART): MAC, CMV, PCP, TB, lymphoma, Bartonella (J Intern Med 1994;236:529.)
   - Elderly: Infections, tumors, and connective tissue diseases (especially temporal arteritis and polymyalgia rheumatica) (J Am Geriatr Soc 1993;41:1187.)
   - Young patients: Many undiagnosed (30%) and long-term follow-up shows benign course (Arch Inter Med 2003;163:1033.)
   - Prolonged fever (>1 year): Lymphoma, factitious, normal variant, granulomatous hepatitis

B. **Etiologic diagnosis** in the 5 standard categories: Infection, neoplasm, connective tissue, miscellaneous, and undiagnosed:

Source	**Petersdorf[1]**	**Larson[2]**	**Barbado[3]**	**Knockaert[4]**	**Likuni[5]**	**DeKleijn[6]**	**Vander[7]**
Period of review	**1952–57**	**1970–80**	**1968–81**	**1980–89**	**1982–92**	**1992–94**	**1991–99**
Location	**U.S.**	**U.S.**	**Spain**	**Belgium**	**Japan**	**Netherlands**	**Belgium**
Number	100	105	133	197	153	167	189
Diagnosis made, %	91	84	78	74	88	69	52
Infection, %*	40	36	39	30	33	37	30
Neoplasm, %*	21	38	25	10	16	18	15
Connective tissue, %*	19	15	19	13	35	33	34

Miscellaneous, %*	21	11	16	29	16	11	20

* % in cases with a final diagnosis
[1] Medicine 1961;40:1
[2] Medicine 1982;61:269
[3] J Med 1984;15:185
[4] Arch Intern Med 1992;152:51
[5] Intern Med 1994;33:67
[6] Medicine 1997;76:392
[7] Arch Intern Med 2003;163:1033

C. **Major conditions** within categories in most contemporary reviews (Arch Intern Med 2003;16:1033.)

1. Infection: Endocarditis, TB, UTI, and intra-abdominal abscess
2. Malignancy ("omas"): Hematologic, solid tumor with hepatic mets
3. Connective tissue: Still disease, polymyalgia rheumatica, and granulomatous disease (sarcoid, Crohn disease, granulomatous hepatitis, and temporal arteritis)
4. Miscellaneous: Pulmonary emboli, drug fever, periodic fever, and "habitual hyperthermia"
5. No diagnosis: Long-term follow-up in 80 cases showed no late sequelae (Arch Intern Med 2003;163:1033.)

D. **Diagnostic tests** (Arch Intern Med 2003;163;545.)

Step 1: Confirm fever (daily temps)

Fever pattern: not helpful (Arch Intern Med 1979;139:1225.)

Stop meds: Fever resolves <72 hrs or there is another cause (Inf Dis Clin N Amer 1996;10:85.)

Step 2: Selected tests

- CT abdomen: Cause found in 19% (Radiology 1980;136:407.) Repeat scan is not helpful
- Nuclar scans: Variable
- Endocarditis: Duke criteria-sensitivity 82% (CID 1995;21:905.)
- Liver biopsy: Yield is 14–17% (Arch Intern Med 1977;137:1001.; J Clin Gastro 1993;17:29.) (but usually with abnormal LFTs)
- Temporal artery bx: 16% (J Am Gastric Soc 1993;41:1187.) (in age >50 yrs)
- Leg doppler: 2–6% (Intern Med 1994;33:67.)

Tests that are usually not helpful: Ultrasound, bone scan, MRI, D-dimer assay, ESR, and CRP

E. **Fever evaluation in critically ill patients** Recommendations of the Society of Critical Care Medicine and the ISDA (Clin Infect Dis 1998;26:1042.)

Blood culture: Two blood cultures (with 10–15 mL each) from separate sites drawn ≥10 minutes apart. For skin preparation, povidine iodine (10%) should be allowed to dry 2 minutes and tincture of iodine (1–2%) should be allowed to dry 30 seconds. Alcohol with no drying time is an alternative. With an intravenous catheter, one peripheral vein sample and one through the catheter is an alternative to 2 peripheral vein samples, but the results provide less precise information.

Intravascular catheters: The risk of fever with central venous catheters is 5–10 per 1000 catheter days and for peripheral IV catheters the risk is <0.2 per 1000 catheter days. If there is evidence of tunnel infection, emboli events, vascular compromise, or sepsis the catheter should be removed.

Pulmonary infection: The evaluation should include a chest x-ray, Gram stain, and culture of respiratory secretions and pleural fluid evaluation (if present)

C. difficile: If ≥2 loose or watery stools/day there should be one stool sample sent for *C. difficile* toxin assay. If this is negative a second specimen can be sent. If disease is severe and the toxin test is negative or delayed, it is appropriate to treat empirically with metronidazole.

Sinusitis: If clinical findings support this diagnosis, there should be a CT scan. With evidence of sinusitis

on CT scan there should be puncture or aspiration of sinuses under sterile conditions for Gram stain and culture for aerobes, anerobes, and fungi.

Urinary tract infection: Urine should be evaluated by quantitative culture for PMNs. Pyuria should be tested by esterase dipstick and Gram stain of centrifuged urine sediment. Urine should be collected from the urine port of a Foley catheter; UTIs almost always show $>10^4$ cfu/mL and pyuria with a catheter collection. If the delay in culture of collected urine >1 hr it should be refrigerated or placed in a preservative.

Postop fever: Noninfectious fever is common during the first 48 hrs. post-operative. Unexplained fever >72 hrs post-operative should be evaluated with chest x-ray, urine culture and urinanalysis, and exam for phlebitis, thrombosis, pulmonary emoblism, and wound infection.

Fever due to non-infectious causes: Blood products (especially RBC's & platelets), drugs, pancreatitis, myocardial infarction, pulmonary emboli, and chemical phlebitis.

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Treatment of Lyme Disease and Potential Exposures

(Recommendations of Med Letter 2000;42:37.; MMWR 1997;46:532.; Ann Intern Med 1998;128:37.)

Prevention: (NEJM 2003;348:2424.):

1. The vaccine (LYMErix has been withdrawn from the market due to poor sales (Nat Med 2002;8:311.).
2. Removal of *I. scapularis* ticks within 36 hrs of attachment using daily tick checks (regarded as most effective preventive strategy) (JID 1997;175:996.; NEJM 2001;345:79.; Am J Epidemiol 1998;147;391.).
3. Prophylactic doxycycline for tick bites (see below).
4. Tick control with acaricide (cardaryl, cyfluthrin, or deltamethrin) in early May reduces *I. scapularis* nymph population by 68–100% (J Med Entomol 2001;38:344.).
5. Note that treatment of early Lyme disease (erythema migrans stage) prevents late sequelae in >95% (Ann Intern Med 1983;99:22.; AAC 1995;39:661.; Am J Med 1992;92:396.; Ann Intern Med 1996;124:785.; NEJM 1997;337:289.; Ann Intern Med 2002;136:421.)

Tick bite: Prophylactic doxycycline 200 mg po × 1 reduces the risk of Lyme disease if given within 72 hours of a bite from a I. scapularis tick vector especially in a high incidence area, and with bites from nymphal ticks that are partially engorged (NEJM 2001; 344:79). Efficacy is 87%. GI intolerance to doxycycline dose is improved if taken with meal

Epidemiology: In 2000 there were 17,730 cases of Lyme disease

reported in the U.S. The number of cases/incidence per 100,000 population by state: CT—3,773/110.8; RI—675/64.4, NJ—2,459/29.2; NY—4,329/22.8; DE—167/21.3, PA—2,343/19.2; MA—1,158/18.2, MD—688/13.0, and WI—631/11.8. The total cases reported for 1991–2000 was 132,438 and the incidence for the U.S. in 2000 was 6.3/100,000 (MMWR 2002; 51:29)

Diagnosis: Recommendations of American College of Physicians (Ann Intern Med 1997;127:110.)

Clinical diagnosis: Patients from an endemic Lyme disease area who present with erythema migrans do not require laboratory confirmation. Seroconversion occurs in 27% with symptoms <7 days, 41% with symptoms 7–14 days and 88% with symptoms >14 days (Ann Intern Med 2002;136:421.). Confirmation of late Lyme disease requires objective evidence of Lyme disease plus laboratory evidence

Culture: Erythema migrans—saline lavage needle aspiration or 2 mm punch biopsy

of the leading edge show *B. burgderfori* by culture or PCR in 60–80% (Ann Intern Med 2002;136:421.)

Serology (MMWR 1999;48 RR–7.; JAMA 1999;282:62.): ELISA testing is standard—sensitivity = 89% and specificity = 72%; when ELISA results are positive or indeterminant, use a Western blot. A positive Western blot confirms the diagnosis and a negative Western blot greatly decreases the probability of Lyme so that treatment is not indicated.

Phases:

Erythema migrans

Early disseminated Lyme disease with carditis and neurologic features including lymphocytic meningitis and radiculoneuropathies

Late Lyme disease with peripheral neuropathies, chronic encephalopathy, or arthritis with migratory polyarthritis and/or monoarthritis. The term "chronic Lyme disease" (in reference to debilitating fatigue) was first applied in 1985 and has no objective findings, but there is considerable support from Internet site advocacy groups and some physicians (Ann Intern Med 2002;136:413.). Multiple studies indicate no evidence of Lyme disease and no benefit from

empiric treatment even with long courses of IV antibiotics (NEJM 2001;345:85.; Ann Intern Med 1998;128:354.; JID 1995;171:356.; JID 1995;171:423.; CID 2000;31:1107.)

TREATMENT OF LYME DISEASE (Med Lett 2000;42:37.)

Stage	***Preferred***	***Comment***
Erythema migrans	Doxy 100 mg po bid × 21 d* (see footnote) Amoxicillin 500 mg po bid × 21 d Cefuroxime axetil 500 mg po bid × 21 d	Goal is shorten duration of rash and prevent late sequelae Doxy is effective vs *Ehrlichia*; beta-lactams are not Amoxicillin preferred for pregnant/lactating women Babesiosis requires clindamycin and quinine
Neurologic		
Bells palsy	Doxy 100 mg po bid × 21–28 d Amoxicillin 500 mg po bid × 21–28 d	Oral treatment is sufficient for facial nerve palsy alone Accounted for 11/503 cases (AM J Otolaryn 2002;23:25)
More serious CNS	Ceftriaxone 2 g/d IV × 14–28 d Cefotaxime 2 g IV q8h × 14–28 d Penicillin G 20–24 mil units/d IV × 14–28 d	"More serious" category includes meningitis, encephalitis, cranial nerve palsies, peripheral nerve palsies, etc.

Cardiac		
1st degree	Doxy 100 mg po bid × 21–28 d Amox 500 mg po tid × 21–28 d	PR interval <0.3 sec can be treated orally
More serious	Ceftriaxone 2 g/d IV × 14–21 d Penicillin G 18–24 mil units/d IV × 14–21 d	PR >0.3 sec gets parenteral drug
Arthritis		
Oral	Doxy 100 mg po bid × 28 d Amox 500 mg po tid × 28 d	Oral therapy usually adequate for arthritis Some require a second course
Parenteral	Ceftriaxone 2 g/d IV × 14–28 d Penicillin G 18–24 mil units IV × 14–28 d	Alternative to second month of oral therapy Arthroscopic synovectomy may be useful in refractory arthritis of knee

* A subsequent study showed that doxycycline (200 mg/d) given for 10 days was as effective as the same regimen given for 20 days or doxycycline given for 16 days with a single 2 g dose of ceftriaxone (Ann Intern Med 2003;289:1533)

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Infections of Epidermis, Dermis, and Subcutaneous Tissue

Condition	*Agent*	*Laboratory diagnosis*	*Treatment*
Superficial erythematous lesions			
Abscess	*S. aureus* Anaerobes	Culture and Gram stain	Drainage
Acne rosacea	?	Appearance	Doxycycline* Metronidazole (0.75% topical) Isotretinoin (Accutane)
Acne vulgaris	*Propionibacterium acnes*	Appearance	Tetracycline* Topical clindamycin 1% gel or erythromycin 2% gel Isotretinoin (Accutane) Tretinoin (Retin-A) Benzoyl peroxide Azelaic acid cream (20%) Adapalene 0.1% gel
Cellulitis: Diffuse spreading infection of deep dermis without sharp demarcation	Group A strep; *S. aureus* (*Vibrio* sp and *Aeromonas* sp with fresh or saltwater exposure; others—*S. pneumoniae, H influenzae*, anaerobes, legionella, *Erysipelothrix rhusiopathiae, Helicobacter cinaed*)	Culture advanced edge of inflammation (rarely positive); 3-mm dermal punch, ulcerated portal of entry, blood; serial DNase titer (Group A strep)	Penicillinase-resistant penicillin*, vancomycin, clindamycin, cephalosporin (first generation), erythromycin, fluoroquinolone MRSA: Vancomycin, daptomycin, linezolid
Erysipelas: Superficial infection with raised and sharply demarcated edge	Group A strep (Groups B, C, and G strep; *S. aureus*)	Appearance, often at sites of lymphedema	Penicillin*, clindamycin, cephalosporin (first generation)
Lymphangitis	Group A strep	As above	As above
Folliculitis: Infected hair follicle(s)	*S. aureus (P. aeruginosa*	Culture and Gram stain	Local compresses or topical antibiotics. Fever, cellulitis, or mild face

	whirlpools, hot tubs, etc)	(usually unnecessary)	involvement—treat as furunculosis
Furunculosis/carbuncle: Abscess that starts in hair follicle; carbuncle is deeper and more extensive	*S. aureus*	Culture and Gram stain	Drainage ± penicillinase-resistant penicillin*, clindamycin, vancomycin, cephalosporin (first generation), erythromycin, amoxicillin-clavulanate MRSA: Vancomycin, daptomycin, linezolid
Mycobacterial furunculosis	*M. fortuitum*	Culture negative boils is clue-culture for mycobacteria at 30° & 37° C	Disease of compromised host especially organ transplant recipients and customers of nail salons (NEJM 2002;346:1366)
Recurrent furunculosis	*S. aureus*		Bathe with hexachlorophene. May be controlled with chronic clindamycin 150 mg qd × 3 mo* Nasal carriers of staph—mupirocin to anterior nares or rifampin 300 mg bid × 5 days
Paronychia: Infection of nail fold	*S. aureus*	Culture and Gram stain	*S. aureus:* Incision and drainage ± antistaph antibiotic *Candida:* Topical nystatin or miconazole
Impetigo: Infection of epidermis with vesicles → pustules on exposed areas ± lymphadenopathy	Group A strep often with *S. aureus*	Culture and Gram stain Average yield of strep even with biopsy is only 25%	Dicloxacillin, cloxacillin, cephalexin, or amoxicillin + clavulanate; topical mupirocin (Am J Dis Child 144:1313, 1990; Arch Dermatol 125:1069, 1989)
Whitlow: Infection of distal phalanx finger	*S. aureus*	Culture and Gram stain	Penicillinase-resistant penicillin*, clindamycin, cephalosporin (first generation)
	H. simplex	Viral culture, Tzanck prep, or FA stain	Acyclovir
Fungal infections:	*Candida*—red, moist, satellite lesions, especially skin folds	Scrapings for KOH prep, culture on Sabouraud medium	Skin: Topical antifungal agent—Miconazole, clotrimazole, econazole, naftifine, or ciclopirox
	Dermatophytes: *Epidermophyton, Trichophyton, Microsporum*, "ringworm"	Scrapings for	Skin: Topical agents (as above) or oral ketoconazole. Nail: Griseofulvin or ketoconazole. Scalp: Selenium sulfide shampoo + griseofulvin

Keratinized tissue—skin, nails, hair (see p 161)		KOH prep and culture: Wood's light	
	Tinea versicolor: *Malas-sezia furfur*— red or hypo-pigmented macules		Skin: Topical agents (as above), oral ketoconazole, or topical selenium sulfide
Bites			
Dog and cat (NEJM 340:85, 1999)	*P. multocida*: Anaerobes, fusobacteria, bacteroides, porphyromonas, *Prevotella streptococci, Capnocytophaga canimorus, S. aureus*	Culture and Gram stain	Risk for tetanus and rabies Lesions should be left open if not potentially disfiguring, if arms or legs involved, or if bite was >6–12 hr before treatment Use of prophylactic antibiotics is controversial (NEJM 340:138, 1999) Amoxicillin + clavulanic acid (Augmentin)*, cefuroxime + metronidazole; TMP-SMX + clindamycin
Human, including clenched-fist injury	Oral flora (strep, anaerobes) *S. aureus, Eikenella corrodens*	Culture and Gram stain	Human bites are usually left open Amoxicillin-clavulanic acid (Augmentin)*, penicillin V ± cephalexin
Rat	*Streptobacillus moniliformis*	*S. moniliformis:* Giemsa stain of blood or pus; culture; serology	Penicillin*, tetracycline
	Spirillum minus	*S. minus*: Giemsa stain of blood or exudate	Penicillin*, tetracycline
Cat-scratch disease	*Bartonella henselae*	Warthin-Starry stain of biopsy	Efficacy of therapy not established. Ciprofloxacin; sulfa-trimethoprim; amoxicillin-clavulanate; macrolides
Burns	*S. aureus*, GNB, *Candida albicans, Aspergillus*, Herpes simplex, group A strep	Quantitative culture and stain of biopsy	Removal of eschar. Topical sulfa (silver sulfadiazine or mafenide) Empiric antibiotics: Aminoglycoside + nafcillin, antipseudomonad penicillin, ticarcillin-clavulanate, vancomycin or cephalosporin *H. simplex*—acyclovir
Sinus tract			

Osteomyelitis	*S. aureus, S. epidermidis*, GNB, anaerobes	Culture of sinus tract drainage does not reliably reflect agent(s) of osteomyelitis	Antibiotics optimally based on bone biopsy
Lymphadenitis	*S. aureus*	Culture and Gram strain	Antistaphylococcal agent
	Mycobacteria (scrofula)	AFB smear and culture	TB—antituberculous drugs MOTT: See pp 185–186
Actinomycosis	*A. israelii, A. naeslundii, A. odontolyticus, Arachnia proprionica*	FA stain, anaerobic culture	Penicillin G*, amoxicillin, clindamycin, tetracycline
Madura foot (tumor masses with draining sinuses)	Actinomycotic: *Nocardia, Actinomadura madurae, A. pelletieri, S. somaliensis*	Culture including AFB stain, culture for *Nocardia*	Antibiotics selected by in vitro sensitivity tests
	Fungi: *Pseudallescheria boydii* (esp U.S.) *Madurella mycetomatis, Phialophora verrucosa*	KOH, culture on Sabouraud's agar	Fungal: Surgical excision; azoles are possibly effective
Nodules/ulcers			
Sporotrichoid (cutaneous inoculation with lymphatic spread)	*Sporothrix schenckii* (thorns) *M. marinum* (tidal water, swimming pool, or tropical fish tank)	Histology (PAS, GMS), culture on Sabouraud's agar Histology, AFB stain and culture (at 30–32°C) TMP-SMX	Oral SSKI Rifampin + ethambutol, Minocycline/doxycycline, TMP-SMX
	Nocardia	Histology, AFB stain; culture for *Nocardia*	Sulfonamide, TMP-SMX
Nodules/ulcers (from hematogenous		Blastomycosis: Endemic area	Culture biopsy on	Ketoconazole, amp itraconazole

dissemination)		Sabouraud's agar	
	Cryptococcus: Defective cell-mediated immunity	Blood for cryptococcal antigen and culture; histopathology and culture of biopsy	Amphotericin B, fluconazole
	Candida: Defective cell-mediated immunity	Blood culture; histopathology and culture of biopsy	Amphotericin B
Diabetic foot ulcer and decubitus ulcer	Mixed aerobes: Anaerobes *S. aureus* Group A strep	Culture and Gram stain of wound edge or dermal punch biopsy	**Local care**: Debridement, bed rest **Antibiotics**: For moderately severe infection *oral*—cephalexin, clindamycin, moxifloxacin, gatifloxacin, levofloxacin, amoxicillin-clavulanate; *parenteral*—beta-lactam-beta-lactamase inhibitor, ciprofloxacin ± clindamycin, levofloxacin ± clindamycin, gatifloxacin, cefepime. For severe infection—imipenem, vancomycin + metronidazole; severe infections with MRSA—vancomycin, daptomycin, linezolid

* Preferred regimen

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Deep Serious Soft Tissue Infections

(From Cecil Textbook of Medicine, Philadelphia: Saunders, 1992:1679)

	Gas-forming cellulitis	***Synergistic necrotizing cellulitis***	***Gas gangrene***	***"Streptococcal" myonecrosis***	***Necrotizing fasciitis***	***Infected vascular gangrene***	***Streptococcal***
Predisposing conditions	Traumatic	Diabetes, prior local lesions, perirectal lesions	Traumatic or surgical wound	Trauma, surgery	Diabetes, trauma, surgery, perineal infection	Arterial insufficiency	Traumatic or surgical wound
Incubation period	>3 days	3–14 days	1–4 days	3–4 days	1–4 days	>5 days	6 hr–2 days
Etiologic organism(s)	Clostridia, others	Mixed aerobic-anaerobic flora	Clostridia, esp *C. perfringens*	Anaerobic streptococci	Mixed aerobic-anaerobic flora	Mixed aerobic-anaerobic flora	*S. pyogenes*
Systemic toxicity	Minimal	Moderate to Severe	Severe	Minimal until late in course	Moderate to severe	Minimal	severe
Course	Gradual	Acute	Acute	Subacute	Acute to subacute	Subacute	Acute
Wound findings, local pain	Minimal	Moderate to severe	Severe	Late only	Minimal to moderate	Variable	Severe
Skin appearance	Swollen, minimal discoloration	Erythematous or gangrene	Tense and blanched, yellow-bronze, necrosis with hemorrhagic	Erythema or yellow-bronze	Blanched, erythema, necrosis with hemorrhagic bullae	Erythema or necrosis	Erythema, necrosis

			bullae				
Gas	Abundant	Variable	Usually present	Variable	Variable	Variable	No
Muscle involvement	No	Variable	Myonecrosis	Myonecrosis	No	Myonecrosis limited to area of vascular insufficiency	No
Discharge	Thin, dark, sweetish, or foul odor	Dark pus or "dishwater," putrid	Serosanguineous, sweet or foul odor	Seropurulent	Seropurulent or "dishwater," putrid PMNs, mixed flora	Minimal	None or serosan-guineous
Gram stain	PMNs, Gram-positive bacilli	PMNs, mixed flora	Sparse PMNs, Gram-positive bacilli	PMNs, Gram-positive cocci		PMNs, mixed flora	PMNs, Gram-positive cocci in chains
Surgical therapy	Debridement	Wide filleting incisions	Extensive excision, amputation	Excision of necrotic muscle	Wide filleting incisions	Amputation	Debridement of necrotic tissue

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Bone and Joint Infections

I. **Osteomyelitis**

A. **Classification and Management: Cierney–Mader classification**

Comp Orthop 10:17, 1985; see Osteomyelitis. Current Opinion 2:187, 2000

Stage	***Example***	***Microbiology***	***Therapy***
1. Medulary	Hematogenous Infected intramedulary rods	Monomicrobial: *S. aureus* (hematogenous), *S. epid* GNB	Antibiotics × 4–6 wk[a] ± surgery; rod–remove when joint is stable
2. Superficial	Exposed bone at bed of soft tissue wound: Diabetic food ulcer Decubitus ulcer	Polymicrobial: Anaerobes, GNB *P. aeruginosa* Streptococci	Debridement + antibiotics

3. Localized	Entire cortex involved: Infected plates for stabilizing fracture	Polymicrobial: GNB, *S. aureus* streptococci	Debridement[b] + antibiotics × 4–6 wk[a]
4. Diffuse	Through-and-through osteo: Non-union	Polymicrobial: GNB *S. aureus*, strep	Debridement[b] + antibiotics × 4–6 wk[a]

[a] Antibiotics often given parenterally × 2 wk, then orally × 4 wk.
[b] Debridement requires removal of necrotic bone; dead space created may be filled with cancellous bone grafts or tissue flaps or antibiotic impregnated beads. Beads are usually replaced by bone grafts at 2–4 wk.

Empiric treatment:

1. Infected prosthetic material: Vancomycin
2. Hemoglopathy: Nafcillin/oxacillin + ampicillin
3. Vascular insufficiency, diabetic foot ulcer, decubitus ulcer: Ciprofloxacin + clindamycin (po or IV), ciprofloxacin + metronidazole (po or IV), imipenem, piperacillin-tazobactam, cefoxitin, gatifloxacin (po)
4. Human bite: Ampicillin-sulbactam, ceftriaxone

B. **Diagnosis**: Surgical sampling or needle biopsy is preferred. Swabs of fistula tracts or ulcers are less reliable (JAMA 239:2772, 1978) The preferred nuclear imaging method is technetium-99 (sensitivity 70–100%; specificity 20–80%). Favored scans CT and MRI (sensitivity 30–100%; specificity 80–90%; best test with diabetic foot or decubitus ulcer: Probe wound for bone, sensitivity 66%, specificity 85% (see JAMA 273: 721, 1995)

C. **Treatment** (CID Suppl 1:S155, 1992; NEJM 336:99, 1997)

ANTIBIOTIC TREATMENT OF OSTEOMYELITIS

Adapted from NEJM 336:999 1997

Pathogen	***Preferred (parenteral)***	***Alternative***
S. aureus		
Methicillin sensitive	Nafcillin or oxacillin 2 g q6h	Cephalosporin—1st gen; clindamycin, vancomycin
Methicillin resistant	Vancomycin 1 g q12h	
Streptococci	Pen G 4 mil units q6h	Clindamycin, vancomycin
S. epidermidis	Vancomycin 1 g q12h	
Enterobacteriaceae	Quinolone–ciprofloxacin 750 mg q12h	third generation cephalosporin
P. aeruginosa	Ceftazidime 2 g q8h plus aminoglycoside ≥ 2 wk	Imipenem, piperacillin, or cefepime plus aminoglycoside ≥2 wk

Anaerobes	Clindamycin 600 mg IV q6h	Metronidazole, beta-lactam-beta-lactamase inhibitor, imipenem/meropenem
Mixed aerobic anaerobic	Imipenem 500 mg q6h or beta-lactam-beta-lactamase inhibitor	Ciprofloxacin + clindamycin

Empiric treatment:

1. Settings in which *S. aureus* is anticipated pathogen

   Preferred: Nafcillin or oxacillin, vancomycin, or clindamycin

2. Patient with hemoglobinopathy

   Preferred: Nafcillin or oxacillin plus ampicillin

   Alternatives: Nafcillin or oxacillin plus cefotaxime or ceftriaxone

3. Osteomyelitis with vascular insufficiency, decubitus ulcer, diabetic foot ulcer, etc

   Preferred: Ciprofloxacin plus clindamycin or metronidazole, cefoxitin, imipenem, or beta-lactam-beta-lactamase inhibitor

   Alternatives: Aztreonam plus clindamycin

4. Animal or human bite

   Preferred: Ampicillin or ampicillin-sulbactam

   Alternative: Ceftriaxone or doxycycline

II. **Bone and joint infections: Associations**

Condition	***Bones/joints***	***Bacteriology***
Sickle cell disease	Multiple bones	*Salmonella, S. pneumoniae*
Injection drug use	Disc space or sternoclavicular joint	*S. aureus* *P. aeruginosa*
Penetrating injury of foot	Foot bones	*P. aeruginosa*
Hemodialysis	Ribs Thoracic vertebrae	*S. aureus*
Ingestion of unpasteurized dairy products	Knee, hip, sacroiliac joint	Brucella
Rash and arthritis	Multiple	*N. gonorrhoeae* *N. meningitis* *H. influenzae* *Moraxella osloenia* *Streptobacillus moniliformis*
Diabetic foot ulcers	Site of ulcer	Streptococci, anaerobes,

		GNB
Foreign body	Site of prosthesis	*Staphylococcus epidermidis*
Dog bite or cat bite	Site of trauma	*Pasteurella multocida* *Anaerobes*
Human bite	Site of trauma	*Eikenella corrodens,* *Anaerobes*
Tick exposure	Large joints esp knees	*Borrelia burgdorferi*

III. **Septic arthritis** (see CID 20:225, 1995)

A. **Acute Monarticular Arthritis**

1. **Differential diagnosis**: Septic arthritis, rheumatoid arthritis, gout, and chondrocalcinosis (pseudogout). All may cause predominance of PMNs in joint fluid. Need joint fluid aspiration for stain culture and analysis for crystals.
2. **Joint analysis**: WBC > 50,000/mm^3 with > 90% PMNs, protein > 3 g/mL, glucose <60%, poor mucin clot, positive Gram stain and culture
3. **Septic arthritis in adults**

Agent	***Treatment (alternatives)[a]***	***Comment***
S. aureus	Methicillin-sensitive: Nafcillin/oxacillin or cefazolin × 3 wk MRSA or beta-lactam allergy: Vancomycin × 3 wk	Accounts for 50–80% of non-gonococcal septic arthritis cases
N. gonorrhoeae	Ceftriaxone (1 g IV daily); alternatives are cefotaxime (1 g IV q8h), ceftizoxime (1 g IV q8h), or spectinomycin (2 g IM q12h) until 24–48 hr after symptoms have resolved, then cefixime (400 mg po bid) or ciprofloxacin (500 mg po bid) to complete 1 wk Doxycycline 100 mg po bid × 1 wk	Most common cause of monarticular arthritis in young sexually active adults. Skin lesions rarely present and blood cultures usually negative with gonococcal monarticular arthritis; genital or joint fluid culture often positive Doxycycline or azithromycin for presumed *C. trachomatis* infection
Streptococci	Penicillin (cephalosporin-first generation, vancomycin, clindamycin) × 2 wk	Accounts for 10–20% of non-gonococcal septic arthritis cases. Group A is most common; groups B, C, or G, *S. milleri* and *S. pneumoniae* are occasional causes

Gram-negative bacilli	Based on in vitro sensitivity tests. Treat × 3 wk	Accounts for 10–20% of non-gonococcal septic arthritis cases. Most commonly in chronically debilitated host, immunosuppressed, prior joint disease, and elderly. Heroin addicts prone to sacroiliac or sternoclavicular septic arthritis caused by *Pseudomonas aeruginosa*

[a] Duration of antibiotic treatment is 2–4 wk; the exception is gonococcal septic arthritis.

4. **Other therapy**:
    a. ***Drainage***: Joint aspiration usually advocated (NEJM 312:764, 1985); repeat needle aspiration at 5–7 days often beneficial. Persistence of effusion >7 days is indication for surgical drainage (CID 20:225, 1995)
    b. ***Weight bearing***: Avoid until inflammation resolves
    c. ***Passive range of motion first week, active ROM at 1–2 wk***
    d. ***Controversies***: Duration of antibiotics; oral vs parenteral route of antibiotics; splinting vs passive ROM; optimal drainage—aspiration, open drainage, or arthroscopy
5. **Prosthetic joint**

a. ***Bacteriology***: *S. aureus* (20–30%), *S. epidermidis* (20–30%), streptococci (15–25%), Gram-negative bacilli (15–25%), anaerobes (5–10%)

b. ***Classification***:

    1. Acute contiguous within 6 mo of surgery: Presumably reflects contamination at time of surgery;

    2. chronic contiguous at 6–24 mo after surgery: Presumably also because of contamination at the time of surgery;

    3. hematogenous at ≥2 yr after surgery

c. ***Diagnosis***: A common presentation is loosening that could be septic but is most commonly mechanical (Curr Opinion 2:2000, 2000). Overlying inflammation or drainage facilitates the distinction. When this is not present diagnostic tests include ESR, C reactive protein, imaging (x-ray, bone scan, MRI, CT scan) and/or joint aspiration. None of these are considered consistently reliable—the best method is biopsy at surgery showing inflammation and culture (Curr Opinion 2:2000,2000)

d. ***Management***

    Single stage revision: Remove all foreign and necrotic material, replace prosthesis with antibiotic impregnated cement, and give antibiotics × 6 wk. Success rate is 20–30%. Relative contraindications: Resistant bacteria, especially *Candida*, GNB, enterococci

    Two stage revision (usually preferred): Remove all foreign and necrotic material, give IV antibiotics 6 wk, then replace prosthesis using antibiotic-impregnated spacer. Success rate: 70–80%

    Resection arthroplasty: Removal of all foreign and necrotic material and fuse joint. Indication is contraindication or refusal for replacement of prosthesis

    Medical management: Debridement cultures and antibiotics. Antibiotics are primarily oral and given ≥6 mo to lifelong. This is advocated only when patient is an extremely poor surgical candidate or refuses preferred procedures

e. ***Antibiotics***: Selection is based on culture and in vitro sensitivity tests. Favored drugs for *S. epidermidis*—vancomycin; *S. aureus*—nafcillin, oxacillin, cefazolin, vancomycin; GNB—fluoroquinolones, betalactams.

Duration is 4–8 wk, usually 6 wk. Role of antibiotic-impregnated polymethyl metuacrylate "cement" (tobramycin and vancomycin) is unclear (Am J Orthop 27:201, 1998; Clin Orthop 295:96,1993).

B. **Chronic Monarticular Arthritis**

1. **Bacteria**: *Brucella, Nocardia*
2. **Mycobacteria**: *M. tuberculosis, M. kansasii, M. marinum, M. avium-intracellulare, M. fortuitum* (see pp 166–176).
3. **Fungi**: *Sporothrix schenckii* (soil contact), *Coccidioides immitis* (endemic area, non-Caucasian immunocompromised men), Blastomyces dermatitidis (endemic area), *Candida* sp (intraarticular steroids or systemic candidiasis), *Pseudallescheria boydii* (penetrating trauma), *Scedosporium* (penetrating trauma) (see pp 151–164).

C. **Polyarticular Arthritis**

1. **Bacteria**: *Neisseria gonorrhoeae* (usually accompanied by skin lesions, positive cultures of blood and/or genital tract, negative joint cultures); *N. meningitidis*; *Borrelia burgdorferi* (Lyme disease, see pp 213–214); pyogenic (10% of cases of septic arthritis have two or more joints involved).
2. **Viral: Hepatitis B** (positive serum HBsAg, seen in pre-icteric phase, ascribed to immune-complexes often in association with urticaria, symmetric arthritis involving hands most frequently, then knees and ankles); rubella (usually small joints of hand, women more than men, simultaneous rash, and tenosynovitis also seen with rubella vaccine in up to 40% of susceptible postpubertal women); Parvovirus B 19 (symmetric arthritis involving hands/wrists and/or knees; adults more than children; women more than men); mumps (0.5% of mumps cases, large and small joints, accompanies parotitis, men more than women); lymphocytic choriomeningitis virus (adults with aseptic meningitis);

arthropod-borne alpha virus: Chikungunya (East Africa, India), O'nyong-nyong (East Africa), Ockelbo agent (Sweden), Ross River agent (Australia), Barmah Forest virus (Australia).

3. **Miscellaneous**: Acute rheumatic fever (Jones' criteria including evidence of preceding streptococcal infection); Reiter's syndrome (conjunctivitis and urethritis, associated infections—*Shigella, Salmonella, Campylobacter, Yersinia*).

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Ocular and Periocular Infections

N. gonorrhoeae	Ceftriaxone, 125 mg IM × 1	Evaluation—4 tests—(1) acuity, (2) external exam, (3) slit lamp biomicroscopy, and (4) diagnostic tests (see below) Most are viral and self-limited
C. trachomatis	Doxycycline 100 mg bid × 7–14 d Azithromycin 1 g po × 1	Pharyngoconjunctival fever—adenovirus 3 and 7 in children Epidemic keratoconjunctivitis—adenovirus 8
Adenovirus (types 8, 11 & 19 in adults)	None (highly contagious)	Diagnostic tests—Culture if severe or recurrent purulent conjunctivitis, especially if not responsive. Smears for special stains and cytology—bacteria—PMNs, viral—mononuclear; herpetic—multi-nucleated cells; chlamydia—mixed; allergic—eosinophils
Allergic or immune-mediated	Topical steroids	*C. trachomatis*: Inclusion conjunctivitis and trachoma
Unknown (empiric)	Topical sulfacetamide or neomycin-bacitracin-polymyxin or bacitracin-polymyxin	*S. pneumoniae:* may cause epidemic conjunctivitis (NEJM 2003;348:1112)

Keratitis	*S. aureus, S. pneumoniae, P. aeruginosa, Moraxella, Serratia*	*P. aeruginosa* (contact lens): topical gentamicin, tobramycin or ciprofloxacin eye drops q15–60 min. *Staphylococcus, S. pneumoniae*, coliforms: topical cefazolin, gentamicin, tobramycin, vancomycin + ceftazidime q15–60 min.	Guidelines: American Academy of Ophthalmology 2000: Management of bacterial keritits requires the expertise of an ophthalmologist due to the risk of vision loss Pain; no discharge; decreased vision Lab—Culture with corneal infiltrate that extends to deep stroma, is chronic or is unresponsive to broad spectrum antibiotics or has features suggesting fungi, amoeba, or mycobacterial infection. Use alginate swab or conjunctival scrapings for stain (Gram, Giemsa, PAS, calcofluor white and methenamine silver) + culture for bacteria and fungi
	Herpes simplex	Trifluridine 1 drop qh (9×/d) for ≤21 d or vidarabine ointment 5×/d ≤21 d; if recurrent—oral acyclovir 400 mg bid	Systemic antibiotics for deep corneal ulcers with bacterial infection Supportive care with cytoplegics, use of corticosteroids controversial
	Herpes zoster	Valacyclovir 1 g po tid, acyclovir 800 mg 5×/d or famciclovir 500 mg tid ×10 d	For topical antibiotics use solutions

	Fungal: *Fusarium solani, Aspergillus, Candida, Acanthamoeba*	Topical natamycin, (5%) or amphotericin B (0.05–0.15%)	Herpes simplex is most common Risks for bacterial keratitis: contact lens, diabetes
	Parasitic: *Acanthamoeba* (contact lens)	Topical propamadine isethionate, 0.1%/ neomycin/gramicidin/polymyxin or polyhexamethylene biguanide 0.02% or chexadine 0.2%: drops qh while awake × 1 wk, then taper	*Acanthamoeba*: Risks or trauma and soft contact lens. Diagnosis by scraping stained with calcofluor white (CID 2002;35:434)
Endophthalmitis	**Bacteria**: Post-ocular surgery:*S. aureus, Pseudomonas, S. epidermidis, P. acnes* Penetrating trauma: *Bacillus* sp. Hematogenous: *S. pneumoniae, N. meningitidis* (others) Injection drug use: *Candida, B.*	Emergent intravitreal antibiotics, and vitrectomy Empiric: Intravitreal vancomycin 1 mg + amikacin 0.4 mg or ceftazidime 2 mg	Lab: Aspiration of aqueous and vitreous cavity for stain (Gram, Giemsa, PAS, methenamine silver) and culture for bacteria and fungi Requires immediate ophthalmology consult: vitrectomy + intravitreal antibiotics Acute: *P. aeruginosa* and *S. aureus* most common Chronic: *P. acnes, S. aureus*, and *S. epidermiditis* most common

	cercus		
Retinitis	**Fungus**: Post-ocular surgery *Neurospora, Candida, Scedosporium, Paecilomyces* Hematogenous: *Candida, Aspergillus* Histoplasmosis	IV amphotericin + topical natamycin ± corticosteroids; vitrectomy (Ophthalmol 85:357, 1978) IV amphotericin B + flucytosine (Arch Ophthalmol 98:1216, 1980) Aspergillus—removal of infected vitreous (Arch Ophthalmol 98:859, 1980) Systemic corticosteroids	
	Parasites: Toxoplasmosis *Toxocara*	Systemic + local corticosteroids ± pyrimethamine and sulfadiazine Systemic or intraocular corticosteroids	
Acute reclinal necrosis	**Virus**: *Herpes zoster* (Herpes simplex)	Acyclovir 10–15 mg/kg IV q8h (CID 1997;24:603)	
Periorbital			
Lid Blepharitis	Multifactorial: Seborrhea,	Topical corticosteroid ± topical bacitracin or erythromycin Lid hygiene	For rosacea—doxycycline po

Lacrimal apparatus Canaliculitis	Anaerobes, especially *Actinomyces*	Topical penicillin by irrigation	
Dacryocystitis	**Acute**: *S. aureus*	Systemic antistaphylococcal agent; then digital massage + antibiotic drops	
	Chronic: *S. pneumoniae, S. aureus, Pseudomonas*, mixed	Systemic antibiotics; digital massage	
Orbital	*S. aureus*, (*S. pneumoniae, S. pyogenes*)	IV antibiotics: Cephalosporin, cefuroxime or third generation (ceftriaxone or cefotaxime)	Over 80% have associated sinusitis Treat sinusitis
	Fungi: Phycomycosis, *Aspergillus, Bipolaris, Curvularia, Drechslera*	Amphotericin B + surgery	

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Infections of Central Nervous System

I. **Cerebrospinal Fluid**

A. **Normal Findings**

1. **Opening pressure**: 5–15 mmHg or 65–195 mmH_2O
2. **Leukocyte count**: <10 mononuclear cells/mm^3 (5–10/mL suspect); 1 PMN (5%)

   Bloody tap: Usually 1 WBC/700 RBC with normal peripheral RBC and WBC counts; if abnormal: true CSF WBC = WBC (CSF) - WBC (blood) × RBC (CSF)/RBC (blood)

   Note: WBCs begin to disintegrate after 90 min
3. **Protein**: 15–45 mg/dL (higher in elderly)

   Formula: 23.8 × 0.39 × age + 15 mg/100 mL or (more simply) less than patient's age (>35 yr)

   Traumatic tap: 1 mg/1000 RBCs
4. **Glucose**: 40–80 mg% of CSF/blood glucose ratio >0.6 (with high serum glucose, usual ratio is 0.3)

B. **Abnormal CSF with Noninfectious Causes**

1. **Traumatic tap**: Increased protein; RBCs; WBC count and differential proportionate to RBCs in peripheral blood; clear and colorless supernatant of centrifuged CSF.

2. **Chemical meningitis (injection of anesthetics, chemotherapeutic agents, air, radiographic dyes)**: Increased protein, lymphocytes (occasionally PMNs).
3. **Cerebral contusion, subarachnoid hemorrhage, intracerebral bleed**: RBCs, increased protein (1 mg/1000 RBCs), disproportionately increased PMNs (peak at 72–96 hr), decreased glucose (in 15–20%).
4. **Vasculitis (SLE, etc)**: Increased protein (50–100 mg/dL), increased WBCs (usually mononuclear cells, occasionally PMNs), normal glucose.
5. **Postictal (repeated generalized seizures)**: RBCs (0–500/mm^3), WBCs (10–100/mm^3 with variable percentage PMNs with peak at 1 day), protein normal or slight increase.
6. **Tumors (especially glioblastomas, leukemia, lymphoma, breast cancer, pancreatic cancer)**: Low glucose, increased protein, moderate PMNs.
7. **Neurosurgery**: Blood; increased protein; WBCs (disproportionate to RBCs with predominance of mononuclear cells) up to 2 wk post-op.
8. **Sarcoidosis**: Increased protein; WBCs (up to 100/mm^3 predominately mononuclear cells); low glucose in 10%.

C. **CSF with Pyogenic Meningitis** (NEJM 1993;328:21.; Lancet 1995;346:1675.)

1. **Findings**: Opening pressure >300 mmH_2O - 40%; WBC > 100/mm^3 - 90%; % PMNs > 20%–98%, most >80%; 80%; protein > 45 mg/dL - 96%; glucose < 40 mg/dL - 50%; Gram stain pos - 60%, culture positive 73%.
2. **Etiologic diagnosis**: Sensitivity of Gram stain 60–80%; antigen assays most helpful in patients with prior antibiotic treatment (Pediatr Emerg Care 1994; 10:67.).
3. **Predictors of bacterial meningitis**: Glucose <34 mg/dL, CSF/serum glucose ratio <0.23, protein >220 mg/dL, WBC >2000 mg/dL or 1180 neutrophils/dL each predict bacterial meningitis with 99% certainty (JAMA 1989;262:2700.).
4. **Response**: CSF cultures should become sterile within 24–36 hr of appropriate therapy (Pediatr Infect Dis J 1992;11:423.).

D. **Practical Issues in Management**

1. **Need for scan prior to LP**: Review of 301 adult cases of suspected pyogenic meningitis showed evidence that pre-LP scans delayed antibiotic admin

istration by an average of 2 hrs, and showed mass effect in only 2% (NEJM 2001;345:1727.). The recommendation was to do the LP with a #22 or #25 needle to minimize risk and restrict pre-LP CT scans to those likely to have an intracranial mass or elevated CSF pressure as indicated by immunosuppression, dilated or poorly reactive pupils, papilledema, ocular palsy, hemiparesis, recent history of seizures, rapid decrease in consciousness, bradycardia, irregular respirations, tonic seizures, or decrebrate or decorticate posture (NEJM 2001;345:1768.; Arch Dis Child 1992;67:1417.)

2. **Dexamethasone in adults with pyogenic meningitis**: Controlled trial showed significant benefit with dexamethasone 10 mg given 15–20 min before first dose of antibiotics and repeated q6h × 4 days. The dexamethasone recipients showed a superior outcome with reduced mortiliaty (11/157 [7%] vs 21/144 [15%]) in placebo recipients (NEJM 2002;347:1549.)

II. **Meningitis**

A. **Pyogenic meningitis: Microbiology**

(NEJM 1993;328:21.)

Agent	***Community acquired (253 cases)***	***Nosocomial (151 cases)***	***Mortality (meningitis related)***
S. pneumoniae	97 (38%)	8 (5%)	25%

Gram-negative bacilli	9 (4%)	57 (38%)	23%
N. meningitidis	35 (14%)	1 (1%)	10%
Streptococci	17 (7%)	13 (9%)	17%
S. aureus	13 (5%)	13 (9%)	28%
Listeria	29 (11%)	5 (3%)	21%
H. influenzae	9 (4%)	6 (4%)	11%
S. epidermidis	0	13 (9%)	0
Culture negative	34 (13%)	16 (11%)	7%

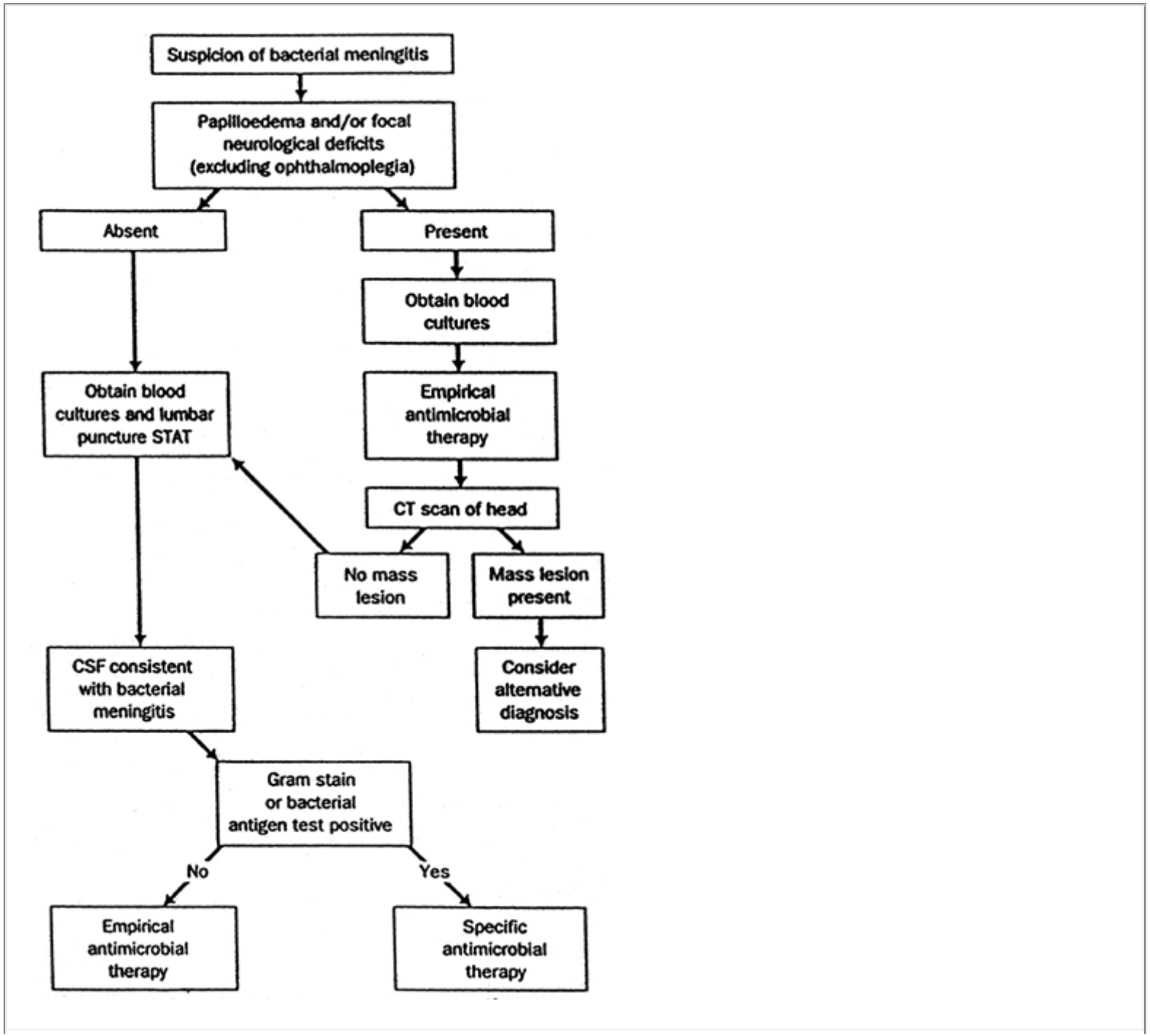
B. **Updated review: 80 cases, Edmonton Canada, 1985–1996** (Medicine 2001;79:360.)

1. **Etiology**: *S. pneumoniae*—42; Listeria—10, *H. influenzae*—6, *S. aureus*—5.
2. **CSF** WBC > 100/mm^3—90%; PMN > 50%–91%; glucose < 50 mg/dL—72%; protein <45 mg/dL—99%; Gram stain positive—48%
3. **Mortality**: 15%

   Mortality in series of pneumococcal meningitis cases was 15/109 (15%) and was

unrelated to penicillin susceptibility of the implicated strain.

C. **Initial management**


Suspicion of bacterial meningitis
Papilloedema and/or focal neurological deficits (excluding ophthalmoplegia)
Absent
Present
Obtain blood cultures
Obtain blood cultures and lumbar puncture STAT
Empirical antimicrobial therapy
CT scan of head
No mass lesion
Mass lesion present
CSF consistent with bacterial meningitis
Consider alternative diagnosis
Gram stain or bacterial antigen test positive
No
Yes
Empirical antimicrobial therapy
Specific antimicrobial therapy

Algorithm for initial management of patient with acute bacterial meningitis. Reprinted from Lancet 1995;346:1675 (with permission).

D. **Doses of antimicrobial agents**

Cephalosporins:

Cefotaxime: 12 g/d in six doses

Ceftizoxime: 9 g/d in three doses

Ceftriaxone: 2–4 g/d in two doses

Ceftazidime: 6–12 g/d in three doses

Chloramphenicol: 4–6 g/d in four doses

Penicillins: Ampicillin: 12 g/d in six doses

Ticarcillin: 18–24 g/d in six doses

Mezlocillin: 18–24 g/d in six doses

Piperacillin: 18–24 g/d in six doses

Nafcillin: 9–12 g/d in six doses

Oxacillin: 9–12 g/d in six doses

Penicillin G: 20–24 mil units/d in six doses

Aztreonam: 6 g/d in four doses

Trimethoprim-sulfamethoxazole: 15–20 mg/kg/d (trimethoprim) in four doses

Metronidazole: 2 g/d in two to four doses

Vancomycin: 2 g/d in two doses

Intrathecal/intraventricular doses:

Gentamicin 4–8 mg q24h

Tobramycin 4–8 mg q24h

Amikacin 5.0–7.5 mg q24h

Vancomycin 5–20 mg q24h

E. **Meningitis: Empiric treatment** *(adapted from* Med Lett 1999;41:95.; NEJM 1996;334:54.)

1. **Adults—immunocompetent**

   Cephalosporin: Cefotaxime 2 g q4h IV or ceftriaxone 2 g q12h IV plus vancomycin 1 g IV q12h ± rifampin 300 mg po or IV bid.

   Note: If isolate is susceptible to cephalosporins, discontinue vancomycin and rifampin.

2. *L. monocytogenes*: Ampicillin 2 g q4h IV ± aminoglycoside plus cefotaxime or ceftriaxone + vancomycin

3. Penicillin allergy: Cefotaxime or ceftriaxone plus vancomycin ± rifampin. If cephalosporins contraindicated then chloramphenicol plus vancomycin ± rifampin. For Gram-negative bacilli then aztreonam. For *Listeria* then TMP-SMX

4. Adjunctive corticosteroid therapy: Dexamethasone (0.15 mg/kg IV q6h × 4 days) has significant benefit in multiple studies in children for reduction of neurologic sequelae, especially hearing loss (NEJM 1991;324:1525.; Pediatr Infect Dis J 1995;14:490.). One study showed a reduction in mortality rates in adults (Pediatr Infect Dis J 1989;8:848.). A. Tunkel and M. Scheld recommend adjunctive dexamethasone for high-risk adult patients: Impaired mental status, cerebral edema, or very high intracranial pressure (Lancet 1995;346:1675.). Dexamethasone reduces vancomycin levels in CSF so rifampin should be added for suspected or established pneumococcal meningitis pending in vitro sensitivity tests (AAC 1995;39:2171.).

   Note: Dexamethasone should be given about 30 min *before* first dose of antibiotics (NEJM 1991;324:1525.).

F. **Treatment by Organism**

(CID 1993;17:603.; Infect Dis Clin Pract 1995;4:423.)

Organism	***Antibiotic selection***	***Comment***
S. pneumoniae **Pen-sensitive** (MIC <0.1 µg/mL)	Preferred Penicillin Cefotaxime Ceftriaxone Alternative Chloramphenicol	Meningitis is the only clinical condition in which intermediate penicillin reistance is relevant Rates of penicillin resistance in U.S.: Intermediate and high level (MIC ≥ 0.1 µg/mL): 40–50% Rates of cefotaxime resistance in U.S. (1998–2002), intermediate and high level: 5–10% (CID 1998;27:764; CID 2003; 36:783; CID 2003;36:1013; AAC 2002;46: 2651; AAC 2003;47:1790); great variation by geography
Pen-resistant (MIC ≥ 0.1 µg/mL)	Preferred Vancomycin ± rifampin Alternative Chloramphenicol Quinupristin/-dalfopristin Linezolid	

		Rate of vancomycin resistant—0 (Nat Med 2003;9:424) Treat ≥10 days LP at 24–36 hr to document eradication of pathogen, especially if cephalosporin resistant
N. meningitidis **Pen-sensitive**	Preferred Penicillin Alternative Cefotaxime Ceftriaxone	Pencillin resistance is rare and found almost exclusively outside U.S. Vaccine reduces infection rate but does not affect outcome (CID 2002;35:1376) Risk in college freshman in dorms (JAMA 2001;286:1894) Intimate and household contacts should receive ciprofloxacin 500 mg
Beta-lactamase-producing	Chloramphenicol	

		× 1 (adults) or rifampin 600 mg po bid × 2 days (adults); 10 mg/kg po bid × 2 days (children) Treat ≥7 days
H. influenzae **Ampicillin-sensitive**	Preferred Ampicillin Alternative Cefotaxime Ceftriaxone Chloramphenicol	Rate of beta-lactamase production 30–40% by type B and nontypable strains (CID 2001; 32:S81) Type B strains: Unvaccinated household contacts <4 yr—rifampin 10 mg/kg po bid × 2 days Treat ≥ 10 days
Ampicillin-resistant	Preferred Cefotaxime Ceftriaxone Alternative Chloramphenicol	
Listeria monocytogenes	Preferred Ampicillin ± gentamicin Alternative Trimethoprim-sulfamethoxazole	Cephalosporins are active in vitro but are not active in vivo Treat 14–21 days Penicillin or ampicillin are 100

		fold more potent when combined with aminoglycoside (J Antimicrob Chemother 1998;41:417) There is no consensus on the need for adding gentamicin to ampicillin. Carbapenems and fluoroquinolones are active in vitro but activity intracellularly is not known (J ClinMicro 2003;41:483) Review of 1808 cases of listerosis showed 47% had CNS infecction with 74% immunocompromised, mean age of 50–76 yrs, and mortality of 36% (Emerg Infect Dis 2002;8:305)
Enterobacteriaceae	Preferred	In vitro sensitivity

	Cefotaxime or ceftriaxone ±aminoglycoside Alternative Aztreonam Antipseudomonad penicillin or ampicillin ± aminoglycoside Trimethoprim-sulfamethoxazole	tests required Bactericidal activity desired Chloramphenicol lacks bactericidal activity vs GNB—not recommended Aminoglycoside given systemically ± intrathecally Effectiveness of quinolones, imipenem, and aztreonam in meningitis is unknown Ceftazidime use is usually restricted to GNB resistant to other 3rd gen cephalosporins Treat ≥21 days
P. aeruginosa	Preferred Aminoglycoside + ceftazidime Alternative Aminoglycoside + antipseudomonad penicillin	In vitro sensitivity tests required Aminoglycoside given systemically ± intrathecally

	Aminoglycoside + aztreonam	Effectiveness of quinolones, imipenem, and aztreonam in meningitis is unknown
Staph aureus Methicillin-sensitive	Preferred Antistaphylococcal penicillin (oxacillin, nafcillin) ± rifampin Alternative Vancomycin + rifampin Trimethoprim-sulfa + rifampin Cefuroxime	Usually post neurosurgery (Eur J Clin Micro Inf Dis 2002;21:864) Efficacy of high dose IV and intrathecal cefuroxime (Scand J Inf Dis 2003;35:311)
Methicillin-resistant	Preferred Vancomycin + rifampin Alternative Linezolid Daptomycin	
S. epidermidis	Preferred Vancomycin + rifampin Alternative Linezolid Daptomycin	

G. **Differential diagnosis of chronic meningitis***

(Adapted from Infect Dis Clin Pract 1992;1:158.)

Infectious disease	*Neoplastic*	*Miscellaneous*
Bacteria	Leukemia	Systemic lupus**
M. tuberculosis	Lymphoma	Wegener's granulomatosis**
Atypical mycobacteria	Metastatic	CNS vasculitis
*Treponema pallidum***	Breast	Granulomatous vasculitis
*Borrelia burgdorferi***	Lung	Sarcoidosis
Leptospira	Thyroid	Behçet's syndrome
*Brucella***	Renal	Vogt-Koyanagi and Harada's syndromes
Listeria	Melanoma	Benign lymphocytic meningitis
Actinomyces/Arachnia	Primary CNS	
Nocardia	Astrocytoma	
Parasites	Glioblastoma	
Toxoplasma gondii	Ependymoma	
Cysticerus	Pinealoma	
Angiostrongylus	Medulloblastoma	
Spinigerum		
Schistosoma		
Fungi		
Cryptococcus		
*Coccidioides***		
Histoplasma**		
Blastomyces		
Sporotrichum		
Pseudoallescheria		

Alternaria *Fusarium* *Aspergillus* *Zygomycetes* *Cladosporium* **Viruses** HIV Echovirus HSV (chronic lymphocytic meningitis and Mollaret's meningitis)		

* Defined as illness present for ≥4 wk with or without therapy; CSF analysis usually shows lymphocytic pleocytosis. Analysis of 83 previously healthy persons in New Zealand showed 40% had tuberculosis, 7% had cryptococcosis, 8% had malignancy, and 34% were enigmatic (Q J Med 1987;63:283).
** Evaluation: Culture, serum serology, CT scan, or MRI (brain abscess, cysticercosis, toxoplasmosis), cytology CSF (lymphoma, metastatic carcinoma), eosinophilic (parasitic, coccidioidomycosis), CSF serology or antigen (cryptococcosis, coccidioidomycosis, syphilis, histoplasmosis), blind meningeal biopsy (rarely positive), empiric treatment (TB, then penicillin, then amphotericin B, then ? corticosteroids).

H. **Aseptic meningitis: infectious and noninfectious causes***

(*from American Academy of Pediatrics, Pediatrics 1986;78 Suppl:970 and updated*)

Infectious Agents and Diseases

Bacteria: Partially treated meningitis, *Mycobacterium* tuberculosis, parameningeal

focus (brain abscess, epidural abscess), acute or subacute bacterial endocarditis

Viruses: Enteroviruses, mumps, lymphocytic choriomeningitis, Epstein-Barr, arboviruses (Eastern equine, Western equine, St. Louis), cytomegalovirus, varicella-zoster, herpes simplex, HIV

Rickettsiae: Rocky Mountain spotted fever

Spirochetes: Syphilis, leptospirosis, Lyme disease

Mycoplasma: *M. pneumoniae, M. hominis* (neonates)

Fungi: *Candida albicans, Coccidioides immitis, Cryptococcus neoformans*

Protozoa: *Toxoplasma gondii*, malaria, amebas, visceral larval migrans (*Taenia canis*)

Angiostrongylus cantonensis: Esophinophilic meningitis (NEJM 2002;346: 688.) Treat with steroids (CID 2000;31:660.)

Nematode: Rat lung worm larvae (eosinophilic meningitis)

Cestodes: Cysticercosis

Noninfectious Diseases

Malignancy: Primary medulloblastoma, metastatic leukemia, Hodgkin's disease

Collagen-vascular disease: Lupus erythematosus

Trauma: Subarachnoid bleed, traumatic lumbar puncture, neurosurgery

Granulomatous disease: Sarcoidosis

Direct toxin: Intrathecal injections of contrast medium, spinal anesthesia

Adverse drug reactions: NSAIDs (Arch Intern Med 1991;151:1309.) and rofecoxib (Arch Intern Med 2002;162:713.)

Poison: Lead, mercury

Adverse drug reaction: High dose (2 g/kg) IV immunoglobulin (Ann Intern Med 1994;121:259.)

Autoimmune disease: Guillain-Barré syndrome

Unknown: Multiple sclerosis, Mollaret's meningitis, Behçet's syndrome, Vogt-Koyanagi syndrome, Harada's syndrome, Kawasaki disease

III. **Brain Abscess** (CID 1997;25:763.)

Associated condition	***Likely pathogens***	***Treatment***
Sinusitis	Anaerobic, microaerophilic and aerobic streptococci, *Bacteroides* sp.	Metronidazole + penicillin or cefotaxime + metronidazole
Otitis	*Bacteroides fragilis, Bacteroides* sp., streptococci, *Entero-bacteriaceae, P. aeruginosa*	Metronidazole + penicillin + ceftazidime
Post-neurosurgery	*Staph. aureus* *S. epidermidis* *Enterobacteriaceae* *P. aeruginosa*	Vancomycin + ceftazidime
Trauma	*Staph. aureus* *Enterobacteraceae*	Nafcillin + cefotaxime or ceftriaxone

Endocarditis	*Staph. aureus*	Penicillinase-resistant penicillin or vancomycin
	Streptococcus sp.	Penicillin or penicillin + aminoglycoside
Cyanotic heart disease	*Streptococcus* sp.	Penicillin or metronidazole + penicillin

RESPIRATORY TRACT INFECTIONS: Recommendations of two panels—one representing the CDC and the other representing the American College of Physicians/American Society of Internal Medicine. Both groups published their recommendations in the same issue of *Annals of Internal Medicine.* They covered the same infections (pharyngitis, bronchitis, sinusitis, and viral URIs). Panel membership overlapped between the two groups, and both said essentially the same thing.

CITATIONS

Topic	Source	Citation
URIs	ACP/ASIM CDC	Ann Intern Med 134:487, 2001 Ann Intern Med 134:490, 2001
Pharyngitis	ACP/ASIM	Ann Intern Med 134:506, 2001

	CDC	Ann Intern Med 134:509, 2001
Sinusitis	ACP/ASIM CDC	Ann Intern Med 134:495, 2001 Ann Intern Med 134:498, 2001
Bronchitis	ACP/ASIM CDC	Ann Intern Med 134:518, 2001 Ann Intern Med 134:521, 2001
Acute exacerbations, chronic bronchitis	ACP/ASIM	Ann Intern Med 134:595, 2001

SUMMARY OF RECOMMENDATIONS (ADULT PATIENTS ONLY)

Diagnosis	Issue	ACP/ASIM	CDC
Sinusitis	Diagnosis	Clinical, no imaging	Same
	Cultures	None	None
	Antibiotics		
	Indications	Nasal pus and face pain/tenderness, + severe	Same

		symptoms or symptoms >7 d	
	Agents	Amoxicillin, doxycycline TMP-SMX	Agents active vs *H. influenzae* and S. pneumoniae
Bronchitis	Diagnosis	Rule out pneumonia X-ray if abnormal vital signs or cough >3 wk or rales	Same
	Culture	None	None
	Antibiotic	None	None
		Exception: Pertussis ? influenza	Same
Pharyngitis	Strep	10%	5–15%
	Diagnosis	Antigen test No culture	Antigen test No culture
	Antibiotic	Centor 2–3* + pos Strep	Same

		antigen Centor 3–4 alone	
	Antibiotic	Penicillin	Penicillin
	Alternative	Erythromycin	Erythromycin

* Centor criteria (Med Decis Making 1981;1:239): 1) Tonsillar exudates, 2) cervical adenopathy; 3) fever; 4) absence of cough. If 0–1: No test, no antibiotics; 2–3: Antigen assay-antibiotic (penicillin) for positives; 3–4: empiric penicillin. Note: The IDSA guidelines for managing pharyngitis do not accept centor criteria as adequate because of a high rate of false positives using clinical criteria (CID 2002;35:113). These guidelines call for evidence of Group A streptococci by culture or rapid antigen detection test. This approach requiring pathogen detection appears to be the most cost effective strategy (Ann Intern Med 2003;139:113)

Exacerbations, chronic bronchitis	ACP/ASIM only (Ann Intern Med 2001;134:595) Diagnosis: Chest x-ray–hospitalized patients and EW Spirometry–not useful to dx Medication: Inhaled B-2 agonist (albuterol) and/or anticholinergic bronchodilator (ipratropium) Severe: Steroids, O_2, and/or positive pressure ventilation Antibiotics: Only for severe cases–increased sputum, sputum purulence, and dyspnea (Anthonism, Ann Intern Med

	1987;106:196) Agents: Amoxicillin, doxycycline, TMP-SMX

Footnote

* Aseptic meningitis is defined as meningitis in the absence of evidence of a bacterial pathogen detectable in CSF by usual laboratory techniques.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Upper Respiratory Tract Infections

Conditions	*Usual pathogens*	*Preferred treatment*	*Alternatives*	*Comment*
EAR AND MASTOIDS				
Acute otitis media (Red Book 2000 pg 457)	*S. pneumoniae* *H. influenzae* *M. catarrhalis* (35% sterile)	Amoxicillin	Failure at 3–5 days: Amoxicillin + clavulanate Cefdinir Erythromycin + sulfisoxazole Cefuroxime axetil Parenteral: Ceftriaxone single dose Penicillin–allergy: Erythromycin–sulfisoxazole, clarithromycin, azithromycin	Tympanocentesis rarely indicated Less frequent pathogens: *S. aureus, Strep. pyogenes*, GNB, and anaerobes Oral or nasal decongestants ± antihistamine
Chronic suppurative otitis media	*Pseudomonas* *Staph. aureus*	Neomycin/polymyxin/hydrocortisone otic drops	Chloramphenicol otic drops	Persistent effusion: Myringotomy
Malignant otitis externa	*P. aeruginosa*	Ciprofloxacin	Tobramycin + ticarcillin, piperacillin, mezlocillin, cefoperazone, ceftazidime, aztreonam, cefepime, imipenem, or ciprofloxacin	Surgical drainage and/or debridement sometimes required Treat 4–8 wk or longer Oral regimen—see J Arch Otolaryngol Head Neck Surg 1989;115:1063
Acute diffuse otitis externa ("swimmer's ear")	*P. aeruginosa* Coliforms *Staph. aureus*	Topical neomycin + polymyxin otic drops	Boric or acetic acid (2%) drops Topical chloramphenicol	Initially cleanse with 3% saline or 70–95% alcohol + acetic acid Systemic antibiotics for significant tissue infection
Otomycosis	*Aspergillus niger*	Boric or acetic acid drops	Cresylate acetic otic drops	Surgery required for abscess

Acute mastoiditis	*S. pneumoniae* *H. influenzae* *S. pyogenes*	Same as for acute otitis media	Cefotaxime or ceftriaxone IV	in mastoid bone *S. aureus* is occasional pathogen, especially in subacute cases
Chronic mastoiditis	Anaerobes *Pseudomonas* sp Coliforms *S. aureus*	None		Surgery often required Pre-op: Tobramycin + ticarcillin or piperacillin
SINUSITIS				
Acute sinusitis (symptoms >4 wk) (see p 241)	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *S. aureus*	Amoxicillin 500 mg tid (up to 1 g tid)	Telithromycin 800 mg qd × 5 d; amoxicillin + clavulanate 875 mg po bid Cefditoren 200–400 mg bid Cefuroxime 250 mg bid Levofloxacin 500 mg qd Moxifloxacin 400 mg qd Gatifloxacin 400 mg qd Clarithromycin 500 mg bid or 1 g qd Azithromycin 500 mg, then 250 mg × 5 days ±; repeat at day 14–18 Cefpodoxime 200 mg bid Cefprozil 500 mg bid Cefdinir 300 mg bid Doxycycline 100 mg bid	Indications to treat: Symptoms severe or symptoms <7 days Most are viral infections; bacterial superinfection in 0.2–10% Frequency of beta-lactamase-producing bacteria is 20–30%, but amoxicillin appears as effective as alternative agents according to a 1999 meta-analysis of antimicrobial trials (www.ahcpr.gov/clinic/) Bacterial pathogens detected in sinus aspirates in about 50%; dominant are *S. pneumoniae* (41%), *H. influenzae*(35%), anaerobes (7%), *M. catarrhalis* (4%), and *S. aureus*(3%) (CID 1997;23:1209) No response after 48–72 hours should lead to an alternative agent such as telithromycin, fluoroquinolones or amoxicillin + clavulanate* Frequency of penicillin or macrolide resistant isolates of *Streptococcus pneumoniae* is 26 or 31% respectively.

				Consider local resistance rates before making empiric antibiotic selections*
Chronic sinusitis (symptoms >3 mo)	Anaerobes *S. aureus* *S. epidermidis*	Penicillin or amoxicillin	Amoxicillin + clavulanate Clindamycin	Usually reserve antibiotic treatment for acute flares Role of anaerobes is controversial (J Clin Microbiol 1991;29:2396; Am J Otolaryngol 1995;16:303) Endoscopic surgery may be required
Nosocomial sinusitis	*Pseudomonas* Coliforms	Aminoglycoside + antipseudo-monad penicillin or aminoglycoside + cephalosporin-3rd generation (ceftazidime)	Imipenem, ceftazidime	Complication of nasal intubation
PHARYNX	*Strep. pyogenes* *A. hemolyticum* *C. diphtheriae*, groups C and G strep	Penicillin po (strep only) × 10 days or benzathine penicillin IM × 1	Erythromycin × 10 days Cephalosporin × 5–10 days (cefditoren, ceftibutin, cephalexin, cefaclor, cefadroxil, cefuroxime, cefixime, cefditoren, cefdinir, cefpodoxime) Clarithromycin × 10 days Azithromycin × 5 days	
	N. gonorrhoeae	Ceftriaxone 125 mg IM × 1 or ciprofloxacin 500 po × 1		
	Mycoplasma, C. pneumoniae	Tetracycline or erythromycin (?)		
	Viruses (EBV etc)	None except influenza: Amantadine, rimantadine, zanamivir, or oseltamivir		

				If compliance questionable, use benzathine penicillin G × 1 IM Penicillin preferred for strep due to established efficacy in preventing rheumatic fever and absence of any penicillin resistance A study of 4782 cases of strep pharyngitis showed a 5-day course of penicillin was as effective as the standard 10-day course (JID 2000;182: 509) Causes: Viral 50–80%, strep 10%, EBV–1% *M. pneumoniae* 2–5%, *C. pneumoniae* 2–5%, *N. gonorrhoeae* 1% (JAMA 2000;284: 2912) Carrier rate *S. pyogenes* (adults) 2–4% (Scand J Prim HC 1997;15:149) Macrolides: About 5% of group A strep are resistant
	HIV	HAART		Acute retroviral syndrome established plasma HIV RNA or p24 Ag
Peritonsillar or pharyngitis tonsillar abscess	*Strep. pyogenes* Peptostreptococci	Penicillin G	Clindamycin	Drainage necessary
Membranous pharyngitis	*C. diphtheriae*	Penicillin or erythromycin		Diphtheria: Antitoxin
	Epstein-Barr virus	None		Mononucleosis associated with airway closure or severe toxicity should be treated with prednisone
	Vincent's angina (anaerobes)	Metronidazole or clindamycin	Penicillin, amoxicillin, or amoxicillin-clavulanate	
Epiglottitis	*H. influenzae*	Cefotaxime, ceftizoxime, ceftriaxone, cefuroxime		Ensure patent airway (usually

	S. pyogenes Viruses	Ampicillin-sulbactam		with endotracheal tube) Rifampin prophylaxis for household contacts <4 yr (×4 days)
Laryngitis	Viruses (*M. catarrhalis*)			For *M. catarrhalis:* Trimethoprim-sulfa, erythromycin, amoxicillin-clavulanate, or cefaclor
PERIMANDIBULAR				
Actinomycosis	*A. israelii*	Penicillin G or V	Clindamycin Tetracycline Erythromycin	Treat for 3–6 mo
Parotitis	*S. aureus* (anaerobes)	Penicillinase-resistant penicillin	Cephalosporin-1st gen Clindamycin, vancomycin	Surgical drainage usually required
Space infections	Anaerobes	Clindamycin Penicillin + metronidazole	Cefoxitin Amoxicillin-clavulanate	Surgical drainage required
Cervical adenitis				
Acute	*Strep. pyogenes*	Penicillin	Erythromycin	
	Anaerobes	Clindamycin	Amoxicillin + clavulanate	
	S. aureus	Penicillinase-resistant penicillin	Oral cephalosporin (not cefixime)	
Chronic	Mycobacteria	TB: INH, rifampin, PZA + Etham MOTT: see pp 170–171		Noninfectious causes include tumors, lymphoma, sarcoid cysts
Cat-scratch disease	*Bartonella henselae*	Ciprofloxacin	TMP-SMX Erythromycin	Role of antibiotics is unclear Treat 2 wk Confirm diagnosis with serology

DENTAL Periapical abscess Gum boil Gingivitis Pyorrhea	Anaerobes Streptococci	Penicillin Clindamycin	Metronidazole × penicillin Amoxicillin-clavulanate	Metronidazole often preferred for periodontal disease, i.e., gingivitis, periodontitis
STOMATITIS Thrush	*C. albicans*	Oral nystatin (swish and swallow) or clotrimazole troches	Ketoconazole po Fluconazole po	
Vincent's angina	Anaerobes	Penicillin Clindamycin	Metronidazole ± penicillin Amoxicillin-clavulanate	
Aphthous stomatitis	No pathogen identified	Topical corticosteroid (Topicort gel), dyclonine (Dyclone) Miles' solution, viscous lidocaine	Systemic corticosteroids (Prednisone 40 mg/d, then rapid taper) Silver nitrate	Miles' solution: 60 mg hydrocortisone, 20 mL nystatin, 2 g tetracycline, and 120 mL viscous lidocaine
Herpetiform ulcers	*H. simplex*	Acyclovir Valacyclovir or famciclovir		Treatment usually reserved for immunocompromised hosts
UPPER RESPIRATORY INFECTION (common cold) (J Clin Microbiol 1999;36:1721; NEJM 2000;343:1715; Ann Intern Med 2001;134:487; Arch Intern Med 2003;163: 278)	Influenza Parainfluenza Rhinovirus Coronovirus	Influenza: Amantadine, rimantadine, oseltamivir, or zanamivir Ipratropium (see comments) Nasal decongestants (see comments)		Antiviral therapy for influenza must be started within 48 hr of onset of symptoms. Amantadine and rimantadine are active against influenza A; oseltamivir and zanamivir are active against influenza A and B Allergic rhinitis—Loratadine 10 mg qd; nasal steroids; avoid allergens Naproxen 500 mg tid × 5 days Ipratropium nasal spray (2 sprays each nostril 3–4 ×/day × 4 days OTC preparations with dexbromphen-iramine 6 mg + pseudoephedrine 120 mg bid × 1 wk Controversial—aspirin and acetaminophen, vitamin C, zinc gluconate lozenges

				Pleconaril is active vs. rhinovirus but failed FDA approval (CID 2003;36: 1523)

* PROTEKT US 2000–01

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COMPARISON OF COMMONLY USED ORAL ANTIMICROBIALS FOR RESPIRATORY TRACT INFECTIONS

	Regimen commonly used			***Antimicrobial activity****					***Adverse drug reactions (%)*****				
Drug	***Regimen****	***Pill count (10 days)***	***Cost AWP** (10 days)***	***Strep. pneumo***	***H. flu***	***Gr A strep***	***Staph. aureus***	***Anae-robes***	***Nausea, vomiting***	***Diarrhea***	***Rash***	***Therapy stopped***	***Other***
Amox-clavulan	875 mg bid	20	$117	++½	+++	+++	+++	+++	1–2	5–10	1	1–3	
Amoxicillin	500 mg tid	30	$13	++½	+	+++	+	++	1–2	5	1	2	
Azithromycin	250 mg qd	6	$48	++	+++	+++	+++	++	1–3	3–4	0.2	1	
Cefaclor	250–500 mg tid	30	$60–130	++	+++	+++	+++	++	1–4	2–6	1–2	2	Serum sickness
Cefdinir	300 mg bid	20	$90	++½	+++	+++	+++	++	3	16	1	3	
Cefditoren	200–400 mg bid	40	$75	+++½	+++	+++	+++	++	1–6	11–15	—	2–3	

Cefixime	200 mg bid	20	$88	+	+++	+++	++	+	5–7	15–20	1–2	2–3	
Cefpodoxime	200 mg bid	20	$108	++½	+++	+++	+++	++	1–2	4	1–2	2	
Cefprozil	250–500 mg bid	20	$90–180	++½	+++	+++	+++	++	1–2	—	—	—	
Cefuroxime	250–500 mg bid	20	$106–196	++	+++	+++	+++	++	2–5	4–8	1	—	
Cephalexin	250–500 mg qid	40	$56	+	+++	+++	+++	++	2–4	1–6	1	1	
Ciprofloxacin	500 mg bid	20	$116	++½	+++	+++	+++	++	2–5	1–2	1–2	1–3	
Clarithromycin	250–500 mg bid	20	$92	++	++	+++	+++	++	3–4	3	—	4	Taste change
Clindamycin	150–300 mg qid	40	$100–200	++½	—	+++	+++	+++	1–2	10–20	—	5–15	*C. difficile colitis*
Doxycycline	100 mg bid	20	$20	++	+++	++	++	++	2–5	1–2	—	1–2	
Erythromycin	250–500 mg qid	40	$11	++	+	+++	++	++	5–30	5	1	5–20	GI intolerance
Gatifloxacin	400 mg qd	10	$94	+++	+++	+++	+++	+++	1–2	1–2	—	1	
Levofloxacin	500 mg qd	10	$106	+++	+++	+++	+++	+	1–2	1–2	—	1	
Loracarbef	400 mg bid	20	$128	++	+++	+++	+++	+	2	4	1	1–2	

Moxifloxacin	400 mg qd	10	$98	+++	+++	+++	+++	111	1–2	1–2	—	1	
Penicillin V	500 mg qid	40	$9	++	+	+++	+	++	3	3	1	2–3	
Telithromycin	800 mg qd	20	$92 est.	+++	+++	+++	+++	++	2–8	10–11	—	4	Headache, dizziness
TMP-SMX	1 DS bid	20	$24	+	+++	++	+++	—	10	—	5–10	4–10	Rash

* Typical regimen for respiratory tract infections (otitis, sinusitis, exacerbations of bronchitis, "walking pneumonia").

** AWP, average whole price Sept 2003.

*** In vitro activity against common respiratory tract community-acquired bacterial pathogens: — indicates minimal activity, + indicates modest activity, ++ indicates moderate activity, +++ indicates activity against nearly all strains or indicates a preferred choice based on clinical trials.

**** Adverse reactions according to package inserts (summarized in Infect Dis Clin Pract 4:S103, 1995); "therapy stopped" indicates percentage that discontinued treatment because of adverse drug reaction.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Pulmonary Infections

A. **Specimens and Tests for Detection of Lower Respiratory Pathogens** (CID 1998;26:611.)

		Test			
Organism	***Specimen***	***Microscopy (stain)***	***Culture***	***Serology***	***Other***
Bacteria					
Aerobic	Expectorated sputum, blood, TTA, empyema fluid	Gram stain Quellung for *S. pneumo*	X		Pneumococcal urine antigen (JCM 2003;41:2810)
Anaerobic	TTA, empyema fluid	Gram stain	X		
Legionella sp.	Sputum, BAL, pleural fluid	FA (*L. pneumophila*)	X	IFA	Urinary antigen (*L. pneumophila* gr1), PCR (experimental)

Nocardia sp.	Expectorated sputum, bronchial washing, BAL fluid, tissue	Gram and modified carbol fuchsin stain	X		
Chlamydia sp.	Nasopharyngeal swab	—	X[a]	CF for *C. psittaci MIF* for *C. pneumo* ≥ 1:64	PCR for *C. pneumoniae* (experimental)
Mycoplasma sp.	Nasopharyngeal swab	—	X[a]	EIA, CF, cold agglutinins in 30–60%	PCR (experimental)
Mycobacteria	Expectorated or induced sputum, bronchial washing, BAL fluid	Fluorochrome stain or carbol fuchsin	X		PPD
Fungi					
Deep-seated					
Blastomyces sp.	Expectorated, sputum, induced sputum, BAL	KOH with phase contrast; Calcofluor white	X	CF, ID	
Coccidioides sp.	As above	As above	X	CF, ID, LA	

Histoplasma sp.	As above	As above	X	CF, ID	Antigen assay BAL, blood, urine
Opportunistic					
Aspergillus sp.	Lung biopsy	H&E, GMS, Calcofluor white	X	ID	CT scan; EIA expected soon
Candida sp.	Lung biopsy	H&E, GMS, Calcofluor white	X		
Cryptococcus sp.	Respiratory secretions, serum, Lung biopsy	H&E, GMS, Calcofluor white	X	LA	Serum or BAL antigen assay
Zygomycetes	Expectorated sputum, tissue	H&E, GMS, Calcofluor white	X		
Pneumocystis carinii	Induced sputum or bronchial brushings, washings, BAL fluid	Toluidine blue, Giemsa, FA, or GMS stain			
Viruses					
Influenza	Nasopharyngeal	FA: Influenza	X	CF, EIA, LA,	Z-Stat Flu

	aspirate	and RSV		FA	
Paraflu, RSV	Nasopharyngeal aspirate				CMV: Shell viral culture, FA stain of BAL or biopsy
CMV	Bronchial aspirate, BAL, or biopsy				
SARS CoV	Respiratory secretions (BSL-3 lab)	EM	X	IFA, EIA	RT-PCR

CF, complement fixation; PPD, purified protein derivative; ID, immunodiffusion; LA, latex agglutination; H&E, hematoxylin and eosin; CIE, coun-terimmunoelectrophoresis; EIA, enzyme immunoassay; FA, fluorescent antibody stain; IFA, indirect fluorescent antibody; MIF, microimmunofluorescence test.

[a] Few clinical microbiology labs offer these cultures, and those that do infrequently recover the indicated organisms.

B. **Empiric Treatment of Lower Respiratory Tract Infections**

1. **Community-acquired pneumonia: Guidelines of Infectious Diseases Society of America** (modified from CID 2003;37:405.)

Outpatient

Generally preferred: Macrolide*, telithromycin,† fluoroquinolone**, or doxycycline

Modifying factors

Suspected penicillin-resistant *S. pneumoniae*: Fluoroquinolone**, telithromycin†

Suspected aspiration: Amoxicillin-clavulanate

Hospitalized Patient

General medical ward

Generally preferred: Beta-lactam*** + macrolide* or fluoroquinolone** (alone)

Hospitalized in the intensive care unit for serious pneumonia

Generally preferred: Erythromycin, azithromycin, or fluoroquinolone** plus cefotaxime or ceftriaxone

Modifying factors

Structural disease of lung: Antipseudomonal penicillin, carbapenem, or cefepime + macrolide or fluoroquinolone** + aminoglycoside

Penicillin allergy: fluoroquinolone** + clindamycin

Suspected aspiration: fluoroquinolone + clindamycin or beta-lactam-beta-lactamase inhibitor (alone)

2. **Nosocomial pneumonia**

   a. **Etiologic diagnosis**: Diagnosis of pneumonia based on clinical criteria of fever, x-ray evidence of an infiltrate, and purulent respiratory secretions is often erroneous based on quantitative brush catheters of bronchoscopic aspirates (Ann Intern Med 2000;132:621.). The debate with ventilator associated pneumonia is empiric treatment vs quantitative bronchoscopic specimens (Lancet 2000;356:874.).

   b. **Empiric treatment** (Med Letter 1999;41:95.)

      Third generation cephalosporin (cefotaxime, ceftizoxime, ceftriaxone, or ceftazidime), cefepime, ticarcillin-clavulanate, piperacillin-tazobactam, meropenem, or imipenem

      With or without aminoglycoside (tobramycin, gentamicin, amikacin)

      Special considerations

      Probable *P. aeruginosa* (especially ICU): Cefepime, meropenem, or imipenem plus aminoglycoside

      Probable *S. aureus*: Add vancomycin

3. **Lung abcess**

   a. **Anaerobic bacteria** (recommendations of IDSA, CID 2000;31:347.)

      1. Clindamycin
      2. Beta-lactam-beta-lactamase inhibitor
      3. Imipinem/meropenem/ertapenem

b. **Other microbial pathogen—see next section**

4. **Acute bronchitis** (Recommendations of ACP and CDC: Ann Intern Med 2001; 134:479 and 521)

   Evaluation of acute cough should focus on ruling out pneumonia

   Chest x-ray if:

   1. Abnormal vital signs,
   2. "asymetrical lung sounds," or
   3. cough ≥3 wks

   Antibiotics are not recommended regardless of duration of cough. Most are viral and self-limited

   Treatment is symptomatic with antipyretics, analgesics, beta-agonist inhalers, antitussives, or vaporizers

   Influenza: Amantadine, rimantadine, zanamivir, or oseltamivir (must start within 48 hr of onset of flu symptoms)

   Pertussis: Erythromycin 500 mg po qid × 14 days or TMP-SMX DS bid × 14 days Antibacterial agents have no documented benefit and should be avoided except with suspected or established pertussis (Am J Med 1999;107:62.)

5. **Exacerbations of chronic bronchitis** (Recommendations of ACP: Ann Intern Med 2001;134:600.)

   a. **Chest x-ray**: Useful in hospitalized patients (up to 23% show new findings) and it may be useful in EW visits; there are not data for or against its use in office practice

   b. **Treatment—hospitalized patients**

      Inhaled anticholinergic bronchodilators or short-acting beta$_2$-agonists; anticholinergics are used first and to maximum dose because of fewer side effects

      Systemic steroids for up to 2 weeks

      Noninvasive positive-pressure ventilation supervised by trained physician

      Cautious administration of O_2 to hypoxemic patients

   c. **Antibiotic decision-making**

      Reserve antibiotics for severe exacerbations

      If used, the preference is narrow-spectrum agents. Prior placebo-controlled trials favored amoxicillin, TMP-SMX, and tetracycline but they were done prior to emergence of multidrug resistant bacteria and excluded nursing home patients and recent hospital discharges

Interventions without documented benefit: mucolytic therapy, chest physiotherapy, and methylxanthine bronchodilators (the latter two may be harmful)

C. **Treatment of Pneumonia by Pathogen** (modified from CID 2003;37:405.)

Agent	*Preferred antimicrobial*	*Alternative antimicrobial*	*Comment*
S. pneumoniae Penicillin-sensitive (MIC ≤ 1.0 µg/mL)	Penicillin G or amoxicillin Cefuroxime Ceftriaxone	Telithromycin† Cephalosporins: Cefepime, Cefotaxime Oral cephalosporins: cefditoren, cefpo-doxime, cefprozil, cefuroxime, cefdinir Macrolides* Ampicillin Doxycycline Clindamycin Imipenem/meropenem/ertapenem	Doses for severe diseases: Penicillin G 0.5–2 mil units IV q4h Ceftriaxone 1–2 g/d IV Cefotaxime 2 g IV q6h Resistance: Penicillin—15%; TMP-SMX—23%; erythromycin—25%; clindamycin—6%; cefotaxime—2%; doxycycline—6%; levofloxacin—1%; vancomycin—0 Data from CDC surveillance with 10,000 strains of *S. pneumoniae* from in diverse regions of U.S. in 2000–02 (Antimicrob Ag Chemother 2003;47:1790)

Penicillin resistance (MIC ≥ 4 µg/mL)	Vancomycin Fluoroquinolone** Telithromycin†	Based on in vitro susceptibility tests Imepenem/meropenem/ertapenem Clindamycin Linezolid	Definition of resistance: Penicillin resistance is defined as an MIC ≥4 µg/mL based on achievable serum levels with nonmeningeal pneumococal infections Risk for resistance: Geographic region; children, immuno-suppressed, chronic antibiotic exposure, clustering (day care, prison, hospital etc), international travel Major resistant serotypes: 6A, 6B, 14, 19A, 19F, 23F (five of six included in vaccine)
H. influenzae	Azithromycin Cephalosporin—2nd or 3rd generation TMP-SMX Telithromycin	Doxycycline Fluoroquinolone** Clarithromycin Beta-lactam-beta-lactamase inhibitor	Betalactamase production by 30–40% of strains Most are nontypable strains
Moraxella catarrhalis	Cephalosporin—2nd or 3rd gen TMP-SMX	Macrolide*: Fluoroquinolone**	Beta-lactamase production by >90%

	Amoxicillin-clavulanate Telithromycin		
Anaerobes	Clindamycin Beta-lactam-beta-lactamase inhibitor	Penicillin G or V Ampicillin/amoxicillin ± metronidazole	Clindamycin is superior to penicillin in putrid lung abscesses (Ann Intern Med 1983;98:466; Arch Intern Med 1990;158:2525) Metronidazole should not be used as a single agent (CID 1993;16:S248). Antibiotics other than penicillin, clindamycin, and metronidazole have not been studied
S. aureus Methicillin sensitive	Nafcillin/oxacillin ± rifampin or gentamicin	Cefazolin or cefuroxime Vancomycin, clindamycin, TMP-SMX, fluoroquinolone**	Beta-lactamase production by >90%. **Methicillin sensitive**: >90% community-acquired strains and 60–70% of nosocomial strains
Methicillin resistant	Vancomycin ± rifampin or gentamicin	Requires in vitro testing: Linezolid	

Enterobacteriaceae (Coliforms: *E. coli Klebsiella, Proteus, Enterobacter*, etc)	Cephalosporin—2nd or 3rd gen ± aminoglycoside Carbapenem***	Aztreonam, imipenem, beta-lactam-beta-lactamase inhibitor Fluoroquinolone**	In vitro sensitivity tests needed
P. aeruginosa	Aminoglycoside + anti-pseu-domonal beta-lactam: ticar-cillin, piperacillin, mezlocillin, ceftazidime, cefepime, or cefoperazone Ciprofloxacin + antipseudomonal beta-lactam	Aminoglycoside + aztreonam, imipenem, or ciprofloxacin	Need in vitro activity test results
Legionella	Fluoroquinolone** Azithromycin	Macrolide* Doxycycline	Fluoroquinolones are superior to erythromycin in animal models Initial erythromycin dose: 4 g/d IV, oral therapy (2 g/d) when improved—total duration 2–3 wk
Mycoplasma pneumoniae	Doxycycline Macrolide* Telithromycin	Fluoroquinolone**	Treat 1–2 wk
Chlamydia pneumoniae	Doxycycline Macrolide*	Fluoroquinolone**	Treat for 2 wk

	Telithromycin		
Chlamydia psittaci	Doxycycline	Erythromycin, chloramphenicol	
Nocardia	Sulfonamide TMP-SMX Sulfonamide + minocycline or amikacin	Imipenem ± amikacin Doxycycline or minocycline	
Coxiella burnetii (Q fever)	Tetracycline	Chloramphenicol	
Influenza (see pp 196)	Amantadine, rimantadine, zanamivir, or oseltamivir		Should be started within 48 hr of onset of symptoms. Oseltamivir and zanamivir are effective against influenza A and B
Hantavirus (see p 200)	Supportive care		Ribavirin (33 mg/kg IV, then 16 mg/kg q6h × 4 days, then 8 mg/kg q8h × 3 days)—experimental. Call CDC 800-532-9929
Cytomegalovirus (see p 194)	Ganciclovir × IVIG or CMV hyperimmune globulin	Foscarnet Cidofovir	

* Macrolide: Erythromycin, clarithromycin, azithromycin; for *H. influenzae*, azithromycin or clarithromycin.
** Fluoroquinolone: Levofloxacin, moxifloxacin, or gatifloxacin show enhanced *S. pneumoniae* and atypical agents.
*** Carbapenems: Imipenem, meropenem and ertapenem.
† Telithromycin is active against multi-drug resistant *Streptococcus pneumoniae*.

Footnotes

*Macrolide: Azithromycin, clarithromycin, or erythromycin

**Fluoroquinolone: Levofloxacin, sparfloxacin, gatifloxacin, or moxifloxacin or other fluoroquinolone with enhanced activity versus *S. pneumoniae.* Preferably reserve for high-risk patients including those with recent antibiotic exposure, the elderly and those with associated underlying diseases such as CHF, chronic lung disease, renal failure or diabetes.

†Telithromycin is also active against multi-drug resistant *Streptococcus pneumoniae*.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Endocarditis

I. **DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS** (Am J Med 1994;96:200.; CID 2000;30:633.)

Note: The Duke criteria have become generally accepted (Am J Med 1994;96:200.) and multiple reviews show a specificity of 99% and a negative predictive value of 92% (Am Heart J 1994;128:1200.; CID 1998;26:1302.).

A. **Definite Infective Endocarditis**

1. **Pathologic criteria**

- Microorganisms: Demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess, or
- Pathologic lesions: Vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

2. **Clinical criteria** (using specific definitions listed below under "Definitions of Terminology")

Two major criteria, or one major and three minor criteria, or five minor criteria

B. **Possible Infective Endocarditis** 1 major + 1 minor or 3 minor

C. **Rejected**

1. Firm alternate diagnosis for manifestations of endocarditis, or

2. Resolution of manifestations of endocarditis with antibiotic therapy for 4 days or less, or
3. No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

Definitions of Terminology

1. **Major Criteria**
    a. ***Positive blood culture for infective endocarditis***
        1. Typical microorganism for infective endocarditis from two separate blood cultures
            a. Viridans streptococci, *Streptococcus bovis*, HACEK group, or
            b. Community-acquired enterococci, in the absence of a primary focus, or
            c. *S. aureus* bacteremia that is community acquired or nosocomial and with or without a primary focus
        2. Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from
            a. Blood cultures drawn more than 12 hr apart or
            b. All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart
        3. Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
    b. **Evidence of endocardial involvement**
        1. Positive echocardiogram for infective endocarditis
            a. Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or

b. Abscess or

c. New partial dehiscence of prosthetic valve, or

2. New valvular regurgitation (increase or change in preexisting murmur not sufficient)

2. **Minor Criteria**

a. Predisposition: Predisposing heart condition or IV drug use

b. Fever: ≥38.0°C (100.4°F)

c. Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

d. Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor

e. Microbiologic evidence: Positive blood culture but not meeting major criterion as noted previously or serologic evidence of active infection with organism consistent with infective endocarditis

f. Echocardiogram: Consistent with infective endocarditis but not meeting major criterion as noted previously (recommended for deletion)

II. **ANTICIPATED AGENTS, ECHO, RISKS**

A. **Microbiology of endocarditis**: Based on literature review (NEJM 2001;345:1318.)

		Prosthetic valve Time postoperative		
	Native valve >16 yrs	***<60 days***	***2–12 mo***	***>12 mo***
Streptococcus species	40–65	1	7–10	30–33
Staph. aureus	22–30	20–24	10–15	15–20
Staph. epidermidis	3–8	10–15	2–4	4–7
Enterococcus	5–17	5–10	10–15	8–12
Fungi	1–3	5–10	10–15	1
Gram-negative bacilli	4–10	10–15	2–4	8–12
HACEK and culture negative	3–10	3–7	3–7	3–8

B. **Culture negative endocarditis**

Microbe	***Methods to establish pathogen***
Atiotrophia (nutritionally deficient strep)	1) Grow in thioglycolate, and 2) as colonies around *S. aureus* in media supplemented with pyridoxal HCI or L-cysteine
Bartonella	1) Serology, 2) Lysis-centrifugation, and 3) PCR of valve or embolized vegetation (may require > 1 month to culture)
Coxiella burnetti	1) Serology, and 2) PCR, Giemsa stain, or immunohistologic stains of op specimen
HACEK	Blood cultures to day 7; may require larger incubation and subculture
Chlamydia	Blood culture using specialized technique described
T. whipplei	1) Silver or PAS stain of valve, and 2) PCR or culture of vegetation
Legionella	1) Subculture of blood, 2) Lysis-centrifugation pellet from blood cult, 3) BCYE agar for valve, 4) FA stain of valve, and 5) serology
Brucella	Serology

Fungi	1) Blood culture-*Candida*, 2) Antigen assay urine or blood for *H. capsulatum* or blood for *C. neoformans*, and 3) culture and histology of valve

C. **Echocardiography**

Transthoracic echo is inadequate in up to 20% of adults due to obesity, chronic lung disease, and chest wall deformities. The sensitivity for vegetations is 60–70% (J Am Coll Cardiol 1991;18:391.; Am J Med 1996;100:90.). Transesophageal echo increases sensitivity for detecting vegetations to 75–95% and shows specificity of 85–98% (Am J Med 1999;107:198.). Guidelines for use (J Am Coll Cardiol 1997;29:862.) suggest the preference for transthoracic echo to evaluate native valves in patients who are good candidates for imaging, especially if the probability of endocarditis is less than 4%. For patients with a probability of 4–60%, initial use of transesophageal echo is more cost-effective. TEE is more sensitive for evaluating periovascular extension in myocardial abscesses.

S. aureus bacteremia: Endocarditis is found in 13–25% (CID 2002;30:633.). TEE is useful in determining the duration of therapy in patients with uncomplicated, intravascular-catheter-associated *S. aureus* bacteremia (Am J Med 1999;107:198.; Ann Intern Med 1999;130:810.; CID 1999;28:106.).

D. **Endocarditis risk/100,000 person years***

- Native valve: 1.7–6.2
- Prosthetic valve: 60 months: 2,000–3,000
- Injection drug use: 700

III. **TREATMENT OF ENDOCARDITIS**

A. **Medical Management by Microbial Pathogen** (Committee on Rheumatic Fever, Endocarditis

and Kawasaki Disease of the American Heart Association's Council on Cardiovascular Disease in the Young: Antimicrobial Treatment of Infective Endocarditis due to Viridans Streptococci, Enterococci, and Staphylococci. JAMA 274:1706, 1995)

1. **Streptococci**
    a. ***Penicillin-sensitive streptococci*** (minimum inhibitory concentration <0.1 µg/mL)
        1. **Penicillin only**: Aqueous penicillin G, 12–18 mil units/day either continuously or in 6 equally divided doses × 4 wk.

            (Preferred regimen for patients with a relative contraindication to streptomycin including age >65 yr, renal impairment, or prior 8th cranial nerve damage.)
        2. Ceftriaxone: 2 g once daily IV × 4 wk
        3. Two-week course: Aqueous penicillin G 12–18 mil units either continuously or in 6 equally divided doses plus gentamicin 1 mg/kg IM or IV q8h. Peak gentamicin level (1 hr after start of 20- to 30-min infusion) should be 3 µg/mL; trough should be <1 µg/mL. Two-week regimen is not recommended for complicated cases, e.g., extracardiac foci or intracardiac abscesses. Aqueous penicillin G, q12h. (Advocated as most cost-effective regimen by Mayo Clinic group for uncomplicated cases with relapse rates of <1%.)
        4. Penicillin allergy: Vancomycin, 30 mg/kg/d IV × 4 wk in 2–4 doses not to exceed 2 g/d unless serum levels are monitored. Vancomycin levels 1 hr post dosing should be 30–45 µg/mL with twice daily dosing. Infuse vancomycin over ≥60 min.

    Note:

    - *Streptococcus bovis* and tolerant streptococci with MIC <0.1 µg/mL may receive any of these regimens
    - Nutritionally deficient should be treated as enterococcal endocarditis
    - Prosthetic valve endocarditis: IV penicillin for 6 wk and gentamicin for at least 2 wk

- Immediate reaction to penicillin or other beta-lactam is major indication for vancomycin
- Penicillin tolerant strains with MBCs that greatly exceed MICs (>32-fold): Recommend usual therapy, meaning routine MBC determination is not recommended for streptococci
- Gentamicin is now the most frequently used aminoglycoside because of ability to monitor levels and ability to give IV or IM. If streptomycin is preferred, test for high-level resistance (≥1000 µg/mL)
- Two-week treatment regimen is not recommended for complicated cases, e.g., shock, extracardiac foci of infection, or intracardiac abscess
- Desired peak serum levels if obtained: Streptomycin—20 µg/mL, gentamicin—3 µg/mL, vancomycin—20–35 µg/mL (qid), or 30–45 µg/mL (bid)
- Ceftriaxone plus gentamicin once daily × 2 wk may be adequate
- Expected bacteriologic cure rate: >95%; expected survival rate: >90%

b. ***Viridans streptococci and Streptococcus bovis relatively resistant to penicillin G*** (minimum inhibitory concentration ≥0.1 µg/mL and ≤0.5 µg/mL)

1. Aqueous penicillin G, 18 mil units/d IV either continuously or in 6 divided doses plus gentamicin 1 mg/kg IM or IV q8h × 4 wk
2. Penicillin allergy: Vancomycin 30 mg/kg/d × 4 wk in 2 daily doses not to exceed 2 g/d
3. Penicillin allergy, cephalosporins: Cefazolin, 1 g IM or IV q8h × 4 wk

c. ***Penicillin-resistant streptococci including enterococci and strains with minimum inhibitory concentrations of >0.5 µg/mL***

1. Aqueous penicillin G 18–30 mil units/d IV either continuously or in 6 divided doses plus gentamicin, 1 mg/kg IM or IV q8h × 4–6 wk

2. Ampicillin 12 g/d IV either continuously or in 6 divided doses plus gentamicin 1 mg/kg IM or IV q8h × 4–6 wk

3. Penicillin allergy: Vancomycin 30 mg/kg/d IV in 2 doses not to exceed 2 g/24 hr unless serum levels are monitored plus gentamicin 1 mg/kg IM or IV q8h × 4–6 wk. Gentamicin is not required for viridans streptococci

   Note:

   - Streptococci, groups B, C, and G: Some recommend routine use of penicillin or cephalosporin × 4–6 wk plus gentamicin × 2 wk
   - Strep bovis endocarditis is associated with colonic carcinoma
   - Patients with symptoms for over 3 mo before treatment and those with prosthetic valve endocarditis should receive combined treatment for 6 wk
   - Aminoglycosides: Gentamicin is usually preferred; MIC should be ≤500–2000 µg/mL for gentamicin or ≤2000 µg/mL for streptomycin. Serum levels should be monitored: Desirable peak levels are streptomycin 20 µg/mL and gentamicin 3 µg/mL. Some authorities recommend gentamicin 1.5 mg/kg q8h with goal for peak serum concentration of 5 µg/mL. Usual dose of streptomycin is 7.5 mg/kg IM q12h, not to exceed 500 mg. Streptomycin is more ototoxic, which is often irreversible. Gentamicin is more often nephrotoxic, which is usually reversible
   - For enterococcal endocarditis, shorter courses of aminoglycosides (2–3 wks vs. 4–6 wks) may be adequate (CID 2002;34:159.)
   - Expected bacteriologic cure rate: >95%; expected survival rate: >90%

2. ***Staphylococcus aureus* or *S. epidermidis***

   a. ***No prosthetic device—methicillin-sensitive***

      1. Nafcillin or oxacillin 2 g IV q4h × 4–6 wk with optional addition of gentamicin 1 mg/kg IV or IM q8h × 3–5 days.

2. Penicillin allergy, cephalosporin: Cefazolin 2 g IV q8h × 4–6 wk with optional addition of gentamicin 1 mg/kg IV or IM q8h × 3–5 days (should not be used with immediate-type penicillin hypersensitivity).
3. Penicillin allergy or methicillin-resistant strains: Vancomycin 30 mg/kg/d

in two daily doses (not to exceed 2 g/d unless serum levels monitored) × 4–6 wk. With inadequate response, add aminoglycoside × 3–5 days.
4. Parenteral drug abuse with tricuspid valve endocarditis: Oxacillin or nafcillin + tobramycin parenterally × 2 wk (Ann Intern Med 1988;109:619.; Eur J Clin Microbiol Infect Dis 1994;13:559.). Vancomycin is not an adequate substitute for nafcillin in this 2-week course (Eur J Clin Microbiol Infect Dis 1994;13:533.). Abbreviated course is not recommended for HIV-positive patients or those with persistent fever >7 days or with vegetations >1–2 cm (NEJM 2001;345:1318.).

b. ***Prosthetic valve or prosthetic material***

1. Methicillin-sensitive strains: Nafcillin or oxacillin 2 g IV q4h × ≥6 wk plus rifampin 300 mg po q8h × ≥6 wk plus gentamicin 1 mg/kg IV or IM q8h (not to exceed 80 mg) × 2 wk.*
2. Methicillin-resistant strains: Vancomycin 30 mg/kg/d in 2–4 doses (not to exceed 2 g/d unless serum levels monitored) × ≥6 wk plus rifampin 300 mg po q8h × ≥6 wk plus gentamicin 1 mg/kg IV or IM q8h (not to exceed 80 mg) × 2 wk.*

Note:

- Methicillin-resistant staphylococci should be considered resistant to cephalosporins
- Vancomycin is considered inferior to oxacillin or nafcillin for methicillin-sensitive strains of *S. aureus* (Ann Intern Med 1991;115:674.)
- Tolerance has no important effect on antibiotic selection

- The occasional strains of staphylococci that are sensitive to penicillin G at <0.1 µg/mL may be treated with regimens advocated for penicillin-sensitive streptococci
- Use of rifampin in prosthetic valve endocarditis will increase required dose of coumadin
- For native valve endocarditis, the addition of gentamicin to nafcillin or oxacillin causes a more rapid clearing of bacteremia in patients with left-sided endocarditis (2.5 vs 4.0 days) but has no impact on cure rates; use of gentamicin (or rifampin) with either methicillin-sensitive or methicillin-resistant strains is sometimes advocated for the first 3–5 days of treatment with a beta-lactam or vancomycin (CID 1993;17:313.)
- Duration of treatment: 4–6 wk, 6 wk commonly recommended for left-sided staphylococcal endocarditis
- Coagulase-negative strains infecting prosthetic valves should be considered methicillin-resistant unless sensitivity is conclusively demonstrated
- Aminoglycoside selection for coagulase-negative strains should be selected on the basis of in vitro sensitivity tests; if not active, these agents should be omitted
- Expected outcome: CID 1992;15:589.

	Bacteriologic cure	***Survival***
Left sided	>80%	>50%
Right sided	>90%	>90%

3. **HACEK group: *Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetem comitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae***
    a. Ceftriaxone 2 g once daily IM or IV × 4 wk
    b. Ampicillin 12 g/d IV either continuously or in 6 divided doses plus gentamicin 1 mg/kg IM or IV q8h × 4 wk
    c. Recent studies show the most active antibiotics in vitro are third generation

    cephalosporins, cefepime, meropenem, rifampin, and fluoroquinolones (Diagn Microbiol Infect Dis 1999;34:73.)
4. **Fungi** (*Candida* sp and *Aspergillus* sp)* (not included in committee recommendations)
    a. Amphotericin B 0.8–1.0 mg/kg/d IV + flucytosine 100–150 mg/kg/d po
    b. Fluconazole 400 mg/d IV or po (susceptible *Candida* sp. only: Experience limited, but anecdotal experience favorable; experience with fluconazole in combination with flucytosine, rifampin, etc also is limited)
5. **Organisms with special culture requirements**: HACEK (see above), *Coxiella burnetii*

(serology), Brucella, *N. gonorrhoeae, Legionella, Bartonella*, corynebacteria, *Listeria*, nutritionally variant streptococci, nocardia, mycoplasma, chlamydia, and mycobacteria

B. **Outpatient Treatment**

1. Ceftriaxone once daily for penicillin-sensitive viridans streptococci
2. Use of portable computerized pumps for multiple dose or continuous-infusion therapy.
3. Dual-lumen central catheter with two portable pumps permits combination therapy.

C. **Empiric Treatment for Acute Endocarditis** Recommendations of Mayo Clinic (Mayo Clin Proc 1997;72:532.)

Setting	***Antibiotic regimen***	***Alternative***
Acute onset, native valve	Nafcillin or oxacillin (2 g IV q4h) plus aminoglycoside*	Vancomycin (1 g IV q12h) plus aminoglycoside*
Subacute Native valve	Ampicillin-sulbactam (2 g q4–6h) (ampicillin) plus aminoglycoside*	Vancomycin (1 g IV q12h) plus ceftriaxone (2 g IV q12h) or cefotaxime (4 g IV q6h) + aminoglycoside*
Prosthetic valve	Nafcillin or oxacillin (2 g IV q4h) plus aminoglyco-side* plus rifampin 300 mg IV q12h)	
Intravenous drug use	Nafcillin or oxacillin (2 g IV q4h) plus aminoglycoside*	Vancomycin (1 g IV q12h) + aminoglycoside*

* Aminoglycoside—usually gentamicin 1 mg/kg IV q8h to achieve peak serum levels of about 3μg/mL.

D. **Monitoring**:

1. Serumcidal activity: Not recommended for routine use—may be useful with unusual etiology or unconventional therapy.
2. Blood culture: To verify response and post-treatment to assure cure. Relapses occur within 4 wk.
3. Most relapses occur within 2 months of discontinuing antibiotic treatment

IV. **INDICATIONS FOR CARDIAC SURGERY IN PATIENTS WITH ENDOCARDITIS** (Am J Med 1985;78(suppl 6B):138.)

A. **Indications for Urgent Cardiac Surgery***

Severe heart failure (especially with aortic insufficiency)

Vascular obstruction

Uncontrolled infection

Fungal endocarditis

Persistent bacteremia (or persistent signs of sepsis)

Lack of effective antimicrobial agents

Unstable prosthetic valve

B. **Relative Indications for Cardiac Surgery**

1. ***Native valve***

Bacterial agent other than susceptible streptococci (especially *P. aeruginosa, Brucella, Coxiella*, fungi, and resistant enterococci)

Relapse (especially if nonstreptococcal agent)

Evidence of intracardiac extension

Rupture of sinus of Valsalva or ventricular septum

Ruptured chordae tendineae or papillary muscle

Heart block (new conduction disturbance)

Abscess shown by echo or catheterization

Two or more emboli

Vegetations demonstrated by echo (especially large vegetation or aortic valve vegetations)

Mitral valve preclosure by echo (correlates with severe acute aortic insufficiency)

2. ***Prosthetic valve***: Surgical therapy is usually superior to medical treatment (Ann Thorac Surg 1994;58:1073.)

Early postoperative endocarditis (<8 wk)

Nonstreptococcal late endocarditis

Periprosthetic leak

Two or more emboli

Relapse

Evidence of intracardiac extension (see above)

Miscellaneous: Heart failure, aortic valve involvement, new or increased regurgitant murmur or mechanical valve versus bioprosthesis

C. **Echocardiographic Findings that Suggest Potential Need for Surgery** (AHA Committee

on Infectious Endocarditis—Circulation 1998; 98:2936.):

1. Persistent vegetations after major embolic event
2. Large vegetations (>1 cm) mitral valve
3. Increase vegetation size after 4 wk of therapy
4. Acute mitral insufficiency
5. Valve perforation or rupture
6. Periannular extension of infection

D. **Point system**: Urgent surgery should be strongly considered with five accumulated points (indications for surgery in infective endocarditis. In Sande MA, Kaye D (Eds). Contemporary Issues in Infectious Disease. New York: Churchill Livingstone, 1984:201–212).

INDICATIONS FOR EMERGENT SURGERY*

	Native valve	***Prosthetic valve***
Heart failure		
Severe	5	5
Moderate	3	5
Mild	1	2

Fungal etiology	5	5
Persistent bacteremia	5	5
Organism other than susceptible strep	1	2
Relapse	2	3
One major embolus	2	2
Two or more systemic emboli	4	4
Vegetations by echocardiography	1	1
Ruptured chordae tendineae or papillary mm	3	—
Ruptured sinus of Valsalva	4	4
Ruptured ventricular septum	4	4
Heart block	3	3
Early mitral valve closure by echo	2	—

Unstable prosthesis	—	5
Early prosthetic valve endocarditis	—	2
Periprosthetic leak	—	2

*Criterion is ≥5 points.
Note: This point system above has never been validated.
Alternative: An alternative point system is based on 6 factors that predict mortality within 6 months: mental status—4; Charlison co-morbidity score—1–6*; CHF-3, pathogen other than *Strep. viridans*—6–8; and medical vs surgical treatment—5.

Footnotes

*NEJM 2001;345:1318; JID 2002;185:1761

*Surgery often required. If strain is resistant to aminoglycosides, avoid these drugs; use fluoroquinolone if susceptible. If surgery performed, examine in vitro sensitivities because these often change during treatment.

***Early surgery virtually always required**

*Note: The validity of these criteria for surgery have never been shown (JAMA 2003;289:1933)

*1 = myocardial infarct, stroke, dementia, ulcer, mild liver disease, diabetes, chronic lung disease; 2 = severe renal disease, complicated diabetes, hemiparesis, tumor; 3 = severe liver disease; 6 = metastatic cancer, immunodeficiency

Validity testing in 513 patients showed the following mortality data at 6 mo: <6: 6%; 7–11: 17%,

12–15: 31%, >15: 63% (JAMA 2003;289:1933). (This system predicts mortality rather than indications for surgery, but the authors suggest utility in surgical decisions.)

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Viral Hepatitis

Types, clinical features, and prognosis

(MMWR 34:313, 1985; MMWR 37:341, 1988; MMWR 39:1, 1990; MMWR 40(RR-12):1, 1991)

Type	*Seroprevalence*	*Incubation period*	*Diagnosis**	*Prognosis/comments*
A (HAV)	Person-to-person fecal-oral Contaminated food and water (epidemic) Seroprevalence: Anti-HAV in adults U.S.: 40–50% Acute viral hepatitis: 40–60% Fulminant	15–50 days Avg: 28 days	Acute HAV: IgM anti-HAV Prior HAV: Total (IgM and IgG) anti-HAV *Sequence*: Viral transmission → HAV viremia and fecal shedding at 2 wk, IgM-HAV at 2 wk, IgG-HAV at 8–16 wk	Self-limited: >99% Fulminant and fatal: 0.6% No carrier state or chronic infection Severity increases with age IgM + elevated ALT is presumptive evidence for acute HAV. IgM remains elevated 3–9 mo; IgG persists for life

	hepatitis: 8%			
B (HBV)	Sexual contact or contaminated needles from HBsAg carrier source (transmission via blood transfusions is rare due to HBsAg screening) Efficiency of transmission increased if source is HBeAg positive Seroprevalence (any marker, U.S.) (see p 116) General population: 3–14% blacks: 14%; whites: 3% IV drug abuse: 60–80%	45–160 days Avg: 120 days	Acute HBV: HBsAg +, IgM anti-HBc+, anti-HBc+, anti-HBs– Chronic HBV: HBsAg+ × 6 mo, anti-HBc+ IgM anti-HBc+, anti-HBs– HBsAg "window": IgM anti-HBc+, anti-HBc+, HBsAg–, anti-HBsAg– Prior HBV: anti-HBc+, anti-HBs+, HBsAg– HBV vaccine response: anti-HBs+, anti-HBc–, HBsAg–, IgM anti-HBc– *Sequence*: Viral transmis-sion → HBsAG at 1–2 mo	Fulminant and fatal: 1.4% Carrier state (defined as HBsAg-pos, 2× separated by 6 mo or HBsAg pos and IgM anti-HBc neg): Develops in 6–10% of infected adults, 25–50% of children <5 yr Chronic carriers: 25% develop chronic active hepatitis that progresses to cirrhosis in 15–30%, fatal cirrhosis in 1%/yr, and/or fatal hepatocellular carcinoma in 0.25%/yr Perinatal with HBsAg-pos and HBeAg-pos mother: 70–90% acquire perinatal HBV infection and 85–90%

	Gay men: 35–80% Hemodialysis patients: 20–80% Health care workers (unvaccinated, frequent blood exposure): 15–30% (unvaccinated, no frequent blood exposure): 3–10% Chronic carriers (HBsAg) U.S.: 0.1–0.2%; developing world: 10–30% Acute viral hepatitis: 30–40% Chronic liver disease: 10–15%		→ IgG anti–HBc, anti–HBe at 3 mo → anti–HBs at 4 mo	of these will become chronic carriers; >25% of these carriers will develop cirrhosis or hepatocellular carcinoma; perinatal transmission rate is <10% if anti-HBe pos Risk of transmission with needlestick from HBsAg-pos source: 6–30%; highest with HBeAg pos source
C (HCV) (parenterally transmitted	Contaminated transfused blood: 10%;	15–150 days (mean 50 days)	Tests: Anti-HCV-EIA-third generation tests	Fulminant and fatal <1% Acute infection:

non-A, non-B) also causes sporadic NANB hepatitis	IVDA—40%; heterosexual contact—10%; unknown—40% Seroprevalence (U.S.): 1.8% Blood donors: 0.2–0.6% General population: 2% Hemophiliacs: 60–90% IV drug abuse: 60–90% Dialysis patients: 15–20% Gay men: 2–6%; Health care workers: 0.5–2.0% Sex contacts of HCV patients: 1–10% Chronic hepatitis: 40% Acute sporadic hepatitis in U.S.:		show specificity and sensitivity of >99%;can confirm with qualitative HCV RNA (or quan-titative HCV RNA) Acute HCV: HCV RNA pos 1–3 wk, anti-HCV at 10–14 wk Active HCV infection: Excluded if ≥ 2 negative HCV RNA assays over 6 mo *Sequence:* Viral transmission → PCR pos for HCV at 1–3 wk, increased ALT at 4–6 wk and anti-HCV at 10–14 wk	Usually mild with moderate elevation ALT Chronic hepatitis: 85%; cirrhosis: in 10–20% within 20 yr Associated with hepatocellular carcinoma: 1–4%/year with HCV associated cirrhosis Evaluation: 1) Confirmed diagnosis with positive EIA ± positive qualitative HCV RNA; 2) liver function test—ALT; 3) candidates for interferon therapy—quantitative HCV RNA genotype and liver biopsy Patients with anti-HCV should be considered infectious: should not be blood or organ donors; risk with

	17% Genotype 1: 70–75%			sex is low—seroconversion rate is 0–0.6%/yr in discordant couples; risk with needlestick injury from HCV infected source is 2%; perinatal transmission rate is 2–7%
Delta	Defective virus that requires presence of active HBV, e.g., co-infection with HBV or superinfection in HBsAg carrier; main source is blood (IV drug abuse, hemophilia) Epidemics: Amazon Basin and Central Africa	Superinfection: 30–60 days Co–infection: same as HBV	Acute HBV-HDV co-infection: HDAg+, HBsAg+, IgM anti-HDV+, IgM anti-HBc+, HBV DNA ± HDV RNA Acute HDV superinfection: HDAg+, HBsAg±, IgM antiHDV+, anti-HDV+, IgM antiHBc–, HBV DNA ± HDV RNA	Acute co-infection with HBV: 1–10% acute fatality; <5% chronic hepatitis Acute superinfection: 5–20% acute fatality, >75% develop chronic hepatitis, with 70–80% developing cirrhosis Epidemics in underdeveloped countries: Fulminant fatal hepatitis in 10–20% of children

	Endemic areas (Mediterranean Basin, Middle East, Amazon Basin): 20–40% Nonendemic areas (U.S.): uncommon Medical care workers and gay men:Low		Chronic HDV: HBsAg+, anti–HDV+, and HDV Ag in liver or HDV RNA in serum	Chronic delta hepatitis: Worsens prognosis of chronic HBV infection; most likely chronic hepatitis to cause cirrhosis
E (HEV) (enterally transmitted non-A, non-B, or ET-NANB)	Epidemic fecal-oral (Burma, Borneo, Mexico, Somalia, Pakistan, China, India, Russia, Peru, throughout Africa) Sporadic (developing countries) U.S.: no documented cases originating in U.S.	20–60 days (mean 40 days)	Anti-HEV (IgM or documented seroconversion). Assays not yet licensed in U.S. but available from CDC (404-639-3048) *Sequence*: Viral transmission → HEV Ag in blood → IgM-anti-HEV at 4–8 wk → IgG-anti-HEV at 6–10 wk; duration of IgG-Ab is unknown	Mortality <2% except for pregnant women who have mortality of 10–20% Usually mild disease predominantly in adults >15 yr; chronic liver disease has not been reported No chronic infection Often cholestatic with high alkaline phosphatase

Non A–E	Cause unknown Fulminant hepatitis 30–40% Chronic hepatitis 15–20%	Unknown	Exclude hepatitis A–E	Candidate virus is SEN virus

* Symptoms or signs of viral hepatitis, serum aminotransferase >2.5 × upper limit of normal, and absence of other causes of liver injury.
CDC Hepatitis Hotline: Automated telephone information system concerning modes of transmission, prevention, serologic diagnosis, statistics, and infection control 404-332-4555.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Intra-Abdominal Sepsis: Antibiotic Selection

I. **PERITONITIS**

A. **Recommended antibiotics for community-acquired intra-abdominal infections**

(Guidelines of the Infectious Diseases Society of America, CID—2003;37:997)

1. Single agent regimens

a. Beta-lactam-beta-lactamase inhibitors

- Ampicillin—sulbactam
- Piperacillin—tazobactam*
- Ticarcillin—clavulanate

b. Carbapenems

- Ertapenem
- Imipenem*
- Meropenem*

2. Combination regimens

a. Cephalosporin-based regimens

- Cefazolin or cefuroxime + metronidazole

- Cefotaxime, ceftriaxone, ceftizoxime, ceftazidime or cefepime + metronidazole*

b. Fluoroquinolone-based regimens

Ciprofloxacin, levofloxacin, moxifloxacin, or gatifloxacin, each in combination with metronidazole

c. Monobactam-based regimen

Aztrenam + metronidazole

B. **Miscellaneous recommendations**

1. Nosocomial intra-abdominal sepsis (healthcare associated): Anticipate resistant pathogens with emperic treatment including *P. aeruginosa Enterobacter*, MRSA, enterococci and *Candida.* Treatment should be based on local resistance patterns (emperic) and culture results (pathogen directed)
2. Anaerobes especially *B. fragilis*: Cefoxitin and cefotetan can no longer be recommended
3. Oral therapy of mixed infections:
    - Quinolone + metronidazole
    - Amoxicillin-clavulanate
4. Microbiology
    - Anaerobes: Culture and sensitivity testing is usually unnecessary. Resistance is increasing to clindamycin, cefoxitin, cefotetan, piperacillin, and fluoroquinolones. Consider in vitro sensitivity testing for anaerobes that persist, cause bacteremia, or require prolonged therapy
    - Blood cultures: Not generally recommended
    - Gram stain: Not recommended for community acquired infections. May be recommended for healthcare associated infections to detect MRSA and enterococci
5. Treatment of specific pathogens

Candida: Antifungal therapy is generally not warranted unless there is immunosuppression, transplantation or with post-op patient

Enterococcus: Community acquired infection—do not treat; healthcare associated—treat based on in vitro susceptibility tests

6. Biliary tract: Direct therapy at Enterobacteraceae, not enterococci; cover anaerobes only with bile duct—bowel anastomosis

7. Necrotizing pancreatitis: Antibiotics as advocated for intra-abdominal sepsis
8. Duration of antibiotics: Until clinical signs of infection resolve including fever and leukocytosis plus a functioning GI tract

C. **Monomicrobial infections**

1. Spontaneous peritonitis or "primary peritonitis" (Arch Intern Med 97:169, 1994)*
    a. Aztreonam 1 g IV q8h × 14 days ± agent for Gram-positive bacteria
    b. Cefotaxime 1.5–2.0 g IV q6h or ceftriaxone 1–2 gm IV qd, each ± ampicillin 2 g IV q6h × 14 days
    c. Ticarcillin-clavulanate 3 g IV q6h × 14 days
    d. Gentamicin or tobramycin 2 mg/kg IV, then 1.7 mg/kg q8h plus a beta-lactam:
        1. Cefoxitin 2 g IV q6h;
        2. cefotaxime 1.5–2.0 mg IV q6h; or
        3. piperacillin 4–5 g IV q6h × 14 days
2. *Candida peritonitis* (diagnostic criteria and indications to treat in absence of peritoneal dialysis are nebulous): Amphotericin B 200–1000 mg (total dose), 1 mg over 6 hr, then maintenance dose of 20–30 mg/d; utility of fluconazole is not established
3. Tuberculous peritonitis (see p 166)

II. **LOCALIZED INFECTIONS**

A. **Intra-abdominal abscess(es)** not further defined: Use regimens recommended for polymicrobial infections with peritonitis (See "I. Peritonitis" above).

B. **Liver Abscess**

1. Amebic

   a. ***Preferred***: Metronidazole 750 mg po or IV tid × 10 days plus diloxanide furoate, 500 mg po tid × 10 days or paromomycin 500 mg po bid × 7 days

   b. ***Alternative***: Emetine 1 mg/kg/d IM × 5 days (or dehydroemetine 1.0–1.5 mg/kg/d × 5 days) followed by chloroquine 500 mg po bid 2 days, then 250 mg po bid × 3 wk plus iodoquinol 650 mg po tid × 20 days

2. Pyogenic: Metronidazole plus ampicillin plus 1) an aminoglycoside, 2) third generation cephalosporin, or 3) aztreonam

C. **Biliary Tract Infections**

1. Cholecystitis

   a. ***Combination treatment***: Gentamicin or tobramycin 2.0 mg/kg IV then 1.7 mg/kg IV q8h plus ampicillin 2 g IV q6h, piperacillin 2–5 g IV q6h, or cefoperazone 1–2 g IV q12h*

   b. ***Single agent***: Cefoperazone 1–2 g IV q12h*. Ampicillin + sulbactam, 1–2 g (ampicillin) IV q6h; ticarcillin-clavulanate 3 g IV q6h; for mild infections the usual recommendation is cefazolin 1–2 g IM or IV q8h, or ampicillin 1–2 g IV q6h

   c. ***Medical Letter consultants*** (Med Lett, 41:95, 1999):

      1. Piperacillin or mezlocillin plus metronidazole,

      2. piperacillin-tazobactam or ampicillin-sulbactam ± aminoglycoside

2. Ascending cholangitis, empyema of the gallbladder, or emphysematous cholecystitis: Treat with regimens advocated for peritonitis or intra-abdominal abscess

D. **Appendicitis: Recommendations of the Surgical Infection Society** (*Arch Surg 127:83, 1992*)

Antibiotic treatment is started pre-op using regimens advocated for peritonitis (p 127)

1. Appendix is normal or inflamed but not perforated: Discontinue antibiotics
2. Gangrene or perforation: Continue antibiotics until clinical improvement with return of bowel function, patient is afebrile, and WBC is <12,000/mm^3

E. **Diverticulitis: Recommendations of the Surgical Infection Society** (*Arch Surg 127:83, 1992*)

1. Hospitalized patients: Use regimens advocated for peritonitis (p 267)
2. Outpatients:
    a. Amoxicillin + clavulanate
    b. Fluoroquinolone plus metronidazole
    c. Trimethoprim-sulfamethoxazole

Footnotes

*Includes severe infections

*Antibiotics should be adjusted according to sensitivities of implicated strain; rate of positive cultures is 30–40% with blood cultures, 40–65% routine culture of ascites fluid, and 90% with ascites fluid inoculated into blood culture bottles (Gastroenterology 95:1351, 1988).

*Other cephalosporins (second and third generation) are probably equally effective. Some authorities add ampicillin (1–2 g IV q6h) to cephalosporin-containing regimens.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Helicobacter pylori: Treatment of Peptic Ulcer Disease

HELICOBACTER PYLORI: TREATMENT OF PEPTIC ULCER DISEASE

(Adapted from Med Letter 1997;39:1; Ann Intern Med 1997;157:87)

Regimen		*Cost*	*Eradication rate*
Bismuth subsalicylate 2 tabs qid plus metronidazole 250 mg qid plus tetracycline 500 mg qid plus ranitidine 150 mg bid or omeprazole 20 mg bid	2 wk	$60	96%
Clarithromycin 500 mg tid plus omeprazole 40 mg qd then omeprazole 20 mg qd × 14 days	2 wk	$289	72%
Clarithromycin 500 mg bid plus metronidazole 500 mg bid or amoxicillin 1 g bid plus omeprazole 20 mg bid or lansoprazole 30 mg bid	10–14 days	$133–$204	89–91%
Clarithromycin 500 mg bid plus ranitidine 400 mg bid × 14 days then ranitidine 400 mg bid × 14 days		$234	NS
Bismuth subsalicylate 2 tabs qid plus metronidazole 500 mg tid plus tetracycline 500 mg qid	2 wk	$15	90%
Omeprazole 40–60 mg qd plus amoxicillin 500 mg tid plus metronidazole 500 mg bid	7 days	$111	84%

Editors: **Bartlett, John G.**
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Infectious Diarrhea

Source: Guidelines from Infectious Diseases Society of America (CID 2001;32:331.)

A. Antimicrobial Treatment

Microbial agent	***Preferred***	***Alternative****	***Comment***
BACTERIA *Aeromonas hydrophila*	Usually none; if treated: Sulfa-trimethoprim 1 DS bid × 3 days Ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 3 days	Tetracycline 500 mg po qid Y × 5 days Gentamicin 1.7 mg/kg IV q8h × 5 days	Efficacy of treatment not established and should be reserved forpatients with severe disease, immunosuppression, extraintestinal infection, or prolonged diarrhea
Campylobacter jejuni	Erythromycin 250–500 mg po qid × 5 days	Doxycycline 100 mg po bid × 7 days Furazolidone 100 mg po qid ×	May not alter course unless given early or for severe symptoms

		7 days Ciprofloxacin 500 mg po bid × 3–5 days	Indications include acutely ill, persistent fever, bloody diarrhea, >8 stools/day, dehydration, symptoms <4 days or to prevent transmission. Resistance to erythromycin has been described.Clinical course not altered in trials when treatment started >4 days after onset of symptoms Resistance: Fluoroquinolone resistance is an increasing problem in the U.S. and other parts of the world (NEJM 340:1525,1999). In Thailand, Spain, and Taiwan the rate of fluoroquin olone resistance is 60–80% (Emerg Infect Dis

			7:24, 2001)
Clostridium difficile	Metronidazole 500 mg po tid or 250 mg po qid× 10 days	Vancomycin 125 mg po q6h × 10–14 days Bacitracin 25,000 units po qid × 10–14 days	Diagnosis: standard is cytotoxin assay for toxin B (most sensitive)or EIA for toxin A and B (less sensitive but more rapid and more generally available) Metronidazole is preferred because of cost, comparable efficacy in clinical trials, and concern for vancomycin-resistant *E. faceum* in nosocomial cases Discontinuation of implicated antibiotic is often adequate. Some strains are resistant to metronidazole and bacitracin. Expected response is afebrile in 24 hr and resolution of diarrhea in mean of 4–5 days

			When oral treatment is not possible metronidazole 500 mg q8h IV(efficacy not established) Antiperistaltic agents: Contraindicated
Multiple relapses	Vancomycin or metronidazole (above doses; ×10 days, then cholestyramine 4 g po tid + lacto bacillus 1 g qid × 4–6 wk or vancomycin 125 mg po every other day × 4–6 wk)	Vanco 500 mg qid × 10 days, day 7 *Saccharomyces boulardii*500 mg bid × 4 wk Vanco or metro treatment, then lactobacillus GG ("Culturella") 75 mg bid ×1 mo IVIG 200–300 mg/kg q3wk	Frequency of relapse: 5–50% (average 25%) with any antibiotic treatment *S. boulardii* and lactobacillus GG are not FDA approved and are not readily available Experience with IVIG is limited but supported by studies showing importance of humoral immune response (NEJM 342:390, 2000;Lancet 357:189, 2001)

E. coli Enterotoxigenic *E. coli* (ETEC) and enteroadherent *E. coli* (EAEC)	Ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 3 days TMP-SMX DS po bid × 3 days	Trimethoprim 200 mg po bid × 3 days Bismuth subsalicylate 1048 mg qid × 5 days	Laboratory confirmation *E. coli*-associated diarrhea is usually unavailable Efficacy of antibiotic treatment established for ETEC (traveler's diarrhea) Diagnosis requires demonstration of LT or ST toxins (EIA, DNA probe, rabbit loop, etc). Many ETEC strains are now resistant to doxycycline and TMP-SMX (see traveler's diarrhea, pp 141–142)
Enterohemorrhagic *E. coli* (EHEC)	None	None	Diagnosis: Culture *E. coli* 0157:H7 using sorbitol—MacConkey agar; for non-0157 species test stool or supernatant with EIA for Shiga toxin Antibiotic treatment is contraindicated

			presumably because of increased toxin release with higher rate of HUS in children Life threatening complications: HUS Antiperistaltic agents: Contraindicated and TTP, esp at age extremes
Enteroinvasive *E. coli* (EIEC)	Usually none, if treated: Sulfa-trimethoprim, 1 DS po bid × 5 days Ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 5 days	Ampicillin 500 mg po or 1 g IV qid × 5 days	Presentation is dysentery as with *Shigella.* Efficacy of treatment not established
Enteropathogenic *E. coli* (EPEC)	Usually none, if treated: Sulfa-trimethoprim, 1 DS po bid × 3–5	Neomycin 50 mg/kg/d po × 3–5 days Furazolidone 100 mg po qid × 3–5 days	Efficacy of treatment not established. Sensitivity testing necessary

	days Ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 3 days		
Food poisoning: *Clostridium perfringens, S. aureus, Bacillus cereus, Listeria*	None		Self-limited and toxin-mediated: antimicrobial treatment is not indicated (see p 279)
Plesiomonas shigelloides	Usually none, but if treated: Sulfa-trimethoprim 1 DS po bid × 3 days Ciprofloxacin 500 mg po bid or ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 3 days	Tetracycline, 500 mg po qid × 5 days	Efficacy of treatment is not established and should be reserved for patients with extraintestinal infection, prolonged diarrhea, or immunosuppression
Salmonella typhi	Chloramphenicol 50 mg/kg/d IV× 10–14 days	Ceftriaxone 1–2 g/d IV× 10–14 days Sulfa-trimethoprim, 1–2 DS po	Steroids: For severe toxicity high-dose antibiotics plus

	Ciprofloxacin 500 mg po bid × 10–14 days	bid × 10–14 days	dexamethasone (3 mg/kg × 1, then 1 mg/kg q6h × 48 hr) or prednisone (60 mg/d with taper to 20 mg/d over 3 days) (NEJM 310:82, 1984)
Salmonella(other) Enteric fever (non-typhoid *Salmonella*) Metastatic infection Chronic bacteremia Enterocolitis in compromised host See comment	Usually none, if indicated: Fluoroquinolone: Ciprofloxacin 500 mg po bid; ofloxacin 300 mg po bid or norfloxacin 400 mg po bid × 5–7 days Cephalosporin: Ceftriaxone, 1–2 g/d IV up to 4 g/d × 14 days	Ampicillin 2–6 g/d po or IV × 14 days Amoxicillin 2–4 g/d po × 14 days Chloramphenicol 3–4 g/d IV or po × 14 days Sulfa-trimethoprim 1 DS po bid × 14 days	Antibiotic treatment is contraindicated except with the following: Severe disease, age > 50 yr, valvular heart disease, sever eatherosclerosis, malignancy, or uremia Duration: 5–7 days unless there is relapsing disease in compromised host—treat ≥14 days
Carrier (*S. typhi*)*	Amoxicillin 6 g/d po + probenecid 2 g/d × 6 wk Ciprofloxacin	Rifampin 300 mg bid + TMP-SMX 1 DS id × 6 wk	Definition of carrier: Positive cultures for 1 yr Cholecystectomy for

	500–750 mg po bid × 6 wk		cholelithiasis and carriers who relapse
Shigella	Ciprofloxacin 500 mg po bid or norfloxacin 400 mg po bid or ofloxacillin 300 mg po bid × 3 days Sulfa-trimethoprim 1 DS po bid × 3 days	Ampicillin 500 mg po or 1 g IV qid × 3–5 days Nalidixic acid 1 g po qid ×5–7 days Cefoperazone 1–2 g IV q12h × 5–7 days	Most important of bacterial enteric pathogens to treat because of severe disease and risk of transmission Ampicillin-resistant strains are common; for ampicillin-susceptible strains, amoxicillin should not be used Sulfa-trimethoprim resistance is increasing and is common in strains from some underdeveloped areas. Use only if susceptibility shown Ciprofloxacin in single, 1 g dose is effective for *Shigella*, other than *S. dysenteriae* (Ann Intern Med 117:727, 1992)

Vibrio cholerae	Tetracycline 500 mg po qid × 3 daysDoxycycline 300 mg po × 1 Sulfa-trimethoprim 1 DS po bid × 3 days Fluoroquinolone		Rare cause of travelers' diarrhea Oral rehydration often critical
Vibrio sp. (*V. parahaemolyticus, V. fluvialis, V. mimicus, V. hollisae, V. furnissii, V. vulnificus*)	Usually none, if indicated: Tetracycline (as above—see comment)	Ciprofloxacin 500 mg po bid × 5 days	Efficacy of treatment is not established and should be reserved for severe disease
Yersinia enterocolitica	Sulfa-trimethoprim 1 DS po bid × 3 days Gentamicin 1.7 mg/kg IV q8h × 3 days Ciprofloxacin 500–750 mg po bid × 3 days Doxycycline 100 mg po bid × 7 days		Efficacy of treatment for enterocolitis or mesenteric adenitis is not established, especially when instituted late; major indications are bacteremia or infection in compromised host Withhold desferoxamine
PARASITES Cryptosporidia	Usually none or symptomatic treatment:	Nitrazoxanide 500 mg bid (Unimed Pharmaceuticals, Buffalo Grove, IL)—not	Diagnosis: Stool for acid-fast stain or monoclonal

	Loperamide, lomotil etc plus nutritional support Compromised host: Paro-momycin 500 mg po tid × 7 days	approved by FDA Compromised host (AIDS): Paromomycin 1 g bid + azithromycin 600 mg po qd × 4 wk then paro-momycin 500 mg po tid	immunoflu-orescent stain; concentration techniques increase yield Treatment: Only for chronic diarrhea in compromised host. Paromomycin is only modestly effective (Am J Med 100:370, 1996) Main treatments in AIDS patient are supportive care and HAART Atovaquone or azithromycin as single agents have not shown good results
*Balantidium coli**	Tetracycline 500 mg po qid × 10 days	Iodoquinol 650 mg tid × 21 days Metronidazole 500 mg po tid × 10 days	No antimicrobial agent has established efficacy
*Cyclospora cayetanenis**		Trimethoprim-sulfamethoxazole 1 DS bid × 3 days	Treatment: Efficacy of TMP-SMX is established Diagnosis: Stool for

			acid-fast stain Reporting: Health departments that identify cases of *Cyclospora* infection should contact CDC 770-488-7760
*Blastocystis hominis** (see comments)	Metronidazole 1.5–2.0 g/d × 7 days	Iodoquinol 650 mg tid × 20 days	Role as enteric pathogen is unclear
Entamoeba histolytica	Metronidazole 750 mg po or IV tid × 5–10 days then iodoquinol 650 mg po tid × 21 days or paromomycin 500 mg tid × 7 days	Dehydroemetine 1.0–1.5 mg/kg/d IM × 5 days, then iodoquinol 650 mg po tid × 21 days	Diagnosis: Stool exam × 3 ± endoscopy with biopsy or scraping; serology (IHA) for colitis or hepatic disease. Patients with colitis or extraintestinal disease need drug for tissue phase (metronidazole or dehydroemetine), then a luminal agent (iodoquinol, or paromomycin)

Cyst passer			No need to treat because most cases are caused by nonpathogenic organisms now reclassified as *E. dispar*
Giardia lamblia (*G. intestinalis*)	Metronidazole, 250–750 mg po tid × 7–10 days	Quinacrine 100 mg po tid × 7–10 days Furazolidone 8 mg/kg/d po × 10 days Tinidazole 1.5–2.0 g single dose	Diagnosis: Stool EIA Metronidazole is less effective than quinacrine, but better GI tolerance and preferred for empiric therapy. Pregnancy: Consider paromomycin 25–30 mg/kg/d × 5–10 days
Isospora belli	Sulfa-trimethoprim, 2 DS po bid × 7–10 days	Pyrimethamine 25 mg + folinic acid, 5–10 mg/d × 1 mo	Diagnosis: Acid-fast stain of stool. Patients with AIDS and other immunosuppressive disorders usually require prolonged maintenance treatment

Microsporidia	Albendazole 400 mg po bid × 3 wk	—	Rare disease in immunocompetent host Response to albendazole is minimal; main treatment in patients with AIDS is support and HAART

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APPROACH TO INFECTION DIARRHEA

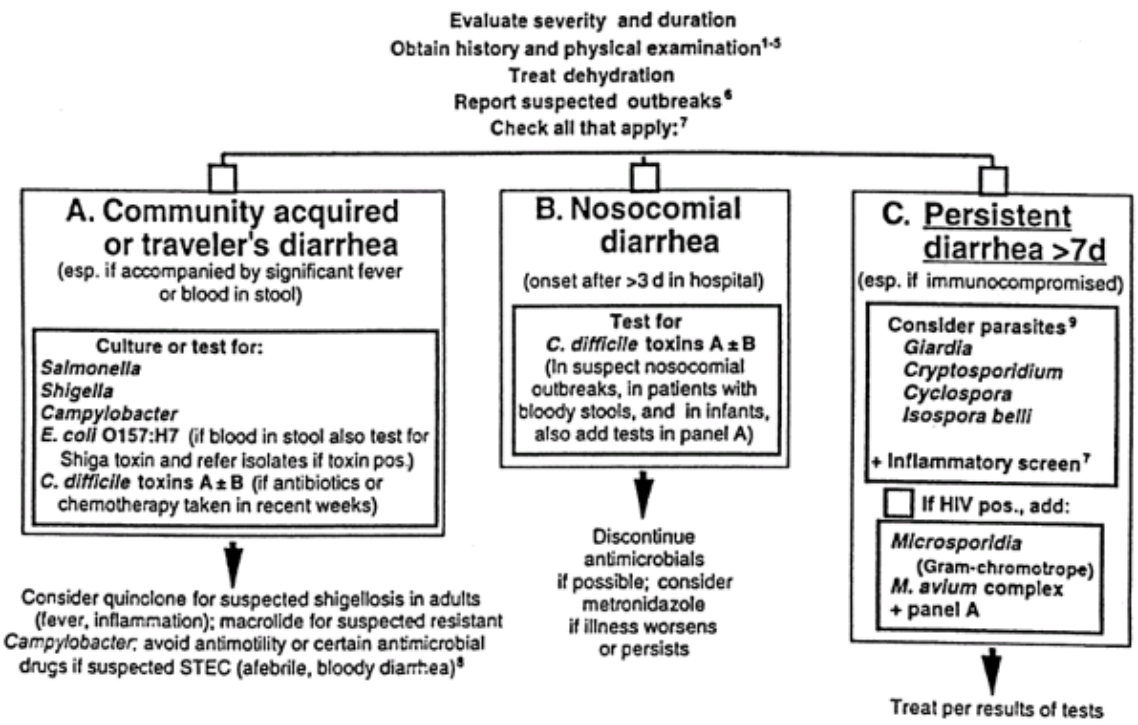

Figure. No caption available

Guidelines from the IDSA (CID 2001; 32:331). (Reprinted with permission)

1. Seafood exposure: culture for vibrio
2. Travelers diarrhea: evaluate if unresponsive to fluoroquinolone or TMP-SMX
3. Abdominal pain: Test for *Yersinia* and enterohemorrhagic *E. coli*
4. Proctitis in gay men: sigmoidoscopy
5. HUS: Test for enterohemorrhagic *E. coli*
6. Outbreaks: Notify health department

7. Fecal lactoferrin test or microscopy
8. Blood diarrhea: Some experts avoid antimicrobials
9. Common tests for parasites: Fluorescence and EIA for *Giardia* and Crypto-sporidium, Cyclospora or Mycobacteria; chromotrope of microsporidia

B. **Nonantibiotic Management**

1. Cholera-like illness: Oral rehydration therapy with Ceralyte, Pedialyte, or generic solutions prepared by mixing in 1L—3.5 g NaCl, 2.5 g $NaHCO_3$, 1.5 g KCl, and 20 g glucose
2. Foods matched to form of stool: Watery—soups, broth, yogurt, soft drinks, vegetables, fresh fruit, Jell-O ± saltine crackers; some form—rice, bread, baked potato, broiled fish or broiled chicken (avoid milk, fried food, spicy food)
3. Drugs: Antiperistaltics are contraindicated with diarrhea because of enterohemorrhagic *E. coli* or *Clostridium difficile*
    a. **Loperamide** 4 mg, then 2 mg/diarrheal stool up to 16 mg/d (avoid with fever and dysentery)
    b. **Diphenoxylate** (no more effective plus potential for opiate toxicity and anti-cholinergic effects)
    c. **Bismuth subsalicylate:** 30 mL (2 tabs) q 30 min × 8 doses, 1–2 days (good safety profile)
    d. **Attapulgite:** 1.2 g (30 cc) with each diarrheal stool up to 8.4 g (good safety profile and preferred to kaolin/pectin)

C. **Fecal Leukocyte Exam** (*Lactoferrin test or stool microscopy*)

Often present	***Variable***	***Not present***
Campylobacter jejuni	*Salmonella*	*Vibrio cholerae*

Shigella	*Yersinia*	Enteroadherent *E. coli*
Enteroinvasive *E. coli*	*Vibrio parahaemolyticus*	Enterotoxigenic *E. coli*
Exacerbations of inflammatory bowel disease	*C. difficile* *Aeromonas* *Plesiomonas* Enterohemorrhagic *E. coli**	Food poisoning: *S. aureus, B. Aeromonas cereus, C. perfringens* Viral gastroenteritis Parasitic infection: *Giardia, E. histolytica**, Cryptosporidia, *Isospora* Small bowel overgrowth "AIDS enteropathy"
* Frequently associated with blood.		

D. **Empiric Antibiotic Treatment** (IDSA Guidelines—CID 32:331, 2001)

1. Domestically acquired infectious diarrhea
    1. Acute diarrhea: Fever and acute diarrhea (nonbloody)—treat for shigellosis
    2. Chronic diarrhea: Diarrhea >10–14 days—treat for giardiasis
    3. Antibiotic treatment in these settings is arbitrary; antibiotic treatment with diarrhea caused by enterohemorrhagic *E. coli* may be harmful.
2. Travelers' diarrhea (CID 2000; 31:1079)
    1. Severity
        - Mild (1–2 stools/24 hr) no systemic sx: No therapy or loperamide or bismuth
        - Moderate (>2 stools/24 hr) + no systemic sx: Loperamide or bismuth

- Moderate (>2 stools/24 hr) + "distressing sx": Loperamide + fluoroquino-lone until diarrhea stops (up to 3 days)
- Severe (>6 stools/24 hr), fever and/or bloody stools: Fluoroquinolone for 1–3 days

3. Agents

- Loperamide 4 mg × 1 then 2 mg with each loose stool (≤16 mg/d) or bismuth subsalicylate (Pepto-Bismol 2 tabs qid, each loose stool)
- Antibiotic regimens: Norfloxacin 400 mg bid × 1–3 days or ciprofloxacin 500 mg bid × 1–3 days or levofloxacin 500 mg qd × 1–3 days
- Alternative antibiotics: TMP-SMX 2 DS × 1 or 1 DS bid × 3 days or azithromycin 1000 mg × 1 or 500 mg qd × 3 days

E. **Clinical Features of Diarrhea**

	Small bowel	***Colon***
Pathogens	*E. coli* (ETEC, EPEC, EAEC), cholera, *Salmonella*, viruses, *Cryptosporidium, Cyclospora, Giardia*	*Shigella, C. difficile, C. jejuni, E. coli* 0157:H7 Enteroinvasive *E. coli, Aeromonas*, *Yersinia, E. histolytica* *V. parahemolyticus*
Pain	Mid abdomen and modest	Lower abdomen with severe cramps Painful defecation
Stools	Watery, large volume	Bloody or mucoid, small volume and frequent

Stool WBC and RBC	Negative	WBC positive; *E. histolytica* and *E. coli* 0157:H7—bloody

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Foodborne Outbreaks

(Source: MMWR 2001;50(RR-2).)

Agent	*Incubation period*	*Syndrome*	*Confirmation**
BACTERIAL			
Bacillus anthracis	2 days–wk	Nausea, vomiting, bloody diarrhea, acute abd pain × wks	Blood culture
Bacillus cereus			
Vomiting toxin	1–6 hr	Vomiting ± diarrhea	Test stool or food for toxin
Diarrhea toxin	10–16 hr	Watery diarrhea ×	Test stool or food for

		24–48 hr	toxin
Brucella	7–21 days	Fever, headache, sweats, myalgias, diarrhea, bloody stools×wks	Blood culture and serology
C. jejuni	2–5 days	Diarrhea, abd pain, fever, vomiting × 2–10 days	Stool culture
C. botulinum	12–72 hr	Diploplia, blurred vision, descending paralysis—bilateral vomiting, diarrhea × days–months	Detect toxin in serum, stool, or food Detect *C. botulinum* in stool or food
C. perfringens	8–16 hr	Diarrhea, cramps × 24–48 hr	Isolate from stool ($>10^6$/g) or food ($>10^5$/g) Detect enterotoxin in stool
E. coli 0157:H7 (EHEC)	1–8 days	Diarrhea—often bloody, cramps no fever × 5–10 days	Stool culture for *E. coli* 0157:H7 or stool assay for Shiga toxin

Enterotoxigenic (ETEC)	days	1–3	Watery diarrhea, cramps, nausea × 5–10 days	Isolate ST or LT producing *E. coli* from stool
Listeria Invasive disease		2–6 wk	Meningitis, fever (elderly, compromised)	Isolate from normally sterile site—blood, CSF
Diarrhea		9–48 hr	Diarrhea, cramps, fever	Listerolysin O antibody
Salmonela Non-typhoid		1–3 days	Diarrhea, cramps, fever × 4–7 days	Stool culture
Salmonella typhi		3–60 days, usually 7–14	Fever, malaise, headache, chills	Stool culture
Shigella		24–48 hr	Diarrhea ± blood, cramps, fever × 4–7 days	Stool culture
S. aureus		1–6 hr	Vomiting, cramps ± diarrhea × 24–48 hr	Toxin/organism in stool, food, and vomitus

Streptococcus group A	1–4 days	Fever, pharyngitis	Isolate organism of same M or T type from ≥2 people
Vibrio cholera 01 or 0139	24–72 hr	Severe watery diarrhea ± vomiting × 2–5 days	Stool culture for *V. cholerae*
Vibrio parahemolyticus	2–48 hr	Diarrhea, cramps, vomiting × 2–5 days	Stool culture for *V. parahaemolyticus*
Vibrio vulnificus	1–7 days	Vomiting, diarrhea, cramps, bacteremia (esp liver disease and comp host) × 2–8 days	Stool and blood culture
Yersinia enterocoliticus	24–48 hr	Diarrhea and cramps Appendicitis-like symptoms with fever, abd pain × 1–3 wk	Isolate organism from stool or food
PARASITIC Cryptosporidia	2–28 days	Diarrhea, nausea, cramps ± fever × days–weeks	Detect organism in stool or food/water
Cyclospora	1–11 days	Protracted diarrhea, fatigue	Demonstrate organisms in stool

E. histolytica	2 days–4 wk	Bloody diarrhea, abd pain × months	Stool exam
Giardia	1–4 wk	Diarrhea, gas, cramps, nausea × wks	Demonstrate organism or antigen in stool
Toxoplasma gondii	6–10 days	Usually asymptomatic compromised host CNS, myo-carditis, pneumonia × months	Serology IgM
Trichinella	Intestinal phase 1–2 days Systemic phase 2–4 wk	Nausea, vomiting, diarrhea, cramps, then fever × mo	Positive serology or demonstrate larvae in muscle of patient or in meat sources; eosinophilia
VIRAL Hepatitis A	15–50 days, median 28 days	Fatigue, anorexia, nausea, jaundice, abnormal LFTs	Detect IgM, ALT
Norwalk agent	24–48 hr	Vomiting, cramps, watery diarrhea × 24–60 hr	Seroconversion

Astrovirus calicivirus	10–70 hr	Vomiting, cramps, diarrhea, headache fever × 2–9 days	Demonstrate virus by immune electron mi-croscopy, PCR, etc.
CHEMICAL Marine toxins Ciguatoxin (esp snapper, grouper, or barracuda)	2–6 hr	GI symptoms, then paresthesias lips, tongue, throat, extremities × days–wk	Demonstrate toxin in fish or typical presentation
Scromboid toxin (histamine)(mahi-mahi, scromboidei fish order)	1 min–3 hr usually <1 hr	Flushing, dizziness, burning mouth, headache, GI symptoms, urticaria, pruritis × 3–6 hr	Demonstrate histamine in food or typical presentation
Paralytic or neurotoxic shellfish poison	30 min–3 hr	Parenthesias of lips mouth, face extremities, GI symptoms × days, weakness, dyspnea	Detect toxin in food or water
Puffer fish	< 30 min	Parenthesias of lips mouth, face, ex-tremities, ascending paralysis, death in 4–6	Demonstrate toxin in fish or clinical presentation

		hr	
Heavy metal: Antimony, cadmium, copper, iron, tin, zinc	5 min–8 hr usually <1 hr	Vomiting and metallic taste ± diarrhea	Demonstrate metal in food
Monosodium glutamate (MSG)	3 min–2 hr usually < 1 hr extremities	Burning of chest, neck, abdomen, or	Clinical presentation plus ingestion of food with MSG
Mushroom toxins Short-acting	< 2 hr	Vomiting and diarrhea, confusion, salivation, hallucinations, visual problems, disulfiram reaction	Clinical syndrome in patients who have eaten mushrooms that represent toxic types
Longer-acting *Amanita* sp	6–24 hr	Diarrhea and cramps, × 24 hr, then hepatic and renal failure; often lethal	Clinical syndrome in patients who have ingested the implicated mushroom
Pesticides	Min–few hr	Nausea, vomiting, cramps, diarrhea, blurred vision, twitch-ing convulsions	Analysis of food and blood

Nitrite poisoning	1–2 hr	Nausea, vomiting, dizzy, weak, uncon-scious, chocolate-colored blood	Food analysis
Mercury	≥ 1 wk	Numbness, leg paresis, spastic paralysis, blindness	Analysis of blood and hair
Arsenic	Few hrs	Vomiting, diarrhea, cramps	Urine test
Shellfish toxins	Minutes–48 hr	GI symptoms, parethesis, CNS	Detect toxins in shellfish
Sodium floride	Minutes–2 hr	Soapy taste, vomiting, diarrhea, shock	Test vomitus and food

* Confirmation to implicate a cause of an outbreak usually requires documentation in ≥2 persons or demonstration of the organism or toxin in the implicated food.

FOODBORNE ILLNESS BY CLINICAL PRESENTATION

MMWR 2001;50(RR-2).

Watery diarrhea: ETEC, *V. cholera, enteric virus, Cryposporidium, Cyclospora*

Dysentery: *Shigella, Salmonella, C. jejuni, EIEC, EHEC, Vibrio parahaemolytica, Yersinia enterocolitica*

Persistent diarrhea (≥14 days): *Cyclospora, Cryptosporidium, E. histolytica, Giardia*

Neurologic syndromes (paresthesias, respiratory suppression): Botulism, poisoning by organophosphate pesticides, thallium, scombroid, ciguatera, tetrodon fish, neurotoxic shellfish, amnesic shellfish, mushroom poisoning, Guillain-Barré syndrome

Systemic illness: *Listeria, Brucella, Trichinella, Toxoplasma, V. vulnificans, hepatitis A*

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Urinary Tract Infections

I. Classicication based on guidelines established by the infectious Diseases Society of America *(CID 15:S216, 1992; CID 29:745, 1999)*

	Criteria for stated category		
Category	***Clinical***	***Laboratory[a]***	***Treatment***
Acute, uncomplicated UTI in women	Dysuria, urgency, frequency, suprapubic pain; no urinary symptoms in last 4 wk; no fever or flank pain	>10 WBC/mm^3 >10^3 cfu/mL uropathogen in MSU	All drugs active vs GNB show cure rates >80% Single dose: No longer favored 3-day treatment: Generally preferred. Expected cure rate[b];>85% at 5–9 days; >65% at 4–6 wk
Acute, uncomplicated	Fever, chills, dysuria, urgency,	>10 WBC/mm^3 >10^4 cfu/mL	Mild symptoms: Oral with agent active vs the

pyelonephritis	frequency, suprapubic pain, CVA tenderness, and/or flank pain Other diagnoses excluded. No history of urologic abnormalities	uropathogen in MSU	uropathogen Seriously ill: Parenteral therapy with agent active vs the uropathogen until afebrile 24–48 hr followed byoral agent × 2 wk total therapy. Expected cure rate[b]:>95% at 3–6 days, >80% at 5–9 days post treatment
UTI in male	Any combination of findings in above categories	>10 WBC/mm^3 >10^5 cfu/mL in MSU	UTI in men: Assume tissue invasion—renal or prostate Regimens: TMP-SMX, trimethoprim or fluoroquinolone for 2–6 wk Expected cure rate[b]: >90% at 3–5 days and 50% at 4–6 wk
Complicated UTI	Above × catheter associated, postvoiding residual>100 mL, calculi, azofemia, or reflux	As above	Regimen: Parenteral—oral or oral using agent active vs uropathogen × 2 wk. Expected cure rate[b]: >90% at 3–5 days, >65% at 5–9 days, and >40% at 4–6 wk
Asymptomatic	No urinary symptoms	>10 WBC/mm^3>	Indications for treatment: Pregnant women, diabetic

		10^5 cfu/mL uropathogen × 2 separated by 24 hr	patients, immunocompromised patients, and children Expected cure rates: >95% at 3–5 days, >75% at 5–9 days, and >50% at 4–6 wk

[a] WBC, white blood cells (unspun urine); MSU, midstream urine culture.

[b] Expected cure refers to eradication of uropathogen andelimination of symptoms. Data provided are expectations based on prior studies with evaluationsduring treatment at 5–9 days post-treatment and 4–6 wk post-treatment. Positive cultures post-treatment are classified as relapse (same strain), usually indicating renal or prostatic nidus of infection or reinfection indicating new uropathogen.

II. **Treatment of cystitis and pyelonephritis** Recommendations of SD Fihn (NEJM 2003;349:3.) and IDSA guidelines (CID 1999;29:745.)

A. **UNCOMPLICATED BACTERIAL CYSTITIS IN NON-PREGNANT WOMEN**

Based on recommendations of SD Fihn (NEJM 2003;349:3.)

1. **Diagnostic tests**: The urinary dipstick has largely replaced the urine culture and urine microscopy because it is cheaper, faster, and more convenient. The relative merits of these tests are summarized in the following table:

a. Diagnostic Tests

	Sensitivity	***Specificity***

Pyuria	95%	71%
Bacteria on Gram stain	40–70%	85–95%
Urinary dipstick	75%	82%
Urine culture	50%	High

Many patients do not need any testing, but can be managed by telephone consultation. Published protocols include women at low risk for complicated infection, who do not have symptoms suggesting vaginitis or cervicitis and in some cases are limited to women >55% years of age (Am J Med 1999;106:636.; Br J Gen Prat 2000;50:635.; J Fam Pract 2001;50:589.).

2. Treatment: (see table below) TMP-SMX for three days results in sterile urine within seven days and about 94%; longer courses do not improve efficacy and increase side effects while the single dose is less effective (CID 1999;29:745.). The alternative for patients with sulfa allergy is trimethoprim, but this may also cause hypersensitivity, and TMP rashes are commonly misidentified as sulfa reactions in patients who get TMP-SMX (Allergy 1992;47:340.). In some areas the pathogens cultured from urine in acute cystitis show rates of TMP-SMX resistance of up to 18% (JAMA 1999;281:736.; NEJM 2001;345:1007.), especially if this drug has been given within the previous six months (J Gen Intern Med 1999;14:606.). The recommendation is to use alternative drugs if the patient has recently received antibiotics or if the local prevalence of urinary isolates exceeds 15–20%. Nevertheless, clinical and bacteriologic cure rates of 80–85% are expected even when the resistance rates approach 30% (Ann Intern Med 2001;135:41.). The major alternative is a fluoroquinolone, but it is not considered “first line” because of its high cost and concern for abuse. Nitrofurantoin is another option, preferably using the

monohydrate macrocrystal formulation because it is taken just twice daily and causes less GI toxicity compared to the macrocrystalline formulation. This drug may assume more importance if there is increasing resistance to fluoroquinolones. Fosfomycin is less effective than the other agents and should only be used when the others cannot be used (CID 1999;29:745.). The expected response rate is symptom relief in 90% within 72 hours and negative cultures (if done)at 7 days in over 90%. Severe dysuria may be treated with phenazopyridine (Pyridium or Uristat) which is now available over-the-counter. Routine follow-up including urine culture is generally not necessary.

3. **Regimens**:

Agent	***Retail Cost***	***Pregnancy Rating***	***Major ADRs***
Acute uncomplicated cystits			
TMP/SMX 1 DS bid × 3 d	$2	C	GI intol, rash
Trimethoprim 100 mg bid × 3 d	$4	C	GI intol
Norfloxacin 250 mg bid × 3 d	$25	C	Dizzy, GI intol, vaginitis
Levofloxacin 250 mg qd × 3 d	$44	C	As above
Ciprofloxacin 250 mg bid × 3	$54	C	As above

d			
Gatifloxacin 400 mg qd × 3 d or 400 mg × 1	$22 $8	C	As above
Nitrofurantoin monohydrate macrocrystals 100 mg bid × 7 d	$30	B	GI intol, pulmonary and liver toxicity
Fosfomycin 3 g po × 1	$34	B	GI intol

B. **PYELONEPHRITIS**

1. **Agent**

a. Oral therapy

Oral agent	*Comment*
Fluoroquinolone	Preferred oral agent for empiric treatment
TMP-SMX	Preferred if pathogen is known to be sensitive

b. Single parenteral dose followed by oral agent Parenteral agent: Ceftriaxone, gentamicin, or fluoroquinolone

Oral agent	*Comment*
Gram-positive pathogen	Amoxicillin or amoxicillin-clavulanate
Gram-negative pathogen	Base on in vitro susceptibility tests

c. Hospitalized patients: Parenteral therapy

Parenteral fluoroquinolone (ciprofloxacin was superior to TMP-SMX in terms of

clinical response, bacteriologic response, and side effects (JAMA 283:1583, 2000))

Aminoglycoside ± ampicillin

Parenteral extended spectrum cephalosporin ± aminoglycoside

Gram-positive pathogen: Ampicillin-sulbactam ± aminoglycoside

After afebrile 48–72 hr: Oral agent based on susceptibility tests

GNB: Fluoroquinolone or TMP-SMX

GPC: Amoxicillin or amoxicillin-clavulanate

2. **Duration**: 14 days; 7 days may be adequate in mild or moderately severe case (JAMA 283:1583,2000)

C. **MANAGEMENT OF BLADDER CATHETER** (Infect Dis Clin Pract 1995;4:446.)

Incidence of infection: 3–10%/day

Prevention

Prevention of infection: Maintain closed system

Prevention of complications of bacteruria: Antibiotics are ineffective

Prevention of catheterization: Condom catheters; intermittent catheterization ± instillations of povidone-iodine and chlorhexidine; suprapubic catheterization

Treatment: Treat only symptomatic infections (fever and/or signs of bacteremia)(symptoms are rare in this population—Ann Intern Med 160:668, 2000)

Treat 7–10 days: Parenteral or oral antimicrobial

D. PROSTATITIS (Guidelines of Assoc Genitourinary Med Society of Venereal Disease London 2002)

1. **Acute prostatitis**

a. Diagnosis: Midstream urine culture and blood culture; do not do prostatic massage

(Pathogens are virtually always in urine)

b. Treatment

    1. Initial antibiotic treatment: Cefotaxime or ceftriaxone + gentamicin—switch to pathogen-specific therapy when sensitivity data available

    2. Oral antibiotics: Switch to oral agent when clinically improved. Usual agent: Ciprofloxacin; alternative: TMP-SMX or trimethoprim × 28 days.

    3. Adjunctive treatment: Catheterize for urinary retention, hydration, analgesics (NSAIDs)

c. Failure to respond: Possible prostatic abscess—transrectal ultrasound or CT scan. Treatment—perineal or transurethral drainage

2. **Chronic prostatitis**

Diagnosis: Symptoms ≥6 months.

Urinary localization procedure (Not often done)

- Patient preparation: No antibiotics × 1 month, no ejaculation × 2 days and no distended bladder
- Specimens: 5–10 mL first voided urine (VB#1), void 100–200 mL then midstream(VB#2), vigorous prostatic massage × 1 minute, then post prostatic massage (PPM) urine of 5–10 mL (VB#3). All three samples have microscopy and quantitative urine cultures.
- Interpretation

    1. Bacterial infection: Culture of VB#3 ≥10 × that of VB#2 and VB#1 Dx: "chronic bacterial prostititis"

    2. Inflammation: >10 PMNs/HPF in prostatic massage specimen or in VB#3. Dx: "Chronic bacterial prostatitis" or "chronic abacterial prostatitis/chronic pelvic pain syndrome—inflammatory"

3. Culture and WBC assessment are negative. Dx: “Chronic abacterial prostatitis/chronicpelvic pain syndrome—inflammatory”.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Sexually transmitted diseases

Recommendations from the CDC (MMWR 2002;51:RR-6.)

I. ***Neisseria gonorrhoeae*** **(Gonococcal Infections)**

A. **Treatment Recommendations for Uncomplicated Localized Infections (urethral, endocervical, and rectal)** (CID 1995;20:S47.; Med Lett 1995;37:117.)

- Ceftriaxone 125 mg IM × 1 or
- Ciprofloxacin* 500 mg po × 1 or
- Ofloxacin* 400 mg po × 1 or
- Levofloxacin 250 mg × 1 or
- Cefixime 400 mg po × 1

All of the above should be combined with treatment for *C. trachomatis* unless this has been ruled out: Doxycycline 100 mg po bid × 7 days; azithromycin (1 g po × 1) is an alternative.

Alternative: 1) Spectinomycin 2 g IM × 1. (Spectomycin may not be commercially available), 2) Cefotaxime 500 mg IM, 3) Gatifloxacin 400 mg po × 1 or norfloxacin 800 mg po. Azithromycin in a dose of 2 g is effective treatment for both gonorrhea and *C. trachomatis*, but GI side effects are frequent, cost is high, and gonococcal cure rates are relatively low (93%)

B. **Special Considerations**

1. Syphilis: All patients with gonorrhea should be screened for syphilis at initial visit. Regimens with ceftriaxone or a 7-day course of doxycycline or erythromycin may cure incubating syphilis.
2. Follow-up: Patients who respond need no follow-up. Patients with persistent symptoms should have

culture for *N. gonorrhoeae* and in vitro susceptibility testing; mostare due to re-infection, indicating need for partner referral or nongonococcal urethritis. Expected response rate ≥95%.

3. Infection control: Patients should avoid sexual intercourse until the patient and partner (see below) are cured. This means no sexual contact until therapy is completed *and* both are asymptomatic.
4. Sex partners: Partners should be referred for evaluation and treatment of *N. gonorrhoeae* and *C. trachomatis.* This includes sex partners within 30 days for symptomatic infection and those within 60 days for asymptomatic infection.
5. Reporting: All states require reporting of *N. gonorrhoeae.*
6. Pregnancy: Quinolones and tetracyclines are contraindicated. For *N. gonorrhoeaea* a cephalosporin or spectinomycin is preferred. For *C. tracho matis*, amoxicillin or erythromycin is preferred.
7. HIV infection: Standard recommendations apply.

C. *Gonococcal Infections at Selected Sites**

1. Pharyngitis: Ceftriaxone 125 mg IM or ciprofloxacin 500 mg po (both withdoxycycline 100 mg po bid × 7 days) or azithromycin 1 g po
2. Conjunctivitis*: Ceftriaxone 1 g IM × 1 plus lavage of infected eye × 1
3. Disseminated gonococcal infections*
    a. Hospitalization is recommended, especially for noncompliant patients, uncertain diagnosis, patients with purulent synovial effusions, or other complications.
    b. Recommended treatment: Ceftriaxone 1 g IV or IM daily

        Alternative regimens: Cefotaxime 1 g IV q8h or ceftizoxime 1 g IV q8h,

        ciprofloxacin 400 mg IV q12h, ofloxacin 400 mg IV q12h, levofloxacin 250 mg IV/d, or spectinomycin 2 g IM q12h

        Duration of parenteral treatment: 24–48 hr after symptoms resolve, then cefixime 400 mg po bid, ciprofloxacin 500 mg po bid, ofloxacin 500 mg po bid, or levofloxacin 500 mg po qd

        Duration of oral treatment: To complete a full week of antibiotic treatment
4. Meningitis*: Ceftriaxone 2 gm IV q12h × 10–14 days

5. Endocarditis*: Ceftriaxone 2 gm IV qd × 4 wk
6. Salpingitis: See pelvic inflammatory disease

II. Syphilis

A. Classification

1. Primary: Ulcer or chancre at site of infection
2. Secondary: Rash, mucocutaneous lesions, adenopathy
3. Tertiary (late): Cardiac, neurologic, ophthalmic, auditory, or gummatous lesions
4. Latent syphilis: No evidence of disease

   Early latent: Acquired syphilis within 1 yr based on seroconversion ≥4–fold increase in titer, history of primary or secondary syphilis, or sex partner with primary, secondary, or early latent syphilis

   Late latent: Infection >1 yr; syphilis of unknown duration should be managed as late latent syphilis

B. Diagnosis

1. Direct exam (lesion exudate or tissue): Dark-field or direct fluorescent antibody tests
2. Serology: Requires treponemal and nontreponemal tests for diagnosis
   a. ***Treponemal***: Fluorescent treponemal antibody absorbed FTA-ABS or microhemagglutinin for antibody (MHATP). Reported as reactive or nonreactive, titers do not correlate with assay disease activity; patients who react usually remain reactive for life regardless of treatment or disease activity
   b. ***Nontreponemal***: Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR). Results should be reported quantitatively. Titers correlate with disease activity. 4-fold changes in titer are required to demonstrate a significant difference. Sequential tests should be done in the same lab. VDRL and RPR are equally valid, although quantitative results cannot be directly compared. It is expected that this test will become nonreactive with treatment, but some stay reactive for long periods, e.g., serofast reaction
   c. ***Neurosyphilis***:

      (1) Positive CSF VDRL or RPR is considered diagnostic if specimen is not contaminated with blood. This test is negative in about one-third with neurosyphilis. Some advocate CSF FTA-ABS, which is less specific but thought to be highly sensitive

(2) CSF leukocytosis (>5 WBC/mm^3) is expected in active neurosyphilis and is a sensitive measure of effectiveness of therapy

d. ***HIV***: Standard serologic tests are usually accurate but rare false negatives are reported. There is an increased risk of neurosyphilis

C. **Treatment**: Penicillin G is preferred for all stages

1. **Primary and secondary**

a. Benzathine penicillin G 2.4 mil units IM × 1

b. Follow-up: Patients should be re-examined clinically and serologically at 6 and12 mo. Patients with HIV should have evaluations at 2, 3, 6, 9, 12 and 24 mo ± LP at 6 mo. Treatment failure or reinfection is diagnosed if symptoms persist, symptoms recur, or 4-fold increase in VDRL or RPR titer by 6–12 mo: 1) Evaluate for HIV, 2) perform LP, and 3) retreat with benzathine penicillin 2.4 mil units IM × 3 (weekly)

c. If titer does not decrease by 4-fold at 6 mo then 1) evaluate for HIV, 2) follow-up clinical and serologic exams at 6 mo (3-mo intervals for HIV-infected patients), and 3) retreat if follow-up cannot be assured—benzathine penicillin 2.4 mil units IM × 3 (weekly)

d. HIV serology: Indicated in all patients with syphilis; patients in high prevalence areas for HIV should be retested at 3 mo

e. LP: Indicated in primary and secondary syphilis only if there are clinical signs and symptoms of neurologic involvement (ophthalmic, auditory symptoms, cranial nerve palsies) or with therapeutic failures

Ophthalmic disease (uveitis): Slit lamp exam

f. Penicillin allergy:

Doxycycline 100 mg po bid × 2 wk or tetracycline 500 mg po qid × 2 wk

Intolerance to tetracyclines (acceptable only in HIV-negative patients):

Erythromycin 500 mg po qid × 2 wk or ceftriaxone 1 g/d for 8- to 10-day course

Pregnancy: Skin test; if positive, desensitize and treat with penicillin*

g. HIV infection: Benzathine penicillin G: 2.4 mil units ×1

h. Jarisch-Herxheimer reaction: Acute febrile reaction accompanied by head ache and myalgias. There are no proven methods to prevent this. Anti pyretics are recommended for treatment. The reaction may induce early labor and cause fetal distress in pregnant women

2. **Latent syphilis** (see "Classification" above)

   a. Early latent (syphilis >1 yr): Diagnosis—documented seroconversion, unequivocal history of primary or secondary syphilis >1 yr previously or sex partner with syphilis>1 yr. Treatment: Benzathine penicillin G 2.4 mil units IM × 1; penicillin allergy, doxycycline 100 mg bid × 4 wk

   b. Late latent (syphilis >1 yr or unknown duration): Benzathine penicillin G 2.4 mil units IM × 3 at weekly intervals; penicillin allergy, doxycycline 100 mg bid × 4 wk

   c. Follow-up: VDRL or RPR at 6, 12, and 24 mo. Patients who develop signs or symptoms of syphilis have a 4-fold increase in titer or an initial titer of ≥1:32 that fails to decrease 4-fold in 12–24 mo should have LP and be retreated

   d. Indications for LP:

      - Neurologic or ophthalmic signs or symptoms (ophthalmic, auditory, cranial nerve symptoms)
      - Other evidence of active disease (aortitis, gumma, iritis, etc)
      - Treatment failure
      - HIV infection

      - Infection >1 yr or unknown duration plus titer ≥1:32
      - Infection >1 yr or unknown duration and nonpenicillin treatment planned

   e. HIV serology: Advocated for all syphilis patients

   f. Penicillin allergy (nonpregnant patients)

      - Infection >1 yr: Doxycycline 100 mg po bid or tetracycline 500 mg po qid × 2 wk
      - Infection >1 yr or unknown duration: Doxycycline 100 mg po bid or tetracycline 500 mg po qid × 4 wk
      - Pregnancy: Skin test; if positive, desensitize and treat with penicillin* (MMWR 1993;42(RR-14):44.)

g. HIV infection: LP, if normal—benzathine penicillin 2.4 mil units IM × 3 (weekly)

h. Evaluation: Patients with latent syphilis should be evaluated for tertiary disease—aortitis, neurosyphilis, gummas, or iritis

3. **Neurosyphilis and ocular syphilis**

   a. Preferred: Aqueous penicillin G 12–24 mil units/d given as 3–4 mil units q4h × 10–14 days

   b. Alternative if outpatient compliance is assured: Procaine penicillin IM 2.4 mil units/d plus probenecid 500 mg po q6h for 10–14 days

   c. Penicillin allergy:

      - Ceftriaxone 2 g/d IV or IM × 10–14 days
      - Skin test; if positive, desensitize and treat with penicillin*

   d. Follow-up: If CSF initially showed pleocytosis, repeat LP q6mo until normal. Also evaluate CSF VDRL and protein, but these respond less rapidly and are of less certain significance. If cell count has not decreased by 6 mo or CSF is abnormal at 2 yr then retreat.

4. Late syphilis (other than neurosyphilis): Gumma, cardiovascular syphilis, etc

   LP: All patients

   Benzathine penicillin 2.4 mil units × 3 at weekly intervals

   Penicillin allergy: Doxycycline 100 mg po bid × 4 wk

D. **Sex partners**

1. Patients sexually exposed to primary secondary or early latent syphilis should be evaluated clinically and serologically: Contacts should be treated if seropositive or if seronegative and exposed <90 days. Presumptive treatment should also be given if exposure was >90 days, serologic test results are unavailable, and source had primary, secondary, or early latent syphilis. Patients with syphilis of unknown duration with a nontreponemal test titer of × 1:32 are considered to have early syphilis for purposes of partner notification

2. Long-term partners of patients with late syphilis should be evaluated clinically and serologically

3. Time periods used to identify at-risk sex partners are 3 mo plus duration of symptoms for primary syphilis, 6 mo plus duration of symptoms for secondary syphilis, and 1 yr for early latent syphilis

E. **Pregnancy**

1. Testing: All women should have screening tests for syphilis in early pregnancy; this should be repeated at 28 wk and at delivery in areas of high prevalence or women with high risk
2. Treatment: Penicillin regimens as summarized above. Penicillin allergy: skin test and desensitize if positive. Note: Some experts recommend a second dose of benzathine penicillin2.4 mil units at 1 wk for pregnant women with primary, secondary, or early latent syphilis
3. Jarish-Herxheimer reaction: Pregnant women treated for syphilis in the second half of pregnancy who have a Jarish-Herxheimer reaction have increased risk of premature labor and fetal distress

MANAGEMENT OF SYPHILIS: SUMMARY

Form	*Initial treatment*	*LP*	*Follow-up VDRL/RPR*	*Expectation VDRL/RPR*	*Indications to retreat*
Primary syphilis	Initial: Benzathine penicillin 2.4 mil units IM × 1 Retreatment: Benzathine penicillin 2.4 mil units IM × 3 (weekly)	Neuro symptoms Treatment failure	3 and 6 mo HIV: 2,3,6,9, 12 and 24 mo	4-fold decrease at 3 mo	Titer increases 4-fold Titer fails to decrease 4-fold at 3 mo + noncompliance or HIV infection Symptoms persist or recur
Secondary syphilis	Initial: Benzathine penicillin 2.4 mil units IM × 1 Retreatment: Benzathine penicillin 2.4 mil units IM × 3 (weekly)	Neuro symptoms Treatment failure	3 and 6 mo HIV: 2,3,6,9, and 12 mo	4-fold decrease at 6 mo	Titer increases 4-fold Titer fails to decrease 4-fold at 6 mo + noncompliance or HIV infection Symptoms persist or recur
Early latent (<1 yr)	Initial: Benzathine	Neuro symptoms	6, 12 mo and q6mo	4-fold decrease if	Titer increases 4-fold

III. Chlamydia Trachomatis (MMWR 1993;42(RR-12).)

A. Spectrum of disease

- Men: Nongonococcal urethritis, epididymitis, proctitis, and proctocolitis (renal intercourse)
- Women: Mucopurulent cervicitis, salpingitis (PID), postpartum endometritis, cystitis (acute dysuria-pyuria or urethral syndrome), perihepatitis (Fitz-Hugh-Curtis syndrome), proctitis, and proctocolitis
- Infants (postexposure): Conjunctivitis and pneumonitis
- Miscellaneous: Reiter's syndrome (reactive arthritis, conjunctivitis, and urethritis), chronic conjunctivitis, pharyngeal colonization (but not pharyngitis)

B. Screening candidates

- Mucopurulent cervicitis
- Sexually active women <20 yr
- Women 20–24 yr who meet the following criteria and those >24 yr who meet both criteria: Inconsistent use of barrier contraceptives or new or >1 sex partner in past 3 mo
- Pregnant females during third trimester

Screening women is the major element of a chlamydial prevention program.

Verification of initial positive test should be performed if the test was not a positive culture and the patient is considered low risk.

C. Detection

1. Polymerase chain reaction (PCR) (Roche Molecular Systems, Branchburg, NJ) and ligase chain reaction (LCR) (Abbott Laboratories, Abbott Park, IL). These assays require about 8 hr and show sensitivity of 86–98%; specificity is 99–100%, and they can be performed on urine. The cost is $14–28/specimen (although commercial labs charge more)
2. Conditions that warrant presumptive diagnosis of chlamydial infection*

Condition	*Chlamydia patients*	*Prevalence in partners*
Nongonococcal urethritis	30–40%	10–43%
Pelvic inflammatory disease	8–54%	36%
Epididymitis (<35 yr)	50%	10–43%
Gonococcal infection: Men	5–30%	40%
Gonococcal infection: Women	25–50%	Unknown

3. Conditions that may not warrant presumptive diagnosis of chlamydial infection

Condition	*Chlamydia patients*	*Prevalence in partners*
Mucopurulent cervicitis	9–51%	2–27%
Proctitis (homosexual men)	8–16%	Unknown
Acute urethral syndrome	13–63%	Unknown

D. Treatment (CID 1995;20:S66.)

1. Preferred*

- Azithromycin 1 g po × 1 day
- Doxycycline 100 mg po bid × 7 days (contraindicated in pregnancy and growing children)

2. Alternatives
   - Levofloxacin 500 mg po qd × 7 days or ofloxacin 300 mg po bid × 7 days (Both are contraindicated in pregnancy and children > 17 yr)
   - Erythromycin ethylsuccinate 800 mg po qid × 7 days
   - Erythromycin base 500 mg po qid × 7 days
3. Pregnancy

   Preferred: Erythromycin base 500 mg po qid × 7 days or amoxicillin 500 mg po tid × 7 days
   - Erythromycin ethylsuccinate 800 mg po qid × 7 days or
   - Erythromycin ethylsuccinate 400 mg po qid × 14 days or
   - If amoxicillin or erythromycin not tolerated: Azithromycin 1 g po
4. HIV infection: As above

E. **Follow-up:** Not indicated unless symptoms persist or recur or erythromycin is used. Failure rates with doxycycline regimen are 0–3% for men and 0–8% for women.

F. **Disease prevention:** Patient should avoid sex for 7 days from initiation of treatment, and until all partners are treated and cured

G. **Partner referral:** Evaluation and treatment of partners within 60 days. Last sex partner should be evaluated, tested, and treated regardless of the time interval

H. **Reporting:** *C. trachomatis* has required reporting in most states

I. **Prevention of ophthalmic neonatorum** (***N. gonorrhoeae and C. trachomatis***): Instill into the eye <1 hr after birth: Silver nitrate (1%) aqueous solution ×1or erythromycin (0.5%) ophthalmic ointment ×1

IV. Lymphogranuloma Venereum

A. **Agent**: Biovar (strain) of *C. trachomatis*, invasive serotypes L1, L2, L3

B. **Symptoms**: Tender inguinal and/or femoral lymphadenopathy; protocolitis in women and gay men

C. **Diagnosis**: Serology: CF titer ≥1:64

D. **Treatment**:

1. Drainage: Bubos may require incision or aspiration
2. Preferred antibiotic: Doxycycline 100 mg po bid × 21 days
3. Alternatives: Erythromycin 500 mg po qid × 21 days

   Expected responses: 50% have healed ulcers at 7 days, 80% at 14 days, and 100% at 28 days. Relapse rate is 3–5%
4. Pregnancy: Use erythromycin regimen

5. Sex partners: Examine and treat partners of 30 days prior to onset of symptoms
6. HIV infection: As above

E. **Sex Partners**: Examine, test, and treat partners within 30 days

F. **Reporting**: Required in most states

V. Genital Herpes Simplex

A. Treatment

	Duration	Acyclovir	Valacyclovir	Famciclovir
First episode	7–10 days	400 mg tid	1 g bid	250 mg tid
Recurrent	5 days	400 mg tid or 800 mg bid	500 mg bid	125 mg bid
Suppressive	>5 yr	400 mg bid	500 mg qd or 1 g/d	250 mg bid
Severe disease	2–7 days*	5–10 mg/kg IV q8h		
* Then oral therapy to complete 10 days				

1. First episode: Acyclovir treatment shortens duration of pain, viral shedding, and systemic symptoms. Treatment has no effect on rate or frequency of relapses
2. Recurrent episodes: Should be started with the prodrome or within 1 day of onset of lesions
3. Prophylaxis: Consider with > 6 recurrences/yr: Safety and efficacy are documented for continuous prophylaxis up to 10 yr without cumulative toxicity or risk of resistance (JID 1994;169:1338.). There is also a significant reduction in viral shedding. Suppressive treatment is contra indicated in pregnancy
4. HIV infection

	Duration	Acyclovir	Valacyclovir	Famciclovir
Recurrent	5–10 days	400 mg tid	1 g bid	500 mg bid

Suppression	—	400–800 mg 2–3 ×/d	500 mg bid	500 mg bid

5. Pregnancy: Registry to report exposure experiences with acyclovir or valacyclovir: 800-722-9292, ext 58465. To date the experience shows no risk to the infant with 601 exposures to acyclovir; this sample size is adequate to detect a 2-fold teratogenic risk over the 3% baseline rate of birth defects (MMWR 1993;42:806.). There are sparse data about famciclovir or valacyclovir in pregnant women, so acyclovir is preferred. Indications for acyclovir in pregnancy:
    - First episode of genital herpes
    - Severe genital HSV or extragenital HSV disease (encephalitis, disseminated disease, etc.)
6. Perinatal infections: Most perinatal HSV infections occur with mothers who have no history of HSV. Risk of transmission is highest with delivery at the time the mother has primary HSV (30–50%); risk with recurrent HSV at the time of delivery is about 3%. Women at risk (HSV negative pregnant woman and HSV infected partner) should be warned of risk of unprotected sexual contact in late pregnancy

B. **Management of pregnancies complicated by genital herpes simplex**
    1. No signs of genital HSV at onset of delivery—vaginal delivery
    2. HSV lesions at onset of labor—most recommend C-section
    3. eSvere genital HSV during pregnancy—oral or IV acyclovir
C. **Neonatal herpes**: Treat infant with acyclovir 30–60 mg/kg/d ×10–21 days

VI. **Chancroid**

A. **Agent**: *Haemophilus ducreyi*

B. **Clinical features**: Painful genital ulcers ± tender inguinal adenopathy with or without suppuration; uncommon in U.S. (MMWR 1995;44:567.)

C. **Diagnosis**: Culture requires specialized media that are not commercially available. Even with these media, the yield is <80%. PCR may soon be available. Presumptive diagnosis: Typical clinical findings plus no evidence of syphilis (dark-field of lesion exudate or negative serology at least 7 days after onset of ulcer) and atypical for herpes simplex or negative tests for herpes simplex. Presence of suppurative inguinal

adenopathy is nearly diagnostic

D. **Treatment** (CID 1995;20:539.)

1. Preferred:
   - Azithromycin 1 g po × 1 or
   - Ceftriaxone 250 mg IM × 1 or
   - Erythromycin base 500 mg po qid × 7 days
   - Ciprofloxacin 500 mg po bid × 3 days (contraindicated in pregnant or lactating women and with age <18 yr)
2. Alternatives: None
3. HIV infection: All regimens are less effective—azithromycin and multiple dose regimens are preferred (STD 1994;21:231.)

E. **Follow-up**: Symptoms improve within 3 days, and objective improvement is seen within 7 days. Examine 3–7 days after treatment. If not improved, consider wrong diagnosis, co-infection (10% coinfected with HSV or *T. pallidum*), HIV infection, noncompliance, *H. ducreyi*, resistance to (rare with recommended treatments), need for needle aspiration of fluctuant adenopathy.

F. **Partner referral**: Examine and treat partners <10 days

G. **HIV infection**: Longer treatment or close follow-up

VII. **Granuloma inguinale (Donovanosis)**

A. **Agent**: *Calymmatobacterium granulomatis*

B. **Geography**: Rare in U.S.; endemic in India, Australia, South Africa, New Guinea

C. **Clinical presentation**: Painless, progressive genital ulcer that is highly vascularized (beefy red) and bleeds easily

D. **Treatment**

- Trimethoprim-sulfamethoxazole 1 DS bid until healed (≥21 days)
- Doxycycline 100 mg bid until healed (≥21 days)
- Alternative: Ciprofloxacin 750 mg bid × 21 days, erythromycin 500 mg po qid × 21 days, or azithromycin 1 g/wk × 3

E. **Sex partners**: Examine partners within 60 days and treat those with symptoms

F. **Pregnancy**: Erythromycin ±aminoglycoside (gentamicin)

G. **HIV infection**: Consider adding gentamicin to treatment regimen

VIII. **Pediculosis Pubis (Pubic Lice)**

A. **Teatment**

- Permethrin (1%) cream rinse (Nix) applied to affected area and washed after 10 min or
- Lindane (1%) shampoo applied 4 min and then thoroughly washed off (not recommended for pregnant or lactating women) or
- Pyrethrins and piperonyl butoxide (nonprescription) applied to affected areas and washed off after 10 min

Note: Permethrin has less potential toxicity with inappropriate use; lindane is least expensive and non-toxic if used correctly

B. **Adjunctive**: Retreat after 7 days if lice or eggs are detected at hair–skin junction. Clothes and bed linen of past 2 days should be decontaminated (machine washed or machine dried using hot cycle or dry cleaned) or removed from body contact at least 12 hr

C. **Follow-up**: Evaluate at 1 wk if symptoms persist. Retreat if lice or eggs are seen at hair–skin junctions

D. **Pregnancy**: Permethrin or pyrethrins

E. **Sex partners**: Treat sex partners within preceding month as above

IX. **Scabies** (*Sarcoptes scabiei*)

A. **Symptoms**: Pruritus

B. **Recommended**: Permethrin (5% cream, 30 g) massaged and left 8–14 hr(preferred—Semin Dermatol 12:22, 1993). Lindane considered preferable drug for scabies by*Medical Letter* consultants (Med Lett 1995;37:117.)

C. **Alternatives**: Lindane (1%) 1 oz lotion or 30 g cream applied thinly to all areas of the body below neck and washed thoroughly at 8 hr (not recommended for pregnantor lactating women) or sulfur (6%) ointment applied thinly to all areas nightly×3; wash off previous application before new applications and wash thoroughly 24 hr after last application. Ivermectin (200 µg/kg po ×1 or 0.8% topical solution)

appears to be effective (NEJM 1995;333:26.)

D. **Sex partners and close household contacts**: Treat as above

E. **Pregnancy**: Avoid lindane

F. **Adjunctive**: Clothing and bed linen contaminated by patient should be decontaminated (machine washed or machine dried using hot cycle or dry cleaned or removed from body contact ×72 hr)

G. **Outbreaks**: Control can usually be achieved only by treating the entire population at risk

X. **Hepatitis B** Rates and risk of HBV are high in patients with STDs. Serologic tests of STD clinic patients show evidence of past infection in 28% of persons ≥25 yr and

7% in those ≥25 yr. HBV vaccination is recommended for 1) sexually active homosexual and bisexual men; 2) men and women diagnosed with another STD, and 3) persons with more than one sex partner in the prior 6 mo (MMWR 1999;48:33.) Usual regimen is three doses at 0, 1, and 6 mo at a cost of about $50/dose (see p 114).

XI. **Human Papillomavirus**: Warts

A. **Types**: Exophytic warts are usually benign and caused by HPB types 6 and 11. Types 16, 18, 31, 33, and 35 are associated with genital dysplasia and carcinoma; these types are usually subclinical

B. **Treatment goals**: No treatment is known to eradicate HPV, reduce risk of cervical dysplasia or cervical carcinoma, or prevent recurrence (CID 1995;20:S91.). The goal of therapy is to eliminate the symptoms and emotional distress associated with exophytic warts

C. **Treatments**: Determined by wart area, wart count, anatomic site, morphology, cost, patient preference, and provider experience. Most treatments are 60–70% effective in clearing exophytic warts and show recurrence rates >25% (Int J Dermatol 1995;34:29.)

1. Patient applied

- Podofilox 0.5% soln or gel (Condylox) apply bid × 3 days, then no therapy × 4 days; repeat cycle up to 4 times. This treatment is relatively brief, inexpensive, safe, and simple. Local pain is common. The wart area should be <10 cm^2 and the total volume of podofilox should be <0.5 mL
- Imiquimod 5% (Aldara) cream (see Med Lett 1997;39:118.)Apply hs 3×/wk—daily for up to 16 wk. Wash with mild soap and water 6–10 hr after application. Local inflammation is common. More expensive than podofilox (AWP $432/16 wk vs $56/4 wk for podofilox)

2. **Provider applied**

- Cryotherapy: liquid nitrogen or cryoprobe, repeat q1–2wk. Requires technical expertise
- Podophyllin resin 10–25% applied to wart and air-dried. Repeat weekly
- Trichloroacetic acid or bichloroacetic acid 80–90% applied to wart and air-dried

3. Alternative treatments
    - Laser surgery
    - Intralesional interferon: Rarely recommended because of systemic reactions and requirement for multiple visits

    Management by anatomical site

    - Cervical warts: Must consult expert to exclude high-grade SIL
    - Vaginal warts: Cryotherapy or podophyllin
    - Meatal warts: Cryotherapy or podophyllin 10–25%
    - Anal warts: Cryotherapy, surgical removal, or TCA/BCA 80–90%
    - Oral warts: Cryotherapy or surgical removal

D. **Follow-up**: Not mandatory after warts have cleared

E. **Sex partners**: Not necessary because there is no curative therapy and treatment does not reduce transmission.

F. **Pregnancy**: Use of podofilox, podophyllin, and imiquimod is contra indicated in pregnancy. HPV types 6 and 11 can cause laryngeal papillomatosis in offspring, but mechanism of transmission is unclear. Cesarean section should not be performed to prevent this complication.

G. **Subclinical warts**: Indirect tests are Pap smear, colposcopy, biopsy, or acetic acid application; definitive diagnosis requires detection of HPV DNA or RNA or capsid proteins. Pap smear diagnosis does not correlate well with detection by HPV DNA in cervical cells; cell changes caused by HPV are similar to mild dysplasia and often regress spontaneously. Therefore, screening for subclinical HPV with nucleic acid or capsid antigen tests for detection of HPV is not recommended. Management is based on results of dysplasia on Pap smear.

H. **Education**: Genital HPV infection is common, usually sexually transmitted, and has a variable incubation period. Most warts are benign; exophytic genital warts are not associated with carcinoma. Recurrence in 3

months post-treatment is common; likelihood of transmission post-therapy is unknown. The value of disclosure to prior partners is also unknown.

XII. Genital Ulcer Disease

Agents	*Diagnosis*	*Treatment**	*Comment*
Herpes simplex	Culture or antigen test for HSV	See p 295	Most common cause in U.S.
Syphilis	Dark-field exam or direct immuno-fluorescence test	See p 288	Second most common identifiable cause in U.S.
Chancroid	Culture for H. *ducreyi*	See p 296	Most labs do not have the appropriate media; rare in U.S.

* Based on results of above tests. About 25% will have no laboratory confirmed diagnosis; in this case treat for the most likely agent.

XIII. Urethritis

A. **Diagnosis**: Any of the following

- Mucoid or purulent urethral discharge
- Positive leukocyte esterase test on first voided urine or microscopic exam of first voided urine showing > 10 WBC/HPF
- Urethral Gram stain showing >5 WBC/HPF

B. **Microbiology**: Evaluate for gonococcal and chlamydial infection.

Gonococcal: Presumptive evidence is urethral discharge with >5 WBC/HPF plus typical Gram-negative diplococci.

Nongonococcal: *C. trachomatis* (20–55%), *Ureaplasma urealyticium* (20%), *Trichomonas vaginalis*

(2–5%), HSV (rare)

C. Management

1. Gram stain of discharge

   a. Gram-negative intracellular displococci +>5 WBC/HPF: Treat for *N. gonorrhoeae* and *C. trachomatis;* refer partners

   b. Negative Gram stain + >5 WBC/HPF: Test for *N. gonorrhoeae* and *C. trachomatis;* treat for *C. trachomatis;* refer partners if tests are positive

   c. Negative tests: Test for *N. gonorrhoeae*, and *C. trachomatis;* defer treatment pending test results unless patient is at high risk and unlikely to return: treat patient and partner for *N. gonorrhoeae* and *C. trachomatis*

2. Gram stain unavailable: Test for *N. gonorrhoeae* and *C. trachomatis;* treat for *N. gonorrhoeae* and *C. trachomatis;* refer partners if tests are positive

3. Nongonococcal urethritis: Treat for *C. trachomatis*

D. **Sex partners**: Evaluate and treat sex partners within ≤60 days of symptomatic patients or last sex partner if last sex preceded intervals.

E. Follow-up and disease prevention: Avoid sex until patient and partner have completed 7 days of therapy.

F. **Persistent or recurrent urethritis**

1. Reexposure or noncompliance with original regimen: Retreat

2. Compliant and no reexposure: Intraurethral swab for wet mount and culture for *T. vaginalis.* Treatment is metronidazole 2 g po × 1 plus either

   Erythromycin base 500 mg po qid × 7 days or

   Erythromycin ethylsuccinate 800 mg po qid ×7 days

XIV. **Epididymitis**

A. Microbiology

Men <35 yr: *N. gonorrhoeae, C. trachomatis;* gay men are likely to have enteric pathogens as well

Men >35 yr: *E. coli* and other urinary tract pathogens

B. Diagnosis: (1) Urethral smear for Gram stain for *N. gonorrhoeae and nongonococcal urethritis* (≥5 WBC/OIF) suggests gonococcal infection, (2)urine LCR for *N. gonorrhoeae*, and *C. trachomatis*, (3) uncentrifuged urine for WBCs and Gram stain for GNB.

C. *Treatment*

- *N. gonorrhoeae*: Ceftriaxone 250 mg IM × 1 plus doxycycline, 100 mg po bid × 10 days
- *C. trachomatis*: Ofloxacin 300 mg po bid × 10 days or levofloxacin 500 mg qd

D. **Follow-up**: Expect improvement within 3 days; swelling >1 wk—evaluate for testicular cancer, TB, fungal infections, abscess, or infarction.

E. **Sex partners**: Evaluate and treat sex partners with sexually transmitted epididymitis if contact was within 60 days and gonococci or *C. trachomatis* is suspected or confirmed. Patient should avoid sexual intercourse until patient and partner are cured.

XV. Proctitis, Proctocolitis, and Enteritis

A. Classification

Condition	*Symptoms*	*Microbiology*
Proctitis*	Anorectal pain, tenesmus, constipation, rectal discharge	*N. gonorrhoeae, C. trachomatis*, syphilis, HSV
Proctocolitis*	Symptoms of proctitis plus diarrhea ± cramps and inflammation of colonic mucosa to 12 cm	*Shigella, E. histolytica, Campylobacter* sp, LGV; C. trachomatis (rare)
Enteritis	Diarrhea without signs of proctitis or colitis	*Giardia;* HIV infection—CMV, *M. avium*, microsporidia, *Cryptosporidium-Isospora, Salmonella*

* Proctitis indicates inflammation limited to the distal 10–12 cm of the colon. Proctocolitis shows inflammation extending beyond 12 cm.

B. **Diagnosis (proctitis)**: Anoscopy with evaluation of anorectal pus for PMNs, Gram stain, and evaluation for gonococci, *C. trachomatis*, syphilis, and HSV

C. **Treatment (proctitis with history of recent receptive anal intercourse plus anorectal pus)**: Ceftriaxone 125 mg IM *plus* doxycycline 100 mg po bid ×7 days

XVI. **Mucopurulent Cervicitis (MPC)**

A. **Agents**: Can be caused by *N. gonorrhoeae* or *C. trachomatis*, but most cases involve neither. Most women with gonococcal and chlamydial infections do not have MPC. MPC is not a sensitive predictor of infection.

B. **Diagnosis**: Yellow endocervical exudate in endocervical canal or in an endocervical swab specimen. Some women have no symptoms, some have vaginal discharge, and some have abnormal vaginal bleeding, especially postcoital bleeding.

C. **Test**: Chlamydia trachomatis and *N. gonorrhoeae*

D. **Treatment**: Recommendations based on results of tests of *N. gonorrhoeae* and *C. trachomatis* unless likelihood of infection with either organism is high or patient is unlikely to return for treatment.

1. Gonococcal endocervicitis: see p 288
2. Chlamydia endocervicitis: see p 293
3. Treat for both if high prevalence of both infections, e.g., many STD clinics
4. Treatment may be delayed for laboratory test results if prevalence of both infections is low and compliance with return visit is likely

E. **Sex partners**: Partners of women treated for gonorrhea or *C. trachomatis* should be examined and treated; patients should avoid sex until treated, i.e., 7 days.

XVII. **Pelvic Inflammatory Disease**

A. **Conditions**: PID includes endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.

B. **Microbiology**: Most common—*N. gonorrhoeae* and *C. trachomatis;* less common—endogenous bacteria including anaerobes, Gram-negative bacilli, and streptococci. Role of mycoplasma is unclear.

C. **Diagnosis**: Sexually active women with uterine/adnexal tenderness or cervical motion tenderness. Additional supporting findings are: (1) oral temperature ≥101°F, (2) cervical/vaginal mucopurulent discharge, (3) WBC's in vaginal secretions, (4) increased ESR, (5)elevated CRP, or (6) lab documentation of *N. gonorrhoeae* or *C. trachmatis*

D. **Indications for hospitalization and/or parenteral antibiotics**:

1. Surgical emergency such as possible acute appendicitis
2. Pregnancy
3. Patient failed oral therapy
4. Patient is unable to follow or tolerate oral therapy
5. Severe illness as indicated by high fever, nausea, and vomiting
6. Tubo-ovarian abscess

E. **Treatment**

1. Parenteral regimen
    - Cefoxitin 2 g IV q6h or cefotetan 2 g IV q12h until at least 24 hr after clinical improvement *plus*

doxycycline 100 mg bid po or IV × 14 days*

- Clindamycin 900 mg IV q8h *plus* gentamicin 2 mg/kg IV or IM followed

by 1.5 mg/kg q8h at least 24 hr after clinical improvement then doxycycline 100 mg po bid × 14 days or clindamycin 450 mg po qid × 14 days clindamycin preferred for tubo-ovarian abscess)

Alternatives/parenteral regimen

- Ofloxacin 400 mg IV q12h or levofloxacin 500 mg IV qd *plus* metronidazole 500 mg IV q12h
- Ampicillin/sulbactam 3 g IV q6h *plus* doxycycline 100 mg IV or po q12h
- Ciprofloxacin 200 mg IV q12h *plus* doxycycline 100 mg IV or po q12h *plus* metronidazole 500 mg IV q12h

2. Oral therapy

- Single dose parenteral plus oral:

  Ceftriaxone 250 mg IM × 1 or cefotaxime or

  Cefoxitin 2 g IM plus probenecid 1 g po

  Plus metronidazole 500 mg po bid × 7 days or

- Oral regimen: Ofloxacin 400 mg po bid or levofloxacin 500 mg qd × 14 days plus metronidazole 500 mg po bid × 14 days

F. **Follow-up**: Patients should show substantial clinical improvement within 3 days. Outpatient evaluation: Follow-up in 72 hr with expectation of substantial clinical improvement or hospitalization. Patients should be examined 7–10 days after therapy.

G. **Sex partners**: Examine all sex partners and treat for *N. gonorrhoeae* and *C. trachomatis*.

H. **Expected clinical cure rates with suggested antibiotic regimens**: 85–95% for PID with most failures ascribed to tubo-ovarian abscesses (CID 1994;19:720.). Response expected within 3 days. Major concern is late sequelae with infertility (16%) and ectopic pregnancy (9%) (STD 1992;19:185.)

XVIII. **Vaginitis/Vaginosis**:

A. **Diagnostic tests**:

Requirement: pH paper and 2 slides for microscopy—one with 2 drops of normal saline and the second

with 10% KOH

Interpretation

- pH >4.5: Bacterial vaginosis or trichomoniasis
- Saline mount—*T. vaginalis* or clue cells of bacterial vaginosis
- KOH—*Candida* pseudohyphae or release of amine odor with bacterial vaginosis

B. **Trichomoniasis**(almost always an STD)

1. Clinical features: Women—malodorous yellow-green discharge with vulvar irritation
2. Diagnosis: Wet mount or culture. PMNs, pH >4.7, and a positive amine odor test. Sensitivity of wet mount is 60–70%; culture is more sensitive.
3. Usual treatment: Metronidazole 2 g po as single dose

   Alternative: Metronidazole 375 mg or 500 mg po bid × 7 days

   Allergy to metronidazole: Desensitization (Am J Obstet Gynecol 174:934, 1996).

   Topical metronidazole is not recommended.
4. Treatment failure: Repeat metronidazole 2 g/d ×3–5 days; if treatment fails again consult CDC 770-488-4115 or http://www.cdc.gov/std
5. Asymptomatic women: Treat as above
6. Pregnant women: Metronidazole 2 g ×1. Note: Treatment of asymptomatic trichomoniasis in pregnant women does not reduce

   preterm delivery and may do harm. Routine screening and treatment should not be done (NEJM 2001; 345:487)
7. Lactating women: Treat with 2 g metronidazole and suspend breastfeeding × 24 hr
8. Sex partners: Treat with 2 g metronidazole or 500 mg po bid × 7 days
9. Disease prevention: Patient and partner should avoid sex until both are cured
10. Treatment failures: Retreat with metronidazole 500 mg po bid × 7 days Persistent failures: 2 g dose daily × 3–5 days

C. **Bacterial vaginosis**

1. Etiology: Dysbiosis of the vaginal flora with reduction in H_2O_2 producing lactobacilli by anaerobic bacteria, *G. vaginalis*, and *Mycoplasma hominis*. Cause is unknown. Frequency is increased with multiple sex partners, but rare cases are seen in virgins. Treatment of male sex partners is not helpful.
2. Frequency: Frequency in sexually active women in STD and gynecology clinics is 5–20% (J Obstet Gynecol 1993;169:446.).
3. Clinical symptoms: Malodorous vaginal discharge; over half of cases are asymptomatic.
4. Diagnosis: Three of the following:
    1. Homogeneous, white non-inflammatory discharge that adheres to vaginal walls
    2. Presence of clue cells
    3. pH of vaginal fluid >4.5
    4. Fishy odor of vaginal discharge with or without addition of 10% KOH ("whiff test")
5. Microscopic exam shows no polymorphonuclear cells, sparse lactobacclli, and numerous coccobacillary forms on epithelial cells (clue cells). Cultures are not indicated.
6. Complications: There is an association between BV and adverse outcome of pregnancy (postpartum endometritis, amnionitis, preterm delivery, preterm labor, premature rupture of membranes) and infectious complications of gynecologic surgery. A large trial designed to examine this issue failed to demonstrate any benefit with metronidazole therapy (NEJM 2000;342:534.).
7. Goals of treatment:

    Non-pregnant women: Relieve symptoms.

    Pregnant women: Relieve symptoms and prevent adverse outcome of pregnancy (especially those with prior preterm birth or maternal age >50).
8. Treatment
    a. Non-pregnant:
        - Metronidazole 500 mg po bid × 7 days
        - Clindamycin 2% (5 g) intravaginal hs × 7 days
        - Metronidazole gel 0.75% (5 g) intravaginal bid × 5 days

- Alternative: Metronidazole 2 g po × 1 or clindamycin 300 mg po bid × 7 days or clindamycin ovules 100 mg intravaginally qd hs × 3 days Cure rates for preferred regimens: 75–84%

b. Pregnant: Bacterial vaginosis is associated with increased risk of preterm delivery. Some studies show treatment is associated with reduced rates of preterm delivery (NEJM 1995;333:1732.; Am J Obstet Gynecol 1994;171:345.) and some do not (NEJM 2000;342:5334.). Therefore, some recommend screening and treatment at the first visit. Recommendations for treatment are:

Preferred: Metronidazole 250 mg po tid × 7 days

Alternatives

- Metronidazole 2 g po × 1
- Clindamycin 300 mg po bid × 7 days
- Metronidazole gel 0.75% (5 g) intravaginal bid × 5 days
- Metronidazole 250 mg po tid ×7 days

9. Sex partners: No evaluation

D. **Vulvovaginal candidiasis (not considered an STD)**

Includes CDC 2002 guidelines and IDSA Guidelines (CID 2000;30:672.)

1. Clinical features: Vaginal discharge and vulvar pruritis
2. Diagnosis: Vulvovaginal erythema and white discharge. KOH wet prep or Gram stain showing yeast or pseudohyphae, or positive culture. (Culture is non-specific) Vaginal pH is usually <4.7 and PMNs increased. About 10–20% of healthy women harbor *Candida* sp in the genital tract.
3. Classification: (CID 2000;30:672.) Uncomplicated–mild to moderate severity, sporadic, **C. albicans**, normal host. Complicated: Severe disease, recurrent, non-albicans species, abnormal host (uncontrolled diabetes, immuno sup pres sion, corticosteroids, HIV, etc)
4. Treatment: Douching is contraindicated (Obstet Gynecol 1993;81:601.) Intravaginal preparation (3- to 7-day regimens are usually more effective than single dose). Topical agents are oil based and may weaken latex condoms and diaphragms. Longer regimens and azoles are advocated for complicated cases.

   Topical agents

- Butoconazole 2% cream (5 g)* at hs × 3 days or 2% sustained release (5%) × 1
- Clotrimazole 1% cream* (5 g)* daily × 7–14 days.
- Clotrimazole 100 mg vaginal tab* daily × 7 days or 2 tabs daily × 3 days or 500 mg tab × 1.
- Miconazole 2% cream* (5 g) daily × 7 days.
- Miconazole 200 mg supp* daily × 3 days or 100 mg supp* daily × 7 days.
- Nystatin 100,000 unit vaginal tablet, one/day × 7–14 days.
- Tioconazole 6.5% ointment (5 g)* × 1.
- Terconazole 0.4% cream (5 g) daily × 7 days or 0.8% cream (5 g) daily × 3 days.
- Terconazole 80 mg supp daily × 3 days.

Systemic agents:

- Preferred: Fluconazole 150 mg po × 1
- Alternatives: Itraconazole 200 mg bid × 1 day or ketoconazole 500 mg po × 5 days (CID 2000;30:672.)

Severe disease:

- Topical azole × 7–14 days
- Fluconazole 150 mg po and repeat at 3 days

5. Expected response rate: 70–90% within 48–72 hr. Patients may be classified as uncomplicated vulvovaginitis (mild to moderate, sporadic, normal host, and sensitive *C. albicans*) vs complicated vulvovaginitis (severe disease, abnormal host, reduced susceptibility of *Candida*). Uncomplicated disease responds well to azoles including single dose and short course (7 days). Patients with complicated vulvovaginitis often require longer therapy (10–14 days).
6. Sex partners: No evaluation

7. Pregnancy: Topical azoles (clotrimazole, miconazole, butoconazole, and terconazole) × 7 days
8. HIV serology: Not indicated for vaginal candidiasis per se.
9. Recurrent or complicated and refractory vulvovaginal candidiasis:

Topical agent × 7–14 days or fluconazole 150 mg po and repeat 3 days later ±maintenance: Clotrimazole 500 mg topically q wk × 6 mo or itraconazole 400 mg q month or itraconazole 100 mg po qd × 6 mo. IDSA guideline is for azole therapy po in standard dose > 2 wk, then fluconazole 150 mg q wk, ketoconazole 100 mg qd, itraconazole 100 mg qod, or daily topical azole. Treatment of sex partners is not effective and should not be conducted unless there is symptomatic balanitis or penile dermatitis

10. HIV infection: Incidence of vaginal candidiasis is increased, but response to therapy isusually good. Standard treatment should be given

XIX. Pap Smears

A. **Frequency** (American College of Obstetrics/Gynecology and American Cancer Society): Annually for sexually active women

B. **HIV infection**: Pap smear on initial evaluation; at least one additional Pap smear should be obtained in the next 6 mo to rule out a false-negative test. If negative, repeat testing at least annually. Results of Pap smears should be managed similarly to those from patients without HIV infection

C. **Classification of results** (Bethesda System, JAMA 1989;262:931.; JAMA 1994;271:1866.):

Low-grade squamous intraepithelial lesion (SIL): Includes cellular changes associated with HPV and mild dysplasia/cervical intraepithelial neoplasia 1 (CIN 1)

High-grade SIL: Includes moderate dysplasia/CIN 2, severe dysplasia/CIN 3, and carcinoma in situ (CIS/CIN 3)

D. **Results**:

- Severe inflammation with reactive cellular changes: Repeat within 3 mo, then repeat every 4–6 mo until there are three consecutive negative smears
- Low-grade SIL or atypical squamous cells of undetermined significance (ASCUS): Referral for colposcopy; an acceptable alternative is repeat Pap smear every 4–6 mo for 2 yr until there are three consecutive negative smears. If smears are persistently abnormal, refer for colposcopy and biopsy
- High-grade SIL or persistent low-grade SIL or ASCUS: Refer to physician who can perform colposcopy

XX. **Pregnancy**

Hepatitis B: Screen for HBsAg (surfase antigen) at first visit

N. gonorrhoeae: Screen in first trimester; repeat in third trimester for high-risk patients

C. trachomatis: Screen in first trimester; repeat in third trimester for high-risk patients

HIV: Test with informed consent at first visit

Bacterial vaginosis: Screen with Gram stain at first visit if history of preterm delivery

Pap smear: First visit if none in prior year

Herpes simplex: Routine cultures are not indicated; see p 295

XXI. **Sexual Assault**

A. **Evaluation**

1. Initial evaluation

a. Cultures of any sites of penetration or attempted penetration for *N. gonorrhoeae* and *C. trachomatis* (a non-culture test that is positive for *C. trachomiatis* must be confirmed with another test using different technol ogy)

b. Wet mount for *T. vaginalis*. If vaginal discharge: Examine wet mount for bacterial vaginosis and *Candida* sp

c. Serum sample for HIV, hepatitis B, and syphilis

Follow-up evaluation at 2 wk: Repeat evaluation

Subsequent evaluation: Serology for syphillis and HIV at 6, 12, and 24 wk

B. **Treatment**

- Ceftriaxone 125 mg IM × 1
- Metronidazole 2 g po × 1
- Azithromycin 1 g po × 1 or doxycycline 100 mg po bid × 7
- Hepatitis B vaccination

Footnots

*Quinolones are contraindicated in persons <17 yr, during pregnancy, and during nursing; they are ineffective vs incubating syphilis; increasing resistance to fluoroquinolones has been reported. (Lancet 2003;262:495)

*Standard recommendations apply for disease control (abstinence from sexual intercourse until treatment completed), partner referral, and concurrent treatment for presumed infection with *C. trachomatis* (doxycycline 100 mg po bid × 7 days).

*Skin test (see desensitization schedule see p 77)

*Patients with these conditions should be immediately treated, including an antibiotic for chlamydia. Sex partners should be treated without waiting for results of tests. Chlamydia tests are encouraged even if a presumed diagnosis is made to 1) ensure proper care, especially if symptoms persist; 2) facilitate counseling; 3) provide better grounds for partner notification; and 4) improve compliance.

*Azithromycin has the advantage of single dose observed therapy. A comparative trial with doxycycline for PID showed azithromycin was significantly better, presumably because of reduced compliance with tetracycline. Ofloxacin is equally effective compared with azithromycin and doxycycline but is relatively expensive and offers no dosing advantage. Erythromycin is less efficacious than azithromycin or doxycycline and causes substantial gastrointestinal toxicity.

*Available over-the-counter.

Editors: **Bartlett, John G.**
Title: ***2004 Pocket Book of Infectious Disease Therapy, 12th Edition***

Duration of Antibiotic Treatment

Location	*Diagnosis*	*Duration (days)*
Actinomycosis	Cervicofacial	4–6 wk IV, then po × 6–12 mo
Arthritis septic	*S. aureus*, GNB Streptococci, H. influenzae N. gonorrhoeae	14–28 days 14 days 7 days
Bacteremia	Gram-negative bacteremia *S. aureus*, portal of entry known *S. aureus*, no portal of entry Line sepsis: Bacteria *Candida* Vascular graft	10–14 days 2 wk 4 wk 3–5 days (post-removal) ≥10 days (post-removal) 4 wk (post-removal)
Bone	Osteomyelitis, acute chronic	4–6 wk IV ≥3 mo or until ESR is normal

Bronchi	Exacerbation of chronic bronchitis	7–10 days
Brucella	Brucellosis	6 wk
Bursitis	*S. aureus*	10–14 days
Central nervous system	Cerebral abscess Meningitis: *Listeria* *N. meningitidis* *S. pneumoniae*	4–6 wk IV, then oral 10 days 14–21 days 7 days 10–14 days
Ear	Otitis media, acute	5–10 days (JAMA 1998; 279:1736)
Gastrointestinal	Diarrhea:*C. difficile* *C. jejuni* *E. histolytica* *Giardia* *Salmonella* *Shigella* Traveler's Gastritis, *H. pylori* Typhoid fever Sprue Whipple's disease	10 days 7 days 5–10 days 5–7 days 14 days 3–5 days or single dose 3 days 10–14 days 5–14 days 6 mo 1 yr

Heart	Endocarditis: Pen-sensitive strep Pen-resistant strep *S. aureus* Microbes, other Prosthetic valve Pericarditis (pyogenic)	14–28 days 4 wk 4 wk 4 wk ≥6 wk 28 days
Intra-abdominal	Cholecystitis Primary peritonitis Peritonitis/intra-abdominal abscess	3–7 days post-cholecystectomy 10–14 days ≤7 days after surgery
Joint	Septic arthritis, gonococcal Pyogenic, non-gonococcal Prosthetic joint	7 days 3 wk 6 wk
Liver	Pyogenic liver abscess Amebic	4–16 wk 10 days
Lung	Pneumonia: *C. pneumoniae* *Legionella* *Mycoplasma* *Nocardia* Pneumococcal *Pneumocystis* Staphylococcal	10–14 days 14–21 days 10–14 wk 6–12 mo Until febrile 3–5 days 21 days ≥21 days

	Tuberculosis Lung abscess	6–9 mo Until x-ray clear or until small stable residual lesion; usually >3 mo
Nocardia	Nocardiosis	6–12 mo
Pharynx	Pharyngitis—group A strep Pharyngitis, gonococcal Diphtheria	10 days 1 dose 7–14 days
Prostate	Prostatitis, acute chronic	2 wk 3–4 mo
Sexually transmitted diseases	Cervicitis, gonococcal Chancroid *Chlamydia* Disseminated gonococcal infection *H. simplex* Lymphogranuloma venereum Pelvic inflammatory disease Syphilis Urethritis, gonococcal	1 dose 7 days 7 days (azithromycin—1 dose) 7 days 7–10days 21 days 10–14 days 10–21 days 1 dose
Sinus	Sinusitis, acute	10–14 days

Systemic	Brucellosis *Listeria:* Immunosuppressed host Lyme disease Meningococcemia Rocky Mountain spotted fever Salmonellosis Bacteremia AIDS patients Localized infection Carrier state Tuberculosis, pulmonary extrapulmonary Tularemia	6 wk 3–6 wk 14–21 days 7–10 days Until afebrile, 2 days 10–14 days ≥3–4 wk 4–6 wk 6 wk 6–9 mo 9 mo 7–14 days
Urinary tract	Cystitis Pyelonephritis	3 days 14 days
Vaginitis	Bacterial vaginosis *Candida albicans* Trichomoniasis	7 days or 1 dose Single dose fluconazole 7 days or 1 dose

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Trade Names of Antimicrobial Agents

For: For trade names see Antimicrobial Agents pp 1–16

Trade name	*Generic name*
Abelcet	amphotericin lipid complex
Abreva	docosanol
Achromycin	tetracycline
A-cillin	amoxicillin
Aerosporin	polymyxin B
Aftate	tolnaftate
Agenerase	amprenavir
A-K-chlor	chloramphenicol
Ala-Tet	tetracycline
Albamycin	novobiocin

Albenza	albendazole
Alferon N	interferon alfa-n3
Alinia	nitazoxide
AmBisome	amphotericin liposome
Amcap	ampicillin
Amficot	ampicillin
Amikin	amikacin
Amoxil	amoxicillin
Amphotec	amphotericin lipid complex
Amplin	ampicillin
Ancef	cefazolin
Ancobon	flucytosine
Anspor	cephradine
Antepar	piperazine
Antiminth	pyrantel pamoate
Aoracillin B	penicillin G

Aralen	chloroquine
Arsobal	melarsoprol
Atabrine	quinacrine
Augmentin	amoxicillin + clavulanic acid
Avelox	moxifloxacin
Azactam	aztreonam
Azulfidine	sulfasalazine
Bactrim	trimethoprim/sulfamethoxa-zole
Bactroban	mupirocin
Beepen-VK	penicillin V
Biaxin	clarithromycin
Bicillin	benzathine peni-cillin G
Biltricide	praziquantel
Bio-cef	cephalexin
Bitin	bithionol
Brodspec	tetracycline

Cancidas	caspofugin
Capastat	capreomycin
Caropen-VK	penicillin V
Ceclor	cefaclor
Cedax	ceftibutin
Cefadyl	cephapirin
Cefanex	cephalexin
Cefizox	ceftizoxime
Cefobid	cefoperazone
Cefotan	cefotetan
Ceftin	cefuroxime axetil
Cefzil	cefprozil
Ceptaz	ceftazidime
Chero-Trisulfa-V	trisulfa- pyrimidines
Chloromycetin	chloramphenicol
Cinobac	cinoxacin

Cipro	ciprofloxacin
Claforan	cefotaxime
Cleocin	clindamycin
Cloxapen	cloxacillin
Cofatrim	TMP-SMX
Coly-Mycin M	colistimethate
Combivir	zidovudine/lamivudine
Concidas	caspofungin
Copegus	ribavirin
Cotrim	TMP-SMX
Crixivan	indinavir
Cytovene	ganciclovir
D-Amp	ampicillin
Daraprim	pyrimethamine
Declomycin	demeclocycline
Diflucan	fluconazole

Doryx	doxycycline
Doxy-caps	doxycycline
Doxy-D	doxycycline
Duricef	cefadroxil
Dycill	dicloxacillin
Dynabac	dirithromycin
Dynapen	dicloxacillin
E-mycin	erythromycin
EES	erythromycin ethylsuccinate
Elimite	permethrin
Emtet-500	tetracycline
Epivir	lamivudine
Erothricin	erythromycin
ERYC	erythromycin
Ery-Tab	erythromycin
Erythrocot	erythromycin

Eryzole	erythromycin-sulfisoxazole
Factive	gemifloxacin
Famvir	famciclovir
Fansidar	pyrimethamine + sulfadoxine
Fasigyn	tinidazole
Femstat	butoconazole
Flagyl	metronidazole
Floxin	ofloxacin
Flumadine	rimantadine
Fortaz	ceftazidime
Fortovase	saquinavir
Forvade	cidofovir gel
Foscavir	foscarnet
Fulvicin	griseofulvin
Fungizone	amphotericin B
Furacin	nitrofurazone

Furadantin	nitrofurantoin
Furamide	diloxanide furoate
Furatoin	nitrofurantoin
Furoxone	furazolidone
G-Mycin	gentamicin
Gantanol	sulfamethoxazole
Gantrisin	sulfisoxazole
Garamycin	gentamicin
Geocillin	carbenicillin indanyl sodium
Germanin	suramin
Grifulvin	griseofulvin
Grisactin	griseofulvin
Gulfasin	sulfisoxazole
Halfan	halofantrine
Hepsera	adofovir
Herplex	idoxuridine

Hetrazan	diethyl-carbamazine
Hiprex	methenamine hippurate
HIVID	zalcitabine
Humatin	paromomycin
Ilosone	erythromycin estolate
Ilotycin	erythromycin
Intron A	interferon alfa-2b
Invanz	ertapenem
Invirase	saquinavir
Jenamicin	gentamicin
Kaletra	lopinavir/rectonavir
Kantrex	kanamycin
Keflex	cephalexin
Keflin	cephalothin
Keftab	cephalexin
Kefurox	cefuroxime

Kefzol	cefazolin
Ketek	telithromycin
Kwell	lindane
Lamisil	terbinafine
Lampit	nifurtimox
Lamprene	clofazimine
Lanacillin	penicillin V
Lariam	mefloquine
Ledercillin VK	penicillin V
Levoquin	levofloxacin
Lice-Enz	pyrethins
Lincocin	lincomycin
Lincorex	lincomycin
Lorabid	loracarbef
Lotrimin	clotrimazole
Lyphocin	vancomycin

Macrobid	nitrofurantoin
Macrodantin	nitrofurantoin
Malarone	atovaquone and proguanil
Mandelamine	methenamine mandelate
Mandol	cefamandole
Marcillin	ampicillin
Maxaquin	lomefloxacin
Maxipime	cefixime
Mectizan	ivermectin
Mefoxin	cefoxitin
Mepron	atovaquone
Merrem	meropenem
Metric	metronidazole
Metro-IV	metronidazole
Mezlin	mezlocillin
Minocin	minocycline

Mintezol	thiabendazole
Monocid	cefonicid
Monodox	doxycycline
Monistat	miconazole
Monurol	fosfomycin
Myambutol	ethambutol
Mycelex	clotrimazole
Mycobutin	rifabutin
Mycostatin	nystatin
MyE	erythromycin
Nafcil	nafcillin
Nallpen	nafcillin
Natacyn	natamycin
Nebcin	tobramycin
NebuPent	pentamidine aerosol
NegGram	nalidixic acid

Netromycin	netilmicin
Neutrexin	trimetrexate
Niclocide	niclosamide
Nilstat	nystatin
Nix	permethrin
Nizoral	ketoconazole
Noroxin	norfloxacin
Nor-Tet	tetracycline
Norvir	ritonavir
Nydrazid	INH
Nystex	nystatin
Omnipen	ampicillin
Ornidyl	eflornithine
Ovide	malathion
Paludrine	proguanil
Panmycin	tetracycline

PAS	aminosalicylic acid
Pathocil	dicloxacillin
Pediamycin	erythromycin ethylsuccinate
Peflacine	pefloxacin
Pen G	penicillin G
Pen-V	penicillin V
Pen-VK	penicillin V
Penamp	ampicillin
Penetrex	enoxacin
Pentam 300	pentamidine isethionate
Pentids	penicillin G
Pentostam	sodium stibogluconate
Permapen	penicillin G benzathine
Pipracil	piperacillin
Plaquenil	hydroxychloroquine
Polycillin	ampicillin

Polymox	amoxicillin
Povan	pyrvinium pamoate
Priftin	rifapentine
Primaxin	imipenem + cilastatin
Principen	ampicillin
Proloprim	trimethoprim
Pronto	pyrethrins
Prostaphlin	oxacillin
Protostate	metronidazole
Pyopen	carbenicillin
Rebetrol	ribavirin
Rebetron	ribavirin
Relenza	zanamivir
Rescriptor	delavirdine
Retrovir	zidovudine
RID	pyrethrins

Rifadin	rifampin
Rifamate	rifampin-INH
Rifater	rifampin, INH, pyrazinamide
Rimactane	rifampin
Robicillin VK	penicillin V
Robimycin	erythromycin
Robitet	tetracycline
Rocephin	ceftriaxone
Rochagan	benznidazole
Roferon-A	interferon alfa-2a
Rovamycine	spiramycin
Seromycin	cycloserine
Silvadene	silver sulfadiazine
Soxa	sulfisoxazole
Spectrobid	bacampicillin
Spectracef	cefditoren

Sporanox	itraconazole
Staphcillin	methicillin
Sterostim	somatropin
Storz-G	gentamicin
Stoxil	idoxuridine
Stromectol	ivermectin
Sulfamar	TMP-SMX
Sulfamylon	mafenide
Sulfamethoprim	TMP-SMX
Sulfimycin	erythromycin-sulfisoxazole
Sumycin	tetracycline
Suprax	cefixime
Suspen	penicillin V
Sustiva	efavirenz
Symadine	amantadine
Symmetrel	amantadine

Synercid	quinupristin-dalfopristin
Tamiflu	oseltamivir
TAO	troleandomycin
Tazicef	ceftazidime
Tazidime	ceftazidime
Teebactin	aminosalicylic acid
Tegopen	cloxacillin
Teline	tetracycline
Tequin	gatifloxacin
Terramycin	oxytetracycline
Tetracap	tetracycline
Tetracon	tetracycline
Tetralan	tetracycline
Tetram	tetracycline
Tiberal	ornidazole
Ticar	ticarcillin

Timentin	clavulanic acid + ticarcillin
Tinactin	tolnaftate
Tobrex	tobramycin
Trecator SC	ethionamide
Triazole	TMP-SMX
Trimox	amoxicillin
Trimpex	trimethoprim
Trisulfam	TMP-SMX
Trizivir	AZT and 3TC and ABC
Trobicin	spectinomycin
Trovan	trovafloxacin
Truxcillin	penicillin G
Ultracef	cefadroxil
Unasyn	ampicillin/sulbactam
Unipen	nafcillin
Urex	methenamine hippurate

Uri-tet	oxytetracycline
Uroplus	TMP-SMX
V-Cillin	penicillin V
Valcyte	valganciclovir
Valtrex	valacyclovir
Vancocin	vancomycin
Vancoled	vancomycin
Vansil	oxamniquine
Vantin	cefpodoxime proxetil
Veetids	penicillin V
Velosef	cephradine
Vermox	mebendazole
Vfend	voriconazole
Vibramycin	doxycycline
Vibratabs	doxycycline
Videx	didanosine

Vira-A	vidarabine
Viracept	nevirapine
Viramune	nelfinavir
Virazole	ribavirin
Viroptic	trifluridine
Vistide	cidofovir
Vitravene	fomivirsen
Wesmycin	tetracycline
Win-cillin	penicillin V
Wintrocin	erythromycin
Wyamycin S	erythromycin
Wycillin	penicillin G
Wymox	amoxicillin
Xigris	drotrecogin
Yodoxin	iodoquinol
Zagam	sparfloxacin

Zartan	cephalexin
Zefazone	cefmetazole
Zentel	albendazole
Zerit	stavudine (d4T)
Ziagen	abacavir
Zinacef	cefuroxime
Zolicef	cefazolin
Zosyn	piperacillin/tazobactam
Zovirax	acyclovir
Zithromax	azithromycin
Zyvox	linezolid

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