Handbook of Antimicrobial Therapy

Selected Articles from *Treatment Guidelines* with updates from *The Medical Letter*®

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Introduction

The Medical Letter, Inc. is a nonprofit company founded in 1958 by Arthur Kallet, the co-founder of Consumers Union, and Dr. Harold Aaron, with the goal of providing health care professionals with objective, independent analyses of both prescription and over-the-counter drugs. In addition to its newsletters, *The Medical Letter on Drugs and Therapeutics* and *Treatment Guidelines from The Medical Letter*, the company also publishes handbooks and software on topics such as adverse drug interactions and antimicrobial therapy. It is supported solely by subscription fees and accepts no advertising, grants or donations.

The Medical Letter on Drugs and Therapeutics offers comprehensive drug evaluations of virtually all new drugs and reviews of older drugs when important new information becomes available on their usefulness or adverse effects. Occasionally, The Medical Letter publishes an article on a new non-drug treatment or a diagnostic aid. Treatment Guidelines from The Medical Letter consists of review articles of drug classes for treatment of major indications. A typical issue contains recommendations for first choice and alternative drugs with assessments of the drugs' effectiveness, safety and cost. The Medical Letter is published every other week and Treatment Guidelines is published once a month. Both are intended to meet the needs of the busy health care professional who wants unbiased, reliable and timely information on new drugs and comprehensive reviews of treatments of choice for major indications. Both publications help health care professionals make decisions based on the best interests of their patients, rather than the commercial interests of the pharmaceutical industry.

The editorial process used for Medical Letter publications relies on a consensus of experts to develop prescribing recommendations. An expert consultant or one of our editors prepares the preliminary report on a drug (for The Medical Letter) or drugs for particular indications (for Treatment Guidelines) in terms of their effectiveness, adverse effects and possible alternatives. Both published and available unpublished studies are carefully examined, paying special attention to the results of controlled clinical trials. The preliminary draft is edited and sent to every member of the Advisory Board of The Medical Letter, to 10-20 other investigators who have clinical and experimental experience with the drug or type of drug or disease under review, to the FDA and sometimes the CDC, to the first authors of all the articles cited in the text, to appropriate representatives of the pharmaceutical companies making the drugs under review, and often to companies that make competitor drugs as well. Many critical observations, suggestions and questions are received from the reviewers and are incorporated into the article during the revision process. Further communication as needed is followed by checking and editing to make sure the final appraisal is not only accurate, but also easy to read.

The Medical Letter and *Treatment Guidelines* are crucial resources for members of the health care community to consult when they are overwhelmed by advertisements and personal visits from sales representatives of the pharmaceutical industry.

The Medical Letter, Inc., is based in New Rochelle, NY. For more information call (800) 211-2769 or visit their Web site at www.medicalletter.org.

ANTIBACTERIAL DRUGS: A BRIEF SUMMARY FOR QUICK REFERENCE

AMINOGLYCOSIDES — Aminoglycosides are effective against many gram-negative bacteria, but not gram-positives or anaerobes. They are often used together with a β -lactam antibiotic such as ampicillin, ticarcillin, piperacillin, a cephalosporin, imipenem or aztreonam. They may be ototoxic and nephrotoxic, especially in patients with diminished renal function.

Amikacin (*Amikin*) — Amikacin is often effective for treatment of infections caused by gram-negative strains resistant to gentamicin and tobramycin, including some strains of *Pseudomonas aeruginosa* and *Acinetobacter*. It is generally reserved for treatment of serious infections caused by amikacin-susceptible gram-negative bacteria known or suspected to be resistant to the other aminoglycosides. Like other aminoglycosides, its distribution to the lungs is limited and when used to treat gram-negative bacilli that cause pneumonia it should be combined with another agent to which the organism is susceptible, such as a ß-lactam. It has also been used concurrently with other drugs for treatment of some mycobacterial infections.

Gentamicin (*Garamycin*, and others) — Useful for treatment of many hospital-acquired infections caused by gram-negative bacteria. Strains of gram-negative bacilli resistant to gentamicin are often susceptible to amikacin or to one of the third-generation cephalosporins, cefepime, or imipenem or meropenem. Gentamicin is also used with penicillin G, ampicillin or vancomycin for treatment of endocarditis caused by susceptible enterococci.

Kanamycin (Kantrex, and others) — Active against some gramnegative bacilli (except *Pseudomonas* or anaerobes), but most centers now use gentamicin, tobramycin or amikacin instead. Kanamycin can be useful concurrently with other drugs for treatment of tuberculosis.

Neomycin — A drug that can cause severe damage to hearing and renal function and has the same antibacterial spectrum as kanamycin. Parenteral formulations have no rational use because of their toxicity. Deafness has also followed topical use over large areas of skin, injection into cavities such as joints, and oral administration, especially in patients with renal insufficiency.

Streptomycin — Streptomycin has been displaced by gentamicin for treatment of gram-negative infections, but it is still sometimes used concurrently with other drugs for treatment of tuberculosis and is occasionally used with penicillin, ampicillin or vancomycin to treat entero-coccal endocarditis.

Tobramycin (*Nebcin*, and others) — Similar to gentamicin but with greater activity *in vitro* against *Pseudomonas aeruginosa* and less activity against *Serratia*. In clinical use, it is not certain that it is significantly less nephrotoxic than gentamicin.

AMINOSALICYLIC ACID (PAS) — Used in antituberculosis regimens for many years, its distressing gastrointestinal effects caused many patients to stop taking it prematurely. An enteric-coated oral formulation *(Paser)* is more tolerable, and is used occasionally in combination with other drugs in treating tuberculosis due to organisms resistant to first-line drugs.

AMOXICILLIN (*Amoxil*, and others) — See Penicillins AMOXICILLIN/CLAVULANIC ACID (*Augmentin*) — See Penicillins

AMPICILLIN (*Principen*, and others) — See Penicillins AMPICILLIN /SULBACTAM (*Unasyn*) — See Penicillins

AZITHROMYCIN (Zithromax) — See Macrolides

AZTREONAM (*Azactam*) — A parenteral monobactam (β-lactam) antibiotic active against most aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*, but not against gram-positive organisms or anaerobes. Aztreonam has little cross-allergenicity with penicillins and cephalosporins.

BACITRACIN — A nephrotoxic drug used in the past to treat severe systemic infections caused by staphylococci resistant to penicillin G. Its use is now restricted mainly to topical application.

CAPREOMYCIN (Capastat) — A second-line antituberculosis drug.

CARBAPENEMS

Ertapenem (*Invanz*) — A parenteral carbapenem with a longer half-life but narrower antibacterial spectrum than imipenem and meropenem. It is more active against some extended-spectrum ß-lacta-mase-producing gram-negative bacilli, but less active against gram-positive cocci, *Pseudomonas aeruginosa* and *Acinetobacter* spp. For empiric treatment of intra-abdominal, pelvic and urinary tract infections and community-acquired pneumonia, it offers no clear advantage over older drugs.

Imipenem/Cilastatin (*Primaxin*) — A parenteral carbapenem β lactam with an especially broad antibacterial spectrum. Cilastatin sodium inhibits renal tubular metabolism of imipenem. This combination may be especially useful for treatment of serious infections in which aerobic gram-negative bacilli, anaerobes, and *Staphylococcus aureus* (but not oxacillin-resistant strains) might all be involved. It is active against many gram-negative bacilli that are resistant to third- and fourth-generation cephalosporins, aztreonam and aminoglycosides. Resistance to imipenem in *Pseudomonas aeruginosa* occasionally develops during therapy.

Meropenem (*Merrem*) — A carbapenem for parenteral use similar to imipenem/cilastatin. It may have less potential than imipenem for causing seizures.

CARBENICILLIN — See Penicillins

CEPHALOSPORINS — All cephalosporins except ceftazidime have good activity against most gram-positive cocci, and all cephalosporins are active against many strains of gram-negative bacilli. All cephalosporins are inactive against enterococci and oxacillin-resistant staphylococci. These drugs are often prescribed for patients allergic to penicillin, but such patients may also have allergic reactions to cephalosporins. Rare, potentially fatal immune-mediated hemolysis has been reported, particularly with ceftriaxone and cefotetan.

The cephalosporins can be classified into four "generations" based on their activity against gram-negative organisms. All first-generation drugs have a similar spectrum, including many gram-positive cocci (but not enterococci or oxacillin-resistant *Staphylococcus aureus*), *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Among the firstgeneration parenteral cephalosporins, **cefazolin** (*Ancef*, and others) is less painful on intramuscular injection than **cephapirin** (*Cefadyl*, and others). The first-generation parenteral cephalosporins are usually given intravenously, and cefazolin is most frequently used because of its longer half-life. The second-generation cephalosporins have broader *in vitro* activity against gram-negative bacteria. **Cefamandole** (Mandol) has increased activity against Haemophilus influenzae and some gram-negative bacilli, but is occasionally associated with prothrombin deficiency and bleeding. **Cefoxitin** (Mefoxin) has improved activity against Bacteroides fragilis, Neisseria gonorrhoeae and some aerobic gram-negative bacilli. **Cefotetan** (Cefotan) has a spectrum of activity similar to that of cefoxitin; it has a side chain that has rarely been associated with prothrombin deficiency and bleeding. **Cefuroxime** (Zinacef, Kefurox), another second-generation cephalosporin, has a spectrum of activity similar to cefamandole. Cefuroxime and cefamandole are less active than third-generation cephalosporins against penicillin-resistant strains of Streptococcus pneumoniae. **Cefoncid** (Monocid) has a longer half-life than the other second-generation cephalosporins, but is less active against gram-positive organisms and less active than cefoxitin against anaerobes.

The third-generation cephalosporins, cefotaxime (Claforan), cefoperazone (Cefobid), ceftizoxime (Cefizox), ceftriaxone (Rocephin) and ceftazidime (Fortaz, and others), and the fourth-generation cephalosporin, cefepime (Maxipime), are more active than the secondgeneration cephalosporins against enteric gram-negative bacilli, including nosocomially acquired strains resistant to multiple antibiotics. These agents are highly active against Haemophilus influenzae and Neisseria gonorrhoeae, including penicillinase-producing strains. Except for ceftazidime, they are moderately active against anaerobes, but often less so than metronidazole, chloramphenicol, clindamycin, cefoxitin, cefotetan, ampicillin/sulbactram, piperacillin/tazobactam, ticarcillin/clavulanic acid, or carbapenems. Ceftazidime has poor activity against gram-positive organisms and anaerobes. Cefotaxime, ceftizoxime, ceftriaxone and cefepime are the most active in vitro against gram-positive organisms, but ceftizoxime has poor activity against Streptococcus pneumoniae that are intermediate or highly resistant to penicillin. Cefoperazone, which can cause bleeding, is less active than other third-generation cephalosporins against many gram-negative bacilli, but more active than cefotaxime, ceftizoxime or ceftriaxone against Pseudomonas aeruginosa. Ceftazidime and cefepime have the greatest activity among the cephalosporins against Pseudomonas aeruginosa. Cefepime has somewhat greater activity against enteric gram-negative bacilli than the third-generation cephalosporins. The third-generation cephalosporins and cefepime are expensive, but are useful for treatment of serious hospital-associated gram-negative infections when used alone or in combination with aminoglycosides such as gentamicin, tobramycin or amikacin. Gram-negative bacteria that produce "broad spectrum" ß-lactamases are resistant to firstgeneration cephalosporins, but are usually sensitive to second and third generation cephalosporins. However, gram-negative bacilli that produce "extended spectrum ß-lactamases", particularly some Klebsiella strains and those that produce chromosomally-encoded β -lactamases, are usually resistant to first, second and third-generation cephalosporins. These organisms are often hospital-associated. Cefipime may be more active than the third-generation cephalosporin against these strains, but imipenem and meropenem are most consistently active against them. Cefotaxime and ceftriaxone are often used for treatment of meningitis. Ceftriaxone has been widely used for single-dose treatment of gonorrhea.

Cephalexin (*Keflex*, and others), **cephradine** (*Velosef*, and others), and **cefadroxil** (*Duricef*, and others) are well-absorbed oral cephalosporins with first-generation antimicrobial activity; cephradine is also available for parenteral use. **Cefaclor** (*Ceclor*, and others), **cefuroxime axetil** (*Ceftin*), **cefprozil** (*Cefzil*) and **loracarbef** (*Lorabid*) are oral second-generation agents with increased activity against *Haemophilus influenzae* and *Moraxella catarrhalis*. **Cefixime**, an oral cephalosporin with activity against gram-positive organisms similar to that of first-generation cephalosporins except for its poor activity against staphylococci; against gram-negative bacteria, it has greater activity than second-generation cephalosporins. It is useful for single-dose oral treatment of gonorrhea. **Cefpodoxime proxetil** (*Vantin*), **cefdinir** (*Omnicef*) and **cefditoren pivoxil** (*Spectracef*) are oral cephalosporins similar to cefixime, but with greater activity against methicillin-susceptible staphylococci. **Ceftibuten** (*Cedax*) is an oral cephalosporin similar to cefixime in its gram-negative activity and poor activity against staphylococci, but it has only inconsistent activity against *Streptococcus pneumoniae*.

CHLORAMPHENICOL (*Chloromycetin*, and others) — An effective drug for treatment of meningitis, epiglottitis, or other serious infections caused by *Haemophilus influenzae*, severe infections with *Salmonella typhi*, for some severe infections caused by *Bacteroides* (especially those in the central nervous system), and for treatment of vancomycinresistant *Enterococcus*. Chloramphenicol is often an effective alternative for treatment of pneumococcal or meningococcal meningitis in patients allergic to penicillin, but some strains of *Streptococcus pneumoniae* are resistant to it. Because it can cause fatal blood dyscrasias, chloramphenicol should be used only for serious infections caused by susceptible bacteria that cannot be treated effectively with less toxic agents.

CINOXACIN (Cinobac, and others) - See Quinolones

CIPROFLOXACIN (Cipro) — See Fluoroquinolones

CLARITHROMYCIN (Biaxin) — See Macrolides

CLINDAMYCIN (*Cleocin*, and others) — A derivative of lincomycin with a similar antibacterial spectrum, clindamycin can cause severe diarrhea and pseudomembranous colitis. It is one of the alternative drugs for anaerobic infections outside the central nervous system, and can also be used as an alternative for treatment of some staphylococcal infections in patients allergic to penicillins. Strains of *S. aureus* that are sensitive to

clindamycin, but resistant to erythromycin become rapidly resistant to clindamycin when it is used. Clindamycin is also used concurrently with other drugs to treat *Pneumocystis carinii* pneumonia and toxoplasmosis. Clindamycin may be beneficial in treatment of necrotizing fasciitis due to Group A streptococcus but, because of the possibility of resistance to clindamycin, it should be used in combination with penicillin G.

CLOFAZIMINE (*Lamprene*) — An oral agent used with other drugs for treatment of leprosy.

CLOXACILLIN — See Penicillinase-resistant Penicillins

COLISTIMETHATE (Coly-Mycin) — See Polymyxins

CYCLOSERINE (*Seromycin*, and others) — A second-line antituberculosis drug.

DAPTOMYCIN (*Cubicin*) — A cyclic lipopeptide antibiotic that is effective for treating complicated skin and soft tissue infections. It is rapidly bactericidal against gram-positive bacteria by causing membrane depolarization. Its anti-bacterial activity includes oxacillin-sensitive and resistant, and vancomycin-sensitive and resistant *S. aureus* and coagulase-negative staphylococci, streptococci and vancomycin-sensitive and resistant enterococci. It is administered intravenously once daily and is excreted unchanged in urine; dose adjustments are required when given to individuals with severe renal insufficiency. Adverse effects include the potential for skeletal muscle damage, with rare reversible CPK elevations. More severe muscle effects, which were seen in preclinical studies, do not seem to occur at the currently approved doses; higher doses may increase the potential for rhabdomyolysis. Daptomycin should not be used to treat pneumonia because it penetrates lung parenchyma poorly and is inactivated by surfactant. Clinical trials are

underway evaluating the drug for treatment of staphylococcal bacteremia and endocarditis.

DEMECLOCYCLINE (*Declomycin*) — See Tetracyclines

DICLOXACILLIN (*Dycill*, and others) — See Penicillinase-resistant Penicillins

DIRITHROMYCIN (Dynabac) — See Macrolides

DOXYCYCLINE (Vibramycin, and others) - See Tetracyclines

ENOXACIN (Penetrex) — See Fluoroquinolones

ERTAPENEM (*Invanz*) — See Carbapenems

ERYTHROMYCIN (Erythrocin, and others) — See Macrolides

ERYTHROMYCIN-SULFISOXAZOLE (*Pediazole*, and others) — See Macrolides

ETHIONAMIDE (*Trecator-SC*) — A second-line antituberculosis drug.

ETHAMBUTOL (*Myambutol*) — Often used in antituberculosis regimens, it can cause optic neuritis.

FLUOROQUINOLONES — Fluoroquinolones are synthetic anti-bacterial agents with activity against gram-positive and gram-negative organisms. With the increased use of fluoroquinolones, resistant organisms have become more frequent, especially among strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Resistance

among *Streptococcus pneumoniae* strains has begun to emerge but is still rare, especially in the US. None of these agents is recommended for use in children or pregnant women. All can cause gastrointestinal disturbances and, less commonly central nervous system toxicity. Tendon effects and hypersensitivity reactions, including vasculitis, serum sickness-like reactions and anaphylaxis, occur rarely. Hypo- and hyperglycemia can also occur rarely.

Ciprofloxacin (*Cipro*, and others) — Used for oral or intravenous treatment of a wide variety of gram-positive and gram-negative bacterial infections in adults, including those due to oxacillin-susceptible and resistant staphylococci, Haemophilus influenzae, Neisseria, enteric pathogens and other aerobic gram-negative bacilli, and Pseudomonas aeruginosa, but not anaerobes. Newer fluoroquinolones such as levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin are preferred for treatment of gram-positive coccal infections such as those caused by S. pneumoniae and S. aureus. Ciprofloxacin is useful for treatment of urinary tract infections caused by enteric gram-negative bacilli or Pseudomonas aeruginosa. Oral ciprofloxacin has been effective in treating patients with neutropenia and fever who are at low risk for mortality. Ciprofloxacin is now one of the preferred prophylactic agents for contacts of patients with meningococcal disease. It is also used for prophylaxis after Bacillus anthracis (Anthrax) exposure. Emergence of resistance in staphylococcal and Pseudomonas strains and other gram-negative organisms is increasingly encountered.

Enoxacin (*Penetrex*) — An oral fluoroquinolone similar to ciprofloxacin that can be used to treat urinary tract infection and uncomplicated gonorrhea.

Gatifloxacin (*Tequin*), **levofloxacin** (*Levaquin*), **moxifloxacin** (*Avelox*) and **gemifloxacin** (*Factive*) — More active than ciprofloxacin

or ofloxacin against gram-positive organisms, such as Streptococcus pneumoniae, including strains highly resistant to penicillin, and Staphylococcus aureus. Like other fluoroquinolones, they are active against Legionella pneumophila, Chlamydia spp., Mycoplasma pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. All are effective for many community-acquired respiratory infections. Levofloxacin, gatifloxacin and moxifloxacin are less active than ciprofloxacin in vitro against enteric gram-negative bacilli and Pseudomonas aeruginosa, but have been effective in treating urinary tract infections and other systemic infections caused by these organisms. Levofloxacin has been used to treat some oxacillin-sensitive and oxacillin-resistant S. aureus infections, although resistance is increasing. Levofloxacin, ofloxacin or ciprofloxacin are sometimes used as second-line anti-tuberculous drugs in combination with other agents. Levofloxacin is more effective for treatment of Legionella pneumophila than azithromycin. Gatifloxacin, levofloxacin and moxifloxacin are available for both oral and parenteral use. Gemifloxacin is only available for oral use. Gatifloxacin, levofloxacin and moxifloxacin have rarely been associated with torsades de pointes arrhythmia. Gemifloxacin has produced more rashes than other fluoroquinolones.

Lomefloxacin (*Maxaquin*) — An oral once-a-day fluoroquinolone promoted for treatment of urinary tract infections and bronchitis, but pneumococci and other streptococci are resistant to the drug.

Norfloxacin (*Noroxin*) — An oral fluoroquinolone for treatment of urinary tract infections due to Enterobacteriaceae, *Enterococcus* or *Pseudomonas aeruginosa*.

Ofloxacin (*Floxin*) — An oral and intravenous fluoroquinolone similar to ciprofloxacin but less active against *Pseudomonas*. Ofloxacin can be used for single-dose treatment of gonorrhea and for seven-day

treatment of chlamydial infections. It is sometimes used as a second-line anti-tuberculous drug in combination with other agents.

Trovafloxacin (*Trovan*) has been associated with rare but fatal hepatitis, and should be restricted to brief (<14 days) inpatient use with liver monitoring.

FOSFOMYCIN (*Monurol*) — Can be used as a single-dose oral agent with moderate effectiveness for treatment of uncomplicated urinary tract infections caused by many strains of enteric gram-negative bacilli, enterococci and some strains of *Staphylococcus saphrophyticus*, but generally not *Pseudomonas*. It is much more expensive than trimethoprim/sulfamethoxazole.

FURAZOLIDONE (*Furoxone*) — An oral nonabsorbable antimicrobial agent of the nitrofuran group that inhibits monoamine oxidase (MAO). The manufacturer recommends it for treatment of bacterial diarrhea. Its safety has been questioned (oral administration induces mammary tumors in rats) and other more effective drugs are available.

GATIFLOXACIN (Tequin) — See Fluoroquinolones

GEMIFLOXACIN (Factive) - See Fluoroquinolones

GENTAMICIN (Garamycin, and others) - See Aminoglycosides

IMIPENEM/CILASTATIN (Primaxin) — See Carbapenems

ISONIAZID (*Nydrazid*, and others) — A major antituberculosis drug that can cause fatal hepatitis. **Rifampin-isoniazid-pyrazinamide** (*Rifater*) and **rifampin-isoniazid** (*Rifamate*) are fixed-dose combinations for treatment of tuberculosis.

KANAMYCIN (Kantrex, and others) - See Aminoglycosides

LEVOFLOXACIN (Levaquin) - See Fluoroquinolones

LINCOMYCIN (*Lincocin*) — Similar to clindamycin in antibacterial activity and adverse effects. Rarely indicated for treatment of any infection because it is less active than clindamycin.

LINEZOLID (*Zyvox*) — An oxazolidinone bacteristatic antibiotic available in both an oral and intravenous formulation. It is active against *Enterococcus faecium* and *E. faecalis* including vancomycin-resistant enterococcal infections. Linezolid is also active against oxacillin-resistant *Staphylococcus aureus*, *S. epidermidis* and penicillin-resistant *Streptococcus pneumoniae*. Reversible thrombocytopenia has occurred, especially with therapy for more than 2 weeks. A serotonin syndrome has been observed in patients taking linezolid together with a selective serotonin receptor inhibitor. Emergence of resistance has been observed with enterococcal and *S. aureus* strains.

LOMEFLOXACIN (Maxaquin) — See Fluoroquinolones

MACROLIDES

Azithromycin (Zithromax) — A macrolide antibiotic that has much less gastrointestinal toxicity than erythromycin and is not associated with drug interactions with the CYP3A cytochrome P-450 enzyme systems. A single dose has been effective for treatment of urethritis and cervicitis caused by *Chlamydia* and for treatment of trachoma. Azithromycin is useful in treating *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila* pneumonias, as well as some respiratory infections due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*. However, an increasing number of *S. pneumoniae* strains have become resistant to the macrolides and azithromycin should not be used alone to treat pneumococcal pneumonia unless the causative strain is known to be sensitive to the macrolides. Azithromycin alone is effective for prevention of *Mycobacterium avium* infections, and combined with other drugs, such as ethambutol, rifabutin or ciprofloxacin, it is effective for treatment.

Clarithromycin (*Biaxin*) — A macrolide antibiotic similar to azithromycin, but with a shorter half-life. It is somewhat more active than azithromycin against gram-positive organisms and less active against gram-negative organisms. Clarithromycin is effective for prevention of *Mycobacterium avium* infections and, combined with other drugs, for treatment of both *M. avium* and *Helicobacter pylori*. It has more adverse drug interactions than azithromycin.

Dirithromycin (*Dynabac*) — Similar to erythromycin; it can be given once a day.

Erythromycin (*Erythrocin*, and others) — Used especially for respiratory tract infections due to pneumococci or Group A streptococci in patients allergic to penicillin, for pneumonia due to *Mycoplasma pneumoniae* or *Chlamydia spp.*, and for treatment of infection caused by *Legionella pneumophila*, erythromycin has few adverse effects except for frequent gastrointestinal disturbances but many drug interactions involving the CYP3A cytochrome P-450 system. Erythromycin given orally or intravenously may rarely be associated with torsades de pointes, a potentially fatal arrhythmia; risk of torsades is increased by concurrent use of CYP3A inhibitors. Use in young infants has rarely been associated with hypertrophic pyloric stenosis. The estolate formulation (*Ilosone*) can cause cholestatic jaundice. Erythromycin is not recommended for treatment of serious staphylococcal infections, even when the organisms are susceptible to the drug *in vitro*, because of potential for rapid development of resistance. Strains of *Streptococcus*

pneumoniae and Group A streptococci resistant to erythromycin have become more frequent and the drug should not be used alone to treat community-acquired pneumonia when pneumococcus is likely, unless susceptibility of the organism has been established.

Erythromycin/Sulfisoxazole (*Pediazole*, and others) — A combination of 100 mg of erythromycin ethylsuccinate and 300 mg sulfisoxazole acetyl per half-teaspoon for oral treatment of acute otitis media.

Troleandomycin (*TAO*) — This oral drug has an antibacterial spectrum like that of the erythromycins, but it can cause cholestatic jaundice, and there are no reasonable indications for its use.

MEROPENEM (Merrem) — See Carbapenems

METHENAMINES (*Mandelamine*, and others) — Oral drugs that can sterilize an acid urine. They are used for prophylaxis of chronic or recurrent urinary tract infections, but trimethoprim/sulfamethoxazole is more effective.

METHICILLIN — See Penicillinase-resistant Penicillins

METRONIDAZOLE (*Flagyl*, and others) — Available in oral form for treatment of trichomoniasis, amebiasis, giardiasis and *Gardnerella vaginalis* vaginitis, metronidazole is also available for intravenous treatment of anaerobic bacterial infections. Good penetration of the blood-brain barrier may be an advantage in treating central-nervous-system infections due to *Bacteroides fragilis*. Metronidazole is the drug of choice for treatment of pseudomembranous enterocolitis due to *Clostridium difficile*. It is sometimes used in combination with other drugs to treat *H. pylori* infection.

MINOCYCLINE (Minocin, and others) - See Tetracyclines

MOXIFLOXACIN (Avelox) — See Fluoroquinolones

NAFCILLIN (*Nafcil*, and others) — See Penicillinase-resistant Penicillins

NALIDIXIC ACID (NegGram, and others) - See Quinolones

NEOMYCIN — See Aminoglycosides

NITROFURANTOIN (*Macrodantin*, and others) — This oral agent is used for prophylaxis or treatment of urinary tract infections, especially those resistant to other agents. Because of its potential toxicity, nitrofurantoin should not be used when renal function is markedly diminished. Nausea and vomiting are often troublesome, and peripheral neuropathy, pulmonary reactions and severe hepatotoxicity may occur.

NORFLOXACIN (Noroxin) - See Fluoroquinolones

OFLOXACIN (*Floxin*) — See Fluoroquinolones

OXACILLIN — See Penicillinase-resistant Penicillins

PENICILLINS

Natural Penicillins — Penicillin remains the drug of choice for Group A streptococcal infections and for treatment of syphilis and some other infections. Clindamycin may be beneficial for treatment of Group A streptococcal necrotizing fasciitis, but it should be combined with penicillin G because of increasing resistance to clindamycin in Group A streptococcus. *Streptococcus pneumoniae* strains frequently show intermediate or high-level resistance to penicillin. Penicillin is effective for fully sensitive strains, and high doses of penicillin, cefotaxime or ceftriaxone are effective for pneumonia due to strains with intermediate sensitivity; vancomycin is added for highly resistant strains, especially for meningitis.

Aminopenicillins:

Amoxicillin (*Amoxil*, and others) — An oral semisynthetic penicillin similar to ampicillin, it is better absorbed and may cause less diarrhea. Amoxicillin is at least as effective as oral ampicillin for the treatment of most infections, with the exception of shigellosis. High doses (at least 3000 mg/day) have been successful in treating pneumococcal respiratory infections caused by strains with reduced susceptibility to penicillin.

Amoxicillin/Clavulanic Acid (Augmentin) — The β -lactamase inhibitor, potassium clavulanate, extends amoxicillin's spectrum of activity to include β -lactamase-producing strains of *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis* and many strains of enteric gram-negative bacilli, including anaerobes such as *Bacteroides* spp. This combination may be useful for oral treatment of bite wounds, otitis media, sinusitis and some lower respiratory tract and urinary tract infections, but it can cause a higher incidence of diarrhea and other gastrointestinal symptoms than amoxicillin alone, and less costly alternatives are available. An oral extended-release form of *Augmentin (Augmentin XR)* containing a higher content of amoxicillin in each tablet (1000 mg) has been successful in treating acute bacterial sinusitis and community-acquired pneumonia caused by strains of pneumococci with reduced susceptibility to penicillin, but high dose amoxicillin which costs much less can also be used.

Ampicillin (*Principen*, and others) — This semisynthetic penicillin is as effective as penicillin G in pneumococcal, streptococcal and meningococcal infections, and is also active against some strains of *Salmonella*, *Shigella*, *Escherichia coli* and *Haemophilus influenzae* and many strains of *Proteus mirabilis*. The drug is not effective against penicillinase-producing staphylococci or β-lactamase-producing gram-negative bacteria. Rashes are more frequent with ampicillin than with other penicillins. Taken orally, ampicillin is less well absorbed than amoxicillin.

Ampicillin /Sulbactam (Unasyn) — A parenteral combination of ampicillin with the ß-lactamase inhibitor sulbactam, which extends the antibacterial spectrum of ampicillin to include ß-lactamase-producing strains of *Staphylococcus aureus* (but not those resistant to oxacillin), *Haemophilus influenzae, Moraxella catarrhalis, Neisseria* and many gram-negative bacilli, including *Bacteroides fragilis*, but not *Pseudomonas aeruginosa, Enterobacter* or *Serratia.* It may be useful for treatment of gynecological and intra-abdominal infections. Some strains of *Acinetobacter* resistant to all other antibiotics may respond to high doses of ampicillin/sulbactam in combination with polymyxins.

Penicillinase-Resistant Penicillins — The drugs of choice for treatment of infections caused by penicillinase-producing staphylococci, they are also effective against penicillin-sensitive pneumococci and Group A streptococci. For oral use, **cloxacillin** or **dicloxacillin** is preferred; for severe infections, a parenteral formulation of **nafcillin** or **oxacillin** should be used. **Methicillin** is no longer marketed in the US. Strains of *Staphylococcus aureus* or *epidermidis* that are resistant to these penicillins ("oxacillin-resistant") are also resistant to cephalosporins, and carbapenems. Infections caused by these strains should be treated with vancomycin, with or without rifampin and/or gentamicin, or with linezolid; complicated skin and soft tissue infections may also be treated with daptomycin. Neither ampicillin, amoxicillin, carbenicillin, piperacillin nor ticarcillin is effective against penicillinase-producing staphylococci.

Extended-Spectrum Penicillins:

Carbenicillin (*Geocillin*) — The oral indanyl ester of carbenicillin; it does not produce therapeutic blood levels, but can be used for treatment of urinary tract infections, including those due to susceptible gramnegative bacilli such as *Pseudomonas aeruginosa* that may be resistant to other drugs.

Piperacillin (*Pipracil*) — A penicillin for parenteral treatment of gram-negative bacillary infections. It is similar to ticarcillin in antibacterial activity, but covers a wider spectrum, particularly against *Klebsiella pneumoniae* and *Bacteroides fragilis*. Its *in vitro* activity against *Pseudomonas* is greater than that of ticarcillin, but increased clinical effectiveness in *Pseudomonas* infections has not been demonstrated. Piperacillin is also active against some gram-positive cocci, including streptococci and some strains of *Enterococcus*. For treatment of serious gram-negative infections, it should generally be used in combination with an aminoglycoside such as gentamicin, tobramycin or amikacin.

Piperacillin/Tazobactam (*Zosyn*) — A parenteral formulation combining piperacillin with tazobactam, a β -lactamase-inhibitor. The addition of the β -lactamase inhibitor extends the spectrum of piperacillin to include β -lactamase producing strains of staphylococci and some gram-negative bacilli, including *Bacteroides fragilis*. Infections caused by gram-negative bacilli that produce "extended spectrum" β -lactamase are often resistant to piperacillin/tazobactam, those that produce chromosomal β -lactamase are always resistant. The combination of the two drugs is no more active against *Pseudomonas aeruginosa* than piperacillin alone.

Ticarcillin (*Ticar*) — A penicillin similar to carbenicillin. Large parenteral doses of this semisynthetic penicillin can cure serious infections caused by susceptible strains of *Pseudomonas*, *Proteus* and some

other gram-negative organisms. *Klebsiella* are generally resistant. Ticarcillin is also active against some gram-positive cocci, including streptococci and some strains of *Enterococcus*. It is often given together with another drug such as gentamicin, tobramycin or amikacin for treatment of serious systemic infections. It is less active than ampicillin, amoxicillin or piperacillin against strains of *Streptococcus pneumoniae* with reduced susceptibility to penicillin and against enterococci.

Ticarcillin/Clavulanic Acid (*Timentin*) — A parenteral preparation combining ticarcillin with potassium clavulanate, a β -lactamase inhibitor. The addition of the β -lactamase inhibitor extends the antibacterial spectrum of ticarcillin to include β -lactamase producing strains of *Staphylococcus aureus, Haemophilus influenzae*, and some enteric gram-negative bacilli, including *Bacteroides fragilis*. The combination is no more active against *Pseudomonas aeruginosa* than ticarcillin alone.

POLYMYXINS B AND E (polymyxin B – various generics; polymyxin E – *Coly-Mycin*; colistimethate; colistin sulfate) — The polymyxins are used topically in combination with other antibiotics for treatment of infected wounds and otitis externa. They should generally not be used parenterally because safer and more effective alternatives are available. However, some strains of *Acinetobacter* are resistant to all other available antibiotics and infections due to those strains have been treated with polymyxin, sometimes combined with high doses of subactam (in the form of ampicillin/subactam), with some reports of benefit.

PYRAZINAMIDE — An antituberculosis drug now often used in the initial treatment regimen. Rifampin-isoniazid-pyrazinamide (*Rifater*) is a fixed-dose combination for treatment of tuberculosis.

QUINOLONES

Nalidixic Acid (*NegGram*, and others) — An oral drug active *in vitro* against many gram-negative organisms that commonly cause urinary tract infections. Development of resistance by initially susceptible strains is rapid, however, and clinical results are much less favorable than would be expected from sensitivity testing alone. Nalidixic acid can cause severe adverse effects, including visual disturbances, intracranial hypertension, and convulsions. Other drugs are generally preferred for treatment of urinary tract infections.

Cinoxacin (*Cinobac*, and others) — An oral drug similar to nalidixic acid for treatment of urinary tract infections.

QUINUPRISTIN/DALFOPRISTIN (Synercid) — Two streptogramin antibacterials marketed in a fixed-dose combination for parenteral use. The combination is active against vancomycin-resistant Enterococcus faecium (but not E. faecalis) as well as Staphylococcus aureus, Streptococcus pneumoniae and S. pyogenes. Adverse effects include frequent thrombophlebitis at the infusion site (it is best given through a central venous catheter) and arthralgias and myalgias. It has a number of drug interactions. The availability of linezolid and daptomycin as alternates have lead to infrequent use of quinupristin/dalfopristin.

RIFABUTIN (*Mycobutin*) — Similar to rifampin, rifabutin is used to prevent and treat tuberculosis and disseminated *Mycobacterium avium* infections in patients with AIDS. It has fewer drug interactions than rifampin.

RIFAMPIN (*Rifadin, Rimactane*) — A major drug for treatment of tuberculosis. To prevent emergence of resistant organisms, it should be used together with other antituberculosis drugs. It is sometimes used concurrently with other drugs for treatment of *Mycobacterium avium* infections in AIDS patients. Rifampin is also useful for prophylaxis in

close contacts of patients with sulfonamide-resistant meningococcal disease and for prophylaxis in children who are close contacts of patients with *Haemophilus influenzae* meningitis. Rifampin is a potent inducer of CYP3A enzymes and may increase the metabolism of the many drugs, particularly some protease inhibitors. **Rifampin-isoniazidpyrazinamide** (*Rifater*) and **rifampin-isoniazid** (*Rifamate*) are fixeddose combinations for treatment of tuberculosis.

RIFAPENTINE (*Priftin*) — A long-acting analog of rifampin used in the treatment of tuberculosis. Studies of its effectiveness are limited. Until more data become available, rifampin is preferred.

RIFAXIMIN (*Xifaxan*) — A non-absorbed oral antibiotic derived from rifampin, it is about as effective as ciprofloxacin for treatment of traveler's diarrhea, which is mostly caused by *E. coli*. It is not effective against gastrointestinal infections associated with fever or blood in the stool or those caused by *Campylobacter jejuni*. It has fewer adverse effects and drug interactions than systemic antibiotics, but should not be taken during pregnancy. Hypersensitivity reactions have been reported.

SPECTINOMYCIN (*Trobicin*) — A single-dose alternative for treatment of urogenital or anal gonorrhea. It is effective for penicillin-resistant infections and for patients who are allergic to penicillin. Spectinomycin is not effective against syphilis.

STREPTOMYCIN — See Aminoglycosides

SULFONAMIDES — Previously used for acute, uncomplicated urinary tract infections sulfonamides are now rarely used because of the increasing frequency of sulfonamide-resistance among gram-negative bacilli and the availability of fluoroquinolone and trimethoprim/sulfamethoxazole. When used, a soluble oral sulfonamide such as sulfisoxazole (*Gantrisin*, and others) is preferred.

TELITHROMYCIN (*Ketek*) — A ketolide antibiotic, derived from erythromycin, it is approved for oral treatment of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis in adults. Telithromycin has good activity against most strains of *S. pneumoniae* that are resistant to penicillin and macrolides (erythromycin, clarithromycin and azithromycin). It is also active against *M. catarrhalis*, *H. influenzae* and the atypical respiratory pathogens (*M. pneumoniae*, *Legionella pneumophilia* and *Chlamydia* spp.). Telithromycin can be an alternative to fluoroquinolones for treatment of respiratory infections, but is expensive and may cause transient visual disturbances. It is an inhibitor of CYP3A enzymes and can cause potentially dangerous increases of serum concentrations of simvastatin, lovastatin, atorvastatin, midazolam and other drugs. It should not be used in patients with myasthemia gravis because it may exacerbate attacks of that disease.

TETRACYCLINES — **Doxycycline** (*Vibramycin*, and others), **oxytetracycline** (*Terramycin*), and **minocycline** (*Minocin*, and others) are available in both oral and parenteral formulations; **tetracycline** and **demeclocycline** (*Declomycin*) are available only for oral use. Parenteral tetracyclines can cause severe liver damage, especially when given to patients with diminished renal function or in pregnancy. **Doxycycline** requires fewer doses and causes less gastrointestinal disturbance than other tetracyclines. It can be used for prophylaxis after *Bacillus anthracis* (anthrax) exposure. Doxycycline and other tetracyclines are effective in treating pneumonia caused by *Mycoplasm pneumoniae*, *Chlamydia pneumoniae* and *Legionella* species and are commonly used to treat Lyme disease in adults and urethritis, cervicitis, proctitis or pelvic inflammatory disease when caused by *Chlamydial* species. **Minocycline** may be useful for prophylactic treatment of close contacts of patients with meningococcal infection, but it frequently causes vomiting and vertigo.

TIGECYCLINE (*Tygacil*) — The first glycylcycline, tigecycline is FDA-approved for parenteral treatment of complicated intra-abdominal infections and complicated skin and skin structure infections in adults. It has a broad spectrum of antimicrobial activity, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

TOBRAMYCIN (Nebcin, and others) - See Aminoglycosides

TRIMETHOPRIM (*Proloprim*, and others) — An agent marketed only for oral treatment of uncomplicated urinary tract infections caused by gram-negative bacilli. Frequent use has the potential for producing organisms resistant not only to this drug but also to trimethoprim/sulfamethoxazole.

TRIMETHOPRIM/SULFAMETHOXAZOLE (*Bactrim, Septra*, and others) — A combination of a folic acid antagonist and a sulfonamide, useful especially for oral treatment of urinary tract infections, shigellosis, otitis media, traveler's diarrhea, bronchitis, and *Pneumocystis carinii* pneumonia. An intravenous preparation is available for treatment of serious infections. Allergic reactions are common, especially in HIV-infected patients. It may occassionally produce elevation of serum creatinine, hyperkalemia and renal insufficiency.

TROLEANDOMYCIN (TAO) — See Macrolides

TROVAFLOXACIN (Trovan) - See Fluoroquinolones

VANCOMYCIN (Vancocin, and others) - An effective alternative to

the penicillins for endocarditis caused by Streptococcus viridans or Enterococcus, for severe staphylococcal infections, and for penicillinresistant S. pneumoniae infections. An increasing number of strains of enterococci (especially E. faecium), however, are resistant to vancomycin. Some strains of S. aureus have reduced susceptibility to vancomycin or are highly resistant. Linezolid or daptomycin may be used to treat infections caused by these strains of enterococci or S. aureus. Vancomycin is the drug of choice for treatment of infections caused by oxacillin-resistant Staphylococcus aureus and epidermidis, but for strains that are oxacillin-sensitive, nafcillin or oxacillin are more effective. For serious infections caused by S. aureus or enterococci higher than the traditional doses of 15 mg/kg every 12 hours IV for adults with normal renal function are being advocated by some consultants, but improved efficacy of such regimens has not yet been demonstrated and when combined with the use of aminoglycosides such higher dose regimens are likely to increase the incidence of nephrotoxicity.

Oral treatment with vancomycin is effective in treating antibiotic-associated colitis due to *Clostridium difficile*, but metronidazole is generally preferred because the increasing use of oral vancomycin has probably promoted the emergence of vancomycin-resistant enterococci.

PATHOGENS MOST LIKELY TO CAUSE INFECTIONS IN SPECIFIC ORGANS AND TISSUES

In many acute and most chronic infections, the choice of antimicrobial therapy can await the results of appropriate cultures and antimicrobial susceptibility tests. In acute life-threatening infections such as meningitis, pneumonia or bacteremia, however, and in other infections that have reached a serious stage, waiting 24 to 48 hours can be dangerous, and the choice of an antimicrobial agent for initial use must be based on tentative identification of the pathogen. Knowing the organisms most likely to cause infection in specific tissues, together with evaluation of gram-stained smears and familiarity with the antimicrobial susceptibility patterns of organisms prevalent in the hospital or community, permits a rational choice of initial treatment.

In the table below, bacteria, fungi, viruses and other pathogens are listed in estimated order of the frequency with which they cause acute infection, but these frequencies are subject to annual, seasonal and geographical variation. The order of pathogens may also vary depending on whether the infections are community or hospital-acquired, and whether or not the patient is immunosuppressed. This listing is based both on published reports and on the experience of Medical Letter consultants. Organisms not listed here may also be important causes of infection.

TABLE OF BACTERIA, FUNGI, AND SOME VIRUSES MOST LIKELY TO CAUSE ACUTE INFECTIONS

BLOOD (SEPTICEMIA) Newborn Infants

- 1. Streptococcus Group B
- 2. Escherichia coli (or other gram-negative bacilli)
- 3. Listeria monocytogenes
- 4. Staphylococcus aureus
- 5. Streptococcus pyogenes (Group A)
- 6. Enterococcal spp.
- 7. Streptococcus pneumoniae

Children

- 1. Streptococcus pneumoniae
- 2. Neisseria meningitidis
- 3. Staphylococcus aureus
- 4. Streptococcus pyogenes (Group A)
- 5. Haemophilus influenzae
- 6. Escherichia coli (or other gram-negative bacilli)

Adults

- 1. Escherichia coli (or other enteric gram-negative bacilli)
- 2. Staphylococcus aureus
- 3. Streptococcus pneumoniae
- 4. Enterococcal spp.
- 5. Non-enteric gram-negative bacilli (*Pseudomonas, Acinetobacter, Aeromonas*)
- 6. Candida spp. and other fungi
- 7. Staphylococcus epidermidis
- 8. Streptococcus pyogenes (Group A)
- 9. Other streptococci (non-Group A and not Lancefield-groupable)
- 10. Bacteroides spp.
- 11. Neisseria meningitidis
- 12. Neisseria gonorrhoeae
- 13. Fusobacterium spp.
- 14. Mycobacteria
- 15. Rickettsia spp.
- 16. Ehrlichia spp.
- 17. Brucella spp.
- 18. Leptospira spp.

MENINGES

- 1. Viruses (enterovirus, mumps, herpes simplex, HIV, arbovirus, lymphocytic choriomeningitis [LCM] virus and others)
- 2. Neisseria meningitidis
- 3. Streptococcus pneumoniae
- 4. Streptococcus Group B (infants less than two months old)
- 5. Escherichia coli (or other gram-negative bacilli)
- 6. Haemophilus influenzae (in children)
- 7. Streptococcus pyogenes (Group A)

Pathogens

- 8. *Staphylococcus aureus* (with endocarditis or after neurosurgery, brain abscess)
- 9. Mycobacterium tuberculosis
- 10. Cryptococcus neoformans and other fungi
- 11. Listeria monocytogenes
- 12. Enterococcal spp. (neonatal period)
- 13. Treponema pallidum
- 14. Leptospira spp.
- 15. Borrelia burgdorferi
- 16. Toxoplasma gondii

BRAIN AND PARAMENINGEAL SPACES

- 1. Herpes simplex (encephalitis)
- 2. Anaerobic streptococci and/or *Bacteroides* spp. (cerebritis, brain abscess, and subdural empyema)
- 3. Staphylococcus aureus (cerebritis, brain abscess, epidural abscess)
- 4. Haemophilus influenzae (subdural empyema)
- 5. Arbovirus (encephalitis)
- 6. Mumps (encephalitis)
- 7. Toxoplasma gondii (encephalitis)
- 8. Human immunodeficiency virus (HIV)
- 9. Mycobacterium tuberculosis
- 10. Nocardia (brain abscess)
- 11. Listeria monocytogenes (encephalitis)
- 12. Treponema pallidum
- 13. Cryptococcus neoformans and other fungi
- 14. Borrelia burgdorferi
- 15. Other viruses (varicella-zoster [VZV], cytomegalovirus [CMV], Ebstein-Barr [EBV] and rabies)
- 16. Mycoplasma pneumoniae
- 17. Taenia solium (neurocysticercosis)
- 18. Echinococcus spp. (echinococcosis)
- 19. Strongyloides stercoralis hyperinfection
- 20. Angiostrongylus cantonensis
- 21. Free-living amoeba (Naegleria, Acanthameoba and Balamuthia spp.)

ENDOCARDIUM

1. Staphylococcus aureus

- 2. Viridans group of *Streptococcus*
- 3. Enterococcal spp.
- 4. Streptococcus bovis
- 5. Staphylococcus epidermidis
- 6. Candida albicans and other fungi
- 7. Gram-negative bacilli
- 8. Streptococcus pneumoniae
- 9. *Streptococcus pyogenes* (Group A)
- 10. Corynebacterium spp. (especially with prosthetic valves)
- 11. Haemophilus, Actinobacillus, Cardiobacterium hominis or Eikenella spp.

BONES (OSTEOMYELITIS)

- 1. Staphylococcus aureus
- 2. Salmonella spp. (or other gram-negative bacilli)
- 3. Streptococcus pyogenes (Group A)
- 4. Mycobacterium tuberculosis
- 5. Anaerobic streptococci (chronic)
- 6. Bacteroides spp. (chronic)

JOINTS

- 1. Staphylococcus aureus
- 2. Streptococcus pyogenes (Group A)
- 3. Neisseria gonorrhoeae
- 4. Gram-negative bacilli
- 5. Streptococcus pneumoniae
- 6. Neisseria meningitidis
- 7. Haemophilus influenzae (in children)
- 8. Mycobacterium tuberculosis and other Mycobacteria
- 9. Fungi
- 10. Borrelia burgdorferi

SKIN AND SUBCUTANEOUS TISSUES Burns

- 1. Staphylococcus aureus
- 2. *Streptococcus pyogenes* (Group A)
- 3. Pseudomonas aeruginosa (or other gram-negative bacilli)

Pathogens

Skin infections

- 1. Staphylococcus aureus
- 2. Streptococcus pyogenes (Group A)
- 3. Dermatophytes
- 4. Candida spp. and other fungi
- 5. Herpes simplex or zoster
- 6. Gram-negative bacilli
- 7. Treponema pallidum
- 8. Borrelia burgdorferi
- 9. Bartonella henselae or quintana
- 10. Bacillus anthracis

Decubitus Wound infections

- 1. Staphylococcus aureus
- 2. Escherichia coli (or other gram-negative bacilli)
- 3. Streptococcus pyogenes (Group A)
- 4. Anaerobic streptococci
- 5. Clostridia spp.
- 6. Enterococcal spp.
- 7. Bacteroides spp.

Traumatic and Surgical Wounds

- 1. Staphylococcus aureus
- 2. Anaerobic streptococci
- 3. Gram-negative bacilli
- 4. Clostridia spp.
- 5. Streptococcus pyogenes (Group A)
- 6. Enterococcal spp.

EYES (Cornea and Conjunctiva)

- 1. Herpes and other viruses
- 2. Neisseria gonorrhoeae (in newborn)
- 3. Staphylococcus aureus
- 4. Streptococcus pneumoniae
- 5. *Haemophilus influenzae* (in children), including biotype *aegyptius* (Koch-Weeks bacillus)
- 6. Moraxella lacunata
- 7. Pseudomonas aeruginosa

- 8. Other gram-negative bacilli
- 9. Chlamydia trachomatis (trachoma and inclusion conjunctivitis)
- 10. Fungi

EARS

Auditory Canal

- 1. Pseudomonas aeruginosa (or other gram-negative bacilli)
- 2. Staphylococcus aureus
- 3. Streptococcus pyogenes (Group A)
- 4. Streptococcus pneumoniae
- 5. Haemophilus influenzae (in children)
- 6. Fungi

Middle Ear

- 1. Streptococcus pneumoniae
- 2. Haemophilus influenzae (in children)
- 3. Moraxella catarrhalis
- 4. Streptococcus pyogenes (Group A)
- 5. Staphylococcus aureus
- 6. Anaerobic streptococci (chronic)
- 7. Bacteroides spp. (chronic)
- 8. Other gram-negative bacilli (chronic)
- 9. Mycobacterium tuberculosis

PARANASAL SINUSES

- 1. Streptococcus pneumoniae
- 2. Haemophilus influenzae
- 3. Moraxella catarrhalis
- 4. Streptococcus pyogenes (Group A)
- 5. Anaerobic streptococci (chronic sinusitis)
- 6. Staphylococcus aureus (chronic sinusitis)
- 7. Klebsiella spp. (or other gram-negative bacilli)
- 8. *Mucor* spp., *Aspergillus* spp. (especially in diabetics and immunosuppressed patients)

MOUTH

- 1. Herpes viruses
- 2. *Candida* spp.

Pathogens

- 3. Leptotrichia buccalis (Vincent's infection)
- 4. Bacteroides spp.
- 5. Mixed anaerobes
- 6. Treponema pallidum
- 7. Actinomyces

THROAT

- 1. Respiratory viruses
- 2. Streptococcus pyogenes (Group A)
- 3. Neisseria meningitidis or gonorrhoeae
- 4. Leptotrichia buccalis
- 5. Candida spp.
- 6. Corynebacterium diphtheriae
- 7. Bordetella pertussis
- 8. Haemophilus influenzae
- 9. Fusobacterium necrophorum

LARYNX, TRACHEA, AND BRONCHI

- 1. Respiratory viruses
- 2. Streptococcus pneumoniae
- 3. Haemophilus influenzae
- 4. Streptococcus pyogenes (Group A)
- 5. Corynebacterium diphtheriae
- 6. Staphylococcus aureus
- 7. Gram-negative bacilli
- 8. Fusobacterium necrophorum

PLEURA

- 1. Streptococcus pneumoniae
- 2. Staphylococcus aureus
- 3. Haemophilus influenzae
- 4. Gram-negative bacilli
- 5. Anaerobic streptococci
- 6. Bacteroides spp.
- 7. Streptococcus pyogenes (Group A)
- 8. Mycobacterium tuberculosis
- 9. Actinomyces, Nocardia spp.
- 10. Fungi
- 11. Fusobacterium necrophorum

LUNGS

Pneumonia

- Respiratory viruses (influenza virus A and B, adenovirus, respiratory syncytial virus, parainfluenza virus, rhinovirus, enteroviruses, cytomegalovirus, Epstein-Barr virus, varicellazoster virus, measles virus, herpes simplex virus, hantavirus and coronavirus [SARS])
- 2. Mycoplasma pneumoniae
- 3. Streptococcus pneumoniae
- 4. Haemophilus influenzae
- 5. Anaerobic streptococci, fusospirochetes
- 6. Bacteroides spp.
- 7. Staphylococcus aureus
- 8. *Klebsiella* spp. (or other gram-negative bacilli)
- 9. Legionella pneumophila
- 10. Chlamydia pneumoniae (TWAR strain)
- 11. Streptococcus pyogenes (Group A)
- 12. Rickettsia spp.
- 13. Mycobacterium tuberculosis
- 14. Pneumocystis carinii
- 15. Fungi (especially *Aspergillus* species in immunosuppressed patients)
- 16. Moraxella catarrhalis
- 17. Legionella micdadei (L. pittsburgensis)
- 18. Chlamydia psittaci
- 19. Fusobacterium necrophorum
- 20. Actinomyces spp.
- 21. Nocardia spp.
- 22. Rhodococcus equi
- 23. Bacillus anthracis (mediastinitis)
- 24. Yersinia pestis

Abscess

- 1. Anaerobic streptococci
- 2. Bacteroides spp.
- 3. Staphylococcus aureus
- 4. *Klebsiella* spp. (or other gram-negative bacilli)
- 5. Streptococcus pneumoniae

Pathogens

- 6. Fungi
- 7. Actinomyces, Nocardia spp.

GASTROINTESTINAL TRACT

- 1. Gastrointestinal viruses
- 2. Campylobacter jejuni
- 3. Salmonella spp.
- 4. Escherichia coli
- 5. Shigella spp.
- 6. Yersinia enterocolitica
- 7. Entamoeba histolytica
- 8. Giardia lamblia
- 9. Staphylococcus aureus
- 10. Vibrio cholerae
- 11. Vibrio parahaemolyticus
- 12. Herpes simplex (anus)
- 13. Treponema pallidum (rectum)
- 14. Neisseria gonorrhoeae (rectum)
- 15. Candida spp.
- 16. Clostridium difficile
- 17. Cryptosporidium parvum
- 18. Cytomegalovirus (CMV)
- 19. Human immunodeficiency virus (HIV)
- 20. Mycobacterium avium complex
- 21. Helicobacter pylori
- 22. Tropheryma whippelii

URINARY TRACT

- 1. Escherichia coli (or other gram-negative bacilli)
- 2. Staphylococcus aureus and epidermidis
- 3. Neisseria gonorrhoeae (urethra)
- 4. Enterococcal spp.
- 5. Candida spp.
- 6. Chlamydia spp. (urethra)
- 7. *Treponema pallidum* (urethra)
- 8. Trichomonas vaginalis (urethra)
- 9. Ureaplasma urealyticum

FEMALE GENITAL TRACT Vagina

- 1. Trichomonas vaginalis
- 2. *Candida* spp.
- 3. Neisseria gonorrhoeae
- 4. Streptococcus pyogenes (Group A)
- 5. Gardnerella vaginalis and associated anaerobes
- 6. Treponema pallidum

Uterus

- 1. Anaerobic streptococci
- 2. Bacteroides spp.
- 3. Neisseria gonorrhoeae (cervix)
- 4. *Clostridia* spp.
- 5. Escherichia coli (or other gram-negative bacilli)
- 6. Herpes simplex virus, type II (cervix)
- 7. Streptococcus pyogenes (Group A)
- 8. Streptococcus, Groups B and C
- 9. Treponema pallidum
- 10. Actinomyces spp. (most common infection of intrauterine devices)
- 11. Staphylococcus aureus
- 12. Enterococcal spp.
- 13. Chlamydia trachomatis
- 14. Mycoplasma hominis

Fallopian Tubes

- 1. Neisseria gonorrhoeae
- 2. Escherichia coli (or other gram-negative bacilli)
- 3. Anaerobic streptococci
- 4. Bacteroides spp.
- 5. Chlamydia trachomatis

MALE GENITAL TRACT Seminal Vesicles

- 1. Gram-negative bacilli
- 2. Neisseria gonorrhoeae

Pathogens

Epididymis

- 1. Chlamydia
- 2. Gram-negative bacilli
- 3. Neisseria gonorrhoeae
- 4. Mycobacterium tuberculosis

Prostate Gland

- 1. Gram-negative bacilli
- 2. Neisseria gonorrhoeae

PERITONEUM

- 1. Gram-negative bacilli
- 2. Enterococcal spp.
- 3. Bacteroides spp.
- 4. Anaerobic streptococci
- 5. Clostridia spp.
- 6. Streptococcus pneumoniae
- 7. Streptococcus Group B

CHOICE OF Antibacterial Drugs

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New drugs for bacterial infections and new information about older drugs continue to become available. Empirical treatment of some common bacterial infections is discussed below. A table listing the drugs of choice and alternatives for each pathogen begins on page 55. These recommendations are based on results of susceptibility studies, clinical trials and the opinions of Medical Letter consultants. Local resistance patterns should be taken into account. Trade names are listed on page 61.

INFECTIONS OF SKIN, SOFT TISSUE AND BONE

CELLULITIS — Uncomplicated skin and skin structure infections in immunocompetent patients are most commonly due to *Staphylococcus aureus, Streptococcus pyogenes* (Group A), or *Streptococcus agalactiae* (Group B). Complicated skin and skin structure infections, such as occur in patients with burns, diabetes, infected decubitus ulcers and traumatic or surgical wound infections, are more commonly due to gram-negative bacilli, including *Escherichia coli* and *Pseudomonas aeruginosa*. Group A *streptococci* or *Clostridium* spp., with and without other anaerobes, can cause fulminant soft tissue infection and necrosis, particularly in patients with diabetes.

For **uncomplicated** infections, an anti-staphylococcal penicillin such as dicloxacillin or a first-generation cephalosporin such as cephalexin would be a reasonable choice. If the patient requires hospitalization, the same classes of drugs (cefazolin, nafcillin) could be given IV. Clindamycin or a fluoroquinolone with good activity against gram-positive organisms (levofloxacin, moxifloxacin or gatifloxacin) would be rea-

sonable choices for patients who are allergic to penicillin (HB Fung et al, Drugs 2003; 63:1459).

Methicillin-resistant *Staphylococcus aureus* (MRSA), an increasing cause of community-onset infections, should be considered if the patient was previously colonized with MRSA, has a history of recent hospitalization, has a delayed response to therapy, or is in a geographic area of high prevalence. Vancomycin is the drug of choice for treatment of severe infections due to MRSA. Linezolid or daptomycin (Medical Letter 2004; 46:11) are reasonable alternatives. Many community-acquired strains of MRSA can also be treated with clindamycin, trimethoprim-sulfamethoxazole or a fluoroquinolone with good gram-positive coverage (levofloxacin, gatifloxacin or moxifloxacin).

For **complicated** infections, piperacillin/tazobactam, ticarcillin/clavulanate, imipenem or meropenem would be reasonable empiric monotherapy; in severely ill patients addition of vancomycin or linezolid to treat MRSA should be considered. If Group A streptococcus is the cause, the combination of clindamycin and penicillin should be used (DL Stevens, Curr Infect Dis Report 2003; 5:379). Surgical debridement is essential to the management of necrotizing skin and skin structure infections (BJ Childers et al, Am Surg 2002; 68:109).

BONE AND JOINT — *S. aureus* is the most common cause of **osteomyelitis**. *Streptococcus pyogenes* is another possible pathogen. *Salmonella* spp. can cause osteomyelitis in patients with sickle cell disease, and other gram-negative bacteria (*E. coli, Pseudomonas*) can also occur, particularly in patients who have had orthopedic procedures. Infections of the feet in diabetic patients often involve both bone and soft tissue and are usually polymicrobial, including both aerobic and anaerobic bacteria.

Septic arthritis in young, sexually active patients is frequently due to *Neisseria gonorrhoeae. S. aureus* or *S. pyogenes*, and gram-negative bac-

teria can also cause septic arthritis (I Garcia-De La Torre, Rheum Dis Clin North Am 2003; 29:61).

For treatment of osteomyelitis, IV administration of an anti-staphylococcal penicillin such as oxacillin or a first-generation cephalosporin such as cefazolin would be appropriate. Ceftriaxone would be a reasonable first choice for empiric treatment of a joint infection to include coverage for *S. aureus* and *N. gonorrhoeae*. For both bone and joint infections, IV penicillin or ceftriaxone can be used to treat *Streptococcus* spp. If MRSA is the pathogen, vancomycin or linezolid (if the patient cannot take vancomycin) should be used. Ceftriaxone, ceftazidime or ciprofloxacin would be a good option for bone and joint infections due to gram-negative bacteria.

MENINGITIS

The organisms most commonly responsible for community-acquired bacterial meningitis in children and adults are *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis*. Meningitis due to *H. influenzae* type b in children has decreased markedly as a result of immunization. Enteric gram-negative bacteria cause meningitis especially in neonates, the elderly, and in those who have had recent neurosurgery or are immunosuppressed. Group B streptococcus often causes meningitis in neonates. *Listeria monocytogenes* may be the cause in pregnant women and newborns, and also in the elderly or immunosuppressed (X Sáez-Llorens and GH McCracken Jr, Lancet 2003; 361:2139).

For treatment of meningitis in adults and in children more than two months old, pending results of cultures, high-dose ceftriaxone or cefotaxime is generally recommended, plus vancomycin to cover cephalosporin-resistant pneumococci. Vancomycin in usual doses may not reach effective levels in cerebrospinal fluid and clinical response should be carefully monitored; some Medical Letter consultants have used 4 grams per day to treat meningitis. Vancomycin should be stopped

if the etiologic agent proves to be susceptible to a third-generation cephalosporin or penicillin. For treatment of nosocomial meningitis, vancomycin and a cephalosporin with good activity against *Pseudomonas* such as ceftazidime are appropriate; if *Pseudomonas* is confirmed, addition of an aminoglycoside such as tobramycin, gentamicin or amikacin is recommended. Meningitis due to *Listeria* should be treated with ampicillin, with or without gentamicin.

Neonatal meningitis is most often caused by group B or other streptococci, gram-negative enteric organisms or *Listeria*. For meningitis in the first two months of life, while waiting for the results of cultures and susceptibility tests, many Medical Letter consultants use ampicillin plus cefotaxime, with or without gentamicin.

Ceftriaxone or cefotaxime is sometimes used to treat meningitis in **penicillin-allergic** patients, but such patients may also have allergic reactions to cephalosporins. Vancomycin with or without rifampin should be added to cover resistant pneumococci. When allergy prevents the use of a cephalosporin, chloramphenicol can be given for initial treatment, but may not be effective if the pathogens are enteric gram-negative bacilli or *Listeria*, or in some patients with pneumococcal meningitis. For enteric gram-negative bacilli, aztreonam could be used. Trimethoprim-sulfamethoxazole can be used for treatment of *Listeria* meningitis in patients allergic to penicillin.

Corticosteroids, usually dexamethasone (*Decadron*, and others), given before or at the same time as the first dose of antibiotics have been reported to decrease the incidence of hearing loss and other neurological complications in children with meningitis (PK Coyle, Arch Neurol 1999; 56:796; T Duke et al, Expert Opin Pharmacother 2003; 4:1227). In addition, a recent study in 301 adults with bacterial meningitis found that dexamethasone, given 15-20 minutes before the first dose of vancomycin and continued every 6 hours for four days, was associated with improved

outcome and decreased mortality (J de Gans et al, N Engl J Med 2002; 347:1549). The benefits were most pronounced in patients with pneumococcal meningitis. All pneumococcal isolates in this study were susceptible to penicillin; a theoretical downside to steroid use in meningitis is that it can decrease antibiotic penetration into the CNS, particularly of vancomycin (V Abril and E Ortega, N Engl J Med 2003; 348:954). A small study in adult patients with bacterial meningitis found that ceftriaxone levels in the CNS were similar in patients who received dexamethasone compared to those who did not (AC Buke et al, Int J Antimicrob Agents 2003; 21:452). A study in animals found that dexamethasone decreases vancomycin levels in the CSF when used alone, but not when vancomycin is combined with rifampin (J Martinez-LaCasa et al, J Antimicrob Chemother 2002; 49:507).

PNEUMONIA

The "atypical" pathogens *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (formerly *Chlamydia pneumoniae*) probably cause most cases of **community-acquired bacterial pneumonia**. *Legionella*, another atypical organism, is less common. Among **hospitalized patients with community-acquired bacterial pneumonia**, *S. pneumo-niae* probably is the most common pathogen. Other bacterial pathogens include *H. influenzae, Klebsiella pneumoniae*, and occasionally other gram-negative bacilli and anaerobic mouth organisms. **Hospitalacquired (nosocomial) pneumonia** is often caused by gram-negative bacilli, especially *P. aeruginosa, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Acinetobacter* spp.; it can also be caused by *S. aureus*.

Guidelines for the treatment of pneumonia have recently been published (Treatment Guidelines 2003; 1:83; LA Mandell et al, Clin Infect Dis 2003; 37:1405). In **ambulatory** patients, an oral macrolide (erythromycin, azithromycin or clarithromycin), doxycycline, or a fluoroquinolone

with good anti-pneumococcal activity such as levo-, gati-, gemi- or moxifloxacin is generally used for otherwise healthy adults. Pneumococci may, however, be resistant to macrolides (JR Lonks et al, J Antimicrob Chemother 2002; 50 suppl 2:87) and to doxycycline, especially if they are resistant to penicillin. For older patients or those with co-morbid illness, a fluoroquinolone may be a better choice. Fluoroquinolone-resistant pneumococci have also been described rarely (MR Jacobs et al, J Antimicrob Chemother 2003; 52:229).

In **community-acquired pneumonia requiring hospitalization**, ceftriaxone or cefotaxime, plus a macrolide (erythromycin, azithromycin or clarithromycin) is recommended pending culture results (RB Brown et al, Chest 2003; 123:1503). Alternatively, a fluoroquinolone with good activity against *S. pneumoniae* (levo-, gati-, gemi- or moxifloxacin) can be substituted. If aspiration pneumonia is suspected, metronidazole or clindamycin can be added. Moxifloxacin, which has anaerobic activity, is a reasonable alternative.

In treating pneumococcal pneumonia due to strains with intermediate degrees of penicillin resistance (minimal inhibitory concentration [MIC] $\leq 2 \mu g/mL$), ceftriaxone, cefotaxime, or high doses of either IV penicillin (12 million units daily for adults) or oral amoxicillin can be used. For highly resistant strains (MIC >2 $\mu g/mL$), an IV fluoroquinolone (levofloxacin, gatifloxacin or moxifloxacin), vancomycin or linezolid may be required, and should be added in severely ill patients (such as those requiring admission to an ICU) and those not responding to a β -lactam.

For initial treatment of **hospital-acquired pneumonia**, in which antimicrobial resistance is frequent and can emerge during treatment, Medical Letter consultants would use piperacillin/tazobactam, ticarcillin/clavulanate or a carbapenem (imipenem or meropenem), all of which have broad gram-positive, gram-negative and anaerobic activity, or cefepime,

which has broader activity than ceftriaxone or cefotaxime against gramnegative organisms. In severely ill patients, an aminoglycoside (tobramycin, gentamicin or amikacin) or ciprofloxacin should be added to improve *Pseudomonas* coverage. Addition of vancomycin or linezolid should be considered in hospitals where MRSA is common.

INFECTIONS OF THE GENITOURINARY TRACT

URINARY TRACT INFECTION — Acute uncomplicated cystitis in women can be effectively and inexpensively treated, before the infecting organism is known, with a three-day course of oral trimethoprim-sulfamethoxazole. In areas where the prevalence of *E. coli* resistant to trimethoprim-sulfamethoxazole exceeds 15% to 20%, a fluoroquinolone can be substituted (K Gupta et al, Ann Intern Med 2001; 135:41). Other alternatives include 5- to 7-day regimens of nitrofurantoin, or a single dose of fosfomycin (TM Hooton, Int J Antimicrob Agents 2003; 22:S65; SD Fihn, N Engl J Med 2003; 349:259). Based on the results of susceptibility testing, nitrofurantoin, amoxicillin or a cephalosporin can be used to treat urinary tract infections in pregnant women (LE Nicolle, Int J Antimicrob Agents 2003; 22:1); nitrofurantoin should not be given near term or during labor or delivery because it can cause hemolytic anemia in the newborn.

Acute uncomplicated pyelonephritis can often be managed with a 7-day course of an oral fluoroquinolone. Urinary tract infections that recur after use of antimicrobial agents or are acquired in hospitals or nursing homes are more likely to be due to antibiotic-resistant gram-negative bacilli, *S. aureus* or enterococci. A fluoroquinolone, oral amoxicillin/clavulanate or an oral third-generation cephalosporin such as cefpodoxime, cefdinir or ceftibuten can be useful in treating such infections in outpatients. In hospitalized patients with urinary tract infections, treatment with a third-

generation cephalosporin, a fluoroquinolone, ticarcillin/clavulanate, piperacillin/tazobactam, imipenem or meropenem is recommended, sometimes together with an aminoglycoside such as gentamicin, especially in patients with sepsis syndromes.

PROSTATITIS — Acute bacterial prostatitis may be due to *E. coli, Klebsiella* spp., *Proteus mirabilis, P. aeruginosa,* or *Enterococcus faecalis* (HS Gurunadha Rao Tunuguntla and CP Evans, Prostate Cancer Prostatic Dis 2002; 5:172), but a bacterial pathogen is often not identified. Chronic prostatitis, although often due to unknown causes, may be caused by the same bacteria as acute prostatitis, or by *S. aureus* and coagulase-negative staphylococci. Sexually transmitted organisms such as *C. trachomatis, Ureaplasma urealyticum* and *N. gonorrhoeae* can also cause chronic prostatitis (JN Krieger et al, Urology 2002; 60 suppl 6A:8).

An oral fluoroquinolone with activity against *Pseudomonas* (ciprofloxacin, levofloxacin) is a reasonable choice for initial treatment of acute bacterial prostatitis in a patient who does not require hospitalization. For more severe disease, an IV fluoroquinolone, third-generation cephalosporin, aminogly-coside or trimethoprim-sulfamethoxazole may be used. Chronic bacterial prostatitis is generally treated with a long (4- to 12-week) course of an oral fluoroquinolone or trimethoprim-sulfamethoxazole (JE Fowler, Jr, Urology 2002; 60 suppl 6A:24).

INTRA-ABDOMINAL INFECTIONS

Most intra-abdominal infections, such as **cholangitis** and **diverticulitis**, are due to enteric gram-negative organisms, most commonly *E. coli*, but also *Klebsiella* or *Proteus* species. Enterococci and anaerobes are also common. Loss of normal flora, such as occurs in hospitalized patients,

leads to an increased risk of infections due to *Pseudomonas* spp. and *Candida*. Many intra-abdominal infections, particularly abscesses, are polymicrobial.

For intra-abdominal infections, treatment with cefoxitin, cefotetan, piperacillin/tazobactam, ticarcillin/ clavulanate, ampicillin/sulbactam or ertapenem would be a reasonable first choice (JS Solomkin et al, Clin Infect Dis 2003; 37:997). Ciprofloxacin plus metronidazole for anaerobic coverage could be used in patients allergic to ß-lactams. When the source of bacteremia is thought to be the biliary tract, some clinicians would use piperacillin/tazobactam or ampicillin/sulbactam, each with or without an aminoglycoside. In severely ill patients and those with prolonged hospitalization, treatment should include coverage for *Pseudomonas;* an antipseudomonal penicillin (ticarcillin/clavulanate, piperacillin/tazobactam), imipenem, meropenem, ceftazidime or cefepime, each plus metronidazole, would be a reasonable choice; an aminoglycoside could be added to any of these regimens.

SEPSIS SYNDROME

For treatment of sepsis syndromes, the choice of drugs should be based on the probable source of infection, gram-stained smears of appropriate clinical specimens and the immune status of the patient. The choice should also reflect local patterns of bacterial resistance.

A third- or fourth-generation cephalosporin (cefotaxime, ceftizoxime, ceftriaxone, cefepime or ceftazidime), piperacillin/tazobactam, ticarcillin/clavulanate, imipenem or meropenem, or aztreonam can be used to treat sepsis caused by most strains of gram-negative bacilli. Ceftazidime has less activity against gram-positive cocci. Cephalosporins other than ceftazidime and cefepime have limited activity against *P. aeruginosa*.

Piperacillin/tazobactam, ticarcillin/clavulanate, imipenem and meropenem are active against most strains of *P. aeruginosa* and are active against anaerobes. Aztreonam is active against many strains of *P. aeruginosa* but has no activity against gram-positive bacteria or anaerobes.

For initial treatment of life-threatening sepsis in adults, Medical Letter consultants recommend either a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidine or cefepime), piperacillin/tazobactam, imipenem or meropenem, each together with an aminoglycoside (gentamicin, tobramycin or amikacin). When MRSA or methicillinresistant *S. epidermidis* are suspected, vancomycin (alone or with gentamicin and/or rifampin) is often added. When bacterial endocarditis is suspected and therapy must be started before the pathogen is identified, a combination of ceftriaxone and vancomycin can be used; some Medical Letter consultants would also add gentamicin.

NEUTROPENIC FEVER — For suspected bacteremia in neutropenic patients, ceftazidime, imipenem, meropenem or cefepime, each alone or in more seriously ill patients with an aminoglycoside (gentamicin, tobramycin or amikacin), would be reasonable first choices (H Link et al, Ann Hematol 2003; 82, suppl 2:S105; WT Hughes et al, Clin Infect Dis 2002; 34:730). Piperacillin/tazobactam or ticarcillin/clavulanate, either combined with amikacin, may be equally effective. Addition of vancomycin may be necessary for treatment of neutropenic patients who remain febrile despite antibiotics or who develop bacteremia caused by methicillin-resistant staphylococci or penicillin-resistant viridans streptococci. Studies in low-risk hospitalized adults show that when neutropenia is expected to last less than 10 days, high-dose oral ciprofloxacin with amoxicillin/clavulanate is as effective as intravenous ceftazidime or ceftriaxone plus amikacin (A Koh and PA Pizzo, Cancer Invest 2002; 20:420).

ANTIBACTERIAL RESISTANCE

MULTIPLE-ANTIBIOTIC-RESISTANT ENTEROCOCCI -Many Enterococcus spp. are now resistant to penicillin and ampicillin, gentamicin or streptomycin or both, and to vancomycin. Some of these strains are susceptible in vitro to chloramphenicol, doxycycline or rarely to fluoroquinolones, but clinical results with these drugs have been variable. Linezolid and daptomycin are active against many grampositive organisms, including both Enterococcus faecium and Enterococcus faecalis (JW Chien et al, Clin Infect Dis 2000; 30:146); resistance has been rare (AH Mutnick et al, Ann Pharmacother 2003; 37:769; Medical Letter 2004; 46:11). Quinupristin/dalfopristin is active against most strains of vancomycin-resistant E. faecium, but not E. faecalis (DJ Winston et al, Clin Infect Dis 2000; 30:790). Polymicrobial surgical infections that include antibiotic-resistant enterococci may respond to antibiotics aimed at the other organisms. When antibioticresistant enterococci cause endocarditis, surgical replacement of the infected valve may be required. Urinary tract infections caused by resistant enterococci may respond nevertheless to ampicillin or amoxicillin, which reach very high concentrations in urine; nitrofurantoin, fosfomycin, or doxycycline can also be used.

STAPHYLOCOCCUS AUREUS WITH REDUCED SUSCEPTIBIL-ITY TO VANCOMYCIN — *Staphylococcus aureus* isolates with decreased susceptibility to vancomycin are uncommon but are increasingly being reported (A Van Griethuysen et al, J Clin Microbiol 2003; 41:2487; K Sieradzki et al, J Clin Microbiol 2003; 41:1687; MMWR Morb Mortal Wkly Rep 2002; 51:565). Many of these isolates, however, can still be treated with high-dose vancomycin. Recently the *vanA* gene, which encodes for vancomycin resistance in enterococci, has been identified in rare isolates of MRSA (S Chang et al, N Engl J Med 2003; 348:1342; MMWR Morb Mortal Wkly Rep 2002; 51:902). These van-

comycin-resistant MRSA (VRSA) have generally remained susceptible to trimethoprim-sulfamethoxazole, as well as to linezolid and daptomycin. It is not yet clear how frequently or easily this mode of resistance will occur; to date there are only two isolates (AP Johnson and N Woodford, J Antimicrob Chemother 2002; 50:621). Susceptibility testing must be used to guide therapy.

COMMUNITY-ACQUIRED MRSA — Community-acquired MRSA is a growing problem in the US. It has recently been implicated in more than 12,000 infections in some prison systems; infections were mostly skin and soft tissue (MMWR Morb Mortal Wkly Rep 2003; 52:992). Community-acquired strains often remain susceptible to drugs such as trimethoprim-sulfamethoxazole and clindamycin; nosocomial strains do not. Treatment should be guided by susceptibility tests.

ANTIBIOTIC-RESISTANT GRAM-NEGATIVE BACILLI — In some hospitals, gram-negative bacilli have become increasingly resistant to aminoglycosides, third-generation cephalosporins and aztreonam; these strains may be susceptible to imipenem, meropenem, ertapenem, piperacillin/tazobactam or trimethoprim-sulfamethoxazole. Of particular concern are multi-drug resistant strains of *Pseudomonas* and *Acinetobacter* (J Quale et al, Clin Infect Dis 2003; 37:214). Resistance is also increasing in some community-acquired organisms such as *Salmonella* spp. and *Shigella* spp. Susceptibility testing and resistance patterns within the region, as reported by public health laboratories, should be used to guide therapy.

Infe	ecting Organism	Drug of First Choice [†]	Alternative Drugs [†]	
GR	AM-POSITIVE COCCI			
Er	terococcus ¹	endocarditis or other severe infection: penicillin G or ampi- cillin + gentamicin or strepto- mycin ²	vancomycin + gentamicin or streptomycin ² ; linezolid; daptomycin ³ ; quinupristin/dalfopristin ⁴	
		uncomplicated urinary tract infection: ampicillin or amoxicillin	nitrofurantoin; a fluoroquinolone ⁵ ; fosfomycin	
*St	aphylococcus aureus or epidermidis	3		
	nethicillin-susceptible	a penicillinase-resistant penicillin ⁶	 a cephalosporin^{7,8}; vancomycin; imipenem or meropenem; clindamycin; linezolid; daptomycin³; a fluoroquinolone⁵ 	
	nethicillin-resistant ⁹	pin	linezolid; daptomycin ³ ; a fluoroquinolone ⁵ ; quinupristin/dalfopristin; a tetracycline ¹⁰ ; trimethoprim- sulfamethoxazole	
	reptococcus pyogenes (group A ¹¹) nd groups C and G	penicillin G or V ¹²	clindamycin; erythromycin; a cephalosporin ^{7,8} ; vanco- mycin; clarithromycin ¹³ ; azithromycin; linezolid; daptomycin ³	
Re	esistance may be a problem; susceptil	bility tests should be used to guide the	rapy.	
† Tr	ade names are listed on page 61.			
-	Disk sensitivity testing may not provide ous infections	adequate information; β-lactamase assays	s, "E" tests and dilution tests for susceptibility should be used in se	
2		alv common among enterococci: treatmen	t options include ampicillin 2 g IV g4h, continuous infusion of amp	
	cillin, a combination of ampicillin plus a	fluoroquinolone, or a combination of amp		
ι.	Daptomycin should not be used to treat			
È.	Quinupristin/dalfopristin is not active ag		in vitro activity against S. pneumoniae, including penicillin- and	
	has become frequent among methicillin infections, norfloxacin, lomefloxacin or	n-resistant strains. Ciprofloxacin has the g enoxacin can be used. For tuberculosis, le	nave good activity against many strains of <i>S. aureus</i> , but resistan reatest activity against <i>Pseudomonas aeruginosa</i> . For urinary trac voltoxacin, diprofloxacin, gatifloxacin or moxifloxacin cou available for IV use. None of these agents is recommended for ch	
i.	be used. Ampicillin, amoxicillin, carbeni tions of clavulanate with amoxicillin or t	cillin, ticarcillin and piperacillin are not eff icarcillin, sulbactam with ampicillin, and ta	ere infections, a parenteral formulation of nafcillin or oxacillin shou ective against penicillinase-producing staphylococci. The combina izobactam with piperacillin may be active against these organism	
7.		ernatives to penicillins in patients allergic	to penicillins, but such patients may also have allergic reactions to	
3.	cephalosporins. For parenteral treatment of staphylococcal or non-enterococcal steptococcal infections, a first-generation cephalosporin such as cetazolin can be used. For oral therapy, cephalexin or cephradine can be used. The second-generation cephalosporin cefamandole, cetroval, cettoreain, cetotatin and tomached are more acute than the first-generation drug against gram-regative bacteria. <i>El</i> (<i>transitions</i>) is active against argum-regative bacteria. <i>El</i> (<i>transitions</i>) and the discover and the second-generation drug against gram-regative bacteria. <i>El</i> (<i>transitions</i>) and the "burth- generation" cetpime have greater activity than the second-generation drug against enteric gram-regative bacili. Ceftazzime and the "burth- generation" cetpime have greater activity than the second-generation drug against enteric gram-regative bacili. Ceftazzime and the "burth- generation" cetpime have greater activity than the second-generation drug against enteric gram-regative bacili. Ceftazzime and the "burth- generation" cetpime have greater activity than the second-generation drug against enteric gram-regative bacili. Ceftazzime and the "burth- generation" cetpime have greater activity than the second-generation drug against enteric gram-regative bacili. The have a distributed activity gainst gram-positive cocci similar to neoflaxizme and ceftazime. Activity against enteric gram-regative bacili. The have no seclul activity against tanary dress or <i>P</i> avarigness, and ceftime and ceftibuten have no useful activity against faultative gram-regative bacili. Then we no useful activity against tanary dress or <i>P</i> avarigness, and ceftime and ceftibuten have no useful activity of all currently available cephalosporins against <i>E</i> averaginos is poor or inconsistent.			
Э.	Many strains of coagulase-positive and resistant to cephalosporins, imipenem a		sistant to penicillinase-resistant penicillins; these strains are also o fluoroquinolones, trimethoprim-sulfamethoxazole and clindamycii -sulfamethoxazole.	
	Tetracyclines are generally not recomm For serious soft-tissue infection due to be resistant to clindamycin; therefore, s ulin, to treat serious soft-tissue infectio	ended for pregnant women or children le group A streptococci, clindamycin may be ome Medical Letter consultants suggest u	ss than 8 years old. more effective than penicillin. Group A streptococci may, howeve sing both clindamycin and penicillin, with or without IV immune glob id for necrotizing soft tissue infections due to Group A streptococc	
12.	Penicillin V (or amoxicillin) is preferred t infections, penicillin G, administered pa pneumococci or Treponema pallidum, p	or oral treatment of infections caused by r renterally, is first choice. For somewhat lo procaine penicillin G, an IM formulation, ca ion, is usually given in a single monthly inj	amnomyon. non-penicillinase-producing streptococci. For initial therapy of sever nger action in less severe infections due to group A streptococci, an be given once or twice daily, but is seldom used now. Benzathin section for prophylaxis of rheumatic fever, once for treatment of Grou	

Pericent G, a slowly absorbed preparation, is usually given in a single m A streptococcal pharyngitis and once or more for treatment of syphilis. 13. Not recommended for use in pregnancy.

Infecting Organism	Drug of First Choice [†]	Alternative Drugs [†]
Streptococcus, group B	penicillin G or ampicillin	a cephalosporin ^{7,8} ; vancomycin; daptomycin ³ ; erythromycin
*Streptococcus, viridans group1	penicillin G ± gentamicin	a cephalosporin ^{7,8} ; vancomycin
Streptococcus bovis	penicillin G	a cephalosporin ^{7,8} ; vancomycin
Streptococcus, anaerobic or Pepto- streptococcus	penicillin G	clindamycin; a cephalosporin ^{7,8} ; vancomycin
*Streptococcus pneumoniae ¹⁴ (pneu- mococcus) penicillin-susceptible (MIC <0.1 µg/mL)	penicillin G or V ¹² ; amoxicillin	a cephalosporin ^{7,8} ; arythromycin; azithromycin; clarith- romycin ¹³ ; levo-, gati-, gemi- or moxifloxacin ¹⁶ ; meropenem, imipenem or artapenem; telithromycin [§] ; trimethoprim-sufamethoxazoic; clindamycin; a tetracy-
penicillin-intermediate resistance (MIC 0.1 - $\leq 2 \ \mu g/mL$)	penicillin G IV (12 million units/day for adults); ceftriaxone or cefotaxime	cline ¹⁰ ; vancomycin levo-, gati-, gemi- or moxifloxacin ¹⁶ ; vancomycin; clindamycin; telithromycin [§]
penicillin-high-level resistance (MIC >2 µg/mL)	meningitis: vancomycin + ceftriaxone or cefotaxime, ± rifampin other infections: vancomycin + ceftriaxone or cefotaxime; levo-, gati-, gemi- or moxifloxacin ¹⁶	linezolid; quinupristin/dalfopristin; telithromycin $\$$
GRAM-NEGATIVE COCCI Moraxella (Branhamella) catarrhalis	cefuroxime7; a fluoroquinolone5	trimethoprim-sulfamethoxazole; amoxicillin/clavulanate; erythromycin; darithromycin ¹³ ; azithromycin; a tetra- cycline ¹⁰ ; cetotaxime ⁷ ; cetifzoxime ⁷ ; cetfraxone ⁷ ; cetpodoxime ⁷ ; telithromycin [§]
Neisseria gonorrhoeae (gonococcus) ¹⁷	ceftriaxone7; ciprofloxacin, gatifloxacin or ofloxacin15,16	cefotaxime7; penicillin G
<i>Neisseria</i> <i>meningitidis</i> ¹⁸ (meningococcus)	penicillin G	cefotaxime ⁷ ; ceftizoxime ⁷ ; ceftriaxone ⁷ ; chloramphenicol ¹⁹ a sulfonamide ²⁰ ; a fluoroquinolone ⁵
GRAM-POSITIVE BACILLI *Bacillus anthracis ²¹ (anthrax)	ciprofloxacin ¹⁶ ; a tetracycline ¹⁰	penicillin G; amoxicillin; erythromycin; imipenem; clin- damycin; levofloxacin ¹⁶
Bacillus cereus, subtilis	vancomycin	imipenem or meropenem; clindamycin
Clostridium perfringens ²²	penicillin G; clindamycin	metronidazole; imipenem, meropenem or ertapenem; chloramphenicol ¹⁹
Clostridium tetani 23	metronidazole	penicillin G; a tetracycline ¹⁰
Clostridium difficile 24	metronidazole (oral)	vancomycin (oral)

14. Some strains of s. pneumoniae are resistant to erytmomycin, clinicamycin, timemoprim-suitametroxazole, clanitromycin, aztitriomycin and chioramphenicol, and resistance to the newer fluoroquinolones is rare but increasing (R Davidson et al, N Engl J Med 2002; 346:747). Nearly all strains tested so far are susceptible to linezolid and quinuprisitrividalforpistin in vitro.

 Fluoroquinolone-resistant strains of gonococcus are increasingly common (MMWR, Morb Mortal Wkly Rep 2002; 51:1041; KA Fenton et al, Lancet 2003; 361:1867).

16. Usually not recommended for use in children or pregnant women.

17. Patients with gonorrhea should be treated presumptively for co-infection with C. trachomatis with azithromycin or doxycycline.

 Rare strains of N. meningitidis are resistant or relatively resistant to penicillin. A fluoroquinolone or rifampin is recommended for prophylaxis after close contact with infected patients.

Because of the possibility of serious adverse effects, this drug should be used only for severe infections when less hazardous drugs are ineffective.

Suttonamide-resistant strains are frequent in the US; suttonamides should be used only when susceptibility is established by susceptibility tests.
 For post-exposure prophylaxis, ciprofloxacin for 4 weeks if given with vaccination, and 60 days if not given with vaccination, might prevent disease; if

 For post-exposure proprylaxis, cipronoxacin for 4 weeks in given with vaccination, and bu days in hot given with vaccination, might prevent disease; if the strain is susceptible, doxycycline is an alternative (JG Bartlett et al, Clin Infect Dis 2002; 35:851; Medical Letter 2001; 43:87).

22. Debridement is primary. Large doses of penicillin G are required. Hyperbaric oxygen therapy may be a useful adjunct to surgical debridement in management of the spreading, necrotizing type of infection.

For prophylaxis, a tetanus toxoid booster and, for some patients, tetanus immune globulin (human) are required.

24. In order to decrease the emergence of vancomycin-resistant enterococci in hospitals and to reduce costs, most clinicians now recommend use of metronidazole first in treatment of patients with C. difficile colitis, with oral vancomycin used only for seriously ill patients or those who do not respond to metronidazole.

Infecting Organism	Drug of First Choice [†]	Alternative Drugs [†]
GRAM-POSITIVE BACILLI (continued)		
Corynebacterium diphtheriae ²⁵	erythromycin	penicillin G
Corynebacterium, JK group	vancomycin	penicillin G + gentamicin; erythromycin
*Erysipelothrix rhusiopathiae	penicillin G	erythromycin; a cephalosporin7,8; a fluoroquinolone5
Listeria monocytogenes	ampicillin ± gentamicin	trimethoprim-sulfamethoxazole
ENTERIC GRAM-NEGATIVE BACILLI		
*Campylobacter fetus	a third-generation cephalosporin8; gentamicin	ampicillin; imipenem or meropenem
*Campylobacter jejuni	erythromycin or azithromycin	a fluoroquinolone5; a tetracycline10; gentamicin
*Citrobacter freundi	imipenem or meropenem ²⁶	a fluoroquinolone ⁵ ; ertapenem; amikacin; a tetracycline ¹⁰ ; trimethoprim-sulfamethoxazole; cefotaxime ^{7,26} , ceftizoxime ^{7,26} , ceftriaxone ^{7,26} , cefepime ^{7,26} , or ceftazidime ^{7,26}
*Enterobacter	imipenem or meropenem ²⁶ ; cefepime ^{7,26}	gentamicin, tobramycin or amikacin; trimethoprim-sul- famethoxazole; ciprofloxacin ¹⁶ ; ticarcillin/clavulanate ²⁷ or piperacillin/sulbactam ²⁷ ; aztreonam ²⁶ ; cefotaxime, cefitizoxime, ceftriaxone, or ceftazidime ^{7,26}
*Escherichia coli ²⁸	cefotaxime, ceftriaxone, cefepime or ceftazidime ^{7,26}	ampicillin ± gentamicin, tobramycin or amikacin; gentamicin, tobramycin or amikacin; amoxiolilin/clavu- lanata ⁶² ; teoricalin/clavu-lane ⁷² ; piperacilin/tazboatam ²⁷ ; ampicillin/sulbactam ²⁶ ; trimethoprim-sulfamethoxaza ²⁶ ; imipenem, meropenem or ertapenem ²⁶ ; aztreonam ²⁶ ; a fluoroquinolone ⁵ ; another cephalospoin ^{7,8}
*Klebsiella pneumoniae ²⁸	cefotaxime, ceftriaxone, cefepime or ceftazidime ^{7,26}	imipenem, meropenem or ertapenem ²⁶ ; gentamicin, tobramycin or amikacin; amoxicillin/clavulanate ²⁶ ; licarcillin/clavulanate ²⁷ ; piperacillin/hazobactam ²⁷ ; ampicillin/subactam ²⁶ ; timethoprim-sultemethoxazole; aztreonam ²⁶ ; a fluoroquinolone ⁵ ; another cephalosporin ^{7,8}
*Proteus mirabilis ²⁸	ampicillin ²⁹	a cephalosporin ^{7,2,226} , ticarcillin/clavulanate or piperacillin/tazobactam ²⁷ ; gentamicin, tobramycin or amikacin; trimethoprim-sulfamethoxazole; imipenem, meropenem or ertapenem ²⁶ , aztreonam ²⁶ , a fluoro- quinolone ⁵ ; chloramphenicol ¹⁹
*Proteus, indole-positive (including Providencia rettgeri, Morganella morganii, and Proteus vulgaris)	cefotaxime, ceftriaxone, cefepime or ceftazidime ^{7,26}	imipenem, meropenem or ertapenem ²⁶ ; gentamicin, tobramycin or amikacin; amoxiciliin/clavulanate ²⁶ ; ticarciliin/clavulanate ²⁷ ; piperaciliin/tzobactam ²⁷ ; ampiciliin/sulbactam ²⁶ ; aztreonam ²⁶ ; trimethoprim-sul- famethoxazole; a fluoroguinolone ⁵
*Providencia stuartii	cefotaxime, ceftriaxone, cefepime or ceftazidime ^{7,26}	imipenem, meropenem or ertapenem ²⁶ ; ticarcillin/clavulanate ²⁷ ; piperacillin/tazobactam ²⁷ ; gentamicin, tobramycin or amikacin; aztreonam ²⁶ ; trimethoprim-sulfamethoxazole; a fluoroquinolone ⁵
*Salmonella typhi (typhoid fever)30	a fluoroquinolone ⁵ or ceftriaxone ⁷	chloramphenicol ¹⁹ ; trimethoprim-sulfamethoxazole; ampicillin; amoxicillin; azithromycin ³¹
*Other Salmonella 32	cefotaxime ⁷ or ceftriaxone ⁷ or a fluoroquinolone ⁵	ampicillin or amoxicillin; trimethoprim-sulfamethoxazole; chloramphenicol ¹⁹
*Serratia	imipenem or meropenem ²⁶	gentamicin or amikacin; cefotaxime, ceftizoxime, ceftriax- one, cefepime or ceftazidime ^{7,26} ; aztreonam ²⁶ ; trimethoprim-sulfamethoxazole; a fluoroquinolone ⁵
 Trade names are listed on page 61. Antitoxin is primary; antimicrobials are u In severely ill patients, most Medical Le In severely ill patients, most Medical Le 	tter consultants would add gentamicin, to tter consultants would add gentamicin, to	therapy. and to prevent the carrier state. bramycin or amikacin.

For an acute, uncomplicated urinary tract infection, before the infecting organism is known, the drug of first choice is trimethoprim-sulfamethoxazole.
 Large doses (6 grams or more daily) are usually necessary for systemic infections. In severely ill patients, some Medical Letter consultants would add add add the second seco

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31. RW Frenck Jr, et al, Clin Infect Dis 2000; 31:1134.

32. Most cases of Salmonella gastroenteritis subside spontaneously without antimicrobial therapy. Immunosuppressed patients, young children and the elderly may benefit the most from antibacterials.

Infecting Organism	Drug of First Choice [†]	Alternative Drugs [†]
*Shigella	a fluoroquinolone ⁵	azithromycin; trimethoprim-sulfamethoxazole; ampicillin; ceftriaxone ⁷
Yersinia enterocolitica	trimethoprim-sulfamethoxazole	a fluoroquinolone ⁵ ; gentamicin, tobramycin or amikacin; cefotaxime ⁷
OTHER GRAM-NEGATIVE BACILLI		
*Acinetobacter	imipenem or meropenem ²⁶	an aminoglycoside; ciprofloxacin ¹⁶ ; trimethoprim- suffamethoxazole; ticarcillin/clavulanate ²⁷ or piperacillin/tazobactam ²⁷ ; ceftazidime ²⁶ ; minocycline ¹⁰ doxycycline ¹⁰ ; subactam ³³ ; polymyxin
Aeromonas	trimethoprim-sulfamethoxazole	gentamicin or tobramycin; imipenem; a fluoroquinolone5
*Bacteroides	metronidazole	clindamycin; imipenem, meropenem or ertapenem; amoxicillin/clavulanate, ticarcillin/clavulanate, piperacillin tazobactam or ampicillin/sulbactam; cefoxitin ⁷ ; chloramphenicol ¹⁹
Bartonella henselae or quintana (bacillary angiomatosis, trench fever)	erythromycin	azithromycin; doxycycline ¹⁰
Bartonella henselae 34 (cat scratch bacillus)	azithromycin	erythromycin; ciprofloxacin ¹⁶ ; trimethoprim-sulfamethoxa zole; gentamicin; rifampin
Bordetella pertussis (whooping cough)	erythromycin; clarithromycin ¹³	azithromycin; trimethoprim-sulfamethoxazole
Brucella	a tetracycline ¹⁰ + rifampin	a tetracycline ¹⁰ + streptomycin or gentamicin; chloram- phenicol ¹⁹ ± streptomycin; trimethoprim-sulfamethoxa- zole ± gentamicin; ciprofloxacin ¹⁶ + rifampin
Burkholderia cepacia	trimethoprim-sulfamethoxazole	ceftazidime7; chloramphenicol19; imipenem
Burkholderia (Pseudomonas) mallei (glanders)	streptomycin + a tetracycline ¹⁰	streptomycin + chloramphenicol ¹⁹ ; imipenem
*Burkholderia (Pseudomonas) pseudomallei (melioidosis)	imipenem; ceftazidime ⁷	meropenem; chloramphenicol ¹⁹ + doxycycline ¹⁰ + trimethoprim-sulfamethoxazole; amoxicillin/clavulanate
Calymmatobacterium granulomatis (granuloma inguinale)	trimethoprim-sulfamethoxazole	doxycycline ¹⁰ or ciprofloxacin ¹⁶ ± gentamicin
Capnocytophaga canimorsus ³⁵	penicillin G	cefotaxime, ceftizoxime or ceftriaxone ⁷ ; imipenem or meropenem; vancomycin; a fluoroquinolone ⁵ ; clin- damycin
Eikenella corrodens	ampicillin	erythromycin; azithromycin; clarithromycin ¹³ ; a tetracy- cline ¹⁰ ; amoxicillin/clavulanate; ampicillin/sulbactam; ceftriaxone ⁷
Francisella tularensis (tularemia) ³⁶	gentamicin or streptomycin either + a tetracycline ¹⁰	chloramphenicol ¹⁹ ; ciprofloxacin ¹⁶
*Fusobacterium	penicillin G; metronidazole	clindamycin; cefoxitin ⁷ ; chloramphenicol ¹⁹
Gardnerella vaginalis (bacterial vaginosis)	oral metronidazole37	topical clindamycin or metronidazole; oral clindamycin
Haemophilus ducreyi (chancroid)	azithromycin or ceftriaxone	ciprofloxacin ¹⁶ or erythromycin
"Haemophilus influenzae	meningitis, epiglottitis, arthritis and other serious infections: cefotaxime or ceftriaxone ⁷	cefuroxime ⁷ (not for meningitis); chloramphenicol ¹⁹ ; meropenem
	upper respiratory infections and bronchitis: trimethoprim-sulfamethoxazole	cefuroxime ⁷ ; amoxicillin/clavulanate; cefuroxime axetii ⁷ ; cefpodoxime ⁷ ; cefaclor ⁷ ; cefotaxime ⁷ ; cefti- zoxime ⁷ ; cefti-axone ⁷ ; cefixime ⁷ ; a tetracycline ¹⁰ ; clarithromycin ¹⁵ ; azithromycin; a fluoroquinolone ⁵ ; ampicillin or amoxicillin; teltihromycin ⁵

33. Sulbactam may be useful to treat multi-drug re able in combination with ampicillin as Una ant Acine t is only a asvn. Mec lical Letter con-Subustanti may be useru to treat multi-roug resistant Academotacier. It is only available in comonation with ampointin as Unasyn. Mis sultants recommend 3 g I vdp. (I U Utane 14. Loi Infect Dis 2003; 8:1286; AS Lewin et al., Int J Antimicrob Agents 2005; 21:58).
 Role of antibiotics in not clear (DA Corrad, Curr Opin Pediatr 2001; 13:56).
 Chers et al., Clin Interc Dis 1996; 23:71.

For post-exposure prophylaxis, doxycycline or ciprofloxacin begun during the incubation period and continued for 14 days might prevent disease (Medical Letter 2001; 43:87).

Metronidazole is effective for bacterial vaginosis even though it is not usually active in vitro against Gardnerella.

Infecting Organism	Drug of First Choice [†]	Alternative Drugs [†]
OTHER GRAM-NEGATIVE BACILLI	(continued)	
*Helicobacter pylori ³⁸	proton pump inhibitor ³⁹ +clarithromycin ¹³ + either amoxicillin or metronidazole	bismuth subsalicylate + metronidazole + tetracycline HCl ¹ + either a proton pump inhibitor ³⁹ or H ₂ -blocker ³⁹
Legionella species	azithromycin or a fluoroquino- Ione ⁵ ± rifampin	doxycycline ¹⁰ ± rifampin; trimethoprim-sulfamethoxa- zole; erythromycin
Leptotrichia buccalis	penicillin G	a tetracycline ¹⁰ ; clindamycin; erythromycin
Pasteurella multocida	penicillin G	a tetracycline ¹⁰ ; a second- or third-generation cephalosporin ^{7,8} ; amoxicillin/clavulanate; ampicillin/ sulbactam
*Pseudomonas aeruginosa	urinary tract infection: ciprofloxacin ¹⁶	levofloxacin ¹⁶ ; ticarcillin/clavulanate or piperacillin/ tazobactam; ceftazidime ⁷ ; cefepime ⁷ ; imipenem or meropenem; aztreonam; tobramycin, gentamicin or amikacin
	other infections: piperacillin/tazobactam or ticarcillin/clavulanate, each plus tobramycin, gentamicin or amikacin ⁴⁰	ceftazidime ⁷ ; ciprofloxacin ¹⁶ ; imipenem or meropenem; aztreonam; cefepime ⁷ each plus tobramycin, gentamicin or amikacin
Spirillum minus (rat bite fever)	penicillin G	a tetracycline ¹⁰ ; streptomycin
*Stenotrophomonas maltophilia	trimethoprim-sulfamethoxazole	minocycline ¹⁰ ; a fluoroquinolone ⁵
Streptobacillus moniliformis (rat bite fever; Haverhill fever)	penicillin G	a tetracycline ¹⁰ ; streptomycin
Vibrio cholerae (cholera)41	a tetracycline ¹⁰	a fluoroquinolone5; trimethoprim-sulfamethoxazole
Vibrio vulnificus	a tetracycline ¹⁰	cefotaxime7; ciprofloxacin13
Yersinia pestis (plague)	streptomycin ± a tetracycline ¹⁰	chloramphenicol ¹⁹ ; gentamicin; trimethoprim- sulfamethoxazole; ciprofloxacin ¹³
ACID FAST BACILLI		
*Mycobacterium tuberculosis	isoniazid + rifampin + pyrazinamide ± ethambutol or streptomycin ¹⁹	a fluoroquinolone ⁵ ; cycloserine ¹⁹ ; capreomycin ¹⁹ or kanamycin ¹⁹ or amikacin ¹⁹ ; ethionamide ¹⁹ ; para-aminosalicylic acid ¹⁹
*Mycobacterium kansasii	isoniazid + rifampin ± ethambutol or streptomycin ¹⁹	clarithromycin ¹³ or azithromycin; ethionamide ¹⁹ ; cycloserine ¹⁹
*Mycobacterium avium complex	treatment: clarithromycin ¹³ or azithromycin + ethambutol ± rifabutin prophylaxis clarithromycin ¹³ or azithromycin ± rifabutin	ciprofloxacin ¹⁶ ; amikacin ¹⁹
*Mycobacterium fortuitum/chelonae complex	amikacin + clarithromycin ¹³	cefoxitin ⁷ ; rifampin; a sulfonamide; doxycycline ¹⁰ ; ethambutol; linezolid
Mycobacterium marinum (balnei) ⁴²	minocycline ¹⁰	trimethopri-sulfamethoxazole; rifampin; clarithromycin ¹³ ; doxycycline ¹⁰
Mycobacterium leprae (leprosy)	dapsone + rifampin ± clofazimine	minocycline ¹⁰ ; ofloxacin ¹⁶ ; clarithromycin ¹³

* Resistance may be a problem; susceptibility tests should be used to guide therapy. † Trade names are listed on page 61.

38. Eradication of H. pylori with various antibacterial combinations, given concurrently with a proton pump inhibitor or H2-blocker, has led to rapid healing of active peptic ulcers and low recurrence rates (Treatment Guidelines 2004; 2:9).

 Proton pump inhibitors available in the US are omeprazole (*Prilosec*, and others), lansoprazole (*Prevacid*), pantoprazole (*Protonix*), esomeprazole (*Nexium*) and rabeprazole (*Aciphex*). Available H₂-blockers include cimelidine (*Tagamet*, and others), famotidine (*Pepcid*, and others), nizatidine (Axid, and others) and ranitidine (Zantas, and others).
 40. Neither gentamicin, tobaranycin, netilimicin or amikacin should be mixed in the same bottle with carbenicillin, ticarcillin, mezlocillin or piperacillin for IV

administration. When used in high doses or in patients with renal impairment, these penicillins may inactivate the aminoglycosides.

41. Antibiotic therapy is an adjunct to and not a substitute for prompt fluid and electrolyte replacement.

42. Most infections are self-limited without drug treatment.

Infecting Organism	Drug of First Choice [†]	Alternative Drugs [†]
ACTINOMYCETES		
Actinomyces israelii (actinomycosis)	penicillin G	a tetracycline ¹⁰ ; erythromycin; clindamycin
Nocardia	trimethoprim-sulfamethoxazole	sulfisoxazole; amikacin ¹⁹ ; a tetracycline ¹⁰ ; ceftriaxone; imipenem or meropenem; cycloserine ¹⁹ ; linezolid
*Rhodococcus equi	vancomycin ± a fluoroquinolone ⁵ , rifampin, imipenem or meropenem; amikacin	erythromycin
Tropheryma whippelii (Whipple's disease)	trimethoprim-sulfamethoxazole	penicillin G; a tetracycline ¹⁰ ; ceftriaxone
CHLAMYDIAE		
Chlamydia trachomatis	trachoma: azithromycin	a tetracycline ¹⁰ (topical plus oral); a sulfonamide (topica plus oral)
	inclusion conjunctivitis:	
	erythromycin (oral or IV)	a sulfonamide
	pneumonia: erythromycin	a sulfonamide
	urethritis, cervicitis:	
	azithromycin or doxycycline ¹⁰	erythromycin; ofloxacin16; amoxicillin
	lymphogranuloma venereum:	
	a tetracycline ¹⁰	erythromycin
Chlamydophila (formerly Chlamydia)	erythromycin; a tetracycline ¹⁰ ;	a fluoroquinolone5; telithromycin§
pneumoniae (TWAR strain)	clarithromycin13 or azithromycin	
Chlamydophila (formerly Chlamydia)	a tetracycline ¹⁰	chloramphenicol ¹⁹
psittaci (psittacosis; ornithosis)		
EHRLICHIA		
Anaplasma phagocytophilum (formerly Ehrlichia phagocytophila)	doxycycline ¹⁰	rifampin
Ehrlichia chaffeensis	doxycycline ¹⁰	chloramphenicol19
Ehrlichia ewingii	doxycycline ¹⁰	
MYCOPLASMA		
Mycoplasma pneumoniae	erythromycin; a tetracycline ¹⁰ ; clarithromycin ¹³ or azithromycin	a fluoroquinolone ⁵ ; telithromycin§
Ureaplasma urealyticum	azithromycin	erythromycin; a tetracycline ¹⁰ ; clarithromycin ¹³ ; ofloxacin ¹⁶
RICKETTSIOSES		
Rickettsia rickettsii		
(Rocky Mountain spotted fever)	doxycycline ¹⁰	chloramphenicol ¹⁹ ; a fluoroquinolone ⁵
Rickettsia typhi	doxycycline ¹⁰	chloramphenicol ¹⁹ ; a fluoroquinolone ⁵
(endemic typhus-murine)		
Rickettsia prowazekii	doxycycline ¹⁰	chloramphenicol ¹⁹ ; a fluoroquinolone ⁵
(epidemic typhus-louseborne)		
Orientia tsutsugamushi (scrub typhus)	doxycycline ¹⁰	chloramphenicol ¹⁹ ; a fluoroquinolone ⁵
Coxiella burnetii (Q fever)	doxycycline ¹⁰	chloramphenicol ¹⁹ ; a fluoroquinolone ⁵
SPIBOCHETES		
Borrelia burgdorferi (Lyme	doxycycline ¹⁰ ; amoxicillin;	ceftriaxone7; cefotaxime7; penicillin G; azithromycin;
disease) ⁴³	cefuroxime axetil ⁷	clarithromycin ¹³
Borrelia recurrentis (relapsing fever)	a tetracycline ¹⁰	penicillin G; erythromycin
Leptospira	penicillin G	a tetracycline ¹⁰ ; ceftriaxone ^{7,44}
Treponema pallidum (syphilis)	penicillin G ¹²	a tetracycline ¹⁰ ; ceftriaxone ⁷
Treponema pertenue (yaws)	penicillin G	a tetracycline ¹⁰
	edical Letter has reviewed telithromycin (i	, , , , , , , , , , , , , , , , , , , ,

§ Since this article was published *The Medical Letter* has reviewed telthromycin (*Kdek*). See page 73. 43. For treatment of erythem anigrans, uncomplicated facial neve pashs, mild cardiad desease and arthritis, oral therapy is satisfactory; for other neuro-logic or more serious cardiac desaes, parenteral therapy with celtriaxone, exblaxime or penciallin G is recommended. For recurrent arthritis after an oral regimen, another course of oral therapy or a parenteral durg may be given (GP Wormser et al., Chin Infect Dis 2000; 31:51). For *The Medical Letter* review of the treatment of Lyme disease, see page 112. 4. UN Vinet, Cin Infect Dis 2003; 36:1514; T Pamaphot et al., Clin Infect Dis 2003; 36:1507.

Norfloxacin - Noroxin

LIST OF SOME GENERIC AND BRAND NAMES

* Amikacin - Amikin * Amikin - Amikacin * Aminosalicylic acid - Paser * Amoxicillin/clavulanate -Augmentin * Ampicillin - Principen * Ancef - Cefazolin * Augmentin - Amoxicillin/clavulanate Avelox - Moxifloxacin Azactam - Aztreonam Azithromycin - Zithromax Aztreonam - Azactam * Bactrim - Trimethoprim-sulfamethoxazole Biaxin - Clarithromycin * Ceclor - Cefaclor Cedax - Ceftibuten * Cefadroxil - Duricef * Cefazolin - Ancef; Kefzol Cefdinir - Omnicef Cefepime - Maxipime Cefixime - Suprax Cefizox – Ceftizoxime Cefobid - Cefoperazone Cefoperazone - Cefobid Cefotan - Cefotetan Cefotaxime - Claforan Cefotetan - Cefotan * Cefoxitin - Mefoxin Cefpodoxime - Vantin Cefprozil - Cefzil Ceftazidime - Fortaz Tazicet Tazidime Ceftibuten - Cedax Ceftin - Cefuroxime axetil Ceftizoxime - Cefizox Ceftriaxone - Rocephin Cefuroxime - Zinacef Cefuroxime axetil - Ceftin Cefzil - Cefprozil * Cephalexin - Keflex * Cephalothin - Keflin * Cephradine - Velosef * Chloramphenicol - Chloromvcetin * Chloromycetin - Chloramphenicol * Cipro - Ciprofloxacin * Ciprofloxacin - Cipro Claforan - Cefotaxime Clarithromycin - Biaxin * Cleocin - Clindamycin * Clindamycin - Cleocin Clofazimine - Lamprene Cubicin - Daptomycin * Cycloserine - Seromycin * Dapsone - generics

* Doxycycline - Vibramycin * Duricef - Cefadroxil * E-Mycin - Erythromycin Enoxacin - Penetrex Ertapenem - Invanz * Erv-Tab - Ervthromvcin * Erythromycin - E-Mycin; Ery-Tab * Ethambutol - Myambutol Ethionamide - Trecator-SC Factive - gemifloxacin * Flagvl - Metronidazole Floxin - Ofloxacin Fortaz – Ceftazidime Fosfomycin – Monurol * Gantrisin - Sulfisoxazole * Garamycin - Gentamicin Gatifloxacin - Tequin Gemifloxacin - Factive * Gentamicin - Garamvcin Imipenem - Primaxin * INH - Isoniazid Invanz – Ertapenem * Isoniazid - INH * Kanamycin - Kantrex: Keflin * Kantrex - Kanamycin * Keflex - Cephalexin * Keflin - Cephalothin * Kefzol - Cefazolin Ketek - telithromycin Lamprene – Clofazimine Levaquin – Levofloxacin Levofloxacin - Levaquin Linezolid - Zvvox Lorabid - Loracarbef Loracarbef - Lorabid * Macrobid - Nitrofurantoin * Macrodantin - Nitrofurantoin Maxipime - Cefepime * Mefoxin - Cefoxitin Meropenem - Merrem Merrem – Meropenem * Metronidazole - Flagyl * Minocin - Minocycline * Minocycline - Minocin Monurol - Fosfomvcin Moxifloxacin - Avelox * Mvambutol - Ethambutol Mycobutin – Rifabutin * Nafcillin - Nallpen * Nallpen - Nafcillin * Nebcin - Tobramvcin

* Nitrofurantoin - Macrobid: Macrodantin

Noroxin - Norfloxacin Ofloxacin - Floxin Omnicef - Cefdinir * Oxacillin - generics Para-aminosalicylic acid - Paser Paser - Para-aminosalicvlic acid Penetrex - Enoxacin * Penicillin G - generics * Penicillin V - Pen-Vee K; Veetids * Pen-Vee K - Penicillin V Piperacillin/Tazobactam - Zosvn Primaxin - Imipenem * Principen - Ampicillin Pyrazinamide - PZA PZA - Pyrazinamide Quinupristin/dalfopristin - Svnercid Rifabutin - Mycobutin Rifadin - Rifampin Rifampin - Rifadin Rocephin - Ceftriaxone * Septra - Trimethoprim-sulfamethovazola * Seromycin - Cycloserine * Streptomycin - generics * Sulfisoxazole - Gantrisin * Sumycin - Tetracycline Suprax - cefixime Svnercid - Quinupristin/dalfopristin Tazicef - Ceftazidime Tazidime - Ceftazidime Telithromycin - Ketek Tequin - Gatifloxacin * Tetracycline - Sumycin Ticar - Ticarcillin Ticarcillin - Ticar Ticarcillin/clavulanate - Timentin Timentin - Ticarcillin/clavulanate * Tobramvcin - Nebcin Trecator-SC - Ethionamide * Trimethoprim - Trimpex * Trimethoprim-sulfamethoxazole -Bactrim: Septra * Trimpex - Trimethoprim * Vancocin - Vancomycin * Vancomycin - Vancocin

- Vantin Cefpodoxime
- * Veetids Penicillin V
- * Velosef Cephradine * Vibramycin - Doxycycline Zinacef - Cefuroxime Zithromax - Azithromycin
- Zosvn Piperacillin/Tazobactam Zyvox - Linezolid

*Also available generically

- Daptomycin Cubicin * Dicloxacillin - generics

	Usual	Pediatric	
Drug	adult dosage	dosage	Cost ¹
AZITHROMYCIN – Zithromax	500 mg day 1, then 250 mg days 2-5	5-12 mg/kg q24h	\$44.64
CEPHALOSPORINS			
Cefaclor – average generic	500 mg q8h	6.6-13.3 mg/kg q8h	89.40
Ceclor	500 mm m10h		131.40 71.40
 average generic (extended-release) Ceclor CD 	500 mg q12h		83.20
Cefadroxil – average generic	1 gram daily	15 mg/kg q12h	62.20
Duricef	i giani ualiy	15 mg/kg q12m	128.80
Cefdinir – Omnicef	300 mg g12h	7 ma/ka a12h	86.00
	ooo nig qizii	or 14 mg/kg g24h	00.00
Cefditoren – Spectracef	400 mg g12h		70.80
Cefpodoxime - Vantin	200 mg q12h	10 mg/kg g24h	106.00
		or 5 mg/kg q12h	
Cefprozil – Cefzil	500 mg q12h	15 mg/kg q12h	173.60
Ceftibuten – Cedax	400 mg daily	9 mg/kg q24h	86.30
Cefuroxime axetil – average generic	500 mg bid	10-15 mg/kg q12h	135.40
Ceftin			187.40
Cephalexin – average generic	500 mg q6h	6.25-25 mg/kg q6h	38.80
Keflex			124.00
Cephradine – average generic	500 mg q6h	6.25-25 mg/kg q6h	41.60
Velosef		or 12.5-50 mg/kg q12h	72.00
l oracarbef – Lorabid	400 mg g12h	7.5-15 mg/kg g12h	120.00
CLARITHROMYCIN – Biaxin	500 mg q12h	7.5 mg/kg q12h	85.80
CLINDAMYCIN – average generic Cleocin	300 mg q6h	2-8 mg/kg q6-8h	73.60 196.00
ERYTHROMYCIN			
base, delayed-release capsules	500 mg q6h	7.5-12.5 mg/kg q6h	
- average generic			10.00
ERYC			44.80
base, enteric-coated tablets	500 mg q6h	7.5-12.5 mg/kg q6h	
E-Mycin			22.40
Ery-tab			16.40
LUOROQUINOLONES			
Ciprofloxacin – average generic	500 mg q12h	see footnote 2	109.20
Cipro			108.40
Cipro XR	1000 mg q24h		94.00
Gatifloxacin - Tequin	400 mg daily		89.50
Levofloxacin – Levaquin	500 mg daily		100.10
Moxifloxacin – Avelox Norfloxacin – Noroxin	400 mg daily		92.90
	400 mg bid		74.20
Ofloxacin - Floxin	400 mg q12h		126.20
FOSFOMYCIN – Monurol	3 grams once		36.36
LINEZOLID – Zyvox	600 mg q12h	10 mg/kg q12h ³	1208.60
NITROFURANTOIN (macrocrystals)	100 mg g6h	1.25-1.75 mg/kg q6h	
- average generic			44.40
Macrodantin			81.20
Nitrofurantoin monohydrate-macrocrystals	100 mg q12h		
Macrobid			42.80

Since this article was published, The Medical Letter has reviewed gemilloxacin (Factive; see page 75) and telithromycin (Ketek; see page 79).
 Cost for 10 days' treatment (5 days with azithromycin and 1 day with fostomycin), for an adult, according to data from retail pharmacies nationwide

provided by NDCHealth, a health care services company, December 2003.

Pediatric dose for post-exposure prophylaxis for anthrax is 10-15 mg/kg bid.
 Not approved for use in children. Limited experience in clinical trials.

	Usual	Pediatric	
Drug	adult dosage	dosage	Cost ¹
PENICILLINS			
Penicillin V ⁴ – average generic	500 mg q6h	6.25-12.5 mg/kg q6h	\$11.20
Veetids			14.80
Amoxicillin – average generic	500 mg q8h	6.6-13.3 mg/kg q8h or 15 mg/kg q12h	9.60
Amoxil			6.00
Amoxicillin/clavulanate5			
Augmentin	875 mg q12h	6.6-13.3 mg/kg q8h	110.00
		or 15 mg/kg q12h	
Augmentin XR ⁶	2000 mg q12h		110.80
Ampicillin – average generic	500 mg q6h	12.5-25 mg/kg q6h	14.80
Principen			15.60
Cloxacillin – average generic	500 mg q6h	12.5-25 mg/kg q6h	27.60
Dicloxacillin – average generic	500 mg q6h	3.125-12.5 mg/kg q6h	47.60
Oxacillin – average generic	500 mg q6h	12.5-25 mg/kg q6h	14.00
TETRACYCLINES			
Tetracycline HCI – average generic	500 mg q6h	6.25-12.5 mg/kg q6h ⁷	3.60
Sumycin			3.60
Doxycycline	100 mg bid	2.2 mg/kg q12-24h ⁷	
capsules – average generic			22.80
Vibramycin			87.80
TRIMETHOPRIM-SULFAMETHOXAZOLE			
- average generic	1 tablet q6h8	4-5 mg/kg (TMP) q6h	16.00
Bactrim			40.40
Septra			42.80
double strength (DS) - average generic	1 DS tablet q12h ⁸		11.60
Bactrim DS			36.00
Septra DS			29.00

 One mg is equal to 1600 units.
 Dosage based on amoxicillin content. For doses of 500 or 875 mg, 500-mg or 875-mg tablets should be used, because multiple smaller tablets would contain too much clavulanate. The 875-mg, 500-mg and 250-mg tablets each contain 125 mg clavulanate. 125-mg chewable tablets and 125 mg/5 mL oral suspension both contain 31.25 mg clavulanate; 250-mg chewable tablets and 250-mg/5 mL oral suspension both contain 62.5 mg clavulanate.

6. Dosage based on amoxicillin content. Each tablet contains 1000 mg amoxicillin and 62.5 mg clavulanate.

7. Not recommended for children <8 years old.

8. Each tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim. Each DS tablet contains 800 mg sulfamethoxazole and 160 mg trimethoprim.

DRUGS FOR Pneumonia

Original publication date - September 2003

The choice of drugs for treatment of pneumonia depends on the most likely pathogens causing the infection and local antimicrobial resistance patterns. Factors such as severity of illness, presence of co-morbid conditions and whether the infection is community- or hospital-acquired also need to be considered.

PATHOGENS

Community-Acquired Pneumonia – "Atypical" pathogens (*Mycoplasma pneumoniae, Chlamydia pneumoniae* and respiratory viruses) probably cause most cases of community-acquired pneumonia (EN Vergis et al, Arch Intern Med 2000; 160:1294). *Legionella*, another atypical organism, is less common. Respiratory viruses, particularly respiratory syncytial virus (RSV) and parainfluenza, are more common in children than adults, but mild community-acquired pneumonia in adults may also be due to a virus, usually influenza A or B, parainfluenza, adenovirus or RSV. Recently, a novel coronavirus has caused pneumonia with severe acute respiratory distress syndrome (SARS) in both children and adults (KL Hon et al, Lancet 2003; 361:1701; TG Ksiazek et al, N Engl J Med 2003; 348:1953).

Among patients hospitalized with community-acquired pneumonia, *Streptococcus pneumoniae* (pneumococcus) is cultured in about 20% of cases (N Sopena et al, Eur J Clin Microbiol Infect Dis 1999; 18:852) and is implicated by other microbiologic techniques in at least another 20%. Other bacterial pathogens that commonly cause community-acquired pneumonia include *Haemophilus influenzae*, *Klebsiella pneumoniae* and

Infecting Organism	Drugs of Choice*	Some Alternatives
Streptococcus pneumoniae Penicilin-susceptible (MIC < 0.1 µg/ml)	Penicillin G or V; amoxicillin	A cephalosporin; azithromycin, clarithromycin or erythromycin; levo-, gati-, gemi- or moxi- floxacin; meropenem, imipenem or ertapenem; clindamycin; doxycycline; trimethoprim/sul- famethoxazole; telithromycin
Penicillin-intermediate resistance (MIC 0.1 - 2 µg/ml)	Penicillin G IV (12 million units/day for adults); ceftriaxone or cefotaxime	Levo-, gati-, gemi- or moxifloxacin; vancomycin; linezolid; clindamycin; telithromyci
Penicillin-high level resistance (MIC > 2 µg/ml)	Vancomycin, ceftriaxone or cefotax- ime; levofloxacin, gatifloxacin, gemifloxacin or moxifloxacin	Linezolid; quinupristin/dalfopristin; telithromycin
Mycoplasma pneumoniae	Azithromycin, clarithromycin or erythromycin; doxycycline	Levo-, gati-, gemi- or moxifloxacin; telithromycin
Chlamydia pneumoniae	Azithromycin; clarithromycin or erythromycin; doxycycline	A fluoroquinolone; telithromycin
Chlamydia psittaci	Doxycycline	A fluoroquinolone
Haemophilus influenzae	A second or third generation cephalo- sporin; amoxicillin/clavulanate	Doxycycline; azithromycin or clarithromycin; a fluoroquinolone; ampicillin or amoxicillin; telithromycin
Legionella pneumophila	Azithromycin or a fluoroquinolone ± rifampin	Doxycycline ± rifampin; erythromycin or clarithromycin
Klebsiella spp. (or other gram-negative bacilli) ¹	Cefotaxime, ceftizoxime, ceftriaxone, cefepime or ceftazidime	Imipenem, meropenem or ertapenem; amoxicillin/clavulanate; ticarcillin/clavulanate; piperacillin/tazobactam; trimethoprim/ sulfamethoxazole; a fluoroquinolone
Staphylococcus aureus Methicillin-sensitive	A penicillinase-resistant penicillin ²	Cefazolin; amoxicillin/clavulanate; ampicillin/sulbactam; ticarcillin/clavulanate; piperacillin/tlazobactam; imipenem or meropenem; clindamycin; levofloxacin, gatilfoxacin or moxifloxacin; vancomycin; linezolid
Methicillin-resistant ³	Vancomycin	Linezolid; quinupristin/dalfopristin; trimethoprim/sulfamethoxazole; levofloxacin, gatifloxacin or moxifloxacin
Anaerobic mouth flora (Bacteroides spp., Fusobacterium spp., Peptostreptococcus spp.)	Metronidazole or clindamycin	Imipenem, meropenem or ertapenem; amoxi- cillin/clavulanate; ticarcillin/clavulanate; piperacillin/tazobactam; cefoxitin; cefotetan; penicillin G; gatifloxacin or moxifloxacin
Influenza A	Oseltamivir, amantadine or rimantadine	Zanamivir
Respiratory Syncytial Virus	Ribavirin	

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occasionally other enteric gram-negative bacilli and anaerobic mouth organisms. Tuberculosis, *Pneumocystis jiroveci* (formerly *carinii*) pneumonia and regionally endemic fungal infections, such as histoplasmosis, blastomycosis or coccidioidomycosis, must also be considered in the differential diagnosis (JG Bartlett et al, Clin Infect Dis 2000; 31:347). The etiology of community-acquired pneumonia is not accurately predicted by clinical and radiographic features; initial therapy is usually empiric.

Hospital-Acquired Pneumonia – Bacterial pneumonia that develops in a hospital is often caused by gram-negative bacilli, especially *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Acinetobacter* spp. and *Pseudomonas aeruginosa*. It can also be caused by *Staphylococcus aureus*.

INITIAL TREATMENT

Ambulatory Community-Acquired Pneumonia – Oral cephalosporins are less useful than in the past for treatment of pneumonia because of pneumococcal resistance and lack of activity against atypical pathogens. In ambulatory patients, an oral macrolide (erythromycin, azithromycin or clarithromycin), doxycycline, or a fluoroquinolone with good anti-pneumococcal activity (such as levo-, gati-, gemi- or moxifloxacin) is generally used in otherwise healthy adults. Pneumococci may, however, be resistant to macrolides (JR Lonks et al, J Antimicrob Chemother 2002; 50 suppl 2:87) and to doxycycline, especially if they are resistant to penicillin. For older patients or those with co-morbid illness such as chronic obstructive pulmonary disease, a fluoroquinolone may be a better choice. Fluoroquinolone-resistant pneumococci have also been described (MR Jacobs et al, J Antimicrob Chemother 2003; 52:229).

Hospitalized Community-Acquired Pneumonia – In patients with community-acquired pneumonia who require hospitalization, the parenteral third-generation cephalosporin ceftriaxone (or cefotaxime) plus a

Drug	Usual Adult dosage	Usual Pediatric dosage	Cost*
CEPHALOSPORINS Cefaclor – average generic Ceclor (Lillv)	250-500 mg q8h	6.6-13.3 mg/kg q8h	\$ 66.78 92.82
Cefdinir – Omnicef (Abbott)	300 mg q12h OR 600 mg q24h	7 mg/kg q12h OR 14 mg/kg q24h	120.12
Cefditoren pivoxil - Spectracef (Tap)	400 mg q12h	See footnote 1	84.56
Cefpodoxime proxetil - Vantin (Pharmacia)	200 mg q12h	5 mg/kg q12h	149.24
Cefprozil – Cefzil (Bristol-Myers Squibb)	500 mg q12h	15 mg/kg q12h	243.88
Cefuroxime – Ceftin (GlaxoSmithKline) Loracarbef – Lorabid (Lilly)	500 mg q12h 200-400 mg q12h	10-15mg/kg q12h 7.5-15mg/kg q12h	253.36 117.32
MACROLIDES			
Azithromycin – Zithromax (Pfizer)	500 mg on day 1, then 250 mg/day on davs 2-5	10 mg/kg on day 1, then 5 mg/kg/day on days 2-5	43.32
Clarithromycin - Biaxin (Abbott)	250-500 mg g12h	7.5 mg/kg g12h	114.80
Biaxin XL Ervthromycin base –	1000 mg q24h x 7d	See footnote 1	62.16
delayed release capsules - average generic	250-500 mg g6h	7.5-12.5 mg/kg g6h	12.32
ERYC (Warner Chilcott)			29.68
enteric-coated tabs – average generic			7.84
E-mycin (Knoll)			15.12
FLUOROQUINOLONES [†] Gatifloxacin – Tequin (Bristol-Myers Squibb)	400 mg g24h	Not recommended	125.44
Levofloxacin – Levaquin (Ortho-McNeil)	500-750 mg g24h	Not recommended	133.84
Moxifloxacin - Avelox (Bayer)	400 mg q24h	Not recommended	130.34
TETRACYCLINES	100	Not recommended	29.40
Doxycycline – average generic Vibramycin (Pfizer)	100 mg q12h	Not recommended	119.28
PENICILLINS			
Amoxicillin – average generic	500 mg-1 g q8h OR 875 mg q12h	8.33-16.67 mg/kg q8h OR 22.5 mg/kg q12h	13.86
Amoxil (GlaxoSmithKline)	500 mm =0h	0.00.10.07	8.40
Amoxicillin/clavulanate – Augmentin (GlaxoSmithKline)	500 mg q8h	8.33-16.67 mg/kg q8h	166.32
	OR 875 mg q12h ²	OR 22.5 mg/kg q12h ²	
Augmentin XR	2000 mg q12h ²	See footnote 1	74.76
OXAZOLIDINONE	00010h	10	1587.04
Linezolid – Zyvox (Pharmacia)	600 mg q12h	10 mg/kg q8h	1567.04
Amantadine – average generic	200 mg q24h	2.5 mg/kg q12h x 5d	5.90
	OR 100 mg g12h x 5d ³	5 5 4	
Symmetrel (Endo)			12.00
Oseltamivir - Tamiflu (Roche)	75 mg q12h x 5d	1-12 yrs old: see footnote 4 ≥ 13 yrs old: 75 mg q12h x 5d	66.30
Ribavirin - Virazole (ICN)	aerosol treatment	aerosol treatment	1416.09 ⁵
	12-18 hrs/d x 3-7d ⁶	12-18 hrs/d x 3-7d ⁶	
Rimantadine – average generic	200 mg q24h	2.5 mg/kg q12h x 5d	16.00
	OR 100 mg q12h x 5d ³		
Flumadine (Forest)			20.50
Zanamivir – Relenza (GlaxoSmithKline)	10 mg q12h x 5d ⁷	10 mg q12h x 5d	24.80

Dosage and Cost of Some Oral Drugs for Pneumonia

Cost for 14 days' treatment (except azilhromycin, Biaxin XL and antivirals) at the lowest adult dosage, according to data from retail pharmacies nationwide provided by NDCHealth, a health care information services company, May 2003.
 Since this table was published, penilloxain (Facility) has been FDA-approved. See page 75 for a review.

 Has not been studied in children.
 Dosace based on amoxicillin content. For doses of 500 or 875 ma. 500-ma or 875-ma tablets should be used, because multiple smaller tablets would ■ contain too much clavulanate. The 875-mg, 500-mg and 250-mg tablets each contain 125 mg clavulanate. 125-mg chavable tablets and 125-mg/5-mL coal suspension both contain 32.5 mg clavulanate, 250-mg chavable tablets and 250-mg/5-mL coal suspension both contain 32.5 mg clavulanate. 30. Decage should be decreased to 100 mg/d for older nursing home residents and for participants. 2 Sign and 200-mg clavulanate.

4. For children 1-13 years of age dosage is by weight as follows: ≤ 15 kg - 30 mg q12h; >15-23 kg - 45 mg q12h; >23-40 kg - 60 mg q12h; > 40 kg -Port contained in 1:13 years to say using to say any any and the say of the

administration. 7. Taken as two 5-mg inhalations using Rotadisk Inhaler.

macrolide or doxycycline is recommended pending culture results, antibiotic susceptibility testing and clinical response (RB Brown et al, Chest 2003; 123:1503). Alternatively, a fluoroquinolone with good activity against *S. pneumoniae* (levo-, gati-, gemi- or moxifloxacin) could be used alone. If aspiration pneumonia is suspected, metronidazole (*Flagyl*, and others) or clindamycin (*Cleocin*, and others) can be added to improve coverage for oral anaerobes.

Patients so ill that they require admission to an ICU can be treated with ceftriaxone, cefotaxime or, to improve gram-negative coverage, ticarcillin/clavulanate or piperacillin/tazobactam, each plus a macrolide or fluoroquinolone to cover atypicals.

In treating pneumococcal pneumonia due to strains with intermediate degrees of penicillin resistance (minimal inhibitory concentration [MIC] 0.1 to 2 µg/ml), ceftriaxone, cefotaxime or high doses of intravenous (IV) penicillin G (12 million units daily for adults) can be used. For highly resistant strains (MIC > 2 µg/ml), an IV fluoroquinolone (levofloxacin, gatifloxacin or moxifloxacin), vancomycin or linezolid may be required, and should be added in all severely ill patients and in those not responding to ceftriaxone, cefotaxime or high-dose penicillin.

Hospital-Acquired Pneumonia — Susceptibility testing and resistance patterns within the region, as reported by hospital microbiology and public health laboratories, should be used to guide therapy. For initial treatment of hospital-acquired pneumonia, in which antimicrobial resistance is frequent and can emerge during treatment, Medical Letter consultants would use piperacillin/tazobactam, ticarcillin/clavulanate or a carbapenem (meropenem, imipenem or ertapenem), which have broad gram-negative activity, or cefepime, which has broader activity than ceftriaxone or cefotaxime against gram-negative organisms. In severely ill

patients, an aminoglycoside (tobramycin, gentamicin or amikacin) should be added.

Ciprofloxacin or aztreonam (*Azactam*), each in combination with clindamycin or vancomycin, can be substituted for the β -lactam in **patients allergic to penicillin**. Addition of vancomycin or linezolid should be considered in hospitals where **methicillin-resistant** *S. aureus* are prevalent. In hospitals where **multi-drug resistant** *P. aeruginosa* frequently cause nosocomial pneumonia, cefepime, imipenem or meropenem combined with an aminoglycoside would be a good first choice. **Nosocomial** *Acinetobacter* may only be sensitive to imipenem or colistin (colistimethate sodium, *Coly-Mycin*) (J Garnacho-Montero et al, Clin Infect Dis 2003; 36:1111).

ADVERSE EFFECTS

Carbapenems – As with other b-lactam antibiotics, rash, diarrhea, nausea, vomiting and reversible increases in aminotransferase activity have occurred with imipenem/cilastatin, meropenem and ertapenem. Meropenem is less likely to cause seizures than imipenem. Imipenem and ertapenem have been associated with low birth weight in animals; use of a carbapenem during pregnancy should be reserved for a strong clinical indication with no good alternative.

Cephalosporins – The most frequent adverse effects of cephalosporins include thrombophlebitis from intravenous infusions, pain at intramuscular injection sites, and transient disturbances in hepatic, renal and hematologic function. Diarrhea, nausea and vomiting can occur. Between 1% and 10% of adult patients with penicillin allergy will also develop allergic reactions to a cephalosporin; no skin testing materials are available to test for cephalosporin allergy. High doses of ceftriaxone can lead to high concentrations of the drug in bile; biliary sludge (biliary

Drug	Usual Adult dosage	Usual Pediatric dosage	Cost ¹
CEPHALOSPORINS			
Cefepime - Maxipime (Elan)	1-2 g q8-12h	50 mg/kg q8-12h	\$ 35.16
Cefotaxime – Claforan (Aventis) Ceftazidime* – Fortaz (GlaxoSmithKline)	1-2 g q8h	50-180 mg/kg/d divided q6-8h 30-50 mg/kg a8h	29.64 13.48
Tazidime (Lilly)	500 mg-2 g q8-12h	30-50 mg/kg qan	13.40
Tazicef (Abbott)			14.2
Ceftriaxone – Rocephin (Roche)	1-2 g q12-24h	50-75 mg/kg/d divided g12h	48.90
Ceftizoxime* - Cefizox (Fujisawa)	1-2 g q12-2-11	50 mg/kg/d alviaed q 1211	23.72
MACROLIDES	12940121	oo nignigidooo qo on	20.71
Azithromycin – Zithromax (Pfizer)	500 mg q24h	Not recommended	25.54
Erythromycin - Erythrocin lactobionate (Abbott)	250 mg-1 g g6h ²	3.75-12.5mg/kg g6h ²	7.40
FLOUROQUINOLONES	200 mg r g qon	otro iztoligitg don	7.10
Ciprofloxacin* – Cipro (Bayer)	400 mg g12h	Not recommended	60.00
Gatifloxacin - Tequin (Bristol Myers Squibb)	400 mg q24h	Not recommended	38.0
Levofloxacin - Levaguin (Ortho-McNeil)	500-750 mg g24h	Not recommended	42.0
Moxifloxacin - Avelox (Bayer)	400 mg q24h	Not recommended	42.50
PENICILLINS			
Penicillin G – average generic	12-24 million units/d	100,000-300,000 units/kg/d	68.8
	divided q4-6h	divided q4-6h	
Pfizerpen (Pfizer)			8.16
Piperacillin/tazobactam ³ – Zosyn (Wyeth)	3.375 g q6h	80 mg/kg of piperacillin q8h	67.40
Ticarcillin/clavulanate ⁴ - Timentin	3.1 g q6h	200-300 mg/kg/d divided g4-6h	58.52
(GlaxoSmithKline)			
CARBAPENEMS			
Ertapenem – Invanz (Merck)	1 g q24h	Not recommended	47.83
Imipenem-cilastatin - Primaxin (Merck)	0.5-1 g q6-8h ⁵	15-25 mg/kg g6h ⁵	82.17
Meropenem - Merrem (AstraZeneca)	1-2 g q8h	20-40 mg/kg q8h	158.04
VANCOMYCIN ⁶			
Vancomycin – average generic	1 g q12h	10 mg/kg q6h	10.3
Vancocin (Lilly)			31.16
DXAZOLIDINONE			
Linezolid – Zyvox (Pharmacia)	600 mg q12h	10 mg/kg q8h	144.00

By slow infusion to minimize thrombophlebitis.

 Combination formulation: a 2.25-g vial contains 2 g piperacillin/250 mg tazobactam; a 3.375-g vial contains 3 g piperacillin/375 mg tazobactam; a 4.5-g vial contains 4 g piperacillin/500 mg tazobactam.
 Combination formulation: a 3.1-g vial contains 3 g ticarcillin/100 mg clavulanate.
 Doses are for imipenem, which is combined with equal weight of cilastatin.

6. Vancomycin should be infused over a period of 60 minutes.

pseudolithiasis), although it is usually asymptomatic and resolves spontaneously, can cause symptoms resembling those of cholelithiasis. Hemolytic anemia has been reported rarely, particularly with cefotetan and ceftriaxone. Cephalosporins are probably safe for use in pregnancy.

Fluoroquinolones - Fluoroquinolones are generally well tolerated, but can occasionally cause skin rashes (particularly gemifloxacin) and gastrointestinal disturbances. Central-nervous-system toxicity, including dizziness, insomnia, confusion, hallucinations and seizures can occur, particularly in elderly patients. Hypersensitivity reactions, including vasculitis, serum-sickness-like reactions and anaphylaxis occur rarely. Fluoroquinolones have been associated with tendinitis, achilles tendon rupture and, in studies with growing animals receiving high doses, cartilage damage; none of them are recommended for use in children less than 18 years old or in pregnant or nursing women. Prolongation of the QT interval has been reported, particularly with moxifloxacin. Moxifloxacin, levofloxacin, gemifloxacin and gatifloxacin should be avoided in patients who are taking other drugs known to prolong the QT interval (www.qtdrugs.org). Fluoroquinolones have been associated rarely with increased liver aminotransferases, acute interstitial nephritis, neutropenia and hypo- and hyperglycemia. [Since this article was published, *The Medical Letter* has reviewed gemifloxacin (*Factive*). See page 75.]

Linezolid – The most troubling adverse effect of linezolid is reversible myelosuppression, which occurs more frequently when the drug is continued for more than 2 weeks. Linezolid can also cause gastrointestinal upset and increases in aminotransferases. It has been associated with decreased fetal survival in animals.

Macrolides – Erythromycin seldom causes any serious adverse effects, but frequent gastrointestinal disturbances make it hard to take. Oral clarithromycin and azithromycin are both better tolerated than oral erythromycin. Neither has the high incidence of disabling nausea that occurs with erythromycin. Some nausea, diarrhea, abdominal pain, headache and dizziness occur occasionally. Clarithromycin can cause abnormal taste and rarely can cause liver failure. Reversible dose-related hearing loss has been reported with the high doses of clarithromycin and azithromycin used to treat *Mycobacterium avium* infections. Erythromycin and clarithromycin are potent inhibitors of CYP450 isozyme 3A4 and have many adverse interactions with other drugs. Azithromycin has fewer interactions. Erythromycin and clarithromycin

can cause prolongation of the QT interval and torsades de pointes. High doses of clarithromycin during pregnancy have caused cardiovascular anomalies in rats, cleft palates in mice, and fetal growth retardation in monkeys. The risk of cholestatic jaundice associated with use of erythromycin estolate (*Ilosone*) is increased in pregnant women. Azithromycin and non-estolate erythromycin are probably safe in pregnancy.

Penicillins – Penicillin and newer semi-synthetic penicillins are generally well tolerated. Diarrhea and rashes are the most common adverse effects. Allergic reactions, including erythema multiforme, Stevens-Johnson syndrome and anaphylaxis can occur; skin testing materials are available to test for penicillin allergy. Other adverse effects of penicillins include thrombophlebitis from intravenous infusions and pain at intramuscular injection sites. Hemolytic anemia has been reported, and platelet dysfunction can occur with high doses. Mild reversible laboratory abnormalities including elevated BUN or creatinine, hyperbilirubinemia, increased aminotransferases, and eosinophilia, leukopenia or thrombocytopenia have all been reported. Piperacillin is less likely to cause fluid retention than ticarcillin. Penicillins are generally considered safe in pregnancy.

Telithromycin – A complete review of telithromycin (*Ketek*), including adverse effects (Med Lett Drugs Ther 2004; 46:66) begins on page 79.

Tetracyclines – Except for frequent gastrointestinal disturbance including nausea and vomiting, oral tetracyclines are generally well tolerated. Doxycycline causes less gastrointestinal disturbance than other tetracyclines. Malabsorption, enterocolitis and esophageal ulcerations occur occasionally. All tetracyclines inhibit bone growth and cause staining and deformity of teeth in children up to 8 years old, and in the newborn when given to pregnant women after the fourth month of pregnancy. They can also cause photosensitivity and allergic reactions including fixed drug eruptions, serum

sickness and anaphylaxis. Exacerbation of renal failure and autoimmune hepatitis have been reported in some patients treated with doxycycline.

Vancomycin – Vancomycin is generally well tolerated. Infusion reactions including fever, chills, "redman" syndrome and thrombophlebitis can occur. The drug must be given over 60 minutes in order to prevent hypotension. Allergic reactions with rash and, rarely, Stevens-Johnson syndrome have been reported. Vancomycin can cause 8th nerve damage, mainly to hearing, when given to elderly patients, those with underlying renal insufficiency, in large doses, or for more than 10 days; serum trough levels should be monitored in these settings. Peripheral neuropathy and, in patients with asthma, cough or bronchospasm, can occur rarely. Vancomycin should be used in pregnancy only if there is a strong clinical indication and no good alternative is available.

Antiviral Drugs – Amantadine may cause anorexia, nausea, peripheral edema and, particularly in the elderly, minor central nervous system effects such as nervousness, anxiety, insomnia, lethargy, difficulty concentrating and lightheadedness. Rimantadine has gastrointestinal adverse effects similar to those of amantadine, but a lower risk of CNS effects. Both amantadine and rimantadine are teratogenic in animals and contraindicated in pregnancy. Adverse effects associated with zanamivir have been uncommon, but include nasal and throat discomfort, headache and cough; bronchospasm has occurred in patients with asthma. Adverse effects due to oseltamivir have been reported in about 15% of treated patients. Nausea, vomiting and headache have been the most common. Nausea occurred less often when the drug was taken with food. Ribavirin is teratogenic and embryotoxic in animals, and is generally contraindicated in pregnancy. Pregnant women should not directly care for patients receiving ribavirin aerosol. Acute deterioration of respiratory function has been reported with ribavirin aerosol in infants and in adults

Drugs for Pneumonia

with bronchospastic lung disease. Systemic ribavirin has been associated with hemolytic anemia.

RECOMMENDATIONS

Atypical organisms such as Mycoplasma pneumoniae, Chlamydia pneumoniae and respiratory viruses cause most cases of community-acquired pneumonia in young people with mild disease. Pneumococci are probably the most common cause in patients sick enough to be hospitalized, and gram-negative bacilli and S. aureus are common in hospital-acquired pneumonia. The increasing resistance of pneumococci to penicillin has made oral cephalosporins unreliable for treatment of pneumonia and has contributed to frequent use of fluoroquinolones, with the predictable result that fluoroquinolone resistance has now become a concern. Before the infecting organism is known, it would be reasonable to treat young healthy patients with mild disease with an oral macrolide (erythromycin, azithromycin or clarithromycin). For older or sicker patients, a fluoroquinolone with good antipneumococcal activity, such as levo-, gati-, gemi- or moxifloxacin, would be a better choice. For hospitalized patients, a parenteral 3rd generation cephalosporin such as ceftriaxone or cefotaxime combined with a macrolide or doxycycline should be effective against many penicillin-resistant pneumococci and atypicals, but with increasing resistance of S. pneumoniae to β -lactams, vancomycin or linezolid is now often added.

In hospital-acquired pneumonia, cefepime, imipenem or meropenem, plus an aminoglycoside, would be a reasonable first choice before the infecting organism is known. Addition of vancomycin should be considered in hospitals with a high prevalence of methicillin-resistant *S. aureus*.

Gemifloxacin (Factive)

Originally published in The Medical Letter - September 2004; 46:78

Gemifloxacin (*Factive* – Oscient), a new oral fluoroquinolone antibiotic, has been approved by the FDA for 5 days' treatment of acute bacterial exacerbations of chronic bronchitis (ABECB) and 7 days' treatment of mild to moderate community-acquired pneumonia (CAP) in adults. For the next 6-8 months it will only be available, presumably for commercial reasons, in states east of the Rocky Mountains.

QUINOLONES FOR RESPIRATORY INFECTIONS — Fluoroquinolones are widely used for treatment of bacterial respiratory infections because of increasing resistance of *Streptococcus pneumoniae* to penicillin, macrolides (erythromycin, azithromycin [Zithromax] or clarithromycin [Biaxin]), doxycycline (Vibramycin, and others), and second-generation cephalosporins such as cefuroxime axetil (*Ceftin*, and others). Resistance to fluoroquinolones is also increasing among pneumococci, but levofloxacin, gatifloxacin and moxifloxacin are still active against the majority of multi-drug resistant strains.

ANTIBACTERIAL ACTIVITY — Like levo-, gati- and moxifloxacin, gemifloxacin is active against pneumococci, including most multi-drug resistant strains; *in vitro* it is more active than other quinolones against these resistant pneumococcal strains, but the clinical significance of this is unknown.¹ Gemifloxacin, like other fluoroquinolones, is also active *in vitro* against other organisms that cause bacterial lower respiratory infections, including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila (Chlamydia) pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* and some strains of *Klebsiella pneumoniae*.

Gemifloxacin (Factive)

PHARMACULOGY	
Class of drug	Fluoroquinolone antibacterial
Mechanism of action	Inhibits bacterial topoisomerase IV and DNA gyrase
Formulation	320-mg tablets
Route	Oral
Bioavailability	71%
Peak plasma levels	1 hour after PO dose
Plasma half-life	7 hours
Metabolism	Hepatic (limited degree, not CYP450)
Excretion	Feces (61%); urine (36%)

CLINICAL STUDIES — Published comparative clinical trials are limited to the non-inferiority studies summarized in the table.²⁻⁶ The studies of CAP included mostly patients with mild to moderately severe illness.

ADVERSE EFFECTS — Gemifloxacin causes a higher incidence of rash (about 3% in all patients) than other fluoroquinolones. In an unpublished study summarized in FDA review documents, women <40 years old were treated for 10 days with gemifloxacin or ciprofloxacin; the incidence of rash was 31.7% with gemifloxacin compared to 4.3% with ciprofloxacin.⁷ The rash usually resolved spontaneously within a week or two, but 5% of patients required treatment with systemic corticosteroids. Progression to life-threatening conditions such as Stevens-Johnson syndrome has not been reported. Photosensitivity has been reported rarely.

Dose-related liver enzyme abnormalities occurred in about 2% of patients treated with gemifloxacin 320 mg daily, about the same inci-

GEMIFLOXACIN CLINICAL STUDIES

STUDY	DESIGN (N)	REGIMENS	RESULTS
Acute bacteria	l exacerbations of	chronic bronchitis (ABECB)	
R Wilson et al ²	Randomized double-blind (712)	Gemifloxacin 320 mg once/d x 5d vs. clarithromycin 500 mg bid x 7d	Bacteriologic cure: gemifloxacin 86.7%, clarithromycin 73.1% Clinical cure: gemifloxacin 85.4%, clarithromycin 84.6%
S Sethi et al ³	Randomized double-blind (360)	Gemifloxacin 320 mg once/d x 5d vs. levofloxacin 500 mg once/d x 7d	Bacteriologic cure: gemifloxacin 78.4%, levofloxacin 85.7% Clinical cure: gemifloxacin 88.2%, levofloxacin 85.1%
R Wilson et al ⁴	Randomized open-label (274)	Gemifloxacin 320 mg once/d x 5d vs. ceftriaxone 1 g IV once/d x 3d max followed by cefuroxime 500 mg PO bid x 7d max	Bacteriologic cure: gemilloxacin 62.5%, cephalosporins 60.8% Clinical cure: gemilloxacin 86.8%, cephalosporins 81.3%
Community-ac	quired pneumonia	(CAP)	
P Leophonte et al ⁵	Randomized double-blind (324)	Gemifloxacin 320 mg once/d x 7d vs. amoxicillin/clavulanate 1 g/125 mg tid x 10d	Bacteriologic cure: gemifloxacin 87.2%, amox/clav 89.1% Clinical cure: gemifloxacin 88.7%, amox/clav 87.6%
H Lode et al ⁶	Randomized open-label (345)	Gemifloxacin 320 mg once/d x 7-14d vs. ceftriaxone 2 g IV once/d x 1-7d followed by cefuroxime 500 mg PO bid x 1-13d	Bacteriologic cure: gemifloxacin 90.6%, cephalosporins 87.3% Clinical cure: gemifloxacin 92.2%, cephalosporins 93.4%

DRUG	DAILY DOSAGE ¹	COST ²
Gatifloxacin -		
Tequin (BMS)	400 mg once/day	\$66.98
Gemifloxacin -		
Factive (Oscient)	320 mg once/day	131.46
Levofloxacin -		
Levaquin (Ortho-	500 mg once/day	74.51
McNeil)		
Moxifloxacin -		
Avelox (Bayer)	400 mg once/day	74.91
1. For treatment of commun	nity-acquired pneumonia.	
 Cost for 7 days' treatment September 2004. 	t, according to AWP listings in R	ed Book Update,

dence as with other fluoroquinolones. Gemifloxacin prolongs the QTc interval by a mean of 2.6 milliseconds, which is less than with levo-floxacin, gatifloxacin or moxifloxacin, all of which have rarely been associated with torsades de pointes.

All fluoroquinolones can cause gastrointestinal disturbances and, less commonly, central nervous system toxicity. Tendinitis and hypersensitiv-

Gemifloxacin (Factive)

ity reactions, including vasculitis, serum-sickness-like reactions and anaphylaxis, occur rarely.

CONCLUSION — Gemifloxacin (*Factive*) probably is at least as effective as other oral fluoroquinolones with good anti-pneumococcal activity for treatment of respiratory infections, but data in patients with severe pneumonia are limited, the drug is expensive and the high incidence of rash is worrisome. Older drugs are preferred.

- JA O'Donnell and SP Gelone. The newer fluoroquinolones. Infect Dis Clin North Am 2004; 18:691.
- R Wilson et al. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. Clin Ther 2002; 24:639.
- S Sethi et al. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Respir Med 2004; 98:697.
- R Wilson et al. Oral gemifloxacin once daily for 5 days compared with sequential therapy with I.V. ceftriaxone/oral cefuroxime (maximum of 10 days) in the treatment of hospitalized patients with acute exacerbations of chronic bronchitis. Respir Med 2003; 97:242.
- P Leophonte et al. Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. Respir Med 2004; 98:708.
- 6. H Lode et al. Oral gemifloxacin versus sequential therapy with intravenous ceftriaxone/ oral cefuroxime with or without a macrolide in the treatment of patients hospitalized with community-acquired pneumonia: A randomized, open-label, multicenter study of clinical efficacy and tolerability. Clin Ther 2002; 24:1915.
- 7. www.fda.gov/cder/foi/nda/2003/21158_factive.htm, Clinical Review, part 1, page 41.

Telithromycin (Ketek) for Respiratory Infections

Originally published in The Medical Letter - August 2004; 46:66

Telithromycin (*Ketek* – Aventis) has been approved by the FDA for oral treatment of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis in patients age 18 and older. The drug is the first in a new class of antibiotics, the ketolides, derived from the macrolide erythromycin. Telithromycin has been marketed in Europe since 2001.

STANDARD TREATMENT — Community-acquired pneumonia (CAP) is most often caused by *Streptococcus pneumoniae* (pneumococci) or the "atypical" pathogens *Mycoplasma pneumoniae*, *Chlamydophila* (*Chlamydia*) *pneumoniae* and *Legionella pneumophila*. For initial treatment of ambulatory patients with CAP, an oral macrolide, doxycycline or a fluoroquinolone with good anti-pneumococcal activity such as gatifloxacin, levofloxacin or moxifloxacin is generally used (Treatment Guidelines from the Medical Letter 2003; 1:83). Cephalosporins, amoxicillin and amoxicillin/clavulanate (*Augmentin*) are also used, but are not effective against atypical pathogens.

Acute bacterial sinusitis (ABS) in adults, usually caused by pneumococci or β-lactamase producing organisms such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and anaerobic streptococci, is generally treated with amoxicillin or amoxicillin/clavulanate, a cephalosporin such as cefuroxime axetil, or a fluoroquinolone with good antipneumococcal activity. **Acute exacerbations of chronic bronchitis** (AECB) may be due to *H. influenzae* or *M. catarrhalis* and are treated with the same antimicrobials used to treat sinusitis.

PNEUMOCOCCAL RESISTANCE — Pneumococci are increasingly resistant to macrolides, penicillin and doxycycline. In a study of 3362

DRUG	DAILY DOSAGE ¹	COST ²
B-LACTAMS		
Amoxicillin – average generic price	500 mg-1g q8h or	\$25.80
	875 mg q12h	17.00
Amoxil (GlaxoSmithKline)	500 mg-1g g8h or	32.40
, ,	875 mg q12h	18.40
Amoxicillin/clavulanate - Augmentin (GlaxoSmithKline)	500 mg/125mg g8h or	130.20
	875 mg/125 mg q12h	116.20
Augmentin XR	2000 mg/125 mg g12h	113.60
Cefuroxime axetil - average generic price	250-500 mg bid	139.20
Ceftin (GlaxoSmithKline)	-	202.60
FLUOROQUINOLONES		
Gatifloxacin – Tequin (Bristol-Myers Squibb)	400 mg once/day	94.80
Levofloxacin - Levaquin (Ortho-McNeil)	500 mg once/day	104.10
	750 mg once/day for 5 days	97.15
Moxifloxacin – Avelox (Bayer)	400 mg once/day	96.40
KETOLIDE	· ,	
Telithromycin – Ketek (Aventis)	800 mg once/day	114.00
MACROLIDES	· ,	
Azithromycin – Zithromax (Pfizer)	500 mg on day 1, then 250 mg once/day for days 2-5	46.86
Clarithromycin – Biaxin (Abbott)	250-500 mg bid	91.40
Biaxin XL	1000 mg once/day for 7 days	65.90
Erythromycin, enteric coated - average generic price	250-500 mg aid	11.20
Ery-Tab (Abbott)	31	17.20
TETRACYCLINES		
Doxycycline – average generic price	100 mg bid	22.40
Vibramycin (Pfizer)	•	95.60
 For treatment of community-acquired pneumonia. Cost for 10 days' (except azithromycin, Biaxin XL and Levaquin 7 most recent data (June 30, 2004) from retail pharmacies nationwi With good antipneumococcal activity. 		

COST OF SOME ORAL ANTIBIOTICS

pneumococcal isolates collected from 25 countries around the world during a one-year period, 22.1% were resistant to penicillin, 31% were resistant to erythromycin and 29.7% were resistant to tetracycline. Similar rates were observed for azithromycin and clarithromycin. Among the isolates that were resistant to penicillin, 72.4% were also cross-resistant to macrolides. The percentage of strains resistant to fluoroquinolones has been less than 1% in the US as a whole, but as high as 5% in some urban centers (D Felmingham et al, J Antimicrob Chemother 2002; 50 suppl S1: 25; MJ Rybak, Ann Pharmacother 2004; 38:epub).

MECHANISM OF ACTION — Telithromycin inhibits bacterial protein synthesis by binding to the 50-S ribosomal subunit (HM Yassin and LL Dever, Expert Opin Investig Drugs 2001; 10:353). It differs from

erythromycin by ketone- and methoxy-group substitutions that make it more acid stable and less susceptible to drug export pumps and increase the drug's ribosomal binding affinity, thereby overcoming the most frequent mechanisms of bacterial resistance to macrolides.

ANTIBACTERIAL ACTIVITY — Telithromycin has good activity *in* vitro against *S. pneumoniae* including most strains that are resistant to penicillin and erythromycin. It is similar to azithromycin and clarithromycin in its activity against *M. catarrhalis*, *H. influenzae*, *Bordetella pertussis* and the atypical respiratory pathogens *M. pneumoniae*, *Legionella* and *Chlamydia* (G Ackermann and AC Rodloff, J Antimicrob Chemother 2003; 51:497). Telithromycin is also active *in vitro* against most strains of group A β-hemolytic streptococci, erythromycin-susceptible strains of *Staphylococcus aureus*, *Helicobacter pylori* and some anaerobes (D Felmingham, Clin Microbiol Infect 2001; 7 suppl 3:2).

PHARMACOLOGY — Following an oral dose, telithromycin is rapidly absorbed from the GI tract, achieving peak serum concentrations in about one hour; absorption is not affected by food. Steady state plasma levels are reached in 2 to 3 days with continued dosing. The drug's halflife is 10 hours. About 37% of the dose and 70% of the absorbed drug are metabolized in the liver, about half by CYP3A4 and half by CYP450-independent pathways. Elimination occurs through multiple pathways including fecal (7%) and renal excretion (13%).

CLINICAL STUDIES — A pooled analysis of 11 controlled and uncontrolled studies in patients with mild to moderate CAP, AECB or ABS compared 2695 patients who received once daily telithromycin (7-10 days for CAP, 5 days for AECB and 5 or 10 days for ABS) to 1190 patients who received a comparator antibiotic (for CAP, amoxicillin t.i.d. for 10 days, clarithromycin b.i.d. for 10 days or trovafloxacin once

daily for 7-10 days; for AECB or ABS, either amoxicillin/clavulanate t.i.d. or cefuroxime axetil b.i.d. for 10 days). Cure rates with telithromycin were similar to the comparators across the three indications studied: 83.3% vs. 80.8% in CAP, 79.5% vs. 74.9% in AECB and 77.3% vs. 69.8% in ABS (CM Fogarty et al, J Antimicrob Chemother 2003; 51:947).

In another pooled analysis of 13 studies (including 8 of the studies mentioned above), a subset analysis of telithromycin use in high-risk patients with CAP, either ≥ 65 years old (154) or with pneumococcal bacteremia (47), found that clinical cure rates were 90.3% and 91.5%, respectively (C Carbon, Infection 2003; 31:308).

ADVERSE EFFECTS — The most common adverse events associated with telithromycin in clinical trials have been GI disturbances, including diarrhea (10% vs. 8% for comparators), nausea (7% vs. 4.1%), and vomiting (2.4% vs. 1.4%). Visual difficulties, particularly slowed ability to accommodate or release accommodation, that manifested as blurred vision, diplopia or difficulty focusing, have occurred in about 1% of patients; women under 40 years of age had the highest incidence (2%). Visual symptoms could occur after any dose, but were most common after the first or second; patients should be warned accordingly. Telithromycin, like erythromycin and clarithromycin, has the potential to prolong the QT interval, but QT prolongation has not been observed in clinical trials and there have been no reports of torsades de pointes or other ventricular arrhythmias (J-L Démolis et al, Clin Pharmacol Ther 2003; 73:242). Exacerbation of myasthenia gravis, including life-threatening respiratory failure, has been reported in patients taking telithromycin during postmarketing surveillance in Europe (RB Neiman et al, Clin Infect Dis 2003; 37:1579); the drug should not be prescribed for patients with myasthenia. Patients who are allergic to macrolides should not take telithromycin.

DRUG INTERACTIONS — Telithromycin is both a substrate and a potent inhibitor of CYP3A4 and can increase serum concentrations of many drugs metabolized by 3A4. It is contraindicated for use with cisapride (Propulsid: no longer marketed but still available in the US) and pimozide (Orap). Simvastatin (Zocor), lovastatin (Mevacor, and others) and atorvastatin (Lipitor) should be stopped while taking the antibiotic. Telithromycin also can markedly increase serum concentrations of the short-acting benzodiazepine midazolam (Versed, and others); although not listed as a contraindication in the telithromycin package insert, it may be prudent to use another shortacting hypnotic instead. Telithromycin can increase serum concentrations of ergot alkaloids used to treat migraine; severe peripheral vasospasm has been reported with concurrent use of macrolides. When coadministered, telithromycin can lead to increased serum concentrations of other substrates of CYP3A4, such as ritonavir (Norvir), sirolimus (Rapamune) or tacrolimus (Prograf), or of the CYP2D6 substrate metoprolol (Lopressor, and others). Telithromycin also increases peak serum levels of digoxin (Lanoxin, and others), probably by inhibition of P-glycoprotein.

Itraconazole (Sporanox) and ketoconazole (Nizoral, and others), both potent CYP3A4 inhibitors, increase telithromycin serum concentrations. Coadministration of the potent CYP3A4 inducer rifampin (Rifadin, and others) should be avoided; other inducers such as carbamazepine (Tegretol, and others) or phenytoin (Dilantin, and others) could decrease serum concentrations of telithromycin to subtherapeutic levels. Theophylline (Theodur, and others) can increase gastrointestinal adverse effects of telithromycin; they should be taken at least one hour apart. Telithromycin decreases absorption and serum levels of sotalol (Betapace). Like erythromycin and clarithromycin, telithromycin should be used cautiously with other drugs that can cause prolongation of the QT interval (www.qtdrugs.org).

DOSAGE — *Ketek* is marketed as a 400-mg tablet. No parenteral formulation is available. The recommended dosage is 800 mg once daily for 7-10 days for CAP and for 5 days for AECB or ABS. The optimal dose in patients with severe renal insufficiency (creatinine clearance <30 ml/min) has not been established; some consultants recommend a dose reduction to 400 mg once daily. No dose adjustment is required in hepatic insufficiency.

CONCLUSION — Oral telithromycin (*Ketek*), the first ketolide antibiotic, is at least as effective as standard drugs for treatment of bacterial respiratory infections, and is also effective for the pneumococcal respiratory infections that are macrolide-resistant. It would be a reasonable alternative to a fluoroquinolone for treatment of such infections. The drug is expensive, however, and visual adverse effects may be troublesome. Telithromycin is a potent inhibitor of CYP3A4 and can cause potentially dangerous increases in the serum concentrations of simvastatin (*Zocor*), lovastatin (*Mevacor*, and others), atorvastatin (*Lipitor*), midazolam (*Versed*, and others) and other drugs.

DRUGS FOR Tuberculosis

Original publication date - December 2004

Tuberculosis (TB) is still a problem in the United States, even though the incidence continues to decline in most of the country (MMWR Morbid Mortal Wkly Rep 2004; 53:209). Treatment of TB can be divided into treatment of latent infection diagnosed by a positive PPD and treatment of active clinical TB. Guidelines with detailed management recommendations are available from the US Centers for Disease Control and Prevention (CDC) (MMWR Morbid Mortal Wkly Rep 2003; 52RR-11:1).

TREATMENT OF LATENT TB INFECTION

The risk of developing clinical tuberculosis is greatest in patients with latent TB who are also infected with HIV or are receiving immunosuppressive therapy. It is also high in close contacts of patients with recent pulmonary tuberculosis, in those with radiographic evidence of prior TB, during the first 2 years after development of a positive tuberculin test, and in recent immigrants (CR Horsburgh Jr, N Engl J Med 2004; 350:2060; K Khan et al, N Engl J Med 2002; 347:1850).

The risk of serious disease, including miliary tuberculosis and tuberculous meningitis, is highest in infants, the elderly, and in patients with HIV infection or other causes of severe immunosuppression. Recent studies also indicate high risk for development of clinical TB, including life-threatening and miliary disease, in persons with latent TB who are treated with the TNF-alpha inhibitors infliximab (*Remicaid*), etanercept (*Enbrel*), and adalimumab (*Humira*). Before beginning therapy with

these drugs, tuberculin skin testing and, if positive, initiation of treatment for latent TB infection, is recommended (MMWR Morbid Mortal Wkly Rep 2004; 53:683; KL Wintrop and JN Siegel, Clin Infect Dis 2004; 39:1256).

Isoniazid – Isoniazid is the drug of choice for treatment of latent TB infection. It should be given for 9 months in a single daily dose of 300 mg for adults and 10 mg/kg (max 300 mg/day) for children, or twice weekly as 10-15 mg/kg (max 900 mg/dose) in adults and 20-30 mg/kg (max 900 mg/dose) in children (MMWR Morb Mortal Wkly Rep 2000; 49 RR-6:1). It is safe for treatment of latent TB in pregnancy (G Bothamley, Drug Saf 2001; 24:553).

Alternatives – Another possible regimen for treatment of latent TB is daily rifampin alone for 4 months, which may be useful in persons intolerant to isoniazid or those found to be tuberculin-positive after exposure to patients with organisms resistant to isoniazid (LB Reichman et al, Am J Respir Crit Care Med 2004; 170:832). The combination of rifampin and pyrazinamide for 2 months, which formerly was used as an alternative to isoniazid treatment of latent infection, should not be given because of its association with potentially lethal hepatotoxicity (MMWR Morbid Mortal Wkly Rep 2003; 52:735).

MDRTB – For patients with known exposure to multi-drug resistant TB (MDRTB) and a high risk of developing active TB, there are no data-based recommendations. Regimens with two drugs to which the organism is susceptible (e.g., pyrazinamide plus ethambutol or a fluoroquinolone for 9 to 12 months) have been used, but may be poorly tolerated (J Papastavros et al, CMAJ 2002; 167:131; R Ridzon et al, Clin Infect Dis 1997; 24:1264).

DIRECTLY OBSERVED THERAPY

In treating TB, poor adherence to therapy is the most important cause of treatment failure and is associated with emergence of drug resistance. Medical Letter consultants recommend that almost all patients, including those with infection due to susceptible strains, take drugs for TB under direct observation ("directly observed therapy" or DOT). DOT has been shown to improve cure rates when compared to self-administered regimens (RM Jasmer et al, Am J Respir Crit Care Med 2004; 170:561). Due to the complexity and duration of treatment regimens, DOT is particularly important for treatment of patients with MDRTB and for patients on intermittent regimens. DOT services are available through most local and state health department TB programs.

TREATMENT OF SUSCEPTIBLE TB

All isolates of *Mycobacterium tuberculosis* should be tested for antimicrobial susceptibility, but results generally do not become available for at least 2 weeks and sometimes much longer (GL Woods, Infect Dis Clin North Am 2002; 16:127). Standard therapy for TB includes a 2-month initial phase of treatment and a continuation phase of either 4 or 7 months, depending on the results of sputum cultures at 2 months. Among the drugs used for treatment of TB, effectiveness is best documented for regimens containing isoniazid and rifampin.

Empiric Initial Therapy – Until susceptibility results are available, empiric initial treatment consists of a 4-drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol (ED Chan and MD Iseman, BMJ 2002; 325:1282). Patients who cannot take pyrazinamide, such as those who have severe liver disease or gout, should receive empiric initial therapy with isoniazid, rifampin and ethambutol.

	Adult dosage Pediatric dosage				Main
Drug/formulation	Daily	Intermittent*	Daily	Intermittent*	adverse effects
lsoniazid (INH) ¹ 100, 300 mg tabs 50 mg/5mL syrup 100 mg/mL inj	5 mg/kg (max 300 mg) PO, IM, IV	15 mg/kg (max 900 mg) 2-3x/week	10-20 mg/kg (max 300 mg)	20-30 mg/kg (max 900 mg) twice/week	Hepatic toxicity, peripheral neuro- pathy
Rifampin (<i>Rifadin,</i> <i>Rimactane</i>) 150, 300 mg caps 600 mg inj powder	10 mg/kg (max 600 mg) PO, IV	10 mg/kg (max 600 mg) 2-3x/week	10-20 mg/kg (max 600 mg)	10-20 mg/kg (max 600 mg) twice/week	Hepatic toxicity, flu-like syndrome, pruritis
Rifabutin ² (Mycobutin) 150 mg caps	5 mg/kg (max 300 mg) PO	5 mg/kg (max 300 mg) 2-3x/week	10-20 mg/kg (max 300 mg)	No data available	Hepatic toxicity, flu-like syndrome, uveitis, neutropenia
Rifapentine (Priftin) 150 mg tabs		10 mg/kg/wk (max 600 mg) PO	No data available	No data available	Hepatic toxicity, hyperuricemia
Pyrazinamide 500 mg tabs	20-25 mg/kg PO	2.5-4 g 2-3x/week	15-30 mg/kg (max 2 g)	50 mg/kg (2 g) twice/week	Arthralgias, hepatic toxicity, hyperuricemia, GI upset
Ethambutol ³ (Myambutol) 100, 400 mg tabs	15-25 mg/kg PO	50 mg/kg 2-3 x/week	15-25 mg/kg	50 mg/kg (max 2.5 g) twice/week	Decreased red-green color discrimination, decreased visual acuity
	ally begun after a few we should be given to preven	2-3 x/week teks or months of treat t neuropathy in main	atment with a daily regin ourished or pregnant p	(max 2.5 g) twice/week men. atients and those with H	Decreased red-gree color discriminatio decreased visual acuity

Susceptible Organisms – When infection proves to be caused by a fully susceptible strain of TB, the initial phase of treatment should include isoniazid, rifampin and pyrazinamide. If pulmonary cavitation is not present on the initial chest X-ray and the patient has a negative AFB smear at 2 months, isoniazid plus rifampin or rifapentine, a long-acting rifamycin, can be given for the next 4 months (continuation phase) to complete a total of 6 months. For patients with a positive AFB culture at 2 months and cavitary lung disease, continuation therapy with isoniazid and rifampin is extended to 7 months (for a total duration of therapy of 9 months). Rifampin, not rifapentine, should be used for continuation therapy if there is cavitary lung disease, a positive AFB smear at 2 months, coinfection with HIV, extrapulmonary disease, or infection in children.

Disseminated TB, tuberculous meningitis and infections in children are usually treated for a total of 9-12 months. Osteomyelitis is usually treated for 6-9 months. Addition of a corticosteroid for 1-2 months is rec-

Cavity or Chest		at 2 mos	Dura	ation
X-ray	AFB smear	AFB culture	Drugs (mo	nths)
No	-	-	INH/RIF	4
			or INH/RPT	4
No	-	+	INH/RIF	4
			or INH/RPT	7
No	+	+	INH/RIF	4
Yes	+	-	INH/RIF	4
Yes	+	+	INH/RIF	7

ommended for tuberculous pericarditis or meningitis (GE Thwaites et al, N Engl J Med 2004; 351:1741).

Drug Intolerance – For patients who cannot tolerate rifampin, alternative regimens include 9-12 months of isoniazid, ethambutol and pyrazinamide, with or without a fluoroquinolone (usually levofloxacin, moxifloxacin, or gatifloxacin); 18 months of isoniazid plus ethambutol has also been given. Rifabutin has been substituted for rifampin in standard regimens for some patients who could not take rifampin because of drug interactions (SV Goldberg et al, Clin Infect Dis 2003; 37:607; A Lopez-Montes et al, Am J Kidney Dis 2004; 44:e59). Patients who cannot take pyrazinamide in the initial phase of treatment should receive continuation therapy with isoniazid and rifampin for a total of 7 months.

Intermittent Treatment – Intermittent 4-drug regimens with 2 or 3 doses per week after at least 2 weeks of daily therapy are also effective for treatment of TB and should always be given by DOT. Once-weekly continuation-therapy regimens including rifapentine (instead of rifampin), started after 2 months of standard initial therapy, may also be effective for susceptible TB (Tuberculosis Trials Consortium, Lancet

Combination Drugs		
Drug	Daily adult dosage	
Rifamate ¹ (isoniazid 150 mg, rifampin 300 mg)	2 capsules	
Rifater ¹	≤44 kg: 4 tablets	
	45-54 kg: 5 tablets	
rifampin 120 mg, pyrazinamide 300 mg)	55-90 kg: 6 tablets	
pyrazinarnide 500 mg)	additional pyrazinamide ²	
malnourished or pregnant alcoholism or diabetes. 2. Six tablets provide 1800 n	nould be given to prevent neuropathy in patients and those with HIV infection, ing of pyrazinamide. Patients should ide tablets to achieve total daily dose of	

2002; 360:528), but the optimal rifapentine dose is not clear, and these regimens have been associated with development of resistance (M Weiner et al, Am J Respir Crit Care Med 2004; 169:1191; FM Gordin, Am J Respir Crit Care Med 2004; 169:1176). Intermittent treatment should never be used for treatment of drug-resistant TB.

Fixed-Dose Combinations – A combination formulation of rifampin, isoniazid and pyrazinamide (*Rifater*) is approved by the FDA for the initial 2 months of daily anti-tuberculosis therapy. A combination of rifampin and isoniazid (*Rifamate*) has been available in the US since 1975. Fixed-dose combinations may be particularly useful for patients self-administering their therapy (B Blomberg and B Fourie, Drugs 2003; 63:535).

TREATMENT OF RESISTANT TB

Resistance to Isoniazid – The most common pattern of resistance is isolated resistance to isoniazid, which can be treated with rifampin, pyrazinamide and ethambutol for 6-9 months. A quinolone is often added if there is extensive disease; streptomycin is an alternative to ethambutol. Patients who cannot tolerate pyrazinamide can take rifampin and ethambutol for 12 months.

Multidrug Resistance – Treatment of MDRTB is based on limited data; patients should be referred, if possible, to clinicians who have experience in treating such cases. MDRTB (resistant at least to isoniazid and rifampin) should be treated with ≥ 4 drugs to which the organism is susceptible. Three drugs are usually given by mouth, the fourth by injection. When MDRTB is likely, or in patients with a history of previous treatment for TB, some clinicians start with combinations of 5, 6 or 7 drugs before laboratory susceptibility data are available.

Typically, empiric therapy for suspected MDRTB includes isoniazid, rifampin, ethambutol, pyrazinamide, an aminoglycoside (streptomycin, kanamycin or amikacin) or capreomycin, a fluoroquinolone (usually levofloxacin, moxifloxacin or gatifloxacin), and either cycloserine, ethionamide or aminosalicylic acid (PAS) (JB Nachega and RE Chaisson, Clin Infect Dis 2003; 36 suppl 1:S24; JS Mukherjee et al, Lancet 2004; 363:474). Even when susceptibility is confirmed, the regimen should include at least 4 active drugs.

Monthly bacteriologic results (AFB smear and culture) should be monitored and treatment continued for 18-24 months, or 12-18 months after the culture becomes negative. The parenteral drug should be continued for 6 months after culture conversion. Surgical

Drug	Daily adult dosage	Daily pediatric dosage	Main adverse effects
Streptomycin ¹	15 mg/kg IM (max 1 g)	20-40 mg/kg	Vestibular and auditory toxicity, renal damage
Capreomycin (Capastat)	15 mg/kg IM (max 1 g)	15-30 mg/kg	Auditory and vestibular toxicity, renal damage
Kanamycin (Kantrex, and others)	15 mg/kg IM, IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Amikacin (Amikin)	15 mg/kg IM, IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Cycloserine ² (Seromycin, and others)	10-15 mg/kg in 2 doses (max 500 mg bid) PO	10-15 mg/kg	Psychiatric symptoms, seizures
Ethionamide (Trecator-SC)	15-20 mg/kg in 2 doses	15-20 mg/kg	GI and hepatic toxicity,
Ciprofloxacin (<i>Cipro</i> , and others) Ofloxacin (<i>Floxin</i>)	(max 500 mg bid) PO 750-1500 mg PO, IV 600-800 mg PO, IV	Not recommended Not recommended	hypothyroidism Nausea, abdominal pain, restlessness, confusion Nausea, abdominal pain, restlessness, confusion
Levofloxacin (Levaquin)	500-1000 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Gatifloxacin ³ (Tequin)	400 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Moxifloxacin ³ (Avelox)	400 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Aminosalicylic acid (PAS; Paser)	8-12 g in 2-3 doses PO	200-300 mg/kg, in 2-4 doses	GI disturbance
week period, and then (if neede is reduced to 10 mg/kg/d (max	d) 2 to 3 times per week (20 to 30 750 mg/d). Dosage should be decre	mg/kg, or a maximum of 1.5 g per eased if renal function is diminished	ximum of 1 g per dose) for an initial 2 to 12 dose). For patients >59 years old, dosage I. ence of adverse neurological effects.

resection has improved outcome in some patients (ED Chan et al, Am J Respir Crit Care Med 2004; 169:1103).

HIV-INFECTED PATIENTS

Because TB therapy is complicated by co-infection with HIV, testing for HIV infection is recommended for all patients with active tuberculosis. To minimize the risk of resistance, treatment in the continuation phase should be given once daily or three times weekly (MMWR Morbid Mortal Wkly Rep 2002; 51:214). Twice weekly regimens should not be given to patients with CD4 cell counts <100 cells/mm³ because they have been associated with rifamycin resistance (RE Nettles et al, Clin Infect Dis 2004; 38:731). Rifapentine is not recommended for TB treatment in HIV-infected patients because it has been associated with development of rifamycin resistance (A Vernon et al, Lancet 1999; 353:1843).

Patients Not on HAART – For HIV-infected patients requiring TB treatment who are not currently being treated with highly active antiretroviral therapy (HAART), it may be prudent to delay HAART (particularly in patients with CD4 cell counts above 100 cells/mm³) for 2 or more months in order to avoid a paradoxical worsening of TB due to immune reconstitution, decrease the risk of overlapping drug adverse effects and interactions, and enhance adherence to both drug regimens (GL Dean et al, AIDS 2002; 16:75; DB Pedial-Sampaio et al, AIDS 2002; 16:1845). The optimal timing for initiating HAART in patients with newly diagnosed TB is not known.

Patients on HAART – Rifamycins induce hepatic CYP3A4 enzymes and can accelerate metabolism of protease inhibitors and some nonnucleoside reverse transcriptase inhibitors (NNRTIs), decreasing their serum concentrations, possibly to ineffective levels. The degree to which each drug activates CYP3A4 differs: rifampin is the most potent and rifabutin the least. In addition, rifabutin is a substrate for CYP3A4; protease inhibitors slow its metabolism, increasing serum concentrations and possibly toxicity.

Options with Rifampin – Standard 4-drug treatment regimens including rifampin can be given to HIV-infected patients with active TB who are simultaneously receiving HAART if the HAART regimen consists of efavirenz (*Sustiva*) and two nucleoside reverse transcriptase inhibitors (NRTIs). Standard doses of rifampin can also be used in patients taking either ritonavir (*Norvir*), ritonavir/saquinavir or ritonavir/lopinavir (*Kaletra*) as the protease inhibitor, combined with 2 NRTIs. Nevirapine (*Viramune*) with two NRTIs can also be given with standard dose rifampin (MMWR Morbid Mortal Wkly Rep 2004; 53:37).

Options with Rifabutin – Two alternative regimens are based on the fact that rifabutin appears to be as effective as rifampin against TB, and has less effect on protease inhibitor levels. The first substitutes low-dose

rifabutin (150 mg once/day or 300 mg 3x/week) for rifampin in the standard regimen (i.e., isoniazid, rifabutin, pyrazinamide and ethambutol) and uses higher than usual doses of indinavir (*Crixivan*) or nelfinavir (*Viracept*), or standard doses of amprenavir (*Agenerase*) or fosamprenavir (*Lexiva*) as the protease inhibitor. The second decreases the rifabutin dose further to 150 mg every other day or 3 times weekly and gives it with standard doses of atazanavir (*Reyataz*), ritonavir/lopinavir (*Kaletra*) or ritonavir alone or combined with other protease inhibitors. Saquinavir (*Fortovase*, *Invirase*) alone should not be used. If the HAART regimen contains nevirapine, the usual dose of rifabutin should be used. Higher rifabutin doses (450-600 mg daily) are needed if the HAART regimen contains efavirenz.

TB IN PREGNANCY

Treatment of TB should be initiated in pregnancy when there is moderate to high suspicion of disease because active infection during pregnancy poses a risk to the fetus that is greater than the risk of adverse drug effects. The initial regimen should include isoniazid, rifampin and ethambutol. Each of these drugs crosses the placenta, but none is teratogenic. Pyrazinamide is also probably safe in pregnancy and some Medical Letter consultants would use it in addition to or as a substitute for ethambutol, depending on results of susceptibility testing (G Bothamlen, Drug Saf 2001; 24:553). If pyrazinamide is not used, treatment should be continued for at least 9 months.

Limited data is available on the treatment of MDRTB in pregnancy. Regimens using combinations of amikacin, ethionamide, PAS, cycloserine, capreomycin and fluoroquinolones have been successful without causing fetal adverse effects, although these drugs are not generally considered safe in pregnancy (S Shin et al, Clin Infect Dis 2003; 36:996; KD Lessnau and S Qarah, Chest 2003; 123:953).

ADVERSE EFFECTS

Isoniazid – Serum aminotransferase activity increases in 10% to 20% of patients taking isoniazid, especially in the early weeks of treatment, but often returns to normal even when the drug is continued. Severe liver damage due to isoniazid is less common than previously thought (CM Nolan et al, JAMA 1999; 281:1014). It is more likely to occur in patients more than 35 years old, but can also occur in younger patients. Routine monitoring is not necessary except for patients with pre-existing liver disease. Medical Letter consultants recommend stopping isoniazid when serum aspartate aminotransferase activity reaches five times the upper limit of normal or if the patient has symptoms of hepatitis, but it can sometimes be re-started later.

Peripheral neuropathy occurs rarely and can usually be prevented by supplementation with pyridoxine (Vitamin B_6 , 10-25 mg/day), which is recommended for patients with chronic alcohol use, diabetes, chronic renal failure or HIV infection, and for those who are pregnant, breast feeding or malnourished.

Rifamycins – Rifampin, like isoniazid, is potentially hepatotoxic, and gastrointestinal disturbances, morbilliform rash and thrombocytopenic purpura can occur. Whenever possible, rifampin should be continued despite minor adverse reactions such as pruritus and gastrointestinal upset. When taken erratically, the drug can cause a febrile "flu-like" syndrome and, very rarely, shortness of breath, hemolytic anemia, shock and acute renal failure. Patients should be warned that rifampin may turn urine, tears and other body fluids reddish-orange and can permanently stain contact lenses and lens implants.

Rifampin is an inducer of CYP isozymes 3A4, 2C9, 2C19, 2D6, 2B6, and 2C8. It can increase the metabolism and decrease the effect of many other drugs, including oral contraceptives (patients should be advised to use another method of contraception), sulfonylureas such as glyburide

(*Diabeta*, and others), corticosteroids, warfarin (*Coumadin*, and others), quinidine, methadone (*Dolophine*, and others), delavirdine (*Rescriptor*), clarithromycin (*Biaxin*), ketoconazole (*Nizoral*, and others), itraconazole (*Sporanox*) and fluconazole (*Diflucan*), as well as protease inhibitors (Medical Letter Adverse Drug Interactions Program).

Rifabutin and **rifapentine** have adverse effects similar to those of rifampin. Rifabutin can also cause uveitis, skin hyperpigmentation and a lupus-like syndrome, but is less likely than rifampin to interact with other drugs.

Other Drugs – Pyrazinamide can cause morbilliform rash, arthralgias and asymptomatic hyperuricemia, and blocks the hypouricemic action of allopurinol (*Zyloprim*, and others). Gastrointestinal disturbances and hepatotoxicity can occur. **Ethambutol** can cause optic neuritis, but this is very rare when using a dosage of 15 mg/kg daily. Testing of visual acuity should be performed at the start of therapy, and monthly if the drug is continued past 2 months. The decision to use ethambutol in children too young to have visual acuity monitored must take into consideration the risk/benefit for each particular patient.

Streptomycin causes ototoxicity (usually vestibular disturbance) and, less frequently, renal toxicity. **Amikacin** and **kanamycin** commonly cause tinnitus and high frequency hearing loss. These drugs and **capreomycin** can also cause nephro- and vestibular toxicity. **Cycloserine** can cause psychiatric symptoms and seizures. **Ethionamide** has been associated with gastrointestinal, hepatic and thyroid toxicity. A delayed-release granular formulation of **aminosalicylic acid** (PAS, *Paser*) is better tolerated than older formulations. **Fluoroquinolones** are usually well-tolerated, but can cause gastrointestinal and CNS disturbances.

CONCLUSION

All isolates of *M. tuberculosis* should be tested for antimicrobial susceptibility. Initial therapy for most patients with active TB should include at least isoniazid, a rifamycin, pyrazinamide and ethambutol until susceptibility is known. Directly observed therapy (DOT) by a health care worker should be considered for all cases of active TB to minimize failure rates and the risk of emergence of drug resistance. Confirmed multidrug-resistant tuberculosis (MDRTB) should be treated with DOT and a regimen that includes at least 4 drugs to which the organism is susceptible; the total duration of therapy usually is 18 to 24 months.

Antimicrobial Prophylaxis for Surgery

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Antimicrobial prophylaxis can decrease the incidence of infection, particularly surgical site infection, after certain operations, but this benefit must be weighed against the risks of toxic and allergic reactions, emergence of resistant bacteria, adverse drug interactions, superinfection and cost. Medical Letter consultants generally recommend antimicrobial prophylaxis only for procedures with high infection rates, those involving implantation of prosthetic material, and those in which the consequences of infection are likely to be especially serious.

Recommendations for prevention of surgical site infection are listed in the table that begins on page 100. Recommendations for prevention of bacterial endocarditis in patients with valvular heart disease, prosthetic heart valves or other cardiac abnormalities are not included here; see page 109.

CHOICE OF A PROPHYLACTIC AGENT

An effective prophylactic regimen should be directed against the most likely infecting organisms, but need not eradicate every potential pathogen. For most procedures, **cefazolin** (*Ancef*, and others), which has a moderately long plasma half-life and is active against most staphylococci and streptococci, has been effective.

Some Exceptions – For procedures that might involve exposure to bowel anaerobes, including *Bacteroides fragilis*, cefotetan (*Cefotan*)

or cefoxitin (*Mefoxin*, and others) are preferred because they are more active than cefazolin against these organisms. In institutions where methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillinresistant coagulase-negative staphylococci are important post-operative pathogens, vancomycin (*Vancocin*, and others) can be used, but routine use of vancomycin for prophylaxis should be discouraged because it may promote emergence of vancomycin-resistant organisms and, at least in one study, was no better than cefazolin at preventing surgical site infection after cardiac surgery in a setting with a high prevalence of MRSA (R Finkelstein et al, J Thorac Cardiovasc Surg 2002; 123:326). Long preoperative hospitalizations are associated with increased risk of infection with an antibiotic-resistant organism; local resistance patterns should be taken into account.

Not Recommended – Third-generation cephalosporins, such as cefotaxime (*Claforan*), ceftriaxone (*Rocephin*), cefoperazone (*Cefobid*), ceftazidime (*Fortaz*, and others), or ceftizoxime (*Cefizox*), and fourthgeneration cephalosporins such as cefepime (*Maxipime*) should not be used for routine surgical prophylaxis because they are expensive, some are less active than cefazolin against staphylococci, their spectrum of activity includes organisms rarely encountered in elective surgery, and their widespread use for prophylaxis would promote emergence of resistance.

PENICILLIN ALLERGY

Cefazolin is often used for prophylaxis in penicillin-allergic patients, but such patients rarely may have allergic reactions to cephalosporins. When allergy prevents use of a cephalosporin, vancomycin or clindamycin can be used, but neither is effective against gram-negative bacteria, so some Medical Letter consultants would add gentamicin (*Garamycin*, and others), ciprofloxacin (*Cipro*, and others), levofloxacin (*Levaquin*, 750 mg

Nature of operation	Common pathogens	Recommended drugs	Adult dosage before surgery
Cardiac	Staphylococcus aureus, S.	cefazolin or	1-2 grams IV ²
	epidermidis	cefuroxime	1.5 grams IV ²
		OR vancomycin ³	1 gram IV
astrointestinal			
Esophageal, gastroduodenal	Enteric gram-negative bacilli,	High risk ⁴ only:	
	gram-positive cocci	cefazolin ⁷	1-2 grams IV
Biliary tract	Enteric gram-negative bacilli,	High risk ⁵ only:	
	enterococci, clostridia	cefazolin ⁷	1-2 grams IV
Colorectal	Enteric gram-negative bacilli,	Oral: neomycin	
	anaerobes, enterococci	+ erythromycin base6	
		OR metronidazole ⁶	
		Parenteral: cefotetan	1-2 grams IV
		or cefoxitin	1-2 grams IV
		OR cefazolin	1-2 grams IV
		+ metronidazole ⁷	0.5-1 grams IV
Appendectomy, non-perforated	Enteric gram-negative bacilli,	cefoxitin or	1-2 grams IV
	anaerobes, enterococci	cefotetan OB cefazolin	1-2 grams IV
		+ metronidazole ⁷	1-2 grams IV
			0.5-1 grams IV
Ruptured viscus	Enteric gram-negative bacilli,	cefoxitin or	1-2 g IV q6h
	anaerobes, enterococci	± gentamicin ^{7,8}	1-2 g IV q12h
		*	1.5 mg/kg IV q8h
Genitourinary	Enteric gram-negative bacilli,	High risk ⁹ only:	
	enterococci	ciprofloxacin	500 mg PO or 400 mg IV
Gynecologic and Obstetric			400 mg rv
Vaginal, abdominal or	Enteric gram-negative bacilli,	cefotetan or	1-2 grams IV
laparoscopic hysterectomy	anaerobes, Gp B strep,	cefoxitin or	1-2 grams IV
aparocoopio nyotorootoniy	enterococci	cefazolin ⁷	1-2 grams IV
Cesarean section	same as for hysterectomy	cefazolin	1-2 grams IV
	,,		after cord
			clamping
Abortion	same as for hysterectomy	First trimester, high risk ¹⁰ :	
		aqueous penicillin G	2 mill units IV
		OR doxycycline	300 mg PO ¹¹
		Second trimester:	1.0
		cefazolin	1-2 grams IV

abditional intradpertative does show be given an interval - 12 times are rained to the duration of the process. In reaconty-on to en-fluoroquinolosis is used, the initiation should be started 60-120 minutes before incision for order to minimize the possibility of an infusion reaction close to the time of induction of anesthesia and to have adequate tissue levels at the time of incision. 2. Some consultants recommend an additional does when patients are removed from typess during open-heart surgery. 3. For hospitals in which methicillin-resistant S. aureus and S. epidermidis are a frequent cause of postoperative wound infection.

for patients previously colonized with MRSA, or for those who are allergic to pericillins or cephalosportins. Rapid IV administration may cause hypotension, which could be especially dangerous during induction of anesthesia. Even when the drug is given over 60 minutes, hypotension may occur; treatment with diphenhydramine (*Benadryl*, and others) and further slowing of the infusion rate may be helpful. For procedures in which

enteric gram-negative bacilitare likely pathogens, such as vascular surgery involving a groin incision, cefarozin or cefurozine should be included in the prophylaxis regimen for patients not allergic to cephalosporins; ciprofloxacin, levofloxacin (750 mg), gentamicin, or aztreonam, each one in com-bination with vancomycin, can be used in patients who cannot tolerate a cephalosporin.
 Morbid obesity, esophageal obstruction, decreased gastric acidity or gastrointestinal motility.

5. Age >70 years, acute cholecystitis, non-functioning gall bladder, obstructive jaundice or common duct stones

After appropriate diet and catharsis, 1 g of neomycin plus 1 g of erythromycin at 1 PM, 2 PM and 11 PM or 2 g of neomycin plus 2 g of metronida-zole at 7 PM and 11 PM the day before an 8 AM operation.

7. For patients allergic to cephalosporins, clindamycin with either gentamicin, ciprofloxacin, levofloxacin (750 mg) or aztreonam is a reasonable alternative.

		Recommended	Adult dosage
Nature of operation	Common pathogens	drugs	before surgery ¹
Head and Neck Surgery Incisions through oral or pharyngeal mucosa	Anaerobes, enteric gram- negative bacilli, S. aureus	clindamycin + gentamicin OR cefazolin	600-900 mg IV 1.5 mg/kg IV 1-2 grams IV
Neurosurgery	S. aureus, S. epidermidis	cefazolin OR vancomycin ³	1-2 grams IV 1 gram IV
Ophthalmic	S. epidermidis, S. aureus, streptococci, enteric gram- negative bacilli, <i>Pseudomonas</i>	gentamicin, tobramycin, ciprofloxacin, gatifloxacin levofloxacin, moxifloxacin, ofloxacin or neomycin- gramicidin-polymyxin B cefazolin	multiple drops topically over 2 to 24 hours 100 mg subcon- junctivally
Orthopedic	S. aureus, S. epidermidis	cefazolin ¹² OR vancomvcin ^{3,12}	1-2 grams IV 1 gram IV
Thoracic (Non-Cardiac)	S. aureus, S. epidermidis, streptococci, enteric gram- negative bacilli	cefazolin or cefuroxime OR vancomycin ³	1-2 grams IV 1.5 grams IV 1 gram IV
Vascular Arterial surgery involving a prosthesis, the abdominal aorta, or a groin incision	S. aureus, S. epidermidis, enteric gram-negative bacilli	cefazolin OR vancomycin ³	1-2 grams IV 1 gram IV
Lower extremity amputation for ischemia	S. aureus, S. epidermidis, enteric gram-negative bacilli, clostridia	cefazolin OR vancomycin ³	1-2 grams IV 1 gram IV

8. Therapy is often continued for about five days. Ruptured viscus in postoperative setting (dehiscence) requires antibacterials to include coverage of nosocomial pathogens.

9. Urine culture positive or unavailable, preoperative catheter, transrectal prostatic biopsy, placement of prosthetic material.

Other culture positive of unavailable, propertaive catenter, unarsectal prosade totops, pacement or prostness
 Divided into 100 mg one hour before the abortion and 200 mg one ahil hour after.
 If a tourning to its provide the provide the abortion and 200 mg on ahil hour after.

once) or aztreonam (*Azactam*), particularly for colorectal procedures, hysterectomies, and vascular surgery involving groin incisions.

TIMING AND NUMBER OF DOSES

It has been common practice to give antibiotics at the time of anesthesia induction, which results in adequate serum and tissue levels of the drugs; there is no consensus on whether the infusion must be completed by the time of incision. For procedures lasting less than 4 hours, Medical Letter consultants recommend a single intravenous dose of an antimicrobial started within 60 minutes before the initial skin incision, which should provide adequate tissue concentrations throughout the procedure. If vancomycin or a fluoroquinolone is used, the infusion should begin 60-120 minutes before the incision is made in order to minimize the risk of antibiotic-associated reactions around the time of anesthesia induction and ensure adequate tissue levels of the drug at the time of incision.

Additional Doses – If the procedure is prolonged (>4 hours), major blood loss occurs, or an antimicrobial with a short half-life is used, redosing every 1-2 half-lives of the drug should provide adequate antimicrobial concentrations during the procedure (cefazolin q2-5 hours, cefuroxime q3-4 hours, cefoxitin q2-3 hours, cefotetan and clindamycin q3-6 hours, and vancomycin q6-12 hours). Published studies of antimicrobial prophylaxis often use one or two doses postoperatively in addition to one dose just before surgery. Most Medical Letter consultants believe, however, that postoperative doses are unnecessary after wound closure and increase the risk of antimicrobial resistance.

CARDIAC

Prophylactic antibiotics can decrease the incidence of infection after cardiac surgery, and intraoperative redosing has been associated with a decreased risk of postoperative infection in procedures lasting >400 minutes (G Zanetti et al, Emerg Infect Dis 2001; 7:828). Antimicrobial prophylaxis for prevention of **device-related infections** has not been rigorously studied. It is, however, generally given before placement of electrophysiologic devices, ventricular assist devices, ventriculoatrial shunts and arterial patches (LM Baddour et al, Circulation 2003; 108:2015). A meta-analysis of seven randomized studies of antimicrobial prophylaxis for **implantation of permanent pacemakers** showed a statistically significant reduction in the incidence of wound infection, inflammation or skin erosion (A DaCosta et al, Circulation 1998; 97:1796).

GASTROINTESTINAL

Antibiotic prophylaxis is recommended for **esophageal** surgery in the presence of obstruction, which increases the risk of infection. After **gastroduodenal surgery** the risk of infection is high when gastric acidity and gastrointestinal motility are diminished by obstruction, hemorrhage, gastric ulcer or malignancy, or by therapy with an H₂-blocker such as ranitidine (*Zantac*, and others) or a proton pump inhibitor such as omeprazole (*Prilosec*, and others), and is also high in patients with morbid obesity (AJ Chong and EP Dellinger, Curr Treat Options Infect Dis 2003; 5:387). A dose of cefazolin before surgery can decrease the incidence of postoperative infection in these circumstances. Prophylactic antibiotics are not indicated for routine **gastroesophageal endoscopy**, but most clinicians use them before placement of a **percutaneous gastrostomy** (WK Hirota et al, Gastrointest Endosc 2003; 58:475; I Ahmad et al, Aliment Pharmacol Ther 2003; 18:209).

Antimicrobials are recommended before **biliary tract** surgery for patients with a high risk of infection — those more than 70 years old and those with acute cholecystitis, a non-functioning gallbladder, obstructive

jaundice or common duct stones. Many clinicians follow similar guidelines for antibiotic prophylaxis of endoscopic retrograde cholangiopancreatography (ERCP) (JS Mallery et al, Gastrointest Endosc 2003; 57:633). Prophylactic antibiotics are generally not necessary for lowrisk patients undergoing elective laparoscopic cholecystectomy (M Koc et al, Surg Endosc 2003; 17:1716; KJ Dobay et al, Am Surg 1999; 65:226; A Higgins et al, Arch Surg 1999; 134:611).

Preoperative antibiotics can decrease the incidence of infection after **colorectal** surgery; for elective operations, an oral regimen of neomycin (not available in Canada) plus either erythromycin or metronidazole appears to be as effective as parenteral drugs. Many surgeons in the US use a combination of oral and parenteral agents (O Zmora et al, Dis Colon Rectum 2001; 44:1537). It is controversial whether the combination is more effective than either alone (RT Lewis, Can J Surg 2002; 45:173). Preoperative antimicrobials can decrease the incidence of infection after surgery for acute **appendicitis** (BR Andersen et al, Cochrane Database Syst Rev 2003; 2:CD001439).

If **perforation** has occurred, antibiotics are often used therapeutically rather than prophylactically and are continued for 5-7 days. In studies of penetrating abdominal and intestinal injuries, however, a short course (12-24 hours) was as effective as 5 days of therapy (EP Dellinger et al, Arch Surg 1986; 121:23; A Bozorgzadeh et al, Am J Surg 1999; 177:125; EE Cornwell 3rd et al, J Gastrointest Surg 1999; 3:648).

GENITOURINARY

Medical Letter consultants do not recommend antimicrobials before most urological operations in patients with sterile urine. When the urine culture is positive or unavailable, or the patient has a preoperative urinary catheter, patients should be treated to sterilize the urine before surgery or receive a single preoperative dose of an appropriate agent. A meta-analysis that included 4260 patients with sterile preoperative urine undergoing **transurethral prostatectomy** concluded that antimicrobial prophylaxis decreased the incidence of postoperative bacteriuria and septicemia (A Berry and A Barratt, J Urol 2002; 167:571). Prophylaxis is recommended before **transrectal prostatic biopsies** because urosepsis has occurred (M Aron et al, BJU Int 2000; 85:682). Surgical prophylaxis is generally used if a **urologic prosthesis** (penile implant, artificial sphincter, synthetic pubovaginal sling, bone anchors for pelvic floor reconstruction) will be placed (A Gomelsky and RR Dmochowski, Curr Pharm Des 2003; 9:989).

GYNECOLOGIC AND OBSTETRIC

Antimicrobial prophylaxis decreases the incidence of infection after **vaginal and abdominal hysterectomy** (C Chongsomchai et al, J Hosp Infect 2002; 52:302; AA Kamat et al, Infect Dis Obstet Gynecol 2000; 8:230). Prophylaxis is also used for **laparoscopic hysterectomies**. Antimicrobials, usually given after cord clamping, can prevent infection after **elective and non-elective cesarean sections** (F Smaill and GJ Hofmeyr, Cochrane Database Syst Rev 2002; 3:CD000933; D Chelmow et al, Am J Obstet Gynecol 2001; 184:656; L French, Curr Womens Health Rep 2003; 3:274). Antimicrobial prophylaxis can also prevent infection after **first- and second-trimester elective abortion**. One meta-analysis found a protective effect of perioperative antibacterials in all women undergoing induced abortions (GF Sawaya et al, Obstet Gynecol 1996; 87:884).

HEAD AND NECK

Prophylaxis with antimicrobials has decreased the incidence of surgical site infection after head and neck operations that involve an incision through the oral or pharyngeal mucosa. One study in 74 patients

undergoing surgery for head and neck cancer who received clindamycin beginning immediately preoperatively found no difference in infectious complications between continuing the drug for 24 hours (3 doses) or 5 days (15 doses); unfortunately, there was no single-dose group (WR Carroll et al, Arch Otolaryngol Head Neck Surg 2003; 129:771).

NEUROSURGERY

An antistaphylococcal antibiotic can decrease the incidence of infection after craniotomy. In **spinal surgery**, the infection rate after conventional lumbar discectomy is low, but the serious consequences of surgical site infection have led many neurosurgeons to use perioperative antibiotics. A meta-analysis concluded that antibiotic prophylaxis is beneficial in preventing infection even in low-risk spinal surgery (FG Barker II, Neurosurgery 2002; 51:391). Infection rates are higher after prolonged spinal surgery or spinal procedures involving fusion or insertion of foreign material, and prophylactic antibiotics are often used (JB Dimick et al, Spine 2000; 25:2544). Studies of antimicrobial prophylaxis for implantation of permanent **cerebrospinal fluid shunts** have produced conflicting results.

OPHTHALMIC

Data are limited on the effectiveness of antimicrobial prophylaxis for ophthalmic surgery, but postoperative endophthalmitis can be devastating. Most ophthalmologists use antimicrobial eye drops for prophylaxis, and some also give a subconjunctival injection or add antimicrobial drops to the intraocular irrigation solution (DV Leaming, J Cataract Refract Surg 2003; 29:1412). There is no consensus supporting a particular choice, route or duration of antimicrobial prophylaxis (TJ Liesegang, Cornea 1999; 18:383). Preoperative povidone-iodine applied to the skin and conjunctiva has been associated with a lower incidence of culture-proven endophthalmitis (TA Ciulla et al, Ophthalmology 2002; 109:13). There is no evidence that prophylactic antibiotics are needed for procedures that do not invade the globe.

ORTHOPEDIC

Prophylactic antistaphylococcal drugs administered preoperatively can decrease the incidence of both early and late infection following **joint replacement**. They also decrease the rate of infection in **compound or open fractures** and when **hip and other fractures** are treated with internal fixation by nails, plates, screws or wires. If a proximal tourniquet is used for the procedure, the antibiotic infusion must be completed prior to its inflation. One large randomized trial found a single dose of a cephalosporin more effective than placebo in preventing wound infection after surgical repair of **closed fractures** (H Boxma et al, Lancet 1996; 347:1133). A prospective randomized study in patients undergoing diagnostic and operative **arthroscopic surgery** concluded that antibiotic prophylaxis is not indicated (JA Wieck et al, Orthopedics 1997; 20:133).

THORACIC (NON-CARDIAC)

Antibiotic prophylaxis is given routinely in thoracic surgery, but supporting data are sparse. In one study, a single preoperative dose of cefazolin before **pulmonary resection** led to a decrease in the incidence of surgical site infection, but not of pneumonia or empyema (R Aznar et al, Eur J Cardiothorac Surg 1991; 5:515). Other trials have found that multiple doses of a cephalosporin can prevent infection after **closed-tube thoracostomy** for chest trauma with hemo- or pneumothorax (RP Gonzalez and MR Holevar, Am Surg 1998; 64:617). Insertion of chest tubes for other indications, such as spontaneous pneumothorax, does not require antimicrobial prophylaxis.

VASCULAR

Preoperative administration of a cephalosporin decreases the incidence of postoperative surgical site infection after arterial reconstructive surgery on the abdominal aorta, vascular operations on the leg that include a groin incision, and amputation of the lower extremity for ischemia. Many experts also recommend prophylaxis for implantation of any vascular prosthetic material, such as grafts for vascular access in hemodialysis. Prophylaxis is not indicated for carotid endarterectomy or brachial artery repair without prosthetic material.

OTHER PROCEDURES

Not indicated – Antimicrobial prophylaxis is generally not indicated for cardiac catheterization, varicose vein surgery, most dermatologic and plastic surgery, arterial puncture, thoracentesis, paracentesis, repair of simple lacerations, outpatient treatment of burns, dental extractions or root canal therapy because the incidence of surgical site infections is low. A study in patients undergoing cosmetic procedures who did not receive prophylactic antibiotics found that infection was more common after longer operations; the authors concluded that a single dose of cefazolin might be helpful before operations that last more than 3 hours (CA Fatica et al, Plast Reconstr Surg 2002; 109:2570).

Controversial – The need for prophylaxis in **breast surgery**, **herniorraphy** and other "clean" surgical procedures has been controversial (R Knight et al, Am J Surg 2001; 182:682; DF D'Amico et al, J Chemother 2001; 13 spec No 1:108). Medical Letter consultants generally do not recommend surgical prophylaxis for these procedures unless prosthetic material (synthetic mesh, saline implants, tissue expanders) will be placed, because of the low rate of infection, the low morbidity of these infections and the potential adverse effects of using prophylaxis in such a large number of patients.

Antibacterial Prophylaxis for Dental, GI and GU Procedures

Antibacterial Prophylaxis for Dental, GI and GU Procedures

Originally published in the Medical Letter - July 2005; 47:59

Many physicians believe that antimicrobial prophylaxis before procedures that may cause transient bacteremia can prevent endocarditis and prosthetic joint infection in patients at increased risk for these disorders. The effectiveness of this common practice has never been established by controlled trials in humans.¹ The drugs and dosages in the table are based on those recommended by the American Heart Association for prevention of endocarditis.²

ENDOCARDITIS — The risk of endocarditis is considered high in patients with previous bacterial endocarditis, prosthetic heart valves, complex cyanotic congenital heart disease such as tetralogy of Fallot, or surgically constructed systemic pulmonary shunts or conduits. The risk is considered sufficient to justify prophylaxis in patients with other forms of congenital cardiac malformation (but not isolated secundum atrial septal defect), acquired valvular disease (such as rheumatic), hypertrophic cardiomyopathy, and mitral valve prolapse with thickened leaflets or regurgitation.

PROSTHETIC DEVICE INFECTIONS — Some infectious disease specialists recommend antimicrobial prophylaxis before procedures in patients with vascular grafts or orthopedic prostheses.³ Guidelines have been suggested for antimicrobial prophylaxis of patients with total joint arthroplasty undergoing dental or genitourinary procedures.^{4,5} No data exist from controlled human trials to support or refute these practices. For patients undergoing other invasive procedures that may result in transient bacteremia, using an approach similar to that for endocarditis prevention seems reasonable.

Antibacterial Prophylaxis for Dental, GI and GU Procedures

	DOSAGE FOR ADULTS	DOSAGE FOR CHILDREN ²
DENTAL, ESOPHAGEAL AND UPPER RESPIRATO	RY PROCEDURES ³	
Oral		
Amoxicillin ^{4,5} (Amoxil, and others)	2 g 1 hour before	50 mg/kg 1 hour before
Penicillin allergy:		
Clindamycin (Cleocin, and others)	600 mg 1 hour before	20 mg/kg 1 hour before
OR		
Cephalexin ⁶ (Keflex, and others)	2 g 1 hour before	50 mg/kg 1 hour before
or Cefadroxil (Duricef, and others)6		
OR		
Azithromycin ⁵ (Zithromax)	500 mg 1 hour before	15 mg/kg 1 hour before
or Clarithromycin ⁵ (Biaxin)		
Parenteral (for patients unable to take oral drugs)		
Ampicillin ⁵ (<i>Omnipen</i> , and others),	2 g IM or IV within	50 mg/kg IM or IV within 30 minutes
	30 minutes before	before
Penicillin allergy:		
Clindamycin	600 mg IV within 30 minutes before	20 mg/kg IV within 30 minutes before
OR		
Cefazolin ⁶ (Ancef, and others)	1 g IM or IV within 30 minutes before	25 mg/kg IM or IV within 30 minutes before
GASTROINTESTINAL (EXCLUDING ESOPHAGEAL) AND GENITOURINARY PROCEDURES ³	
Oral		
Amoxicillin ^{4,5}	2 g 1 hour before	50 mg/kg 1 hour before
Parenteral ⁷		
Ampicillin ^{5,8}	2 g IM or IV within	50 mg/kg IM or IV within 30 minutes
	30 minutes before	before
±Gentamicin ⁹ (Garamycin, and others)	1.5 mg/kg (120 mg max.) IM or IV	1.5 mg/kg IM or IV within 30 minutes
	within 30 minutes before	before
Penicillin allergy:		
Vancomycin (Vancocin, and others)	1 g IV infused slowly over 1 hour starting 1 hour before	20 mg/kg IV infused slowly over 1 hour starting 1 hour before
	÷	÷
±Gentamicin ⁹	1.5 mg/kg (120 mg max.) IM or IV within 30 minutes before	 1.5 mg/kg IM or IV within 30 minutes before

Prophylaxis for Endocarditis and Prosthetic Device Infection¹

enterococci are the most common cause after gastrointestinal or genitourinary procedures.

2. Should not exceed adult dosage.

3. For a review of the risk of bacteremia with various procedures, see AS Dajani et al, JAMA 1997; 277:1794 and WK Hirota et al, Gastrointest Endosc 2003; 58:475. Among dental procedures, some experts believe that endocarditis prophylaxis should only be offered to at-risk patients undergoing tooth extractions and gingival surgery, including implant placement, and to those with prosthetic cardiac valves or a history of previous endocarditis (DT Durack, Ann Intern Med 1998; 129:829).

4. Amoxicillin remains the drug of choice for patients without penicillin allergy because of its excellent bioavailability and generally good activity against streptococci and enterococci.

5. Resistance and tolerance to penicillins and macrolides is increasing among viridans streptococci. Failure of appropriate prophylaxis has been reported, but remains rare (RM Prabhu et al, Antimicrob Agents Chemother 2004; 48:4463; MJ Kennedy et al. Clin Pediatr 2004; 43:773; T Hanslik et al. Clin Microbiol Infect 2003; 9:852).

6. Not recommended for patients with history of recent, severe or immediate-type (urticaria, angioedema, anaphylaxis) allergy to penicillin. 7. Parenteral regimens are preferred for patients at high risk for endocarditis.

8. High-risk patients given parenteral ampicillin before the procedure should receive a dose of ampicillin 1 g IM or IV or amoxicillin 1 g PO six hours afterwards.

9. Gentamicin is usually added for patients with a high risk of endocarditis.

Antibacterial Prophylaxis for Dental, GI and GU Procedures

The risk of hematogenous joint infection is thought to be increased in the first two years after a total joint replacement and in patients with a history of previous prosthetic joint infection. Prophylaxis is not indicated for those who have only orthopedic pins, plates or screws. Most experts would not recommend prophylaxis for patients with other implanted foreign bodies, such as dialysis catheters, ventriculoperitoneal shunts, cardiac pacemakers and/or defibrillators.

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Treatment of Lyme Disease

Originally published in the Medical Letter - May 2005; 47:41

Lyme disease in North America is caused by the spirochete *Borrelia burgdorferi*, which is transmitted to humans by *Ixodes scapularis* or *pacificus* ticks. These ticks may also carry other pathogens; coinfection with *Babesia microti* or *Anaplasma phagocytophilum* (formerly *Ehrlichia*) has been reported.¹ In 2001 and 2002, 12 states (CT, DE, ME, MD, MA, MI, NH, NJ, NY, PA, RI, WI) reported about 95% of all the Lyme disease in the US, but cases occurred in all states except HI, MT and OK.² Most Lyme disease in North America occurs between May and September.

THE DISEASE — About 70-80% of patients infected by *B. burgdor-feri* develop the characteristic skin lesion, erythema migrans, which occurs at the site of the tick bite 3 to 30 days after the tick has detached.³ Fever, headache, malaise, arthralgias and myalgia usually accompany early disease. Multiple (secondary) skin lesions occur in about 15% of patients. Patients with untreated Lyme disease may develop cardiac involvement, neurologic disease or migratory musculoskeletal pain. Late manifestations of Lyme disease include arthritis, typically of the knee, and various neurologic conditions, including peripheral neuropathy and subtle encephalopathy with cognitive defects. Clinical manifestations of the disease are somewhat different in Europe because other borrelia species cause human infection there.⁴

DIAGNOSIS — In endemic areas, Lyme disease is diagnosed by recognition of erythema migrans. IgG antibodies to *B. burgdorferi* are usually detectable 4 to 6 weeks after the initial infection. If an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent assay (IFA) is positive or equivocal, the specimen should also be tested with a standardized Western blot.⁵

PROPHYLAXIS — No vaccine is currently available to prevent Lyme disease in humans. Avoidance of ticks and use of tick repellents such as DEET or picaridin, or the insecticide permethrin on clothing can prevent Lyme disease.⁶ Since transmission of *B. burgdorferi* is more likely with prolonged tick attachment, prompt removal of ticks can also prevent disease.⁷ Whether early antibiotic prophylaxis is indicated after a tick bite is controversial; the strongest indication is in a highly endemic area when an engorged tick is attached for 48 hours or more. In one study of 482 patients who had removed an attached I. scapularis tick, a single 200-mg dose of doxycycline (Vibramycin, and others) within 72 hours of tick removal was 87% effective in preventing development of erythema migrans at the site of the bite.⁸ In another prophylactic study, 10 days of amoxicillin (Amoxil, and others) appeared to be effective (no treated patients developed the disease), but the incidence of infection in the placebo group was too low to permit any conclusions.9

ERYTHEMA MIGRANS — Oral antibiotic therapy shortens the duration of the rash and generally prevents development of late sequelae. Among the 3 drugs used for this indication, only doxycycline is also effective against *A. phagocytophilum* infection; it should not be used in pregnant women or children less than eight years old. One double-blind controlled trial in 180 patients with erythema migrans showed that 10 days treatment with doxycycline was as effective as 20 days. Some patients remained symptomatic at the end of antibiotic therapy, but they continued to improve after treatment at the same rate regardless of whether they were treated for 10 or 20 days. One patient in the 10-day group developed meningitis.¹⁰

Amoxicillin is as effective as doxycycline and is preferred for children less than 8 years old and pregnant or lactating women. Cefuroxime axetil (*Ceftin*) is also effective, but much more expensive. Macrolides such as

		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE ²
ERYTHEMA MIGRANS		Doxycycline ³ (Vibramycin,	100 mg PO bid x 10-21d	≥8 yrs; 1-2 mg/kg bid
		and others)	100 Hig1 O bld x 10-210	20 yra, 1-2 mgrkg blu
	or	Amoxicillin (Amoxil, and others)	500 mg PO tid x 14-21d	25-50 mg/kg/d divided tid
	or	Cefuroxime axetil (Ceftin)	500 mg PO bid x 14-21d	30 mg/kg/d divided bid
NEUROLOGIC DISEASE				
Facial nerve palsy		Doxycycline ³	100 mg PO bid x 14-21d	≥8 yrs; 1-2 mg/kg bid
	or	Amoxicillin	500 mg PO tid x 14-21d	25-50 mg/kg/d divided tid
More serious disease		Ceftriaxone4 (Rocephin)	2 g/d IV once/d x 14-28d	75-100 mg/kg once/d IV
CARDIAC DISEASE				
Mild (first degree		Doxycycline ³	100 mg PO bid x 14-21d	≥8 yrs: 1-2 mg/kg bid
AV block)	or	Amoxicillin	500 mg PO tid x 14-21d	25-50 mg/kg/d divided tid
More serious disease ⁵		Ceftriaxone ⁴	2 g once/d IV x 14-21d	50-100 mg/kg once/d IV
ARTHRITIS ⁶				
		Doxycycline ³	100 mg PO bid x 28d	>8 yrs: 1-2 mg/kg bid
	or	Amoxicillin	500 mg PO tid x 28d	25-50 mg/kg/d divided tid
	or	Ceftriaxone ⁴	2 g once/d IV x 14-28d	50-100 mg/kg once/d IV
		Lyme disease, complete response to tre s with objective signs of relapse may n	eatment may be delayed beyond th	e treatment duration. Relapse ha
 Should not exceed adult dosage. 				
		eight years old or for pregnant or lactatin 8d for adults and 150-200 mg/kg/d in 3		

A semiconary contrastry c gri y con a resource and similarity 150-200 mg/gg in 3-4 cueeds for Children.
 A temporary pacemaker may be necessary. Oral treatment may be substituted for IV therapy after resolution of the heart block in a stable patient.
 In late disease, the response to treatment may be delayed for several weeks or months.

azithromycin (Zithromax) have been less effective in controlled trials.¹¹ Patients in whom bacterial cellulitis cannot be excluded could be treated with cefuroxime axetil or amoxicillin/clavulanic acid (Augmentin), since these drugs are active against Lyme disease as well as Streptococcus pyogenes and most community-acquired strains of Staphylococcus aureus. Fluoroquinolones are ineffective against B. burgdorferi.

NEUROLOGIC DISEASE - For patients with facial nerve palsy alone, oral doxycycline or amoxicillin may be effective. Patients with other neurologic involvement, such as meningitis, other cranial nerve palsies, radiculopathy or cognitive deficits, should be treated with IV ceftriaxone (Rocephin) or cefotaxime (Claforan).12

CARDIAC DISEASE — Cardiac conduction abnormalities associated with Lyme disease are generally self-limited. Patients with minor cardiac involvement (first-degree atrioventricular block) can usually be treated with oral doxycycline or amoxicillin. Those with more severe cardiac involvement should receive IV ceftriaxone or cefotaxime.

ARTHRITIS — Oral therapy with doxycycline or amoxicillin for 28 days is usually effective for treatment of Lyme arthritis. Patients who have not responded to oral treatment may respond to a second one-month course of oral therapy or to IV therapy with ceftriaxone or cefotaxime. One trial found similar efficacy in eradicating signs and symptoms with 14 and 28 days of ceftriaxone in patients with late Lyme disease, the majority of whom had Lyme arthritis.¹³

POST-LYME DISEASE SYNDROME — Some treated patients whose objective manifestations of Lyme disease have resolved with antibiotic treatment report subjective symptoms such as fatigue, musculoskeletal pain or cognitive difficulties of varying intensity that may persist over prolonged periods. Microbiologic evaluation of these patients has failed to find evidence of either persistent *B. burgdorferi* infection or of co-infection with another tick-borne pathogen. Two controlled studies, one in 78 patients seropositive for IgG antibodies to *B. burgdorferi* and another in 51 seronegative patients, both with a history of treated Lyme disease and persistent symptoms for at least 6 months, compared 1 month of IV ceftriaxone plus 2 additional months of oral doxycycline with placebo and found no clinical benefit of antibiotic therapy.¹⁴

CONCLUSION — Use of repellents and avoidance and early removal of ticks are the first steps in prevention of Lyme disease. In highly endemic areas, when an engorged *Ixodes scapularis* tick is attached for at least 48 hours, prophylaxis with a single dose of doxycycline would be reasonable in adults and children at least 8 years old. With a less compelling indication, it would be reasonable not to prescribe antibiotics unless erythema migrans develops. Recommended doses of antibiotics cure almost all patients with erythema migrans without complications. Antibiotic therapy is not recommended for patients with a history of appropriately treated Lyme disease and persistent subjective symptoms.

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Antifungal Drugs

Original publication date - February 2005

The drugs of choice for treatment of some fungal infections are listed in the table that begins page 119. Some of the indications and dosages recommended here have not been approved by the FDA.

POLYENES: AMPHOTERICIN B

Amphotericin B products are the only polyenes currently available for systemic treatment of fungal infections. Nystatin, another polyene, is only available topically. A liposomal formulation of nystatin is in clinical development for treatment of systemic fungal infections including invasive aspergillosis (F Offner et al, Antimicrob Agents Chemother 2004; 48:4808).

Polyenes act by binding to ergosterol in the fungal cell membrane, leading to loss of membrane integrity and leakage of cell contents. Conventional amphotericin B and the newer lipid-based formulations have the same spectrum of activity and are active against most pathogenic fungi and some protozoa. Exceptions include *Aspergillus terreus*, *Fusarium* spp., *Pseudallescheria boydii* and some strains of *Candida lusitaniae*. Amphotericin is used for treatment of many fungal disorders including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis (including meningitis), histoplasmosis, paracoccidioidomycosis, sporotrichosis and zygomycosis. It is also used as empiric therapy in febrile neutropenic patients.

Conventional amphotericin – Amphotericin B deoxycholate (*Fungizone*, and others), the old non-lipid formulation of amphotericin, is by far the least expensive, but the development of better tolerated lipid-based formulations has led to a decrease in its use.

Intravenous infusion of amphotericin B deoxycholate frequently causes fever and chills, and sometimes headache, nausea, vomiting, hypotension and tachypnea, usually beginning 1 to 3 hours after starting the infusion and lasting about 1 hour. The intensity of these infusion-related acute reactions tends to decrease after the first few doses. Pretreatment with acetaminophen (*Tylenol*, and others) or aspirin, diphenhydramine (*Benadryl*, and others) 25 mg IV and/or hydrocortisone 25 mg IV can decrease the severity of the reaction. Treatment with meperidine (*Demerol*, and others) 25-50 mg IV can shorten the duration of rigors.

Nephrotoxicity is the major dose-limiting toxicity of amphotericin B deoxycholate; sodium loading with normal saline may prevent or ameliorate it and is generally recommended for patients who can tolerate a fluid load. The nephrotoxicity of amphotericin B may add to the nephrotoxicity of other drugs including cyclosporine (*Sandimmune, Neoral*), tacrolimus (*Prograf*) and aminoglycoside antibiotics such as gentamicin (*Garamycin*, and others). Hypokalemia and hypomagnesemia are common and are usually due to a mild renal tubular acidosis. Weight loss, malaise, anemia, thrombocytopenia and mild leukopenia can occur. Cardiac toxicity and myopathy have been reported (PJ Danaher et al, J Antimicrob Chemother 2004; 53:115).

A small, non-blind study comparing a conventional 4-hour infusion with a 24-hour continuous infusion of amphotericin B deoxycholate found that infusion-related reactions and nephrotoxicity were less frequent and less severe with continuous infusions (U Eriksson et al, BMJ 2001; 322:579), but the comparative efficacy of the 24-hour infusion has not been established.

	Treatment of Fun	igal Infections	
Infection			
Drug of Choice	Dosage ¹	Duration ²	Alternatives
ASPERGILLOSIS			
Amphotericin B or	1-1.5 mg/kg/d IV ³	≥10 wks	Itraconazole 200 mg IV bid x 2d, then
Voriconazole ⁴	6 mg/kg IV q12h x 1d, then 4 mg/kg IV q12h, then 200 mg PO bid		200 mg IV qd x 12d or 200 mg PO tid x 3d; either followed by 200 mg PO bid Caspofungin 70 mg IV x 1d, then 50 mg IV once/d
BLASTOMYCOSIS5			
Itraconazole or	200 mg PO bid	6-12 mos	Fluconazole 400-800 mg PO once/d
Amphotericin B	0.5-1.0 mg/kg/d IV ³	6-12 wks	
CANDIDIASIS			
Oropharyngeal or Esophageal 6,7			
Fluconazole ⁷	200 mg IV or PO once, then 100 mg once/d	1-3 wks	Itraconazole ⁸ 200 mg PO once/c
or			
Amphotericin B or	0.3-0.5 mg/kg/d ³		Voriconazole ⁹ 200 mg PO bid
Caspofungin	50 mg IV once/d		
Vulvovaginal ¹⁰			
topical therapy Butoconazole, clotrimazole, miconazole, tioconazole, or terconazole	once/d (available as intravaginal creams, ointments, tablets, ovules or suppositories)	1-7d	
systemic therapy			
Fluconazole	150 mg PO once ¹¹	1d	Itraconazole 200 mg PO bid x 1d Ketoconazole 200 mg PO bid x 5d
Candidemia ⁷			
Fluconazole ¹²	400-800 mg IV once/d, followed by PO	2 wks after afebrile and blood cultures negative	
or			
Caspofungin ¹³	70 mg IV x 1d, then 50 mg IV once/d		
or			
Amphotericin B	0.5-1 mg/kg/d IV ³		
Urinary ¹⁴			
Fluconazole or	200 mg IV or PO once/d	7-14d	Flucytosine 25 mg/kg PO qid ¹⁶
Amphotericin B ¹⁵	0.3-0.5 mg/kg/d IV3	7-14d	

1. Usual dosage. Some patients may need dosage adjustment for renal or hepatic dysfunction or when used with interacting drugs.

2. The optimal duration of treatment with these drugs is often unclear. Depending on the disease and its severity, they may be continued for weeks or months or, particularly in immunocompromised patients, indefinitely. 3. Dosage of amphotericin B deoxycholate. Usual doses of lipid-based formulations for treatment of invasive fungal infection are: amphotericin B

lipid complex (Abelcet) 5 mg/kg/d; liposomal amphotenicin B (AmBisome) 3-5 mg/kg/d; amphotenicin B cholesteryl sulfate (Amphotec) 3-4 mg/kg/d. For treatment of aspergiliosis, husariosis and mucormycosis, he dosage of AmBisome is 5 mg/kg/d and doses up to 15 mg/kg/d have been used. For treatment of cryptococcal mengilis in HIV patients, the dosage of AmBisome is 6 mg/kg/d.

4. In one large controlled trial, voriconazole was more effective than amphotericin B for treatment of invasive aspergillosis (R Herbrecht et al, N Engl J Med 2002; 347:408).

5 Patients with severe illness or CNS involvement should receive amphotericin B.

3. Failing and series invises of vota involvement sinual to be a series and series an

resistant to low doses, but may be susceptible to high doses of fluconazole. C. lusitaniae may be resistant to amphotericin B.

8. For patients with oropharyngeal disease, itraconazole oral solution 200 mg (20 mL) given once daily without lood is more effective than itraconazolo consulos

9. R Ally et al, Clin Infect Dis 2001; 33:1447.

10. Non-albicans species, such as C. glabrata and C. krusei, respond to boric acid 600 mg intravaginally daily x 14d or to topical flucytosine cream (JD Sobel et al, Am J Obstet Gynecol 2003; 189:1297). 11. May be repeated in 72 hours if patient remains symptomatic

12. Non-neutropenic patients only. In one large controlled trial, fluconazole plus amphotericin B was somewhat more effective than fluconazole alone

for patients with candidemia (JH Rex et al, Clin Infect Dis 2003; 36:1221). 13. In a large controlled that, caspolungin was at least as effective as amphotencin B for treatment of invasive candidiasis or candidemia (J Mora-Duarte et al, N Eng I Med 2002; 347:2202).

or 67 6100000000 6100000000 61000000000 6100000000	0 mg PO bid 0-800 mg PO once/d 5-0.7 mg/kg/d IV ³ 5-1 mg/kg/d IV ³ 0 mg/kg/d PO ¹⁶	>1 yr >1 yr >1 yr 2 wks	
Itraconazole 200 or Fluconazole 400 or Amphotericin B 0.5 CRYPTOCOCCOSIS Amphotericin B 0.5 ±Flucytosine 100 followed by	0-800 mg PO once/d 5-0.7 mg/kg/d IV ³ 5-1 mg/kg/d IV ³	>1 yr >1 yr	
or Amphotericin B 0.5 CRYPTOCOCCOSIS Amphotericin B 0.5 ±Flucytosine 100 followed by	5-0.7 mg/kg/d IV ³	>1 yr	
CRYPTOCOCCOSIS Amphotericin B 0.5 ±Flucytosine 100 followed by	5-1 mg/kg/d IV ³		
Amphotericin B 0.5 ±Flucytosine 100 followed by		2 wks	
±Flucytosine 100 followed by		2 wks	
followed by	0 mg/kg/d PO ¹⁶		
	0 mg PO once/d	8 wks	Itraconazole 200 mg PO bid
maintenance ¹⁸			
Fluconazole 200	0 mg PO once/d		Amphotericin B 0.5-1 mg/kg IV wkly ³
FUSARIOSIS			
Amphotericin B 1-1 or	I.5 mg/kg/d IV qd ³		
	ng/kg IV q12h x 1d, nen 4 mg/kg q12h		
HISTOPLASMOSIS5			
	0 mg PO bid	6-18 mos	Fluconazole 400-800 mg PO once/d ¹⁹
Amphotericin B ²⁰ 0.5	5-1.0 mg/kg/d IV ³	10-12 wks	
chronic suppression ¹⁸			
	0 mg PO once/d or bid		Amphotericin B 0.5-1 mg/kg IV wkly ³
MUCORMYCOSIS			,
Amphotericin B 1-1	I.5 mg/kg/d IV ³	6-10 wks	Posaconazole ²¹ 200 mg PO gi
ONYCHOMYCOSIS ^{22, 23}			
	0 mg PO once/d	12 wks	
Itraconazole 200	0 mg PO once/d	3 mos ²⁴	Fluconazole 150-300 mg PO
200	0 mg PO bid x 1 wk/mo	3-4 mos ²⁴	once wkly x 6-12 mos24
PARACOCCIDIOIDOMYCOSIS5			
	0-200 mg PO once/d	6-12 mos	Ketoconazole 200-400 mg PO once/d
or			
	I-0.5 mg/kg/d IV ³		
PSEUDALLESCHERIASIS (scedospor			
	ng/kg IV g12h x 1d,		Itraconazole 200 mg IV bid x 2

21. An investigational drug, posaconazole has been used after mucormycoses was clinically improved and oral almentation was sufficient to enhance absorption (AM Tobon et al. (clinited Dis 2003; 51:488).
22. Nail speciments should be obtained prior to any drug therapy to confirm the diagnosis of onychomycosis.
23. Topical treatment with clicipoirs (%) nail lauger (Privalce) is indicated for treatment of mid-on-derate onychomycosis caused by *T. rubium* that does not involve the lunula. Cicliptions (is less effective than systemic therapy, but has no systemic side effects or drug interactions.
24. Duration for toenal interiction. Duration of treatment of fingernal interior. S weeks with terioratine, 2 months with traconazole and 3-6 months

with fluconazole. 25. Initial treatment of severely ill patients. To be followed by itraconazole.

Infection			
Drug of Choice	Dosage ¹	Duration ²	Alternatives
SPOROTRICHOSIS cutaneous			
Itraconazole	200 mg PO once/d	3-6 mos	Saturated solution of potassium iodide 1-5 mL PO tid
extracutaneous5			
Amphotericin B or	0.5-0.7 mg/kg/d IV3	6-12 wks	
Itraconazole	200 mg PO bid	12 mos	
TINEA PEDIS ²⁶			
Terbinafine cream ²⁷ or	twice daily application	1-2 wks	Fluconazole PO 150 mg once/wk for 1 to 4 wks
Topical azoles (i.e. clotrimazole, miconazole, econazole)	once or twice daily application	4 wks	

Lipid Formulations – Three lipid formulations of amphotericin B are marketed in the US: amphotericin B lipid complex (ABLC, *Abelcet*), liposomal amphotericin B (L-AmB, *AmBisome*), and amphotericin B colloidal dispersion (ABCD, *Amphotec*). In clinical trials, these formulations have been at least as effective as amphotericin B deoxycholate (TJ Walsh et al, N Engl J Med 1999; 340:764; PC Johnson et al, Ann Intern Med 2002; 137:105).

Compared to conventional amphotericin B, acute infusion-related reactions are worse with *Amphotec*, less with *Abelcet*, and least with *AmBisome*. Nephrotoxicity is less common with lipid-based products and, when it occurs, less severe than with amphotericin B deoxycholate (JR Wingard et al, Clin Infect Dis 2000; 31:1155). Liver toxicity, which is generally not associated with amphotericin B deoxycholate, has been reported with the lipid formulations.

Cost comparisons of amphotericin formulations should take into account the fact that conventional amphotericin B deoxycholate may cause renal failure, which can increase the length of hospital stay, healthcare costs and mortality rates (DW Bates et al, Clin Infect Dis 2001; 32:686). The superior tolerability of the lipid-based products permits more patients to receive high doses and complete the recommended course of therapy.

Amphotericin B Drug	Formulations Daily dosage	Cost [*]
Amphotericin B deoxycholate generic (Abbott) <i>Fungizone</i> (Sandoz) Amphotericin B lipid complex	1-1.5 mg/kg IV	\$23.28 40.90
(ABLC) Abelcet (Enzon)	5 mg/kg IV	920.00
Liposomal amphotericin B (L-AmB) AmBisome (Fujisawa)	3-5 mg/kg IV	1318.80
Amphotericin B colloidal dispersion (ABCD) Amphotec (InterMune)	3-4 mg/kg IV	480.00
* For one day's treatment of a 70-kg pa according to AWP listings in <i>Red Boo</i> tutions based on formulary contracts.	ok 2004. Cost may vary	

AZOLES

Systemic azole antifungals currently available in the US include fluconazole (*Diflucan*, and others), itraconazole (*Sporanox*), voriconazole (*Vfend*) and ketoconazole (*Nizoral*, and others). All act by blocking the activity of 14-alpha-demethylase, leading to inhibition of ergosterol synthesis. They differ in their spectrum of activity, bioavailability, adverse effects and potential for drug interactions.

FLUCONAZOLE — Fluconazole is active against most *Candida* species other than *C. krusei*, which is intrinsically resistant, and many strains of *C. glabrata*, which are increasingly resistant. Fluconazole has good activity against *Cryptococcus* spp. but no clinically significant activity against most molds, including *Aspergillus* spp., *Fusarium* spp. and Zygomycetes.

Fluconazole, which is available in both oral (tablets and suspension) and intravenous preparations, is approved by the FDA for treatment of cryptococcal meningitis, vaginal, oropharyngeal and esophageal candidiasis, and for prophylaxis against candidiasis in patients undergoing bone marrow transplantation. Although not FDA-approved, it is also

0 mg IV once \$162.19 I IV once 203.44 g IV q12h 315.18 IV once 372.68
\$162.19 IV once 203.44 g IV q12h 315.18
203.44 g IV q12h 315.18
315.18
IV once 372.68
0 mg PO once
28.77
30.74 PO bid
39.60
PO q12h
67.36

widely used to treat systemic infections due to *Candida*, such as candidemia and peritonitis.

Adverse Effects – Fluconazole is generally well tolerated. Gastrointestinal distress and rash can occur. Stevens-Johnson syndrome, anaphylaxis and hepatic necrosis have been reported.

Interactions – Fluconazole is a weaker inhibitor of CYP3A4 than itraconazole or ketoconazole but may still increase serum concentrations of drugs metabolized by 3A4, such as cyclosporine, simvastatin (*Zocor*) and lovastatin (*Mevacor*, and others). Fluconazole is a strong inhibitor of CYP2C9 and can therefore increase serum concentrations of tacrolimus, phenytoin (*Dilantin*, and others), zidovudine (*Retrovir*), warfarin (*Coumadin*, and others) and other drugs metabolized by 2C9. Concomitant administration of rifampin (*Rifadin*, and others) can lower serum concentrations of fluconazole.

ITRACONAZOLE — Itraconazole has a broader spectrum of activity than fluconazole. It is active against a wide variety of fungi including *Cryptococcus neoformans, Aspergillus* spp., *Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis, Pseudallescheria boydii, Sporothrix* spp., and dermatophytes. It also has good activity against most *Candida* spp., including some strains of fluconazole-resistant *C. glabrata.* Itraconazole has no clinically meaningful activity against *Fusarium* spp. or Zygomycetes. Itraconazole is not recommended for treatment of meningitis because it does not cross the blood-brain barrier.

Itraconazole is available orally in both capsules and solution and in an intravenous formulation. Absorption after oral dosing is variable; the solution is more bioavailable than the capsules and is generally preferred. The capsules should be taken with food, while the solution is absorbed best without food.

Itraconazole is FDA-approved for treatment of blastomycosis, histoplasmosis (non-meningeal) and aspergillosis in patients who are intolerant of or refractory to amphotericin B. It is also indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. The oral solution is approved for treatment of oropharyngeal and esophageal candidiasis and may have an additional benefit as a topical treatment of this disease. Itraconazole capsules are approved for treatment of fingernail and toenail onychomycosis due to dermatophytes.

Adverse Effects – The most common adverse effects of itraconazole are dose-related nausea and abdominal discomfort. Rash and serious hepatic toxicity can occur. The drug can cause hypokalemia, edema and hypertension. Congestive heart failure has been reported with itraconazole and the drug should not be used in patients with ventricular dysfunction. Thrombocytopenia and leukopenia have also been reported. The intra-

venous formulation contains cyclodextrin, which can accumulate in azotemic patients; its use is not recommended in patients with creatinine clearance <30 mL/min.

Interactions – The absorption of itraconazole capsules is reduced with concurrent use of drugs that decrease gastric acidity, such as antacids, H2-receptor blockers, proton pump inhibitors or didanosine (*Videx*).

Itraconazole is a potent inhibitor of the hepatic isozyme CYP3A4 and may increase serum concentrations of drugs that are metabolized by this enzyme. For this reason, itraconazole is contraindicated with the following drugs: cisapride (*Propulsid*), dofetilide (*Tikosyn*), ergot alkaloids, levomethadyl (*Orlaam*), lovastatin, oral midazolam (*Versed*, and others), pimozide (*Orap*), quinidine, simvastatin, and triazolam (*Halcion*, and others). Itraconazole is itself also a substrate of CYP3A4; its metabolism may be affected by both inducers of the enzyme, such as rifampin and carbamazepine (*Tegretol*, and others), and by other inhibitors.

When some protease inhibitors, such as ritonavir (*Norvir*), amprenavir (*Agenerase*) or indinavir (*Crixivan*) are taken with itraconazole, serum concentrations of both drugs may increase. Itraconazole can increase serum concentrations of digoxin (*Lanoxin*, and others). Possible decreased contraceptive effect has been reported in patients taking oral contraceptives with itraconazole. Other azole antifungals have increased plasma concentrations of loratadine (*Claritin*), oral anticoagulants and oral hypoglycemics, suggesting that itraconazole should be used with caution in patients taking any of these drugs.

VORICONAZOLE — Voriconazole has a spectrum of activity similar to itraconazole but appears to be more active against *Aspergillus* spp. and some species of *Candida*, including *C. glabrata* and *C. krusei* (The

Medical Letter 2002; 44:63). Unlike itraconazole, voriconazole is active against *Fusarium* spp. Zygomycetes, such as *Mucor* spp. and *Rhizomucor* spp., are generally resistant to voriconazole, and infection with these organisms has developed during treatment with the drug.

Voriconazole is FDA-approved for treatment of invasive aspergillosis and esophageal candidiasis, and for treatment of refractory infections caused by *Scedosporium apiospermum* and *Fusarium* spp. It is also indicated for treatment of candidemia in non-neutropenic patients and for disseminated *Candida* infections involving the skin, abdomen, bladder and kidney.

Adverse Effects – Transient visual disturbances, including blurred vision, photophobia and altered perception of color or image, are common with voriconazole. Rash, photosensitivity, increased transaminase activity and hallucinations have also occurred. In patients with creatinine clearance <50 mL/min the drug should be given orally if possible, instead of intravenously, because the solubilizing agent (sulfobutyletherb-cyclodextrin), not voriconazole itself, can accumulate. Patients with mild to moderate hepatic cirrhosis should receive a normal loading dose of voriconazole, but half of the maintenance dose.

Interactions – Voriconazole is metabolized in the liver by CYP2C19, CYP2C9 and CYP3A4. CYP2C19 is genetically variant (about 3% to 5% of Caucasians and African-Americans and about 15% of Asians do not express it) and patients deficient in this enzyme may be exposed to higher concentrations of the drug. Voriconazole is contraindicated in patients taking rifampin, rifabutin, ergot alkaloids, long-acting barbiturates, carbamazepine, pimozide, quinidine, efavirenz (*Sustiva*), ritonavir (400 mg q12h) or sirolimus (*Rapamune*). Clinical monitoring or dose adjustment is required in patients taking warfarin (*Coumadin*, and others), sulfonylureas, statins, benzodiazepines, vinca alkaloids, nevirapine

(*Viramune*) and HIV protease inhibitors other than indinavir. Omeprazole (*Prilosec*, and others), cyclosporine and tacrolimus require dose reductions when given with voriconazole. Patients taking phenytoin require increased doses of voriconazole and more frequent monitoring for phenytoin toxicity.

KETOCONAZOLE — Ketoconazole is now seldom used. The other azoles have fewer adverse effects and are generally preferred. Ketoconazole remains an option for treatment of infections with dimorphic fungi (histoplasmosis, blastomycosis or coccidioidomycosis), but, as with itraconazole, is not recommended for treatment of meningitis due to these organisms because it does not cross the blood-brain barrier. Ketoconazole is also FDA-approved for treatment of paracoccidioidomycosis, candidiasis and severe cutaneous dermatophyte infections that do not respond to topical therapy.

Adverse Effects – Anorexia, nausea and vomiting are common with higher doses (>400 mg/day) of ketoconazole; taking the drug with food or at bedtime may improve tolerance. Pruritus, rash and dizziness may occur. Ketoconazole can decrease plasma testosterone concentrations and cause gynecomastia, decreased libido and loss of potency in men and menstrual irregularities in women. High doses may inhibit adrenal steroidogenesis and decrease plasma cortisol concentrations. Mild hepatic toxicity is fairly common with ketoconazole. If jaundice or symptoms of hepatitis appear, the drug should be stopped promptly or fatal hepatic necrosis may occur.

Interactions – Drug interactions with ketoconazole are similar to those with itraconazole.

POSACONAZOLE — Posaconazole (SCH 56592), an unapproved azole available from the manufacturer for compassionate use, is

under review by the FDA for oral treatment of invasive fungal infections, including aspergillosis, fusariosis, and zygomycosis in patients who are intolerant of or refractory to other therapy. Posaconazole appears to have similar activity to fluconazole and itraconazole against *Candida* spp. but is more active against Zygomycetes (*Mucor* spp. and *Rhizomucor* spp.). Currently, amphotericin B is the only drug available to treat *Mucor*.

ECHINOCANDINS

Echinocandins inhibit synthesis of β (1,3)-D-glucan, an essential component of the fungal cell wall. The potential for adverse effects in humans is low due to the absence of this substance in mammalian cells. The only echinocandin currently on the market is caspofungin (*Cancidas*).

CASPOFUNGIN — Caspofungin is available only for intravenous administration and is FDA-approved for treatment of esophageal candidiasis, candidemia, and intra-abdominal abscesses, peritonitis, and pleural space infections due to *Candida*. It is also indicated for empirical treatment of presumed fungal infections in febrile, neutropenic patients and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies. Caspofungin is active against *Candida* spp. and *Aspergillus* spp., but not *Cryptococcus neoformans*.

Adverse Effects – Although generally well tolerated, caspofungin occasionally causes rash, fever and mild hepatic toxicity (Medical Letter 2001; 43:58). Anaphylaxis has occurred. Dosage should be reduced in patients with moderate hepatic dysfunction. Liver function tests should be monitored in patients taking cyclosporine with caspofungin.

Interactions – Rifampin, carbamazepine, dexamethasone, efavirenz, nevirapine and phenytoin may increase the clearance of caspofungin. An increase in caspofungin dosage to 70 mg should be considered when co-administered with these drugs.

MICAFUNGIN (*Mycamine*) — Micafungin is an echinocandin indicated for treatment of esophageal candidiasis and prophylaxis of invasive *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT). [Since this article was published, *The Medical Letter* has reviewed micafungin (*Mycamine*). See page 133.]

OTHER DRUGS

FLUCYTOSINE (*Ancobon*) – Potentially lethal, dose-related bone marrow toxicity, colitis and rapid development of resistance when used alone limit the use of flucytosine. Keeping serum concentrations below 100 mcg/mL (some clinicians recommend staying below 50 mcg/mL) decreases toxicity, but delays in obtaining assay results often limit their utility.

TERBINAFINE (*Lamisil*) – Terbinafine is a synthetic allylamine approved by the FDA for treatment of onychomycosis of the toenail or fingernail due to dermatophytes. It likely acts by inhibiting squalene epoxidase and blocking ergosterol synthesis. The most commonly reported adverse effects of oral terbinafine have been headache, gastrointestinal symptoms including diarrhea, dyspepsia and abdominal pain, and occasionally a taste disturbance that may persist for weeks after the drug is stopped. Rash, pruritus and urticaria, usually mild and transient, have occurred. Toxic epidermal necrolysis and erythema multiforme have been reported. Liver function should be assessed before initiation and occasionally during treatment with terbinafine. Anaphylaxis, pancytopenia and severe neutropenia have also been reported.

Interactions – Terbinafine is an inhibitor of CYP2D6 and may increase the effect or toxicity of drugs metabolized by this enzyme, including tricyclic antidepressants. Cimetidine (*Tagamet*, and others) may reduce the clearance of terbinafine. Enzyme inducers such as rifampin may enhance terbinafine clearance.

SPECIAL CIRCUMSTANCES

Pregnancy – Amphotericin B is the preferred treatment for deep fungal infections during pregnancy. Fluconazole is teratogenic in animals and a similar pattern of craniofacial and cardiac anomalies has been reported in a few infants exposed to high doses of the drug during pregnancy. In rats, itraconazole, ketoconazole and voriconazole are teratogenic, and caspofungin is embryotoxic. None of these drugs should be used in pregnancy unless there is a strong clinical indication for which no suitable alternative is available.

Prophylaxis – High-risk neutropenic patients, such as those undergoing allogeneic and certain autologous stem cell transplants, and those with hematologic malignancy who are expected to have prolonged profound neutropenia, may require prophylactic treatment with antifungal drugs (CA Diekewicz, Clin Infect Dis 2001; 33:139). The drug of choice for these patients is fluconazole 400 mg PO or IV once daily (JH Rex et al, Clin Infect Dis 2000; 30:662). Itraconazole solution, 200 mg PO or IV once daily, is an alternative but may not be well tolerated (KA Marr et al, Blood 2004; 103:1527). Micafungin has also been effective in this population (JH van Burik et al, Clin Infect Dis 2004; 39:1407).

HIV-infected patients with frequent or severe recurrences of oral or esophageal candidiasis may also require prophylaxis. For these patients the regimen of choice is fluconazole 100-200 mg PO once daily. Itraconazole solution 200 mg PO once daily is an alternative (H Masur et al, Ann Intern Med 2002; 137:435).

Recurrent vaginal candidiasis in any population can often be controlled by maintenance therapy with fluconazole 150 mg PO once weekly (JD Sobel et al, N Engl J Med 2004; 351:876).

Fever and Neutropenia – For neutropenic patients with fever that persists despite treatment with antibacterial drugs, empiric addition of an antifungal drug is common practice (JR Wingard, Clin Infect Dis 2004; 39 suppl 1:S38). Amphotericin B has been used for this indication; the liposomal formulations are better tolerated, but much more expensive. Caspofungin was not inferior to liposomal amphotericin B (*AmBisome*) in a randomized comparative trial (TJ Walsh et al, N Engl J Med 2004; 351:1391). In another randomized trial, voriconazole appeared to be about as effective as liposomal amphotericin B (TJ Walsh et al, N Engl J Med 2002; 346:225). Fluconazole and itraconazole have also been used as alternatives to amphotericin B for this indication (DJ Winston et al, Am J Med 2000; 108:282; M Boogaerts et al, Ann Intern Med 2001; 135:412).

Combination therapy – Use of combination therapy for treatment of immunosuppressed patients with invasive aspergillosis (IA), which has a high morbidity and mortality despite current treatments, is controversial. Theoretically, combining two drugs with different mechanisms of action might be more effective than either one alone.

Amphotericin B and azoles both act on ergosterol, but in different ways. *In vitro* and animal data indicate that if an azole is started before a polyene, they antagonize each other (MD Johnson et al, Antimicrob Agents Chemother 2004; 48:693). If they are given simultaneously, however, antagonism may not occur. A clinical trial in patients with candidemia

showed that patients who received high-dose fluconazole in combination with 5-6 days of amphotericin B were more likely to clear the infection from the blood than those who received high-dose fluconazole alone (JH Rex et al, Clin Infect Dis 2003; 36:1221).

In vitro studies and animal data suggest a potential benefit of combining an echinocandin with either an azole or amphotericin B, but clinical studies are lacking. One small observational study in patients with refractory invasive aspergillosis showed that a combination of voriconazole and caspofungin was associated with a lower mortality than voriconazole alone (KA Marr et al, Clin Infect Dis 2004; 39:797). The comparative efficacy of this combination in previously untreated invasive aspergillosis is unknown (MD Johnson et al, Antimicrob Agents Chemother 2004; 48:693).

Micafungin (Mycamine) for Fungal Infections

Originally published in The Medical Letter - June 2005; 47:51

Micafungin sodium (*Mycamine* – Astellas), the second echinocandin antifungal¹ to become available in the US, has been approved by the FDA for intravenous treatment of esophageal candidiasis and prophylaxis of invasive *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT).

MECHANISM OF ACTION — Echinocandins block the biosynthesis of (1,3)- β -D-glucan, a polysaccharide component of the cell wall in many pathogenic fungi.²

FHANMACOLOGI	
Drug class	Echinocandin antifungal
Mechanism of action	Blocks cell wall synthesis
Formulation	50-mg, single-use vials
Route	Intravenous
Elimination half-life	11-17 hours
Metabolism	Predominantly hepatic by non-CYP450 pathways
Elimination	Fecal

PHARMACOLOGY

IN VITRO ACTIVITY — Standardized susceptibility testing methods for echinocandins have not been established, and results of *in vitro* susceptibility tests do not necessarily correlate with *in vivo* or clinical outcomes. Micafungin is active *in vitro* against most isolates of *Candida* spp. and *Aspergillus* spp. It has good activity against fluconazoleresistant *Candida albicans* and against non-*albicans Candida* spp. inherently resistant to fluconazole, such as strains of *C. glabrata* or *C. krusei*, all of which are increasing, particularly in immunocompromised patients. Micafungin is also active against *Pneumocystis jiroveci* (formerly *carinii*).^{3,4}

CLINICAL STUDIES — **Treatment of esophageal candidiasis** – A randomized dose-response study compared 14 to 21 days treatment with micafungin 50, 100, or 150 mg IV once daily with fluconazole (*Diflucan*, and others) 200 mg IV daily in 245 HIV-positive patients with endoscopically- and culture-proven esophageal candidiasis. Endoscopic cure rates with micafungin were 68.8% (50 mg), 77.4% (100 mg) and 89.8% (150 mg), compared to a cure rate of 86.7% with fluconazole.⁵

A second clinical trial randomized 523 patients with endoscopically proven candidiasis to either micafungin 150 mg/day IV or fluconazole 200 mg/day IV. After a median of 14 days, micafungin was comparable to fluconazole in endoscopic (87.7% vs. 88%) and clinical (94.2% vs. 94.6%) cure.⁶

Fungal Prophylaxis in HSCT – A prospective randomized doubleblind trial in 882 adults and children compared prophylaxis with micafungin 50 mg IV once daily (1 mg/kg for patients weighing <50 kg) to fluconazole 400 mg IV once daily (8 mg/kg for patients weighing <50 kg) during the neutropenic phase of HSCT. The treatment success rate for patients receiving micafungin was 80.0% compared to 73.5% with fluconazole, a statistically significant difference, but most patients who failed treatment had received empiric therapy for a suspected, not a confirmed, fungal infection.⁷

Other – A small, open-label study of micafungin to treat deep-seated mycoses found overall clinical response rates of 57% in aspergillosis and 71% in esophageal candidiasis; rates were similar in patients with and without prior treatment.⁸ No randomized controlled trials are available comparing micafungin with standard antifungals in the treatment of deep-seated candidiasis, candidemia, or invasive aspergillosis, or with caspofungin for any indication.

ADVERSE EFFECTS — Micafungin is generally well tolerated. Adverse events have included fever, headache, nausea, vomiting, diar-

rhea, leukopenia, hepatic enzyme abnormalities, and phlebitis at the injection site. Possible histamine-mediated symptoms such as rash, pruritus, facial swelling and vasodilatation have also occurred. Isolated cases of anaphylaxis and hemolysis have been reported.

DRUG INTERACTIONS — Micafungin is not metabolized by the CYP450 system and is not a P-glycoprotein substrate or inhibitor. In the presence of steady-state micafungin, serum concentrations (AUC) of sirolimus (*Rapamycin*) and nifedipine (*Adalat, Procardia,* and others) were increased by 21% and 18%, respectively. Micafungin does not interact with tacrolimus (*Prograf*),⁹ cyclosporine (*Sandimmune,* and others) or mycophenolate mofetil (*Cellcept*).

The other echinocandin, caspofungin, decreases serum levels of tacrolimus by about 20-25% when the two are given together.¹ Co-administration of caspofungin with cyclosporine increases caspofungin plasma concentrations by 35% and can cause transient liver abnormalities, but 2 small studies in a total of 54 patients who took both drugs for two weeks did not find serious adverse effects or significant transaminitis.^{10,11}

DOSAGE AND COST — The recommended dosage of micafungin is 50 mg/day for prophylaxis and 150 mg/day for treatment, both given IV as a single dose over 1 hour.

CHOICE OF DRUGS — Oral fluconazole remains the drug of choice for initial treatment of *Candida* esophagitis. Micafungin (*Mycamine*) could be used as an alternative for patients needing intravenous treatment and those with fluconazole-resistant strains. Caspofungin and amphotericin B could also be used for such patients. For HSCT prophylaxis, fluconazole remains the drug of choice. The utility of micafungin alone or in combination with other antifungal drugs to treat aspergillosis remains to be established. Drug-drug interactions may be less of a problem with micafungin than with caspofungin, but comparative trials are lacking.

ESOPHAGEAL CANDIDIASIS				
DRUG	DOSAGE	COST ¹		
Oral				
Fluconazole - generic	200 mg once, then	\$167.18		
Diflucan (Pfizer)	100 mg once/d	210.41		
Itraconazole ² -				
Sporanox (Janssen)	200 mg once/d	382.20		
Voriconazole -				
Vfend (Pfizer)	200 mg bid (100 mg bid if <40 kg)	1461.60		
Intravenous				
Amphotericin B deoxycholate				
generic	0.3-0.5 mg/kg/d	16.43		
Liposomal amphotericin B (L				
AmBisome (Astellas)	3-5 mg/kg/d	28,848.75		
Amphotericin B lipid complex				
Abelcet (Enzon)	5 mg/kg/d	18,614.40		
Amphotericin B colloidal dispersion (ABCD) -				
Amphotec (Intermune)	3-4 mg/kg/d	10.527.93		
Caspofungin -	3*4 mg/kg/u	10,527.55		
Cancidas (Merck)	50 ma once/d	8485.26		
Fluconazole – generic	200 mg once, then	935.00		
Diflucan (Pfizer)	100 mg once/d	1089.00		
Micafungin -				
Mycamine (Astellas)	150 mg once/d	5890.50 ³		
Voriconazole4 -				
Vfend (Pfizer)	3 mg/kg bid	3783.78		
1. For 21 days' treatment of a 70- ing to the most recent data (Ap nationwide available from NDC company. Cost may vary amon 2. Only the PO solution is FDA-ap 3. Wholesale acquisition cost, acc cost will be higher. 4. IV administration is not FDA-ap	ril 30, 2005) from retail ph Health, a healthcare info g institutions based on for proved for this indication. sording to the manufacture	narmacies rmation services rmulary contracts.		

DRUGS FOR TREATMENT OF ESOPHAGEAL CANDIDIASIS

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DRUGS FOR HIV Infection

Original publication date - January 2004

New drug approvals as well as continuing concerns about drug toxicity and the development of resistance have prompted new antiretroviral treatment guidelines (Panel on Clinical Practices for Treatment of HIV Infection, November 10, 2003, www.aidsinfo.nih.gov).

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) — The treatment of HIV infection requires combination therapy known as highly active antiretroviral therapy (HAART) along with interval monitoring of the patient's HIV RNA levels ("viral load") and CD4 cell count. Increases in viral load or decreases in CD4 count may indicate development of drug resistance and the need for susceptibility testing and a change in treatment regimen. The dosage and cost of drugs for HIV infection are listed in the table on pages 141 and 143. The regimens of choice are listed on page 146. [Since this article was published, *The Medical Letter* has reviewed two oncedaily fixed dose NRTI combinations—abacavir/lamivudine (*Epzicom*) and emtricitabine/tenofovir (*Truvada*). See page 155.]

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs) — Nucleoside analogs inhibit HIV reverse transcriptase and decrease or prevent HIV replication in infected cells. All NRTIs except didanosine are taken without regard to meals and generally do not interact with other drugs.

Class adverse effects – All NRTIs can all cause a potentially fatal syndrome of lactic acidosis with hepatic steatosis, probably due to mitochondrial toxicity (HCF Côté et al, N Engl J Med 2002; 346:811); they have also been associated with fat redistribution and hyperlipidemia.

Abacavir (ABC, Ziagen) - Abacavir is available alone or in a fixed-dose combination with lamivudine (Epzicom) or with lamivudine and zidovudine (Trizivir). Although generally recommended for twice-daily use, some clinical data indicate that abacavir could be given once daily (B Gazzard et al, Intersci Conf Antimicrob Agents Chemother [ICAAC] 2003: abstract H-1722b). In one study, the combination of abacavir/lamivudine/efavirenz was as effective as zidovudine/lamivudine/efavirenz for initial anti-HIV therapy (E Dejesus et al, Intersci Conf Antimicrob Agents Chemother [ICAAC] 2003; abstract H-446). Abacavir should not be used in a three-drug combination with lamivudine and tenofovir because of high rates of virologic failure (JE Gallant et al, Intersci Conf Antimicrob Agents Chemother [ICAAC] 2003; abstract H-1722a). Treatment with Trizivir alone has been associated with higher rates of virologic failure regardless of baseline viral load compared to Trizivir/efavirenz and lamivudine/zidovudine/efavirenz (RM Gulick et al, Antivir Ther 2003, 8 suppl 1:S194, abstract 41). HIV strains resistant to zidovudine, lamivudine, stavudine, didanosine, and tenofovir may also be resistant to abacavir. Patients with extensive prior NRTI therapy are less likely to respond to abacavir.

Adverse effects – In 3-9% of patients, a severe hypersensitivity reaction, usually with fever and sometimes with respiratory or gastrointestinal symptoms, malaise and rash, develops early in treatment (median of 11 days), but can occur at any time and may be fatal. Patients who experience a hypersensitivity reaction should not be rechallenged. It is controversial whether hypersensitivity reactions can occur when restarting abacavir after a hiatus in patients who previously tolerated the drug (PHJ Frissen et al, AIDS 2001; 15:289; AE Loeliger et al, AIDS 2001; 15:1325; J Berenguer et al, AIDS 2002; 16:1299). When rash occurs without the systemic symptoms associated with hypersensitivity, the drug can sometimes be continued (PG Clay et al, Ann Pharmacother 2000; 34:247).

Didanosine (**ddl**, *Videx*) – Didanosine is available as buffered tablets, buffered or non-buffered powder, and non-buffered enteric-coated capsules (*Videx EC*).

Adverse effects – Treatment-limiting toxicities of didanosine have been dose-related peripheral neuropathy, pancreatitis and gastrointestinal disturbances. The risk of pancreatitis, neuropathy and lactic acidosis is increased when didanosine is combined with stavudine or tenofovir; the combination of didanosine and stavudine is no longer recommended for initial treatment or treatment of pregnant women. The combination of didanosine is not recommended because of overlapping toxicities.

Didanosine buffered tablets can interfere with absorption of drugs that require gastric acidity, including dapsone, ketoconazole, ciprofloxacin, delavirdine, indinavir, nelfinavir, atazanavir and others; they should be taken at least 1 to 2 hours apart. Use of the enteric-coated preparation should eliminate these drug interactions. Didanosine buffered tablets must be chewed or crushed into water. Gastrointestinal tolerance may be improved by using either *Videx EC* or the buffered powder formulation, or by preparing the pediatric powder in water with a liquid antacid (final concentration 10 mg/ml). The dose of *Videx EC* should be decreased to 250 mg/d when combined with tenofovir since didanosine levels are increased.

Emtricitabine (FTC, *Emtriva***)** – Emtricitabine (Medical Letter 2003; 45:89) is the 5-fluorinated derivative of lamivudine. It has similar safety and efficacy, and can be given once daily. It is available alone or in a fixed dose combination with tenofovir (*Truvada*). Resistance to emtricitabine is conferred by the M184V mutation, which is the main cause of resistance to lamivudine, so cross-resistance is expected.

An unpublished randomized controlled trial in 571 treatment-naïve patients, summarized in the package insert, compared emtricitabine to

	Drugs for HIV Infection	n	
	Usual	Total tablets or	
Drug	adult dosage	capsules/day	Cost ¹
NUCLEOSIDE REVERSE TRANSCRIP	TASE INHIBITORS (NRTIS)		
Abacavir (ABC)			
Ziagen - GlaxoSmithKline*	300 mg bid ²	2	\$13.46
Didanosine (ddl)	3		
Videx - Bristol-Myers Squibb*	200 mg bid ³	2	9.14
Videx EC - Bristol-Myers Squibb	400 mg once/day ³	1	10.22
Emtricitabine (FTC)	3 1 1 1		
Emtriva - Gilead	200 mg once/day4	1	9.65
Lamivudine (3TC)	· · ·		
Epivir - GlaxoSmithKline*	150 mg bid ⁵ or	2	10.04
	300 mg once/day5	1	9.98
Stavudine (d4T)	, ,		
Zerit - Bristol-Myers Squibb*	40 mg bid ⁶	2	11.38
Zalcitabine (ddC)			
Hivid - Roche	0.75 mg tid ⁷	3	8.10
Zidovudine (AZT, ZDV)			
Retrovir - GlaxoSmithKline*	200 mg tid ⁸ or	6	11.64
	300 mg bid ⁸	2	11.74
Zidovudine/lamivudine			
Combivir - GlaxoSmithKline	1 tablet bid9	2	21.84
Zidovudine/lamivudine/abacavir			
Trizivir - GlaxoSmithKline	1 tablet bid ¹⁰	2	35.24
NUCLEOTIDE REVERSE TRANSCRIPT	TASE INHIBITOR [†]		
Tenofovir (TDF)			
Viread - Gilead	300 mg once/day ¹¹	1	14.52
* Available in a liquid or oral powder formulation. † Since this table was published, <i>Epzicom</i> (a comt) approved. See page 155. †† Tipranavir (<i>Aptivus</i>) was recently FDA-approved. 1. Daily cost according to data from retail pharmac 2003.	The Mediacl Letter has not yet review ies nationwide provided by NDCHealth	ed this drug. n, a health care information service	
2. Available in 300-mg tablets. Some clinical data in		00 mg once daily. ng PO bid or 250 mg once daily, ≥€	20 km 000 mm DO hid

stavudine, each taken in addition to didanosine and efavirenz. At 48 weeks, 81% of the emtricitabine group had achieved and maintained viral suppression compared to 68% in the stavudine group. In a doubleblind trial, emtricitabine was as effective as lamivudine in 468 treatment-naïve patients. An open-label trial found that of 440 treatment-experienced patients maintained on lamivudine, those who switched to emtricitabine had slightly lower rates of viral suppression than those who continued taking lamivudine (77% vs. 82%) (I Sanne et al, Int Conf AIDS 2002; July 7-12; 14:abstract TuPeB4432).

Adverse effects – Emtricitabine can cause hyperpigmentation of the palms and soles, particularly in dark-skinned patients. Because emtricitabine is also active against hepatitis B virus (HBV), HIV-positive patients with chronic HBV infection may experience a flare of hepatitis if emtricitabine is withdrawn or if their HBV strain becomes resistant to the drug.

Lamivudine (3TC, *Epivir*) – Lamivudine is probably the best tolerated of the NRTIs and can be taken once or twice daily. An increase in viral load during treatment with a lamivudine-containing regimen is often an indication of resistance to lamivudine (DV Havlir et al, JAMA 2000; 283:229). Lamivudine-resistant strains may be cross-resistant to zalcitabine and emtricitabine, and may have low-level resistance to abacavir, ddI and ddC.

Adverse effects – Because lamivudine is also active against hepatitis B virus (HBV), HIV-positive patients with chronic HBV infection may experience a flare of hepatitis if lamivudine is withdrawn or if their HBV strain becomes resistant to the drug. Other adverse effects are uncommon; pancreatitis has been reported rarely in children.

Stavudine (d4T, *Zerit*) – Stavudine can be given either in initial combination therapy or after failure of regimens containing other NRTIs. Cross-resistance with zidovudine is frequent, however.

Adverse effects – Fatal lactic acidosis may occur more frequently with stavudine than with other NRTIs. Serum aminotransferase activity may increase with stavudine treatment, and pancreatitis has occurred rarely. Stavudine commonly causes dose-related peripheral sensory neuropathy, which often disappears when the drug is stopped and may not recur when it is restarted at a lower dose. Stavudine is associated with risk of lipoatrophy and increased serum lipids, and has been associated with the development of diabetes (AM Brambilla, AIDS 2003; 17:1993). Lactic acidosis and pancreatitis are more common when

Drug	Usual adult dosage	Total tablets or capsules/day	Cost ¹
			0031
NON-NUCLEOSIDE REVERSE TRANS Delavirdine (DLV)	CRIPTASE INHIBITORS (NI	irits)	
Rescriptor - Agouron Efavirenz (EFV)	400 mg tid ¹²	6	\$10.02
Sustiva - Bristol-Myers Squibb Nevirapine (NVP)	600 mg once/d ¹³	1	14.72
Viramune - Boehringer Ingelheim* PROTEASE INHIBITORS ^{††} Amprenavir (APV)	200 mg bid ¹⁴	2	12.76
Agenerase - GlaxoSmithKline* Atazanavir (ATV)	1200 mg bid ¹⁵	16	23.20
Reyataz - Bristol-Myers Squibb Fosamprenavir	400 mg once/d ¹⁶	2	26.26
Lexiva - GlaxoSmithKline Indinavir (IDV)	1400 mg bid ¹⁷	4	20.00
Crixivan - Merck Lopinavir/ritonavir (LPV/RTV)	800 mg tid ¹⁸	6	17.46
Kaletra - Abbott* Nelfinavir (NFV)	400/100 mg bid ¹⁹	6	22.32
Viracept - Agouron*	750 mg tid ²⁰ or 1250 mg bid ²⁰	9 10 (250-mg tablets) or 4 (625-mg tablets)	21.69 24.10 24.21
Ritonavir (RTV)		, ,	
Norvir - Abbott*	100 mg bid- 400 mg bid ²¹	2 8	4.08 16.32
Saguinavir hard gel cap (SQV hgc)			
Invirase - Roche	400 mg bid ²² or	4	9.48
	1000ma bid ²²	10	23.70
Saquinavir soft gel cap (SQV sgc)			
Fortovase - Roche FUSION INHIBITOR Enfuvirtide (T20)	1200 mg tid ²³	18	23.70
Fuzeon - Roche	90 mg SC bid ²⁴		66.51

mg capsules

14.200 mg oncelday for the first 2 weeks of treatment to decrease the risk of rash. Available in 200-mg tablets. 15. With or without food, but not with a fatty meal. Available in 50-mg capsules. Also FDA-approved for administration with ritonavir: 1200 mg AP/U200 mg RTV onceldary or 600 mg AP/V100 mg RTV but.

16. With food. Available in 100-, 150- and 200-mg capsules. When taken with EFV or TDF, the recommended dose is 300 mg ATV/100 mg RTV. 17. With or without food. Can also be given as 1400 mg onceiday plus ritonavir 200 mg onceiday or 700 mg bid plus ritonavir 100 mg bid plus

of fosamprenavir plus ritonavir once/day is 1400 mg fosamprenavir/300 mg RTV. 18. With water or other liquids, 1 hour before or 2 hours after a meal, or with a light meal. Patients should drink at least 48 ounces (1.5 L) of water

daily, Available in 100-, 200-, 333- and 400-mg capsules. 19. Each capsule contains 133.3 mg of lopinavir and 33.3 mg of ritonavir. The recommended dose is 533/133 mg bid when taken with efavirenz or nevirapine. The higher dose can also be tried if lopinavir resistance is suspected.

20. Nelfinavir is available in 250-mg and 625-mg tablets (available 1st quarter 2004) and should be taken with food.

21. Taken in combination with other protease inhibitors. Taken with food. Available as a 100-mg soft-gelatin capsule. The liquid formulation has an unpleasant taste: the manufacturer suggests taking if with chocolate milk or a liquid nutritional supplement.

22. 200-mg hard-gelatin capsules. Taken in combination with ritonavir: 400 mg SQV/400 mg RTV bid or 1000 mg SQV/100 mg RTV bid. Invirase should be taken with or within 2 hours after a full meal.

23. 200-mg soft-gelatin capsules. Fortovase should be taken with or within 2 hours after a full meal.

24. Available in kits containing a one-month supply of syringes and single-use vials with powder for a 90-mg dose and sterile water for reconstitution.

stavudine is combined with didanosine; this regimen is no longer recommended for initial treatment or treatment of pregnant women.

Zalcitabine (ddC, *Hivid*) – Zalcitabine appears to be less effective, less convenient and more toxic than the other NRTIs; it is used rarely.

Adverse effects – Dose-related peripheral neuropathy can be severe and persistent, and is more likely in patients also taking didanosine or stavudine. Other adverse effects include rash, stomatitis, esophageal ulceration and pancreatitis.

Zidovudine (AZT, ZDV, *Retrovir*) – Zidovudine is available alone and in fixed-dose combinations with lamivudine as *Combivir* and with lamivudine and abacavir as *Trizivir*. It can be given in combination with any other NRTI except for stavudine, which causes antagonism. Zidovudine plus lamivudine with or without a protease inhibitor has been recommended for post-exposure prophylaxis (PEP) against HIV infection after needlestick exposures (MMWR Recomm Rep 2001; 50 RR-11:1); most Medical Letter consultants would include a protease inhibitor in the PEP regimen. This combination has also been used after sexual exposure, although data are limited (JO Kahn et al, J Infect Dis 2001; 183:707).

Adverse effects – Adverse effects of zidovudine include anemia, neutropenia, nausea, vomiting, headache, fatigue, confusion, malaise, myopathy, hepatitis, and hyperpigmentation of oral mucosa and nail beds.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR — Nucleotides are phosphorylated nucleosides; nucleoside and nucleotide RTIs have similar mechanisms of action.

Tenofovir disoproxil fumarate (TDF, Viread) – Tenofovir DF is the only nucleotide RTI available for treatment of HIV. It is a prodrug of tenofovir, a potent inhibitor of HIV replication. Tenofovir DF is given once daily and is generally well tolerated. It is effective as part of initial

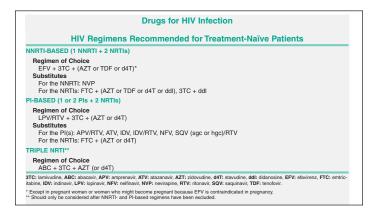
HIV therapy and has activity against some HIV strains that are resistant to other NRTIs. It is available alone or in combination with emtricitabine (*Truvada*). Tenofovir should not be used in three-drug combinations with abacavir/lamivudine or didanosine/lamivudine because of high rates of virologic failure (C Farthing et al, Antivir Ther 2003; 8 suppl 1: S195, abstract 43; www.fda.gov/medwatch/SAFETY/2003/ viread_dear-doc.pdf). Tenofovir is also active against HBV, even strains that are resistant to lamivudine (M Nunez et al, AIDS 2002; 16:2352; R Bruno et al, AIDS 2003; 17:783).

Adverse effects – The most common adverse effects have been nausea, vomiting and diarrhea. Renal failure, including a Fanconi-like syndrome, has been reported (A Karras et al, Clin Infect Dis 2003; 36:1070); tenofovir dosage must be decreased in patients with renal failure. *In vitro* studies suggest that mitochondrial toxicity with tenofovir may be less than with other NRTIs, but fatal lactic acidosis has been reported (P Rivas et al, BMJ 2003; 327:711).

When tenofovir is used in combination with ddI, the dose of ddI should be decreased. Tenofovir lowers the serum levels of atazanavir; the manufacturer recommends adding ritonavir (100 mg) to boost atazanavir levels when given in combination with tenofovir.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (**NNRTIs**) — These drugs are direct, non-nucleoside inhibitors of HIV-1 reverse transcriptase. Combinations of an NNRTI with NRTIs tend to be at least additive in reducing HIV replication *in vitro*.

HIV isolates that are resistant to NRTIs and protease inhibitors remain sensitive to NNRTIs, but cross-resistance is common within the NNRTI class. Resistance to NNRTIs develops rapidly if they are used alone or in combinations that do not completely suppress viral replication.



Class adverse effects – All NNRTIs can cause a rash that is sometimes severe. NNRTIs are metabolized by and can affect hepatic CYP 450 isozymes; drug interactions can occur with protease inhibitors and many other drugs (*The Medical Letter Adverse Drug Interactions Program*). Rifampin (*Rifadin*, and others) decreases levels of NNRTIs and should generally be avoided.

Delavirdine (DLV,*Rescriptor)* – Delavirdine is the least potent NNRTI. A study comparing delavirdine/zidovudine/didanosine, delavirdine plus either zidovudine or didanosine, and zidovudine/didanosine in patients with mean CD4 cell counts of 295 cells/mm³ and <6 months prior HIV treatment showed only modest benefit from the triple combination (GH Friedland et al, J Acquir Immune Defic Syndr 1999; 21:281). Unlike other NNRTIs, delavirdine increases serum concentrations of protease inhibitors.

Efavirenz (EFV, *Sustiva*) – Efavirenz is the only NNRTI approved for once-daily dosing. Efavirenz in combination with zidovudine/lamivudine has been more effective than indinavir/zidovudine/lamivudine or nelfinavir/zidovudine/lamivudine in lowering HIV RNA levels, even among

patients with high baseline RNA levels (>100,000 copies/mL), and has been better tolerated. Brief studies in treatment-experienced patients or those failing other regimens have shown that efavirenz in combination with at least two other new agents can be effective in suppressing plasma HIV RNA levels and raising CD4 cell counts.

Adverse effects – The most common adverse effects have been rash, dizziness, headache, insomnia and inability to concentrate. Vivid dreams, nightmares and hallucinations also occur frequently. CNS effects tend to occur between 1 and 3 hours after each dose, and often stop within a few weeks. Hypertriglyceridemia has occurred. Fetal abnormalities occurred in pregnant monkeys exposed to efavirenz; the drug should not be given to women who are, or are considering becoming, pregnant. Methadone dosage often needs to be increased if efavirenz is used concurrently.

Nevirapine (**NVP**, *Viramune*) – Nevirapine is most effective at raising CD4 cell counts and lowering viral load when combined with 2 NRTIs for initial HIV therapy.

Adverse effects – Nevirapine can cause severe hepatotoxicity, hepatic failure and death, particularly in patients with previously elevated transaminases or underlying hepatitis B or C, and when used for post-exposure prophylaxis (E Martinez et al, AIDS 2001; 15:1261; MMWR Morb Mortal Wkly Rep 2001; 49:1153). Fever, nausea and headache can occur. Rash is common early in treatment with nevirapine and can be more severe than with other NNRTIs; it may progress to Stevens-Johnson syndrome. To decrease the incidence of rash, nevirapine should be given 200 mg once daily for the first 2 weeks, and then 200 mg twice daily. In one study, 400 mg once daily was as effective as b.i.d. dosing (F Raffi et al, Antivir Ther 2000; 5:267), although hepatotoxicity and rash may be more frequent with once-daily dosing (F van Leth et al, 10th Conference on Retroviruses and Opportunistic Infections 2003, abstract 176). As

with efavirenz, the dose of methadone often needs to be increased if nevirapine is used concurrently.

PROTEASE INHIBITORS (PIs) — Protease inhibitors prevent cleavage of protein precursors essential for HIV maturation, infection of new cells and viral replication. Use of a protease inhibitor in combination with other drugs has led to marked clinical improvement and prolonged survival even in patients with advanced HIV infection. Most protease inhibitors potently suppress HIV *in vivo*. Combinations of two protease inhibitors are increasingly being used; one is usually ritonavir, which inhibits the metabolism and increases serum concentrations of other PIs.

Class adverse effects – Many protease inhibitors can cause gastrointestinal distress, increased bleeding in hemophiliacs, hyperglycemia, insulin resistance and hyperlipidemia and have been associated with increased risk of coronary artery disease (DC Rhew et al, Clin Infect Dis 2003; 37:959; L Calza et al, Int J Antimicrob Agents 2003; 22:89). They have also been associated with a syndrome of lipodystrophy including fat wasting, reaccumulation and redistribution. All, especially higher doses of ritonavir, can cause hepatotoxicity, which may occasionally be severe and is more common in patients who are co-infected with HBV or HCV (MS Sulkowski et al, JAMA 2000; 283:74).

All protease inhibitors are metabolized by and are inhibitors of hepatic CYP3A4; drug interactions are common and can be severe (*The Medical Letter Adverse Drug Interactions Program*). Rifampin (*Rifadin*, and others), which decreases the plasma levels of protease inhibitors, should generally be avoided. If a rifamycin must be used, rifabutin (*Mycobutin*) is preferred (M Narita et al, Clin Infect Dis 2000; 30:779).

Amprenavir (APV, *Agenerase*) – Amprenavir is available in large capsules and in an oral solution; full doses require 16 capsules or 187 mL

daily. Both preparations contain amounts of vitamin E that exceed the recommended daily allowance (RDA), so patients should be advised not to take vitamin E supplements concurrently. The total number of daily amprenavir tablets can be reduced by co-administering it with low doses of ritonavir (C Goujard et al, Antimicrob Agents Chemother 2003; 47:118).

Adverse effects – The most common adverse effects have been nausea, vomiting (especially in combination with zidovudine), perioral paresthesias and rash (JC Goodgame et al, Antivir Ther 2000; 5:215). Many patients with rash can continue or restart amprenavir if the rash is mild or moderate, but about 1% of patients have developed severe rashes, including Stevens-Johnson syndrome.

Atazanavir (ATV, *Reyataz*) – Atazanavir (Medical Letter 2003; 45:89) is the first single-agent protease inhibitor with once-daily dosing (amprenavir/ritonavir in combination was previously FDA-approved for oncedaily treatment). In clinical trials it has been similar to efavirenz or nelfinavir in lowering viral load in treatment-naïve patients (I Sanne et al, J Acquir Immune Defic Syndr 2003; 32:18). Atazanavir alone was less effective than lopinavir/ritonovir, but atazanavir/ritonavir was comparable to lopinavir/ritonavir in treatment-experienced patients (L Nieto-Cisneros et al and R Badaro et al, Antivir Ther 2003, 8 suppl 1:S212, abstracts 117 and 118).

Adverse effects – Atazanavir causes indirect hyperbilirubinemia. It has had no adverse effects on lipid profiles, but the drug's long-term effects are unknown. It can cause PR prolongation and should be used with caution in patients with cardiac conduction abnormalities. Co-administration with tenofovir or efavirenz decreases serum levels of atazanavir; this may be overcome by addition of low-dose ritonavir. Atazanavir should not be used in combination with indinavir, which also can cause hyperbilirubinemia.

Fosamprenavir calcium (*Lexiva*) – Fosamprenavir calcium, a prodrug of amprenavir, was recently approved by the FDA for use in HAART. In patients who have not previously been treated with a protease inhibitor, fosamprenavir can be taken once daily combined with ritonavir, or twice daily with or without ritonavir. In patients who are treatment-experienced, it should be taken twice daily with ritonavir. If coadministered with ritonavir and efavirenz, the ritonavir dosage should be increased. Fosamprenavir will likely replace amprenavir, because the total number of pills taken each day is lower (4 versus 16).

Adverse effects – Adverse effects are similar to those with amprenavir, but in clinical studies the incidence of nausea, vomiting and severe rash was lower. Unlike amprenavir, which should not be taken with a fatty meal, fosamprenavir has no food restrictions.

Indinavir (**IDV**, *Crixivan*) – Indinavir has good oral bioavailability. Indinavir 800 mg combined with ritonavir 100 mg (both b.i.d. for ease of use) was comparable in effectiveness to indinavir alone in the usual dosage of 800 mg t.i.d. (JA Arnaiz et al, AIDS 2003; 17:831).

Adverse effects – In addition to adverse effects similar to those of other protease inhibitors, indinavir causes elevation of indirect bilirubin, indinavir-containing kidney stones and renal insufficiency, dermatologic changes including alopecia, dry skin and mucous membranes, and paronychia and ingrown toenails (J Garcia-Silva et al, Drug Saf 2002; 25:993). Patients should drink at least 1.5-2 liters of water daily to minimize renal adverse effects. Gallstones have also been reported (R Verdon et al, Clin Infect Dis 2002; 35:e57).

Lopinavir/ritonavir (LPV/RTV, Kaletra) – Lopinavir is available in the US only in a fixed-dose combination with ritonavir (Medical Letter 2001; 43:1). In treatment-naïve patients a regimen with lopinavir/ritonavir was more effective than a nelfinavir-containing regimen (S Walmsley et al, N

Engl J Med 2002; 346:2039). A regimen containing lopinavir/ritonavir is a first choice in patients with previous HIV treatment and moderate or no protease inhibitor resistance (≤5 resistance mutations).

Adverse Effects – Lopinavir/ritonavir is generally well tolerated. Mild diarrhea, nausea, headaches and asthenia have occurred.

Nelfinavir (**NFV**, *Viracept*) – Nelfinavir is a commonly used protease inhibitor because it is well tolerated. It appears to be less potent than lopinavir/ritonavir or efavirenz.

Adverse effects – Diarrhea, which may resolve with continued use, and increased food intake, are its main adverse effects.

Ritonavir (**RTV**, *Norvir*) – Ritonavir is well absorbed from the gastrointestinal tract and at full doses potently inhibits HIV, but due to poor tolerability it is now used mainly in doses of 100 to 400 mg b.i.d. to increase the serum concentrations and decrease the dosage frequency of other protease inhibitors.

Adverse effects – Adverse reactions are common to full doses of ritonavir, but less common with the low doses used in PI combinations. Ritonavir can cause hypertriglyceridemia, altered taste, nausea, vomiting and, rarely, circumoral and peripheral paresthesias. It has frequent adverse interactions with other drugs.

Saquinavir (SQV, Fortovase, Invirase) – When administered as a single protease inhibitor, a soft-gel preparation (Fortovase) with improved bioavailability and potency has largely replaced the older hard-gelatin capsule formulation (Invirase), which is poorly absorbed. In healthy volunteers, plasma levels of Invirase and Fortovase were comparable when combined with ritonavir, and Invirase was better tolerated (M Kurowski et al, HIV Med 2003; 4:94). In one study, saquinavir 1000 mg b.i.d. combined with ritonavir 100 mg b.i.d. had similar virologic efficacy and superior tolerability compared to indinavir 800 mg b.i.d.

combined with ritonavir 100 mg b.i.d. (UB Dragsted et al, J Infect Dis 2003; 188:635). Aside from the large number of capsules daily with *Fortovase*, saquinavir is usually well tolerated.

FUSION INHIBITOR — After HIV binds to the host cell surface, a conformational change occurs in the transmembrane glycoprotein subunit (gp41) of the viral envelope, facilitating fusion of the viral and host cell membranes, and entry of the virus into the cell. Fusion inhibitors bind to gp41 and prevent the conformational change (JM Kilby and JJ Eron, N Engl J Med 2003; 348:2228).

Enfuvirtide (T-20, *Fuzeon)* – Enfuvirtide (Medical Letter 2003; 45:49) is the first fusion inhibitor approved by the FDA for treatment of HIV infection and is indicated for treatment-experienced patients with ongoing HIV replication despite current antiretroviral use. It is administered by subcutaneous injection twice daily. In two open-label trials in highly treatment-experienced patients, the addition of enfuvirtide to a background regimen optimized by resistance testing resulted in superior virologic suppression and CD4 cell count increases compared to optimized background regimen alone (JP Lalezari et al, N Engl J Med 2003; 348:2175; A Lazzarin et al, N Engl J Med 2003; 348:2186).

Adverse effects – Almost all patients develop local injection site reactions to enfuvirtide, usually consisting of mild or moderate pain, erythema, induration, nodules and cysts (RA Ball et al, J Am Acad Dermatol 2003; 49:826). Other adverse effects include eosinophilia, systemic hypersensitivity reactions, and possibly an increased incidence of bacterial pneumonia.

PREVENTION OF PERINATAL TRANSMISSION — Zidovudine alone, started at 14-34 weeks of gestation and continued in the infant for the first 6 weeks of life, reduced HIV transmission from 26% to 8% (EM Connor

et al, N Engl J Med 1994; 331:1173). Zidovudine alone taken orally for just 3-4 weeks before delivery and during labor has been reported to decrease the risk of HIV transmission by 50% (N Shaffer et al, Lancet 1999; 353:773).

Most clinicians now would give combination therapy with **zidovudine plus another NRTI and either a protease inhibitor or nevirapine throughout pregnancy** to prevent transmission of HIV to the offspring. Women not already on therapy should consider waiting until after 10-12 weeks of gestation to begin.

Already in labor - For women who are already in labor and have had no antiretroviral therapy, **zidovudine** given to the mother and continued in the infant for 6 weeks or given only to the infant for 6 weeks beginning within 48 hours after birth decreased HIV transmission (NA Wade et al, N Engl J Med 1998; 339:1409). A combination of zidovudine plus lamivudine given at the onset of labor and to the infant for one week is also effective (Petra Study Team, Lancet 2002; 359:1178). Single-dose nevirapine given to the mother at the onset of labor and to the infant within 72 hours of delivery can also decrease the risk of perinatal transmission and was more effective than zidovudine alone given to the mother during labor and to the infant for 7 days (LA Guay et al, Lancet 1999; 354:795; JB Jackson et al, Lancet 2003; 362:859). Single-dose nevirapine, however, has been associated with the emergence of nevirapine-resistant strains in 15-20% of women and 46% of infants; this may not be long-lasting but theoretically could compromise future treatment of mother and child (SH Eshleman et al, AIDS 2001; 15:1951). It is not a good choice unless no other options are available.

Drugs not to be used – Fatal lactic acidosis from the combination of stavudine and didanosine has occurred in pregnant women; this combination should not be used. Efavirenz should be avoided in pregnancy because of potential teratogenicity.

SUMMARY — For initial therapy of HIV infection, reasonable first choices include either an NNRTI, often efavirenz because it has fewer adverse effects than nevirapine, or the PI combination lopinavir/ritonavir *(Kaletra)*, each combined with 2 NRTIs. If an NNRTI- or PI-based regimen cannot be used, a final option for initial therapy would be abacavir plus lamivudine and either zidovudine or stavudine. For more advanced disease, combinations should include three or more active drugs based on resistance testing. Enfuvirtide-based regimens may be particularly helpful in heavily pretreated patients. For all patients, regular monitoring of HIV viral load and CD4 cell count should be used to guide therapy. NNRTIs and protease inhibitors have many adverse interactions with each other and with other drugs *(The Medical Letter Adverse Drug Interactions Program)*.

Two NRTI Combinations for HIV

Two Once-Daily Fixed-Dose NRTI Combinations for HIV

Originally published in The Medical Letter - February 2005; 47:19

The FDA has approved emtricitabine/tenofovir (*Truvada* – Gilead) and abacavir/lamivudine (*Epzicom* – GSK), two new fixed-dose combinations of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), for oncedaily use in treatment of HIV infection. Two other fixed-dose NRTI combinations were previously approved for twice-daily dosing. Dual NRTI therapy is generally used in either an NNRTI (non-nucleoside reverse transcriptase inhibitor)-based or a PI (protease inhibitor)-based regimen.¹

CLINICAL STUDIES — No clinical studies with these combinations have been published. A 48-week non-inferiority study in treatment-naïve HIV patients also treated with efavirenz found virologic suppression (HIV RNA <400 copies/mL) in 84% of patients treated with fixed-dose emtricitabine/tenofovir once daily and in 73% with zidovudine/lamivudine (*Combivir*) twice daily.² In similar patients, fixed-dose abacavir/lamivudine plus efavirenz produced virologic suppression in 77% after 24 weeks.³ Two non-inferiority studies in treatment-experienced patients with HIV found that, in combination with other antiretrovirals, taking fixed-dose abacavir/lamivudine once daily was not inferior to taking abacavir twice daily with lamivudine once or twice daily.^{4,5}

ADVERSE EFFECTS — Adverse effects with the combinations have generally been similar to those with the drugs taken separately. In one study, more severe hypersensitivity reactions and severe diarrhea occurred with abacavir once daily than with twice-daily dosing. Abacavir/lamivudine is contraindicated in patients with hepatic impairment and those with a CrCl <50 mL/min. Emtricitabine/tenofovir is contraindicated in patients with a CrCl <30 mL/min; the dosing interval should be increased to once every 48 hours in patients with a CrCl of 30-49 mL/min.

Two NRTI Combinations for HIV

DRUG	TAB/CAPS SIZE	USUAL ADULT DOSAGE	COST*
Abacavir (ABC) – Ziagen (GSK)	300 mg	300 mg bid or 600 mg once daily	\$421.80
amivudine (3TC) – Epivir (GSK)	150 or 300 mg	150 mg bid or 300 mg once daily	315.30
Abacavir/lamivudine – Epzicom (GSK)	600 mg/300 mg	1 tablet once daily	737.10
Emtricitabine (FTC) - Emtriva (Gilead)	200 mg	200 mg once daily	293.40
Tenofovir (TDF) – Viread (Gilead)	300 mg	300 mg once daily	473.70
Emtricitabine/tenofovir - Truvada (Gilead)	200 mg/300 mg	1 tablet once daily	770.40
Zidovudine (AZT) – Retrovir (GSK)	100 or 300 mg	200 mg tid or 300 mg bid	368.40
Zidovudine/lamivudine – Combivir (GSK)	300 mg/150 mg	1 tablet bid	687.60
Zidovudine/lamivudine/abacavir – Trizivir (GSK)	300 mg/150 mg/300 mg	1 tablet bid	1108.20

CONCLUSION — Emtricitabine/tenofovir (*Truvada*) and abacavir/lamivudine (*Epzicom*) can simplify HIV treatment regimens by reducing pill burden and potentially increasing adherence. Because of the risk of hypersensitivity reactions with abacavir, *Epzicom* should not be the first choice for initial treatment of HIV infection.

- 1. Drugs for HIV infection. Treat Guidel Med Lett 2004; 2:1.
- Gilead announces 48-wk data from Study 934. Press Release; Feb 3, 2005. www.gilead.com
- JE Gallant et al. Efficacy of once-daily abacavir/lamivudine fixed-dose combination (ABC/3TC) + efavirenz and subsequent treatment of tenofovir DF and ABC/3TC non-responders (NRs): ESS3009 planned 24-week analysis. 44th Intersci Conf Antimicrob Agents Chemother (ICAAC); Oct 30-Nov 2, 2004; Washington DC. Abstract H-567.
- C Hill-Zabala et al. Abacavir and lamivudine (ABC/3TC) fixed dose combination once daily compared to ABC and 3TC twice daily in HIV-1 infected subjects (ESS30008). 7th International Congress on Drug Therapy in HIV Infection; Nov 14-18, 2004; Glasgow. Abstract P45.
- N Clumeck et al. Safety and efficacy of a once daily (OAD) fixed-dose combination of ABC/3TC versus ABC twice daily and 3TC OAD as separate entities in ART-experienced HIV-1 infected patients. 44th ICAAC; Oct 30-Nov 2, 2004; Washington, DC. Abstract H-558.

DRUGS FOR Non-HIV Viral Infections

Original publication date - April 2005

The drugs of choice for non-HIV viral infections with their dosages and cost are listed in the tables that begin on page 159. Some of the indications and dosages recommended here have not been approved by the FDA.

DRUGS FOR HERPES SIMPLEX AND VARICELLA-ZOSTER VIRUS

ACYCLOVIR (*Zovirax*, and others) — Available in topical, oral, and intravenous (IV) formulations, acyclovir is used to treat herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. Acyclovir cream reduces the duration of herpes labialis by about half a day (SL Spruance et al, Antimicrob Agents Chemother 2002; 46:2238). Oral acyclovir is effective for both primary and recurrent genital HSV infections (A Wald et al, Clin Infect Dis 2002; 34:944). Long-term oral suppression with acyclovir decreases the frequency of symptomatic genital recurrences and asymptomatic viral shedding. Oral acyclovir begun within 24 hours after the onset of rash, decreases the severity of primary varicella infection and can also be used to treat localized zoster. IV acyclovir is the drug of choice for treatment of HSV infections that are visceral, disseminated or involve the central nervous system (CNS) and for serious or disseminated VZV infections.

Adverse Effects – By any route of administration, acyclovir is generally well tolerated. Gastrointestinal (GI) disturbances and headache can occur. Given IV, the drug may cause phlebitis and inflammation at sites of infusion or extravasation. IV acyclovir can also cause reversible renal dysfunction due to crystalline nephropathy; rapid infusion, dehydration,

renal insufficiency and high dosage increase the risk. IV and rarely oral acyclovir have been associated with encephalopathy, including tremors, hallucinations, seizures and coma.

In rats, high doses of acyclovir cause testicular atrophy and high concentrations cause chromosomal damage, but no adverse effects on sperm production or cytogenetic alterations in peripheral blood lymphocytes have been detected in patients who have taken the drug orally for more than 10 years to suppress recurrent genital herpes.

Pregnancy – Although acyclovir is not approved for treatment of pregnant women, its use during pregnancy has not been associated with an increased risk of congenital abnormalities, and many clinicians prescribe the drug for treatment of first episodes of genital herpes during pregnancy. Suppression of recurrent genital herpes in pregnant women near term reduces the need for cesarean sections to avoid neonatal herpes infections.

Resistance – Acyclovir-resistant HSV occurs mainly in immunocompromised patients treated with the drug; isolates are usually also resistant to valacyclovir and famciclovir. Resistant HSV infection in HIV-positive patients has been associated with progressive mucosal disease and, rarely, visceral involvement. Acyclovir-resistant VZV strains in HIV-positive patients have been associated with chronic cutaneous lesions and, rarely, invasive disease.

Infections with acyclovir-resistant HSV or VZV may respond to foscarnet or cidofovir, which are primarily used for treatment of CMV infection and are discussed on page 165.

FAMCICLOVIR (Famvir) — Famciclovir, which is rapidly converted to penciclovir after oral administration, is an alternative to acyclovir. It is

and a set a se	Deven	A dute days and	0
Infection	Drugs	Adult dosage ¹	Cost ²
Orolabial Topical	Acyclovir – Zovirax	5% cream 5x/d x 4d	\$33.06 ³
	Docosanol – <i>Abreva</i> ⁴ Penciclovir – <i>Denavir</i>	10% cream 5x/d until healing 1% cream applied q2h while	15.99 ⁵
		awake x 4d	23.546
Oral	Acyclovir – generic	400 mg PO 5x/d q4h x 5d	45.25
	Zovirax Famciclovir – Famvir	500 mg PO bid x 7d	83.50 119.14
	Valacyclovir – Valtrex	2 g PO q12h x 1d	35.36
Genital	valacyclovii – valitex	2 91 0 4121 X 10	00.00
first episode	Acyclovir – generic	400 mg PO tid or 200 mg	31.50
	Zovirax	PO 5x/d x 7-10d ⁷	59.85
	Famciclovir ⁸ – Famvir	250 mg PO tid x 7-10d	89.25
	Valacyclovir – Valtrex	1 g PO bid x 7-10d	123.76
	Valadyolovii Valitox	igi o blaxi iba	120.70
episodic treatment	Acyclovir – generic	800 mg tid x 2d	16.29
of recurrences9	Zovirax	or 400 mg PO tid x 3-5d ¹⁰	30.06
	Famciclovir - Famvir	125 mg PO bid x 3-5d ^{10,11}	23.40
	Valacyclovir - Valtrex	500 mg PO bid x 3d	29.04
		-	
suppression of	Acyclovir – generic	400 mg PO bid	108.60 ¹³
recurrences12	Zovirax		200.4013
	Famciclovir - Famvir	250 mg PO bid	255.0013
	Valacyclovir - Valtrex	500 mg - 1 g PO 1x/d ¹⁴	145.20 ¹³
Mucocutaneous	Acyclovir – generic IV	5 mg/kg IV q8h x 7-14d ¹⁵	900.00
(immunocom-	Zovirax IV generic PO	or 400 mg PO 5x/d x 7-10d	1,118.10 ¹⁶ 63.35
promised)	Zovirax PO	or 400 mg PO 5x/d x 7-10d	116.90
	Famciclovir – Famvir	500 mg bid x 7-10d	119.14
	Valacyclovir ⁸ - Valtrex	500 mg or 1 g bid x 7-10d	67.76
Encephalitis	Acyclovir – generic Zovirax	10-15 mg/kg IV q8h x 14-21d ¹⁷	3,540.00 4,397.86 ¹⁶
Neonatal	Acyclovir – generic Zovirax	10-20 mg/kg IV q8h x 14-21d	180.00 ¹⁸ 223.62 ^{16,18}
Keratoconjunctivitis ¹⁹	Trifluridine – generic	1% solution 1 drop q2h	81.98 ²¹
	Viroptic	(max 9 drops/d) ²⁰	94.88 ²¹
Acyclovir-resistant (severe infection, immunocompromised)	Foscarnet – Foscavir	40 mg/kg IV q8h x 14-21d	1,500.00
wide, available from NDC1 administration may increas 3. Based on purchase of 2-g 4. Available without a prescrip 5. Based on purchase of 0.07 6. Based on purchase of 1.5- 7. For severe initial genital he 8. Not approved by the FDA 1 9. Antiviral therapy is variably 0. No published data are ava 1. For recurrent HSV in HIV- 2. Some clinicians discontinu 3. For 30 darsy therapy.	leatith, a healthcare information : se the total cost. For generic dru tube. Dition. 7 or (20) tube on drugstore.com g tube containing 15 mg of penc rypes, IV acyclovir (5-10 mg/kg of or this indication. effective and only if started eart liable to support 3 day's use. ostite patients, 500 mg bid for the treatment for 1-2 mos/yr to as:	(March 10, 2005). iclovir. 8h for 5-7d) can be used. y.	drugs, the cost of

An ophthalmic preparation of acyclovir is available in some countries. Treatment of HSV ocular infections should be supervised by an ophthalmicologist, duration of therapy and dosage depend on response.
 Once the cornea has re-epithelialized the dose can be decreased to 1 drop q4h x 7d.
 Based on purchase of a 7.5-m bottle.

Infection	Drugs	Adult dosage ¹	Cost ²
Varicella	Acyclovir – generic Zovirax	20 mg/kg (800 mg max) PO qid x 5d	\$69.40 128.40
Herpes zoster	Valacyclovir - Valtrex	1 g PO tid x 7d	185.64
	Famciclovir – Famvir	500 mg PO tid x 7d	178.71
	Acyclovir – generic Zovirax	800 mg PO 5x/d x 7-10d	121.45 224.70
Varicella or zoster in immunocom- promised	Acyclovir – generic Zovirax	10 mg/kg IV q8h x 7d ³	1,602.00 2,236.20 ⁴
Acyclovir-resistant zoster	Foscarnet ⁵ – Foscavir	40 mg/kg IV q8h x 10d	1,050.00

Cost based on AWP listings in Red Book 200

5. Not approved by the FDA for this indication.

effective in treating first episodes and recurrences of genital HSV and for chronic suppression. In immunocompromised patients with herpes zoster, famciclovir, begun within 72 hours after onset of rash is effective in speeding the resolution of zoster-associated pain and shortening the duration of postherpetic neuralgia (SK Tyring et al, Arch Fam Med 2000; 9:863).

Adverse Effects – Famciclovir has been generally well tolerated. Headache, nausea and diarrhea have been reported. Like acyclovir, famciclovir has been associated with dose-related adverse effects on testicular function in animals, but not in humans. In female rats, 600 mg/kg/day of famciclovir for 2 years increased the incidence of mammary adenocarcinoma.

Resistance – HSV and VZV strains resistant to acyclovir are generally also resistant to famciclovir.

VALACYCLOVIR (Valtrex) — Valacyclovir is an L-valyl ester of acyclovir that is metabolized to acyclovir after oral administration, resulting

in higher serum concentrations than with oral acyclovir. Acyclovir serum concentrations following high doses of oral valacyclovir resemble those following IV administration of acyclovir. A one-day treatment regimen of valacyclovir reduced the duration of oral herpes by about 1 day (Med Lett Drugs Ther 2002; 44:95). In first-episode or recurrent genital herpes, valacyclovir twice daily is as effective as acyclovir given 5 times a day. Valacyclovir 500 mg once daily is effective for suppression of genital HSV and one study of discordant couples found that 8 months of suppressive valacyclovir taken by the infected partner reduced the risk of HSV transmission to the susceptible partner by about half (L Corey et al, N Engl J Med 2004; 350:11). A higher dose (500 mg b.i.d. or 1 g once/d) may be needed for suppression in patients with frequent recurrences.

Adverse Effects – Valacyclovir is generally well tolerated; adverse effects are similar to those with acyclovir. GI disturbance, headache, rash, CNS effects such as hallucinations and confusion, and nephrotoxicity can occur. A thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in some severely immunocompromised patients taking high doses.

Resistance – Isolates resistant to acyclovir are also resistant to valacyclovir.

TOPICAL DRUGS FOR HERPES SIMPLEX — **Penciclovir** (*Denavir*) – Topical penciclovir 1% cream applied every 2 hours while awake decreases the healing time of recurrent orolabial herpes by about 0.7 days in immunocompetent adults (SL Spruance et al, JAMA 1997; 277:1374).

Docosanol (*Abreva*) – Topical docosanol cream, available without a prescription, started within 12 hours of prodromal symptoms, decreases

Drugs for Cytomegalovirus				
Infection	Drugs	Adult dosage ¹	Cost ²	
Cytomegalovirus (CMV) ³	Diugs	Addit dosage	0031	
Cytomegalovirus (CMV)	Valganciclovir - Valcyte	900 mg PO bid x 21d	\$2630.88	
	·	followed by 900 mg once/d	1.879.20 ⁴	
or	Ganciclovir – Cytovene	5 mg/kg IV g12h x 14-21d	836.00	
0.	danololotti oytotoho	followed by 5 mg/kg IV once/d	836.00 ⁴	
		or 6 mg/kg IV 5x/wk	710.604	
		or 1 g PO tid ⁶	1,631.284	
	average generic	1 g PO tid ⁶	1,362.484	
	Vitrasert implant7	4.5 mg intraocularly g5-8 mos	5,000.00 ^{5,8}	
or	Foscarnet - Foscavir	60 mg/kg IV q8h or 90 mg/kg IV		
		q12h x 14-21d followed by	2,250.00	
		90-120 mg/kg IV once/d ⁹	2,400.004	
or	Cidofovir – Vistide	5 mg/kg IV once/wk x 2 then	1,622.70	
		5 mg/kg IV q2wks ¹⁰	1,622.704	
or	Fomivirsen ⁷ – Vitravene	330 mcg intravitreally q2wks x 2	2,000.005	
		then 1x/mo	1,000.00 ^{4,5}	
3. Chronic suppression is recor	nended dosage for a 70-kg patient, mmended in AIDS and in other high	according to NDCHealth (January 31, 2005) ly immunocompromised patients with retiniti d for prevention of CMV disease in solid org	s. Both oral gan-	
recipients.				
 Based on 4 wks' maintenand Based on AWP listings in Re 				
		enia in renal transplant patients with renal ins	sufficiency who	
are also taking azathioprine		(CellCept) (SM Flechner et al, Transplantation		
66:1682).				
 Systemic therapy is recomm Cost of one implant. 	ended to prevent CMV disease in t	ne contralateral eye and other organ system	S.	
	may be more effective but less wel	tolerated.		
 To minimize renal toxicity pa should also receive oral prot who can tolerate additional f sion. Not recommended for 	tients should receive 1 L 0.9% salir benicid 2 g 3 hours prior to infusion fluid should receive a second 1 L of patients with serum creatinine >1.5	the over 1-2 hrs prior to a 1-hour cidofovir inft of cidofovir and 1 g 2 and 8 hrs after the inf 0.9% saline, started immediately after the c mg/dL, creatinine clearance ≤55 mL/min or ded for serum creatinine 0.3-0.4 mg/dL abor	usion. Patients idofovir infu- proteinuria ≥100	

healing time by about half a day in recurrent orolabial herpes (Med Lett Drugs Ther 2002; 44:95).

Trifluridine (*Viroptic*) – Trifluridine is a nucleoside analog active against herpes viruses, including acyclovir-resistant strains. Marketed in an ophthalmic preparation, it is approved for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. It is also active against vaccinia virus and has been used to treat accidental ocular infection following smallpox vaccination (JS Pepose et al, Am J Ophthalmol 2003; 136:343).

DRUGS FOR CYTOMEGALOVIRUS

GANCICLOVIR (*Cytovene*) — IV ganciclovir is approved for both induction and maintenance treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients and for prevention of CMV infection in transplant recipients. It is also used to treat CMV infections of other sites (colon, esophagus, lungs, etc) and for preemptive treatment of immunosuppressed patients with CMV antigenemia or viremia (MMWR Recomm Rep 2000; 49[RR-10]:1). Oral ganciclovir is less effective than IV because of lower bioavailability. It has largely been replaced by oral valganciclovir, which achieves plasma concentrations similar to those with IV ganciclovir.

Prophylactic oral ganciclovir, or IV ganciclovir followed by either oral ganciclovir or high-dose oral acyclovir, reduces the risk of CMV in patients who have had liver transplantation, including seronegative recipients of seropositive donations (E Gane et al, Lancet 1997; 350:1729; DJ Winston and RW Busuttil, Transplantation 2003; 75:229).

An intraocular implant that releases ganciclovir (*Vitrasert* – Bausch & Lomb) has been more effective than IV ganciclovir for CMV retinitis in the eye with the implant, but is not effective systemically.

Adverse Effects – Ganciclovir is teratogenic, carcinogenic and mutagenic and causes aspermatogenesis in animals. Granulocytopenia and thrombocytopenia, which are usually reversible, are more common with the IV formulation. Severe myelosuppression may occur more frequently when the drug is given concurrently with zidovudine (AZT, *Retrovir*), azathioprine (*Imuran*) or mycophenolate mofetil (*CellCept*). Granulocyte-colony-stimulating factors (GM-CSF; G-CSF) have been used to treat ganciclovir-induced neutropenia. Other adverse effects of

systemic ganciclovir include retinal detachment in patients with CMV retinitis, fever, rash, phlebitis, confusion, abnormal liver function, renal dysfunction, headache, GI toxicity and, rarely, psychiatric disturbances and seizures.

Resistance – Ganciclovir resistance may be associated with persistent viremia and progressive disease. Ganciclovir-resistant CMV can emerge and cause late morbidity in transplant recipients given prophylactic ganciclovir (AP Limaye et al, Lancet 2000; 356:645). CMV strains resistant to ganciclovir *in vitro* may be susceptible to foscarnet or cidofovir.

VALGANCICLOVIR (*Valcyte*) — Oral valganciclovir, an oral prodrug of ganciclovir, achieves plasma concentrations similar to those following IV administration of ganciclovir; it has largely replaced oral ganciclovir (MD Pescovitz et al, Antimicrob Agents Chemother 2000; 44:2811). Valganciclovir is as effective as IV ganciclovir for induction and maintenance therapy of CMV retinitis in patients with AIDS and has replaced both IV and oral ganciclovir for treatment of patients with CMV retinitis whose lesions are peripheral and not immediately sight threatening (DF Martin et al, N Engl J Med 2002; 346:1119; MMWR Recomm Rep 2004; 53[RR-15]:1). Valganciclovir once daily is as effective as oral ganciclovir t.i.d. in prevention of CMV disease in mismatched (D+, R-) solid organ transplant recipients (C Paya et al, Am J Transplant 2004; 4:611), but has not been approved by the FDA for use in liver transplant recipients.

Adverse Effects - Adverse effects are similar to those of IV ganciclovir.

Resistance – Isolates that are resistant to ganciclovir are also resistant to valganciclovir.

FOSCARNET (*Foscavir*) — Foscarnet is an alternative to ganciclovir and valganciclovir for treatment of CMV infection. It is approved for use in CMV retinitis, including progressive disease due to ganciclovir-resistant strains, and for treatment of acyclovir-resistant HSV or VZV infections. Foscarnet is more expensive and generally less well tolerated than ganciclovir, and requires controlled infusion rates and large volumes of fluid. In allogeneic stem cell transplant recipients who develop CMV infection, treatment with foscarnet is as effective as IV ganciclovir and causes less hematologic toxicity (P Reusser et al, Blood 2002; 99:1159).

Adverse Effects – Renal dysfunction often develops during treatment with foscarnet and is usually reversible, but renal failure requiring dialysis may occur. Renal toxicity is increased in patients receiving other nephrotoxic drugs; adequate hydration may decrease the risk. Nausea, vomiting, anemia, fatigue, headache, genital ulceration, CNS disturbances, hypo- and hypercalcemia, hypo- and hyperphosphatemia, hypokalemia and hypomagnesemia have also occurred. The risk of severe hypocalcemia, sometimes fatal, is increased by concurrent IV pentamidine (*Pentam*). Foscarnet given with zidovudine may increase the risk of anemia. It causes chromosomal damage *in vitro* and *in vivo*.

Resistance – HSV, VZV and CMV strains resistant to foscarnet can emerge during treatment. Combined use of foscarnet and ganciclovir may benefit some patients, but CMV strains resistant to both ganciclovir and foscarnet have been reported.

CIDOFOVIR (*Vistide*) — IV cidofovir given once weekly for 2 weeks and then once every 2 weeks for maintenance therapy can delay progression of CMV retinitis in patients with AIDS.

Adverse Effects – About 25% of patients discontinue cidofovir because of adverse effects such as nephrotoxicity, neutropenia and metabolic acidosis. Iritis, uveitis or ocular hypotony can occur. To decrease the risk of nephrotoxicity, IV 0.9% saline and oral probenecid must be given with each cidofovir dose. Cidofovir is contraindicated in patients taking other nephrotoxic agents. Adverse effects are more common in patients simultaneously taking antiretroviral drugs. The drug is oncogenic in animals. Topical cidofovir (not commercially available) causes local irritation and ulceration, especially in concentrations of 3% or higher.

Resistance – Ganciclovir-resistant CMV isolates may be cross-resistant to cidofovir. Acyclovir-resistant HSV or VZV frequently are susceptible to cidofovir.

FOMIVIRSEN (*Vitravene*) — Fomivirsen, an antisense oligonucleotide, is FDA-approved for intravitreal treatment of CMV retinitis in HIV-infected patients who cannot tolerate or have not responded to other drugs. The manufacturer recommends not giving fomivirsen to patients who have been treated with cidofovir in the previous 2 to 4 weeks because of increased risk of ocular inflammation. The most commonly reported adverse effects include iritis, vitritis, increased intraocular pressure and vision changes. *In vivo* resistance has not been observed (CM Perry and JA Balfour, Drugs 1999; 57:375).

DRUGS FOR INFLUENZA

AMANTADINE (*Symmetrel*, and others) and RIMANTADINE (*Flumadine*, and others) — Treatment with oral amantadine or rimantadine begun within 48 hours after the onset of illness decreases the duration of fever and symptoms by about 1 day. Whether these drugs decrease influenza-related complications or are effective in treating severe influen-

za pneumonia is unknown. Neither amantadine nor rimantadine is effective against influenza B virus.

Either amantadine or rimantadine is 70% to 90% effective in preventing influenza A when started before exposure (RB Couch, N Engl J Med 2000; 343:1778). Prophylaxis with amantadine or rimantadine has been used to control institutional influenza outbreaks and to protect high-risk patients immunized after or <2 weeks before an epidemic has begun. The drugs can also be used as prophylaxis for immunodeficient patients who may respond poorly to influenza vaccine, and in unvaccinated persons who are at high risk for influenza or are caring for highrisk patients.

Adverse Effects – Amantadine may cause anorexia, nausea, peripheral edema and, particularly in the elderly, minor CNS effects such as nervousness, anxiety, insomnia, lethargy, difficulty concentrating, and lightheadedness. These effects usually diminish after the first week of use and rapidly disappear after the drug is stopped. Serious CNS effects (confusion, hallucinations, seizures) can occur, especially with old age, renal insufficiency, seizure disorders, concomitant CNS stimulant or anticholinergic drug therapy and underlying psychiatric illness. Amantadine is excreted mainly in urine, and dosage must be reduced for creatinine clearance below 50 mL/min.

Rimantadine has GI adverse effects similar to those of amantadine, but a lower risk of CNS effects. It is extensively metabolized by the liver before renal excretion, so dosage reductions are not needed until the creatinine clearance falls below 10 mL/min.

Pregnancy – Both amantadine and rimantadine are teratogenic in animals and contraindicated during pregnancy.

Drugs for Influenza A and B				
Infection	Drugs	Adult dosage ¹	Cost ²	
Influenza A and B V	ïrus			
treatment	Oseltamivir - Tamiflu	75 mg PO bid x 5d ³	\$73.00	
	Zanamivir – Relenza	10 mg bi x 5d by inhaler ⁴	58.00	
prevention	Oseltamivir - Tamiflu	75 mg PO once/d ³	306.60 ⁵	
	Zanamivir – Relenza	10 mg once/d by inhaler4	290.00 ⁵	
nfluenza A Virus				
treatment	Rimantadine – generic	100 mg PO bid or	16.30	
	Flumadine	200 mg PO 1x/d x 5d ^{6,7}	22.70	
	Amantadine – generic	100 mg PO bid or	7.90	
	Symmetrel	200 mg PO 1x/d x 5d ⁸	13.60	
prevention	Rimantadine – generic	100 mg PO bid or 200 mg PO once/d ⁶	136.92 ⁵	
	Flumadine		190.68 ⁵	
	Amantadine – generic	100 mg PO bid or 200 mg PO once/d ⁸	66.36 ⁵	
	Symmetrel		114.24 ⁵	
after the end of the treatment of infection treatment of infection 2. Based on the lowest 3. Pediatric dose is lowed were a conserved for between doses shou mL/min. See also for 4. Approved for treatme prophylaxis. 5. Cost of prophylaxis i 6. Pediatric dosage of 1 severe hepatic dyst. Not FDA-approved for	outbreak. For post-exposure prophylaxis in the duration is usually 56 (3-56 with an recommended dosage, according to ND imp bid for weight (3-56, 4-56 mg bid for: treatment of children 2-1 yro d age, appr 16 be every other day for prophylaxis and othorte 1. and of children 2-7 yrs old. Taken as two 5 or 6 wks. 9 yrs) is 5 mg/kg/d up to a maximum of 1 00 mg/d is recommended for older nurs nuction or CrCl <10 mL/min. See also for the atment of hildren, bot according to the atment of hildren bot according to the atment of hil	15 to 23 kg, 60 mg bid tor 523 to 40 kg, and 75. owed for prophytaxis in children 213 yso 40 ag. Th d onceld for treatment in patients with CrCl betwee •mg inhalations using Rotadisk Inhaler. Not FDA- 150 mg/d. Children ≥10 yrs old and ≥40 kg can tai ng home residents, for patients ₂ 65 yrs old, and 1	fective. For i resistance). ng bid for e interval en 10-30 upproved for we the adult or patients w oppropriate.	
the adult dosage. Do		ith diminished renal function (creatinine clearance		

Resistance – Influenza A viruses cross-resistant to both amantadine and rimantadine can emerge when either drug is used to treat influenza infection; they only occur rarely in nature. Viruses resistant to amantadine and rimantadine are transmissible from person to person and retain their pathogenicity; up to now, they have remained susceptible to oseltamivir and zanamivir. Resistance to amantadine and rimantadine has occurred in human isolates of avian H5N1 influenza virus (TH Tran et al, N Engl J Med 2004; 350:1179).

OSELTAMIVIR (*Tamiflu*) — This oral neuraminidase inhibitor, started within 36 hours of symptom onset, can decrease the severity and duration of symptoms caused by either influenza A or B in both children and adults and decreases the risk of respiratory complications, antibiotic use and hospitalization (RJ Whitley et al, Pediatr Infect Dis J 2001; 20:127; L Kaiser et al, Arch Intern Med 2003; 163:1667).

Taken prophylactically once daily for 7 days, it appears to be effective in preventing clinical influenza (R Welliver et al, JAMA 2001; 285:748). The indications for prophylaxis with oseltamavir are the same as those for amantadine. Oseltamavir has been effective against some avian strains of influenza in animal studies and is an option for prophylaxis and treatment of H5N1 disease (IA Leneva et al, Antiviral Res 2000; 48:101).

Adverse Effects – Nausea and vomiting can occur. Taking the drug with food decreases the incidence of nausea. In juvenile rats, very high doses of oseltamivir (~250 times the recommended pediatric dose) have been associated with deaths and unexpectedly high concentrations in brain, possibly related to an immature blood-brain barrier. Oseltamivir has been used in infants, but is FDA-approved only for patients 1 year and older (M Kiso et al, Lancet 2004; 364:759).

Resistance – During treatment, resistant variants emerge in about 1% of immunocompetent adults and in about 9% of children. No person-to-person transmission of resistant variants has been documented to date.

ZANAMIVIR (*Relenza*) — Started within 2 days after onset of symptoms, this orally inhaled neuraminidase inhibitor can shorten the duration of illness and may decrease the incidence of lower respiratory complications. It is FDA-approved only for treatment of acute uncomplicated influenza A or B in patients \geq 7 years of age. Once-daily inhaled zanamivir is effective for prophylaxis of influenza (AS Monto et al, J Infect Dis 2002; 186:1582), but is not FDA-approved for this indication. Zanamivir has been effective against some avian strains of influenza in animal studies and is also an option for prophylaxis and treatment of H5N1 disease (IA Leneva et al, Antimicrob Agents Chemother 2001; 45:1216).

Adverse Effects – Nasal and throat discomfort can occur. Bronchospasm, sometimes severe, has been reported uncommonly in patients with reactive airway disease; zanamivir should be avoided in

such patients. It has rarely caused bronchospasm in previously healthy persons with influenza.

Resistance – Zanamivir is active against amantadine/rimantadine-resistant influenza A and some oseltamivir-resistant strains. Zanamivir resistance has been described in an immunocompromised patient.

DRUGS FOR HEPATITIS B AND C

INTERFERON ALFA — Interferon alfa is available as alfacon-1 (*Infergen*), alfa-n3 (*Alferon N*), alfa-2a (*Roferon-A*), alfa-2b (*Intron A*), pegylated alfa-2b (*PEG-Intron* – Med Lett Drugs Ther 2001; 43:54), and pegylated alfa-2a (*Pegasys* – Med Lett Drugs Ther 2003; 45:19).

In about one third of adults and children with chronic **hepatitis B**, treatment with interferon alfa-2b leads to loss of HBeAg, return to normal aminotransferase activity, sustained histological improvement and, in adults, a lower risk of progressive liver disease. However, AIDS patients coinfected with hepatitis B virus (HBV) generally respond poorly to interferon. Hepatitis D (hepatitis delta virus), which occurs only in patients infected with HBV, may respond to treatment with high doses of interferon alfa, but relapse is common.

Peginterferon alfa-2a may be superior to conventional interferon (WG Cooksley et al, J Viral Hepat 2003; 10:298) and has been associated with higher rates of sustained response than lamivudine in patients with HBeAg-negative chronic hepatitis B (P Marcellin et al, N Engl J Med 2004; 351:1206). Peginterferon alfa-2b monotherapy has been effective for patients with HBeAg-positive chronic hepatitis B; addition of lamivudine was not superior to monotherapy (HL Janssen et al, Lancet 2005; 365:123).

Peginterferon plus ribavirin is the treatment of choice for chronic **hepatitis C**; it provides sustained viral responses (SVRs) of 54% to 63%. When used as monotherapy, peginterferons once weekly are more effective than standard interferon 3 times a week, producing SVRs of 30% to 40%. The combination of peginterferon plus ribavirin is more effective than combinations of standard interferons and ribavirin in patients co-infected with HIV and hepatitis C virus (HCV) (FJ Torriani et al, N Engl J Med 2004; 351:438; RT Chung et al, N Engl J Med 2004; 351:451; F Carrat et al, JAMA 2004; 292:2839). In a retrospective study, use of interferon appeared to decrease the risk of hepatocellular carcinoma in patients with chronic HCV infection, especially among patients with sustained responses (Y Shiratori et al, Ann Intern Med 2005; 142:105; H Yoshida et al, Ann Intern Med 1999; 131:174).

In one study, interferon alfa-2b treatment of acute hepatitis C prevented chronic infection in most patients (E Jaeckel et al, N Engl J Med 2001; 345:1452).

Adverse Effects – Intramuscular or subcutaneous injection of interferon is commonly associated with an influenza-like syndrome, especially during the first week of therapy. High-dose or chronic therapy may be limited by bone marrow suppression, profound fatigue, myalgia, weight loss, rash, cough, increased susceptibility to bacterial infections, psychiatric syndromes including depression, anxiety, psychosis, mania, agitation and neurocognitive impairment, increased aminotransferase activity, alopecia, hypo- or hyperthyroidism, tinnitus, reversible hearing loss, auto-antibody formation, retinopathy, pneumonitis and possibly cardiotoxicity. Injection-site reactions and dose-related neutropenia and thrombocytopenia have been more common with pegylated interferon. Autoimmune chronic hepatitis and other autoimmune diseases like thyroiditis may be induced or exacerbated by treatment with interferon. Granulocyte-colony stimulating factors and erythropoietin (*Procrit*, *Epogen*) have been used to treat interferon-induced bone marrow suppression. Depression caused by interferon alfa might be treatable with an antidepressant without stopping the interferon.

RIBAVIRIN (*Copegus, Rebetol*, and others) — Combination treatment of **HCV** with peginterferon alfa and oral ribavirin has produced higher sustained response rates than peginterferon alone and is now considered the regimen of choice for chronic HCV. Patients relapsing after interferon monotherapy may still respond to the combination. Ribavirin is not effective as monotherapy for HCV.

Adverse Effects – Systemic ribavirin has been associated with hemolytic anemia. Oral ribavirin plus interferon appears to cause a higher incidence of cough, pruritus and rash than interferon alone. Acute deterioration of respiratory function has been reported with ribavirin aerosol in infants and in adults with bronchospastic lung disease.

Pregnancy – Ribavirin is teratogenic and embryotoxic in animals, and is contraindicated in pregnancy. Pregnant women should not directly care for patients receiving ribavirin aerosol. Patients exposed to the drug should not conceive children during or for 6 months after treatment.

LAMIVUDINE (3TC; *Epivir HBV*) — This oral antiretroviral nucleoside analog used to treat HIV is also FDA-approved for treatment of chronic HBV infection. A trial in Asian patients with chronic HBV infection treated for 2 years found that 52% taking lamivudine 100 mg daily had sustained suppression of HBV DNA, 50% had normalization of aminotransferase activity and seroconversion to anti-HBeAg occurred in 27% (YF Liaw et al, Gastroenterology 2000; 119:172). In patients with cirrhosis or advanced fibrosis, treatment for up to 42 months reduces the risk of clinical progression and hepatocellular carcinoma development by about half

	Drugs for Hepatitis B and C				
Infection	Drugs	Adult dosage ¹	Cost ²		
Hepatitis B Virus (HBV))				
Chronic hepatitis*	Lamivudine ³ – <i>Epivir HBV</i> Interferon alfa-2b – <i>Intron A</i>	100 mg PO 1x/d x 1-3 yrs ⁴ 5 million units/d or 10 million	\$2,452.80		
	0	units 3x/wk SC or IM x 4 mos ⁵	7,292.40		
	Peginterferon alfa-2a ⁶ – Pegasy	s180 mcg once/wk SC x 48 wks	18,712.80		
	Adefovir – Hepsera	10 mg PO 1x/d x 1-3 yrs ⁴	6,486.05		
Hepatitis C Virus (HCV)					
Chronic hepatitis	Peginterferon alfa-2b – PEG-Intron	1.5 mcg/kg once/wk SC x 48 wks ⁷	19,043.04		
	plus ribavirin – generic	800-1200 mg PO/d x 48 wks7	9,932.16		
	Rebetol	-	13,749.12		
	or Peginterferon alfa-2a - Pegasys	180 mcg once/wk SC x 48 wks7	18,712.80		
	plus ribavirin - generic	800-1200 mg PO/d x 48 wks ⁷	9,932.16		
	Copegus	-	9,354.24		
Acute hepatitis	Interferon alfa-2b ⁶ – Intron A	5 million units/d x 3 wks,	1,875.32		
		then 3x/wk x 20 wks	4,688.30		

 Pediatric dosage is 3 million units/m² 3x/wk SČ for first wk, then 6 million units/m² (maximum 10 million units) 3x/wk for 16 to 24 wks.

6. Not approved by the FDA for this indication. 7. Shorter courses (24 rather than 48 wks) and lower ribavirin doses (800 rather than 1000 or 1200 mg/d) appear to be effective for HCV genotypes 2 and 3 but not genotype 1, which is the most common in North America (SJ Hadziyannis et al, Ann Intern Med 2004; 140:340.

(YF Liaw et al, N Engl J Med 2004; 351:1521). Lamivudine is also active in chronically infected children aged ≥ 2 years, with 55% showing sustained normalization of aminotransferase levels, 61% DNA suppression, and 22% anti-HBe seroconversion at 1 year of therapy (MM Jonas et al, N Engl J Med 2002; 346:1706). Lamivudine appears to reduce the risk of HBV reinfection in liver transplant recipients. Combination therapy with lamivudine and peginterferon alfa-2b, but not standard interferon alfa, may lead to higher response rates than lamivudine monotherapy (HL Chan et al, Ann Intern Med 2005; 142:240). However, in one study the combination of peginterferon alfa-2b and lamivudine was no better than peginterferon alfa-2b alone (HL Janssen et al, Lancet 2005; 365:123).

Adverse Effects – Lamivudine is generally well tolerated. Headache, nausea and dizziness are rare. Pancreatitis has been reported in adults and children coinfected with HIV.

Resistance – Resistance emerges in 14% to 32% of HBV-infected patients receiving lamivudine for one year and increases at 5 years to 69% (EB Keeffe et al, Clin Gastroenterol Hepatol 2004; 2:87). Resistant variants have been associated with hepatitis flares (YF Liaw et al, Hepatology 1999; 30:567) and progressive liver disease in both chronic hepatitis patients and liver transplant recipients.

ADEFOVIR DIPIVOXIL (Hepsera) — This phosphonate nucleoside analog, administered as the oral prodrug, inhibits replication of HBV, including variants resistant to lamivudine (Med Lett Drugs Ther 2002; 44:105). Adefovir treatment of HBeAg-positive or -negative chronic hepatitis B is associated with marked reductions in HBV DNA levels, aminotransferase normalization in 48% to 72% of patients, and histologic improvements in 53% to 64% at 48 weeks (SJ Hadziyannis et al, N Engl J Med 2003; 348;800; P Marcellin et al, N Engl J Med 2003; 348:808). More prolonged therapy results in higher rates of response; anti-HBeAg seroconversion occurs in 23% by 72 weeks. The antiviral effects of adefovir are similar in lamivudine-susceptible and -resistant HBV infections (MG Peters et al, Gastroenterology 2004; 126:91). Some experts recommend adefovir over lamivudine for long-term treatment of HBeAg-negative or cirrhotic patients because of the high risk of emergence of lamivudine resistance (EB Keeffe et al, Clin Gastroenterol Hepatol 2004; 2:87). Combination studies with other anti-HBV drugs are in progress.

Adverse Effects – Doses of adefovir used for HBV are generally well tolerated but may be associated with asthenia, headache, diarrhea and abdominal pain. Higher than recommended doses (30-60 mg/d) and preexisting renal impairment are risk factors for azotemia and renal tubular dysfunction. Hepatitis flares may occur after adefovir is stopped.

Resistance – Adefovir-resistant variants emerge at a low frequency (3.9% of patients after 3 years of use) and have been associated with a

rebound in HBV DNA levels (P Angus et al, Gastroenterology 2003; 125:292); these variants may remain susceptible to lamivudine.

ENTECAVIR (*Baraclude*) — A carbocyclic analogue of guanosine, entecavir is a new drug for treatment of chronic hepatitis B. [Since this article was published, *The Medical Letter* has reviewed entecavir (*Baraclude*). See page 177.]

DRUGS FOR PAPILLOMAVIRUS, RESPIRATORY SYNCYTIAL VIRUS, AND OTHER VIRUSES

IMIQUIMOD (*Aldara*) — This immunomodulator is FDA-approved for topical treatment of external and perianal genital warts, which are caused by papillomavirus (Med Lett Drugs Ther 2004; 46:42). Gradual clearance of warts occurs in about 50% of patients over an average of 8 to 10 weeks. Recurrences are less common than after ablative therapies. Imiquimod is also effective for a high percentage of patients with too many actinic keratoses to be treated with liquid nitrogen.

Adverse Effects – Application site reactions (irritation, pruritus, flaking, erosion) are generally mild to moderate in intensity and resolve within 2 weeks of cessation. Pigment changes may persist. Systemic adverse effects including fatigue and influenza-like illness have been reported (Med Lett Drugs Ther 2004; 46:92).

RIBAVIRIN — A synthetic nucleoside, ribavirin used as an aerosol (*Virazole*) may decrease morbidity in some children hospitalized with respiratory syncytial virus (RSV) bronchiolitis and pneumonia (American Academy of Pediatrics Committee on Infectious Diseases eds, *Report of the Committee on Infectious Diseases* 26th ed, Evanston, Ill: American Academy of Pediatrics, 2003, page 523), but because of its

Drugs for Papillomavirus and RSV					
Infection	Drugs	Adult dosage	Cost ¹		
Papillomavirus - Anogenital warts					
	Imiquimod – Aldara	3x/wk (wash off 6-10 hrs after application) x 16 wks max	\$181.44 ²		
	Interferon alfa-2b - Intron A	1 million units intralesionally 3x/wk x 3 wks max	911.55 ³		
Respiratory Syncytial V	'irus ⁴				
	Ribavirin - Virazole	aerosol treatment 12-18 hrs/d x 3-7d	⁵ 4,248.27 ⁶		
Hibavinn – Virazole aerosol treatment 12-18 hrs/d x 3-7d ⁹ 4,248.27 ⁹ 1. According to NDCHeath (January 31, 2005), 2. Oost of a box containing 12 250-mg packets. 3. Cost to treat one lesion. 4. Immunoprophylaxis with IM palivizumata (Synagis – Medimmune), a monoclonal antibody given by monthly injection, can prevent liness in children -24 mos old with choroic lung disease, in infants who were premature (-25 wkg gestation), and in some children -24 mos old with choroic lung disease. (Committee on Infectious Diseases in LK Pickening eds. 2003, Page 523. Med Lett Drugs Ther 2001; 43:13). 5. Requires registratory therapy monitoring for administration and a special aerosol-generating device (Spag-2 – Viratek) that delivers an aerosol containing 190 mog/L at arte of 12.5 L/min. 6. Cost of 3 dws's treatment using one 6-q vial(L) based on AVP listings in <i>Red Book</i> 2004.					

potential adverse effects it is not generally recommended for such use. Pregnant women should not directly care for patients receiving ribavirin aerosol. (For adverse effects and use in pregnancy, see page 172.)

Other viruses – IV ribavirin appears to decrease mortality in Lassa fever and in hantavirus hemorrhagic fever with renal syndrome. *In vitro*, high concentrations inhibit West Nile virus, but clinical data are lacking. There are case reports of systemic ribavirin use with some success in cases of LaCrosse encephalitis, Nipah virus encephalitis, and Congo-Crimean hemorrhagic fever, but it is ineffective in SARS and hantavirus cardiopulmonary syndrome (GJ Mertz et al, Clin Infect Dis 2004; 39:1307).

CIDOFOVIR — IV and topical cidofovir (3% cream once daily; not commercially available) have been reported to produce resolution of molluscum contagiosum in immunosuppressed patients (E De Clercq, Clin Microbiol Rev 2003; 16:569). Cidofovir has also been used for adenovirus infection in allogeneic stem cell transplant recipients (P Ljungman et al, Bone Marrow Transplant 2003; 31:481). *In vitro*, cidofovir is active against vaccinia, variola, and other pox viruses and has been effective in animal models of lethal infection (M Bray and CJ Roy, J Antimicrob Chemother 2004; 54:1). (For adverse effects, see page 166.)

Entecavir (Baraclude) for Chronic Hepatitis B

Originally published in the Medical Letter - June 2005; 47:47

Entecavir (*Baraclude* – Bristol-Myers Squibb), a nucleoside analog, has been approved by the FDA for treatment of adults with active chronic hepatitis B virus (HBV) infection.

DRUGS FOR HEPATITIS B — Chronic HBV infection is currently treated with interferon alfa, lamivudine or adefovir.¹ Lamivudine is much better tolerated than interferon and much less expensive, but resistance to the drug occurs in about 15%-30% of patients after one year and in about 50% after 3 years.² Resistance has been less of a problem with adefovir, which is active against lamivudine-resistant strains, but can cause nephrotoxicity.³

PHARMACOLOGY	,
Mechanism of action	Inhibition of HBV polymerase
Formulation	0.5- and 1-mg film-coated tablets and oral solution 0.05 mg/mL
Tmax	0.5-1.5 hour
Metabolism	Minimal
Excretion	Renal (62%-73% excreted unchanged)

CLINICAL STUDIES — FDA approval was based on 3 unpublished randomized, double-blind trials (described in the package insert) comparing treatment with entecavir to lamivudine in adults with chronic HBV. Some patients had previously been treated with interferon alfa. These studies are summarized in the table on page 178. No studies comparing entecavir to adefovir have been published. HBV isolates from lamivudine-refractory patients failing entecavir therapy remained susceptible to adefovir *in vitro*. Unlike lamivudine and adefovir, entecavir has no activity against HIV.

ADVERSE EFFECTS — Lactic acidosis and severe hepatomegaly with steatosis have been reported with use of other nucleoside analogs. The most common adverse effects of entecavir have been headache,

Entecavir (Baraclude) for Chronic Hepatitis B

SOME CLINICAL STUDIES OF ENTECAVIB

Population (N)	Regimen (52 wks)	Patients with Histologic Improvement ¹	Patients with Undetectable HBV DNA ²	Patients with ALT Normalization ³
HBeAg-positive,	Entecavir 0.5 mg/d	72%	67%	69%
nucleoside-naïve (709)4	Lamivudine 100 mg/d	62%	36%	60%
HBeAg-negative,	Entecavir 0.5 mg/d	70%	90%	78%
HBeAb-positive, nucleoside-naïve (638)	Lamivudine 100 mg/d	66%	72%	71%
Lamuvidine-refractory (286)	Entecavir 1 mg/d	55%	19%	61%
	Lamivudine 100 mg/d	28%	1%	15%
 Histologic improvement = ≥ 2-point r Undetectable HBV DNA = <300 cop ALT permaination = <1 × upper lim 		y Score with no worsening in K	nodell Fibrosis Score at w	eek 48.

ALT normalization = ≤ 1 x upper limit of normal.
 21% of entecavir-treated patients seroconverted by week 48; 82% of these patients had a sustained response at 24 weeks post-treatment.

Drug	Dosage	Cost ¹		
Adefovir - Hepsera (Gilead)	10 mg once/d	\$552.60		
Entecavir – Baraclude	0.5 mg once/d ²	714.60		
(Bristol-Myers Squibb)				
Lamivudine – Epivir-HBV (GlaxoSmithKline)	100 mg once/d	201.90		

ORAL DRUGS FOR HEPATITIS B

fatigue, dizziness and nausea. Severe acute exacerbations of HBV have been reported after discontinuation of anti-hepatitis B drugs, including entecavir. Entecavir is not a substrate, inhibitor or inducer of the cytochrome P450 enzyme system. It is carcinogenic in rodents.

CONCLUSION - Entecavir (Baraclude) taken orally once a day as monotherapy appears to be superior to lamivudine for patients with chronic HBV infection, but susceptibility to entecavir may be reduced in patients refractory to lamivudine. How it compares with adefovir remains to be established, but HBV isolates from lamivudine-refractory patients failing entecavir therapy have remained susceptible to adefovir in vitro.

- 1 Drugs for non-HIV viral infections. Treat Guidel Med Lett 2005; 3:23.
- 2 GV Papatheodoridis et al. Nucleoside analogues for chronic hepatitis B: antiviral efficacy and viral resistance. Am J Gastroenterol 2002; 97:1618.
- 3. Adefovir (Hepsera) for chronic hepatitis B infection. Med Lett Drugs Ther 2002; 44:105.

Drugs for Parasitic Infections

DRUGS FOR Parasitic Infections

Original publication date - August 2004

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections. The brand names and manufacturers of the drugs are listed on page 190.

	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Acanthamoeba keratiti:	s		
Drug of choice:	See footnote 1		
AMEBIASIS (Entamoel	oa histolvtica)		
asymptomatic			
Drug of choice:	lodoquinol	650 mg tid x 20d	30-40 mg/kg/d (max. 2g) in 3 doses x 20d
OR	Paromomycin	25-35 mg/kg/d in 3 doses x 7d	25-35 mg/kg/d in 3 doses x 7d
Alternative:	Diloxanide furoate2*	500 mg tid x 10d	20 mg/kg/d in 3 doses x 10d
mild to moderate inte	astinal disease ³		0 0 0
Drug of choice:4	Metronidazole	500-750 mg tid x 7-10d	35-50 mg/kg/d in 3 doses x 7-10d
OB		2 g once daily x 3d	50 mg/kg/d (max. 2g) in 1 dose x 3d
	extraintestinal disease		oo nigrigra (max. 2g) in r accor x ca
Drug of choice:	Metronidazole	750 mg tid x 7-10d	35-50 mg/kg/d in 3 doses x 7-10d
OB	Tinidazole ⁵	2 g once daily x 5d	50 mg/kg/d (max. 2 g) x 5d
			55
	CEPHALITIS, primary a	no granulomatous	
Naegleria	Annahasiain D67	1. Carefue (die Ordense v. Od. Here	1. C. martha (d. in O. danaa v. Od. Ahan
Drug of choice:	Amphotericin B6,7	1.5 mg/kg/d in 2 doses x 3d, then	1.5 mg/kg/d in 2 doses x 3d, then
		1 mg/kg/d x 6d	1 mg/kg/d x 6d
Acanthamoeba			
Drug of choice:	See footnote 8		
 Availability problems. Set 	e table on page 190.	urrent topical use of 0.1% propamidine isethional	e (Brolene) plus neomycin-polymyxin B-gramicidin oph-
Availability problems. So: For treatment of knailitis dime (Desmotive) has been dime (Desmotive) has been used successfully in a large warenue Pharmany, San Ja cessfull (K Kilagawa et al. (800-247-9767: www.pano (Treatment should be follow Nilazovanide is TDA-apper (Med Leit Drugs Ther 200 (Med Leit Drugs Ther 200 (Med Leit Drugs Ther 200 A nitro-imidance) similar is should be laken with fo with cherry syrue (Marco drug, is also used outsidd	table on page 190. aused by Acanthamoeba, conc successful GS. Hargene et al., successful GS. Hargene et al., successful GS. Hargene et al., per sumber of patients (GTabin), per sumber of patients (GTabin), per Johnson 2003; 47:01 as a service commerciality, but as a service commerciality, but as a service and a service of the service of the service of a second the service of the service of the second the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the service of the se	Ophthalmology 1999: 106/952), In some Europea B30]. In addition, Oxi25 Ipolaia polyheaxemethyle et al., Cornes 2001: 20737; YS Wynerbeek et al., Corne encome Tecore Ministration of drithorheadmin, na a). Can be compounded by Panorama Compoundiny al Center Hmarmay, New Haver, CT (20-38-884 a). Can be compounded by Panorama Compoundiny al Center Hmarmay, New Haver, CT (20-38-884 a). Can be compounded by Panorama Compounding al Center Hmarmay, New Haver, CT (20-38-884 a). Can be compounded by Charlos Compounding and the compounded by Charlos Compounded and the compounded by Charlos Compounded as recently approved by the FDA and appears to compounded by the FDA and appears to compounded by the Charlos Compounded by the Charlos Labies and Informations and the Charlos Labies and Informative and an and compounded by the Charlos Charlos Compounded by the Charlos Compounded by the Charlos C	n countries, progamidine is not available and hexami- te bigunide (PHMB) and/or chichrosadine has been rinea 2000; 19:464). PHMB is available from Leiter's Park amyoin (pimaricin) and debridement also has been suc- g Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 6: www.medcenterpharmacy.com).

Drugs for Parasitic Infections

INFECTION		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
AMEBIC MENING Balamuthia mai		EPHALITIS (continued) is		
Drug of choice:		See footnote 9		
Sappinia diploi	dea			
Drug of choice:		See footnote 10		
	caninu	m (Eosinophilic enterod		
Drug of choice:		Albendazole ⁷	400 mg once	400 mg once
	OR	Mebendazole	100 mg bid x 3d	100 mg bid x 3d
	OR	Pyrantel pamoate ⁷	11 mg/kg (max. 1g) x 3d	11 mg/kg (max. 1g) x 3d
Anavlaatama du		Endoscopic removal e, see HOOKWORM		
			onensis, Angiostrongylus costaricensis)	
Drug of choice:	LIAOI	See footnote 11	nenaia, Angioarongyida coatancenaia)	
ANISAKIASIS (A	nisakis			
Treatment of choi		Surgical or endoscopi	c removal	
		mbricoides, roundworm		
Drug of choice:		Albendazole7	, 400 mg once	400 mg once
	OR	Mebendazole	100 mg bid x 3d or 500 mg once	100 mg bid x 3d or 500 mg once
	OR	Ivermectin ⁷	150-200 mcg/kg once	150-200 mcg/kg once
BABESIOSIS (Ba				
Drugs of choice:1	3	Clindamycin7	1.2 g bid IV or 600 mg tid PO	20-40 mg/kg/d PO in 3 doses x
			x 7-10d	7-10d
		plus quinine ⁷	650 mg tid PO x 7-10d	25 mg/kg/d PO in 3 doses x 7-10d
	OR	Atovaquone ⁷	750 mg bid x 7-10d	20 mg/kg bid x 7-10d
		plus azithromycin7	600 mg daily x 7-10d	12 mg/kg daily x 7-10d
			GOENCEPHALITIS, PRIMARY	
BALANTIDIASIS	(Balani	Tetracvcline ^{7, 14}	500 mg gid x 10d	
Drug of choice:				40 mg/kg/d (max. 2 g) in 4 doses x 10d
Alternatives:		Metronidazole7	750 mg tid x 5d	35-50 mg/kg/d in 3 doses x 5d
		lodoquinol ⁷	650 mg tid x 20d	40 mg/kg/d in 3 doses x 20d
Drug of choice:	515 (D	aylisascaris procyonis) See footnote 15		
BLASTOCYSTIS	homin			
Drug of choice:		See footnote 16		
	(Capilla	aria philippinensis)		
Drug of choice:	(Oupine	Mebendazole ⁷	200 mg bid x 20d	200 mg bid x 20d
Alternatives:		Albendazole ⁷	400 mg daily x 10d	400 mg daily x 10d
	see TE	RYPANOSOMIASIS	too ng dany x rod	too nig daily x rod
		e FLUKE infection		
		table on page 190.		
treated with flucy gical resection of A free-living amel tosine combined Most patients hav toms from increa patients have wo	tosine, pe the CNS ba not pro with surg /e a self-l sed intra rsened w	entamidine, fluconazole and su lesion (TR Deetz et al, Clin Inf eviously known to be pathoge gical resection of the CNS lesi imited course and recover cor cranial pressure (V Lo Re III ar tiht herapy (TJ Slom et al, N Er	Ifadiazine plus either azithromycin or clarithromyci ec Dis 2003: 37:1304: 5 Jung et al, Arch Pathol Lai nic to humans. It has been successfully treated with on (BB Gelman et al, J Neuropathol Exp Neurol 20 mgletely. Analgesics, conticosteroids and careful re of SJ Gluckman, Am J Med 2003: 114:217). No ant ng J Med 2002: 346:668). In one report, however, n	azithromycin, IV pentamidine, itraconazole and flucy
	et al, Gas	C Tsai et al, Am J Med 2001; 1 troenterol Hepatol 2003; 26:34		sis with albendazole has been reported (DA Moore e
 Exchange transfu who were not sev ated (PJ Krause e 	sion has /erely ill, et al, N Er	combination therapy with ato Igl J Med 2000; 343:1454).	vaquone and azithromycin was as effective as cline	atcher et al, Clin Infect Dis 2001; 32:1117). In patients damycin and quinine and may have been better tole
 No drugs have be clinical disease ar 50:1153; PJ Gavin available. Steroid tion therapy to de 16. Clinical significan 	een demo nd is reco and ST S therapy stroy the ice of the	ommended for children with k Shulman, Pediatr Infect Dis 200 may be helpful, especially in e intraretinal larvae. se organisms is controversial;	ndazole 25 mg/kg/d x 20d started as soon as possil nown exposure (ingestion of racoon stool or conta 35 :22:651). Mebendazole, thiabendazole, levamisol aye and CNS infections. Ocular baylisascariasis has metronidazole 750 mg tid x 10d, iodoquinol 650 n	ble (up to 3d after possible infection) might prevent minated soli) (MMWR Morb Mortal Wkly Rep 2002; e or ivermedin could be trief all albendazole were no been treated successfully using laser photocoagula- ng tid x 20d or trimethoprim-sulfamethoxazole 1 DS
	sistance i			63; UZ Ok et al, Am J Gastroenterol 1999; 94:3245). has been effective in children (E Diaz et al, Am J Tro

RYPTOSPORIDIOSIS (DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Non-HIV infected	Cryptosporidium)		
Drug of choice:	Nitazoxanide4	500 mg bid x 3d ⁷	1-3yrs: 100 mg bid x 3d
		9 · · · ·	4-11yrs: 200 mg bid x 3d
HIV infected Drug of choice:	See footnote 17		
UTANEOUS LARVA MI	GRANS (creeping erup	tion, dog and cat hookworm)	
Drug of choice:18	Albendazole7	400 mg daily x 3d	400 mg daily x 3d
OR	Ivermectin ⁷	200 mcg/kg daily x 1-2d	200 mcg/kg daily x 1-2d
Alternative:	Thiabendazole	Topically	Topically
YCLOSPORIASIS (Cyc	lospora cayetanensis)		
Drug of choice:19	Trimethoprim-	TMP 160 mg/SMX	TMP 5 mg/kg, SMX
•	sulfamethoxazole7	800 mg (1 DS tab) bid x 7-10d	25 mg/kg bid x 7-10d
YSTICERCOSIS, see T/	APEWORM infection	• • •	
DENTAMOEBA fragilis i			
Drug of choice:	lodoquinol	650 mg tid x 20d	30-40 mg/kg/d (max. 2g) in 3 doses x 20d
OB	Paromomvcin7	25-35 ma/ka/d in 3 doses x 7d	25-35 ma/ka/d in 3 doses x 7d
	Tetracycline ^{7,14}	500 mg gid x 10d	40 mg/kg/d (max. 2g) in 4 doses x 10d
	Metronidazole	500-750 mg tid x 10d	20-40 mg/kg/d in 3 doses x 10d
Diphyllobothrium latum,			
RACUNCULUS medine			
Drug of choice:	See footnote 21		
chinococcus, see TAPE			
ntamoeba histolytica,			
NTEROBIUS vermicular			
Drug of choice:22	Pyrantel parnoate	11 mg/kg base once (max. 1 g); repeat in 2wks	11 mg/kg base once (max. 1 g); repeat in 2wks
OR	Mebendazole	100 mg once: repeat in 2wks	100 mg once: repeat in 2wks
OB	Albendazole7	400 mg once; repeat in 2wks	400 mg once; repeat in 2wks
ILARIASIS ²³			··· • • • • • • • • • • • • •
Tasciola hepatica, see F TLARIASIS ²³ Wuchereria bancrofti, E Drug of choice: ²⁴ Loa loa		<i>timori</i> 6 mg/kg in 3 doses x 14d ²⁵	6 mg/kg in 3 doses x 14d ²⁵
ILARIASIS ²³ Wuchereria bancrofti, B Drug of choice: ²⁴ Loa loa Drug of choice: ²⁶ Availability problems. See t	Brugia malayi, Brugia Diethylcarbamazine* Diethylcarbamazine table on page 190.		6 mg/kg in 3 doses x 14d ²⁵ 6 mg/kg in 3 doses x 14d ²⁵

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
FILARIASIS (continued)2	3		
Mansonella ozzardi			
Drug of choice:24	See footnote 27		
Mansonella perstans			
Drug of choice:24	Albendazole ⁷	400 mg bid x 10d	400 mg bid x 10d
OR	Mebendazole ⁷	100 mg bid x 30d	100 mg bid x 30d
Mansonella streptocer			
Drug of choice:24,28	Diethylcarba-	6 mg/kg/d x 14d	6 mg/kg/d x 14d
	mazine*		
	Ivermectin ⁷	150 mcg/kg once	150 mcg/kg once
Tropical Pulmonary Eo		a	
Drug of choice:	Diethylcarba- mazine*	6 mg/kg/d in 3 doses x 12-21d	6 mg/kg/d in 3 doses x 12-21d
Onchocerca volvulus (
Drug of choice:	Ivermectin ³⁰	150 mcg/kg once, repeated every	150 mcg/kg once, repeated every
Drug of choice.	Ivermecunas	6-12mos until asymptomatic	6-12mos until asymptomatic
LUKE, hermaphroditic, i	infaction	0=12mos unui asymptomatic	6-12mos unui asymptomatic
Clonorchis sinensis (C			
Drug of choice:	Praziguantel	75 mg/kg/d in 3 doses x 1d	75 mg/kg/d in 3 doses x 1d
OR	Albendazole ⁷	10 mg/kg x 7d	10 mg/kg x 7d
Fasciola hepatica (she		To hig/kg x 7u	TO HIG/KG X 70
Drug of choice:31	Triclabendazole*	10 mg/kg once or twice32	10 mg/kg once or twice ³²
Alternative:	Bithionol*	30-50 mg/kg on alternate days	
Alternative:	Bithionol		30-50 mg/kg on alternate days
		x 10-15 doses	x 10-15 doses
		hyes, Metagonimus yokogawai (intestina	
Drug of choice:	Praziquantel ⁷	75 mg/kg/d in 3 doses x 1d	75 mg/kg/d in 3 doses x 1d
Metorchis conjunctus	Praziguantel ⁷		75 4 41 0 1 41
Drug of choice:		75 mg/kg/d in 3 doses x 1d	75 mg/kg/d in 3 doses x 1d
Nanophyetus salminco		00	
Drug of choice:	Praziquantel ⁷	60 mg/kg/d in 3 doses x 1d	60 mg/kg/d in 3 doses x 1d
Opisthorchis viverrini			
Drug of choice:	Praziquantel	75 mg/kg/d in 3 doses x 1d	75 mg/kg/d in 3 doses x 1d
Paragonimus westerm			
Drug of choice:	Praziquantel ⁷	75 mg/kg/d in 3 doses x 2d	75 mg/kg/d in 3 doses x 2d
Alternative: ³⁴	Bithionol*	30-50 mg/kg on alternate days	30-50 mg/kg on alternate days
		x 10-15 doses	x 10-15 doses
GIARDIASIS (Giardia du			
Drug of choice:	Metronidazole7	250 mg tid x 5d	15 mg/kg/d in 3 doses x 5d
	Nitazoxanide4	500 mg bid x 3d	1-3yrs: 100 mg q12h x 3d
			4-11yrs: 200 mg q12h x 3d
	Tinidazole ⁵	2 g once	50 mg/kg once (max. 2 g)
Alternatives:35	Paromomycin7,36	25-35 mg/kg/d in 3 doses x 7d	25-35 mg/kg/d in 3 doses x 7d
	Furazolidone	100 mg qid x 7-10d	6 mg/kg/d in 4 doses x 7-10d
	Quinacrine ²	100 mg tid x 5d	2 mg/kg tid x 5d (max. 300 mg/d)
GNATHOSTOMIASIS (Gr			
Treatment of choice:37	Albendazole7	400 mg bid x 21d	400 mg bid x 21d
OR	Ivermectin ⁷	200 mcg/kg/d x 2d	200 mcg/kg/d x 2d
±	Surgical removal		
GONGYLONEMIASIS (G	ongylonema sp.) ³⁸		
Treatment of choice:	Surgical removal		
OR	Albendazole ⁷	10 mg/kg/d x 3d	10 mg/kg/d x 3d
* Availability problems. See table	e on nage 190		
27. Diethylcarbamazine has no ef	fect. Ivermectin 200 mcg/kg	once, has been effective.	
		gainst both adult worms and microfilariae. Ivermectin is on	ly active against microfilariae.
 Relapse occurs and can be tre Appual treatment with increase 	eated with diethylcarbamazi	ne. It blindness due to ocular onchocerciasis (D Mabey et al, C	Ophtholegology 1006: 102:1001)
Diethylcarbamazine should no			philialihology 1990, 103.1001).
1. Unlike infections with other flu	kes, Fasciola hepatica infec	tions may not respond to praziguantel. Triclabendazole (Eg	aten - Novartis) may be safe and effective
		1; 33:1). It is available from Victoria Pharmacy, Zurich, Swit	
32) and should be given with	food for better absorption	A single study has found that nitazoxanide has limited	efficacy for treating fascioliasis in adults and childre
(L Favennec et al, Aliment Pha 32. J Richter et al, Curr Treat Opti	armacol Ther 2003; 17:265).		
 J Hichter et al, Curr Treat Opti 33. JD MacLean et al, Lancet 199 			
 Triclabendazole may be effecti 	ive in a dosage of 5 mg/kg	once/d x 3d or 10 mg/kg bid x 1d (M Calvopiña et al, Trans	R Soc Trop Med Hyg 1998; 92:566). See foot-
note 31 for availability.			
Albendazole 400 mg daily x 5	d alone or in combination wi	th metronidazole may also be effective (A Hall and Q Nah	ar, Trans R Soc Trop Med Hyg 1993; 87:84; AK
		t al, Clin Ter 1995; 146:761). Combination treatment with st	
given for 3wks has been effect	tive for a small number of rel	ractory infections (TE Nash et al, Clin Infect Dis 2001; 33:2 to metronidazole and albendazole (P Abboud et al, Clin In	 In one study, nitazoxanide was used suc- fact Die 2001; 32:1792)
 Not absorbed; may be useful f 			

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INFECTION		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
HOOKWORM infec	tion	(Ancylostoma duodena	ale, Necator americanus)	
Drug of choice:		Albendazole ⁷	400 mg once	400 mg once
		Mebendazole	100 mg bid x 3d or 500 mg once	100 mg bid x 3d or 500 mg once
		Pyrantel pamoate7	11 mg/kg (max. 1g) x 3d	11 mg/kg (max. 1g) x 3d
Hydatid cyst, see				
		TAPEWORM infection		
SOSPORIASIS (Is	ospor		THE 444 (014) 444 (1 10 1 1)	
Drug of choice:39		Trimethoprim- sulfamethoxazole ⁷	TMP 160 mg/SMX 800 mg (1 DS tab) bid x 10d	TMP 5 mg/kg, SMX 25 mg/kg bid x 10d
LEISHMANIA infec	ction			
Visceral ⁴⁰ Drugs of choice:		Sodium stibo-	20 mg Sb/kg/d IV or IM x 28d ⁴¹	20 mg Sb/kg/d IV or IM x 28d ⁴¹
	OR	gluconate* Meglumine antimonate*	20 mg Sb/kg/d IV or IM x 28d ⁴¹	20 mg Sb/kg/d IV or IM x 28d ⁴¹
	0.0	Amphotericin B ⁷	0.5-1 mg/kg IV daily or every	0.5-1 mg/kg IV daily or every
	UR	Amphotencin B'	u.5-1 mg/kg IV daily or every second day for up to 8wks	second day for up to 8wks
	OR	Liposomal amphotericin B42	3 mg/kg/d IV (d 1-5) and 3 mg/kg/d d 14 and 2143	3 mg/kg/d IV (d 1-5) and 3 mg/kg/d d 14 and 2143
Alternative:44		Pentamidine ⁷	4 mg/kg IV or IM daily or every	4 mg/kg IV or IM daily or every
Cutaneous45			second day for 15-30 doses	second day for 15-30 doses
Drugs of choice:		Sodium stibo- gluconate*	20 mg Sb/kg/d IV or IM x 20d ⁴¹	20 mg Sb/kg/d IV or IM x 20d ⁴¹
	OR	Meglumine antimonate*	20 mg Sb/kg/d IV or IM x 20d ⁴¹	20 mg Sb/kg/d IV or IM x 20d ⁴¹
Alternatives:46		Pentamidine ⁷	2-3 mg/kg IV or IM daily or every	2-3 mg/kg IV or IM daily or every
/ atomativoo.		1 ontamidino	second day x 4-7 doses ⁴⁷	second day x 4-7 doses47
	OB	Paromomycin7,48	Topically 2x/d x 10-20d	Topically 2x/d x 10-20d
Mucosal ⁴⁹		,,	.,,	
Drugs of choice:		Sodium stibo- gluconate*	20 mg Sb/kg/d IV or IM x 28d ⁴¹	20 mg Sb/kg/d IV or IM x 28d ⁴¹
	OR	Meglumine antimonate*	20 mg Sb/kg/d IV or IM x 28d41	20 mg Sb/kg/d IV or IM x 28d41
	OR	Amphotericin B7	0.5-1 mg/kg IV daily or every	0.5-1 mg/kg IV daily or every
		P	second day for up to 8wks	second day for up to 8wks
by bid x 3wks) and lo been effective.	patients ng-term	s usually a self-limited illness. I maintenance. In sulfonamide-	mmunosuppressed patients may need higher doses, lo sensitive patients, pyrimethamine 50-75 mg daily in div	ided doses (plus leucovorin 10-25 mg/d) has
			pecies L. donovani (kala-azar) and L. infantum and the ecies and area of the world where infection was acquire	
1. May be repeated or c	ontinue	d; a longer duration may be ne	eded for some patients (BL Herwaldt, Lancet 1999; 35	4:1191).
			r treatment of visceral leishmaniasis. Largely based on o	
tum, the FDA approve lipid complex (Abelce dition by the FDA.	ed liposi et) and a	mai amphotericin B (AmBisor mphotericin B cholesteryl sulfa	ne) for treatment of visceral leishmaniasis (A Meyerhoft ate (Amphotec) have also been used with good results in	r, Gim intect Dis 1999; 28:42). Amphotericin B but are considered investigational for this con-
43. The FDA-approved d			ed patients (e.g., HIV infected) is 4 mg/kg/d (d 1-5) and re is no consensus as to dosage or duration.	4 mg/kg/d on d 10, 17, 24, 31 and 38. The relapse
44. For treatment of kala-	-azar in	adults in India, oral miltefosine	100 mg/d (~2.5 mg/kg/d) for 3-4wks was 97% effective	
The dose of miltefosi	ne in an	open-label trial in children in I	3; 51:686). Gastrointestinal adverse effects are commor ndia was 2.5 mg/kg/d x 28d (SK Bhattacharya et al, Cli rmany at Impavido@zentaris.de).	
45. Cutaneous infection i	s most o	commonly due to the Old Work	d species L. major and L. tropica and the New World sp ost immune status, species and area of the world wher	
			ost immune status, species and area of the world when niltefosine was effective for the treatment of cutaneous	
Colombia but not L(N	V.) brazi	liensis in Guatemala at a dosa	ge of about 2.5 mg/kg/d for 28d. "Motion sickness," nau	usea, headache and increased creatinine were
neous lesions, a stud	y in Sau	di Arabia found that oral flucor	Dis 2004; 38:1266). See footnote 44 regarding miltefosin azole, 200 mg once/d x 6wks, appeared to speed healin maniasis in Colombia where the likely organism was L	ng (AA Alrajhi et al, N Engl J Med 2002; 346:891).
			994; 50:107); its effect against other species is not well	
			gions where cutaneous leishmaniasis species have low	

48. Topical paromorpici handu be used only in geographic regions where cutaneous isistmaniais species have low potential for muosal special. A formation of 15% paromorpicit?3% methybrazzhonium, michoid (e.aducular) in oit Mithe parafillo for topical special be partially effective in some patients against cutaneous alestmaniais due to L. major in Israel and against L. mexicana and L. (U) braziliensis in Guatemala, where much special percent and a special percent and the work of the percent before they improve.

INFECTION		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
LICE infestation (Pediculus I	umanus, P. capi	itis, Phthirus pubis) ⁵⁰	
Drug of choice:	0.5	5% Malathion ⁵¹	Topically	Topically
	OR 1%	Permethrin ⁵²	Topically	Topically
Alternative:	p	rethrins with iperonyl utoxide ⁵²	Topically	Topically
	OR Ive	rmectin7, 53	200 mcg/kg x 3, d 1, 2 and 10	200 mcg/kg x 3, d 1, 2 and 10
Loa loa, see FILA	RIASIS			
MALARIA, Treatm	nent of (Pla	asmodium falcip	arum, P. ovale, P. vivax, and P. malariae)	
			oquine-resistance	
Drugs of choice:		tovaquone/ proguanil ⁵⁶	2 adult tabs bid ⁵⁸ or 4 adult tabs once daily x 3d	-5kg: not indicated 5-8kg: 2 peds tabs once/d x 3d 9-10kg: 3 peds tabs once/d x 3d 11-20kg: 1 adult tabs once/d x 3d 21-30kg: 2 adult tabs once/d x 3d 31-40kg: 3 adult tabs once/d x 3d >40kg: 4 adult tabs once/d x 3d
		luinine sulfate lus	650 mg q8h x 3-7d ⁵⁷	30 mg/kg/d in 3 doses x 3-7d ⁵⁷
		oxycycline ^{7,14} r plus	100 mg bid x 7d	4 mg/kg/d in 2 doses x 7d
		r plus	250 mg qid x 7d	6.25 mg/kg qid x 7d
	cl	indamycin7,59	20 mg/kg/d in 3 doses x 7d ⁶⁰	20 mg/kg/d in 3 doses x 7d
Alternatives:	N	lefloquine61	750 mg followed 12 hrs later by 500 mg	15 mg/kg followed 12 hrs later by 10 mg/kg
		rtesunate ^{62*} Ius	4 mg/kg/d x 3d	4 mg/kg/d x 3d
		nefloquine61	750 mg followed 12 hrs later by 500 mg	15 mg/kg followed 12 hrs later by 10 mg/kg

 For infestation of eyelashes with P pubs Ice, use petrolatum; TMP/SMX has also been used (TL Meinking and D Taplin, Curr Probl Dermatol 1996; 24:157). For public lice, treat with 5% permethrin or ivermectin as for scables (see page 187). TMP/SMX has also been effective together with permethrin for head lice (RB Hipolito et al. Pediatrics 2001; 107:E30)

51 KS Yoon et al. Arch Dermatol 2003: 139:994

52. A second appl n is rec d one week later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (TL Meinking et al, Arch Dermatol 2002: 138:220)

Ivermectin is effective against adult lice but has no effect on nits (KN Jones and JC English III, Clin Infect Dis 2003; 36:1355).

 Chloroquine-resistant P falciparum occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Halli, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yernen, Oman, Saudi Arabia and Iran). For treatment of multiple-drug-resistant P. falciparum in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, arte sunate plus mefloquine or artemether plus mefloquine may be used (C Luxemburger et al, Trans R Soc Trop Med Hyg 1994; 88:213; J Karbwang et al, Trans R Soc Trop Med Hyg 1995; 89:296) Uncomplicated or mild malaria may be treated with oral drugs.
 Altorapone plus proguant is available as a faxel-dose combination tablet: adult tablets (*Malarone*; 250 mg atovaquene/100 mg proguanii) and pediatric tablets

Malarone Pediatrice 62.5 mg atovaquone/25 mg programii). To enhance absorption, it should be taken with food or a miky drink. Atovaquone/programi should Industrie routing, the program when or patients with severe real impairment (creating cleaned of an impairment and patients). There have been several isolated reports of resist-ance in *P* faloparum in Africa (E Schwartz et al, Clin Infect Dis 2003; 37:450; A Farnert et al, BMJ 2003; 326:628).

In Southard Asia, relative resistance to durine has increased and treatment should be continued for 7d.
 In Southard Asia, relative resistance to qurine has increased and treatment should be continued for 7d.
 Although approved for once daily dosing, Medical Letter consultants usually divide the dose in two to decrease nausea and vomiting.

50 For use in pregnancy.

60. B Lell and PG Kremsner. Antimicrob Agents Chemother 2002; 46:2315.

61. At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis and seizures can occur. Melloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (F Nosten et al, Clin Infect Dis 1999; 28:808). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric liness. Melloquine can be given to patients taking b-blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Melloquine should not be given together with quinine, quindine or halofantrine, and caution is required in using quinine, quinidine or halofantrine to treat patients with malaria who have taken melloquine for prophylaxis. Resistance to melloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the US, a 250-mg tablet of mefloquine contains 228 mg mefloquine base. Outside the US, each 275-mg tablet contains 250 mg base.

F Nosten et al, Lancet 2000; 356:297; M van Vugt et al, Clin Infect Dis 2002; 35:1498.

		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
MALARIA, Treatr <i>P. vivax</i> ⁶³ acqui ORAI ⁵⁵		(continued) reas of chloroquine	-resistance	
Drug of choice:		Quinine sulfate	650 mg q8h x 3-7d ⁵⁷	30 mg/kg/d in 3 doses x 3-7d ⁵⁷
	OR	doxycycline ^{7,14} Mefloquine ⁶¹	100 mg bid x 7d 750 mg followed 12 hrs later by 500 mg	4 mg/kg/d in 2 doses x 7d 15 mg/kg followed 12 hrs later by 10 mg/kg
Alternatives:		Chloroquine	25 mg base/kg in 3 doses over 48 hrs	25 mg base/kg in 3 doses over 48 hrs
		plus primaguine ⁶⁴	00	
All Plasmodiun ORAL ⁵⁵	n except		30 mg base daily x 14d tant P. falciparum ⁵⁴ and Chloroquine-re	0.6 mg/kg/d x 14d sistant P. vivax ⁶³
All Plasmodium		Chloroquine phosphate ⁶⁵	1 g (600 mg base), then 500 mg (300 mg base) 6 hrs later, then 500 mg (300 mg base) at 24 and 48 hrs	10 mg base/kg (max. 600 mg base), then 5 mg base/kg 6 hrs later, then 5 mg base/kg at 24 and 48 hrs
PARENTERAL				
Drug of choice:66	3	Quinidine gluconate ⁶⁷	10 mg/kg loading dose (max. 600 mg) in normal saline over 1-2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg loading dose (max. 600 mg) in normal saline over 1-2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
	OR	Quinine dihydro- chloride ^{67*}	20 mg/kg loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2-4 hrs q8h (max. 1800 mg/d) until PO therapy can be started	20 mg/kg loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2-4 hrs q8h (max. 1800 mg/d) until PO therapy can be started
Alternative:		Artemether ^{68*}	3.2 mg/kg IM, then 1.6 mg/kg daily x 5-7d	3.2 mg/kg IM, then 1.6 mg/kg daily x 5-7d
Drug of choice:	elapses	Primaquine phosphate ⁶⁴	30 mg base/d x 14d	0.6 mg base/kg/d x 14d
÷				
MALARIA, Preve				
MALARIA, Preve Chloroquine-se Drug of choice:	ensitive	areas ⁵⁴ Chloroquine phosphate ^{70,71}	500 mg (300 mg base), once/wk 72	5 mg/kg base once/wk, up to adult dose of 300 mg base ⁷²
VALARIA, Preve Chloroquine-se Drug of choice: Availability problem Availability problem Availability problem and the program Arrite program (Co Miler et al. N Gostionen Earth (Co Miler et al. N Gostionen Earth men. The loading of is required, the qui carbon et al. N Gostionen Earth men. The loading of is required, the qui carbon et al. United studies of Med Hyg 2001; 59. No drug regimen g	ns. See table ased susce e Solomon hate can ca A African, Ar ancy. sphate is no lion has bee Engl J Mec blood press manufactu lose should inline or qui efficacy exx: 637; K Mai juarantees j	areas ⁵⁴ Chloroquine phosphate ^{70,71} de on page 190. Biblilly to chloroquine is a Island, Yunatu, Guyan e hemotyla camenia, esp aian and Medlerannean pe et available, hydroxycholog area and phose patient 1 989, 22 450). um and phose monitorie rer (El Luy, 800-565-597). be devasated or omitted in niche dos should he redu be devasated or omitted in niche dos should he redu petter M. P. Alleganarm, noti ma, East Ar Med 3 2002;	significant problem in Papua New Guinea and Indonesia. Saturation of the second of the second of the descendent of collection of second of the second of the second of the Collection of the second of the second of the Collection of the with high-dentity (>10%) parasitemia, altered mental att are recommended, especially in pregnant women and y of the COC Matter Monte (77-048-778). Durindre mi hose patients with how received quarks or melocitiants of the COC Matter and a second second quarks or melocitiants of the COC Matter and a second quarks or melocitiants 0x39. Second second and the the US (Arterenther-Quarkson 0x39.)	adult dose of 300 mg base? ² There are also a tew reports of resistance from 4-phosphate dehydrogenase. This deficiency before treatment. Primagune should not be suitate is equivatent to 500 mg of chloro- tus, pulmonary edema or renat complications mung chlidhen. For problems with quintidine hware greater antimatival activity than qui- more than 46 hours of parenteral treatment Meta-Analysia Study Group, Trans R Soc Top norothy all der tavet to malarious areas,
MALARIA, Preve Chloroquine-se Drug of choice: Availability problem Is most common in Primaquine phosp tas most common in SI of choroquine phor quine phosphate. Exchange translus (KD Milee et al. N Continuous EKG, availability, cal the mine. The loading di Limited studies of travelers shudle be prophystas (Med 1 not be avoided.	ensitive Ins. See table ased susce e Solomon hate can ca e African, Ar ancy. sphate is no cion has bee Engl J Mec blood press e manufactu lose should inne or qui efficacy exx c637; K Mai juarantees e advised to .ett Drugs T	areas ⁵⁴ Chloroquine Discopate ^{70,71} bi on rape 180. philligh to chloroquine 1 as laidand, Vancatala, Gayara, ase hemolyti amenta, seg- ati available, hydraxychloroq at available, hydraxyc	agglicant problem in Papua New Guinea and Indonesia. Brazil, Colonbia and Peru. Calabi In patients whose red cells are deficient in glucose generative structures and the screment for Co 6-PD deficiency are suitate is as effective. 400 mg of hydroxychioroquine with high-dentity (-10%) parasitemia, altered metal tait as an encommendad, especially in gragmatic somen and y or the CDC balancies Istolme (77-MER-7780). Coundes more are scrementared on wencebed quarine or melociquine. If development and the screen and the screme and para edb by 30-S05. Development on walkable in the US (Attemether-Caurine Beitig). There destings within a yang (attricularly within the first in the Beitig).	adult dose of 300 mg base? ² There are also a lew reports of resistance from 45-phosphate dehydrogenase. This deficiency between teatiment. Phomagene include not be suitate is equivalent to 500 mg of chioro- tus, pulmonary edema or renal complications umg childens. For problems with quintidne my have orgeneter antimaturial activity than qui- more than 48 house of parenteral treatment Meta-Analysis Study Group. Trans R Soc Top on monthaj after transfer to malaria
Availability problem Chloroquine-ses Drug of choice: Availability problem Availability problem Availability problem Myannar, India, th Primaquine phosp India, th Primaquine, the qu India dudas of India dudas India India dudas	Ins. See table ased susce e Solomon hate can ca a African, As ancy. sphate is no sion has ber Engl J Mec Solo has be Has ber H	areas ⁵⁴ Chloroquine phosphate ^{70,71} le on page 180. piblithy to chronouthe as a use hemolytic aventive, exp sian and Mediternanen per sian and mediternanen per per sian per per sian per sian and per per sian and sian and per sian and per sian and per per sian and per sian and per sian and per sian and per per sian and per sian and pe	agglicant problem in Papua New Guinea and Indonesia. Brazil, Colonbia and Peru. Calabi In patients whose red cells are deficient in glucose generative structures and the screment for Co 6-PD deficiency are suitate is as effective. 400 mg of hydroxychioroquine with high-dentity (-10%) parasitemia, altered metal tait as an encommendad, especially in gragmatic somen and y or the CDC balancies Istolme (77-MER-7780). Coundes more are scrementared on wencebed quarine or melociquine. If development and the screen and the screme and para edb by 30-S05. Development on walkable in the US (Attemether-Caurine Beitig). There destings within a yang (attricularly within the first in the Beitig).	adult dose of 300 mg base? ² There are also a lew reports of revisitance from 4-phosphate dehydrogenase. This deficiency before treatment. Phomagnine should not be suitate is equivalent to 500 mg of chloro- tus, putmonary edema or mail complications ung chlidten. For problem with quickfore my have greater antimatarial activity than qui- more than 48 house of parenteral treatment Meta-Analysis Study Group. Trans R Soc Top to monthal after travel to malarian s; therefore, prophysiks is indicated if exposure can tail areas where mataria is fording except prefer

NFECTION		DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
ALARIA, Preve				
Chloroquine-re Drug of choice:	sistant a	Atovaguone/	1 adult tab/d73	11-20kg: 1 peds tab/d ^{56,73}
Sing of choice.		proguanil56,71	i addit tab/d·=	21-30kg: 2 peds tabs/d56,73
		proguani		31-40kg: 3 peds tabs/d ^{56,73}
				>40kg: 1 adult tab/d56,73
	OR	Mefloquine61,71,74	250 mg once/wk72	5-10kg: 1/8 tab once/wk72
				11-20kg: ¼ tab once/wk72
				21-30kg: 1/2 tab once/wk72
				31-45kg: 34 tab once/wk72
	OB	Doxycycline7,71	100 mg daily ⁷⁵	>45kg: 1 tab once/wk ⁷² 2 mg/kg/d, up to 100 mg/d ⁷⁵
Alternatives:	UH	Primaguine ^{7,64}	30 mg base daily ⁷⁶	0.6 mg/kg base daily
Alternatives.		Chloroquine	500 mg (300 mg base) once/wk ⁷²	5 mg/kg base once/wk, up to
		phosphate	coo mg (coo mg base) choo ma	300 mg base ⁷²
		plus proguanil77	200 mg once/d	<2yrs: 50 mg once/d
		1	3	2-6yrs: 100 mg once/d
				7-10yrs: 150 mg once/d
				>10yrs: 200 mg once/d
	resump	tive Treatment ⁷⁸		
Orug of Choice:		Atovaquone/	4 adult tabs daily x 3d	<5kg: not indicated
		proguanil7,56		5-8kg: 2 peds tabs once/d x 3d 9-10kg: 3 peds tabs once/d x 3d
				9-10kg: 3 peds tabs once/d x 3d 11-20kg: 1 adult tab once/d x 3d
				21-30kg: 2 adult tabs once/d x 3d
				31-40kg: 3 adult tabs once/d x 3d
				>40kg: 4 adult tabs once/d x 3d
	OR	Quinine sulfate	650 mg q8h x 3-7d ⁵⁷	30 mg/kg/d in 3 doses x 3-7d ⁵⁷
		plus		-
		doxycycline7,14	100 mg bid x 7d	4 mg/kg/d in 2 doses x 7d
	OR	Mefloquine ⁶¹	750 mg followed 12 hrs later by 500 mg	15 mg/kg followed 12 hrs later by 10 mg/kg
	alitozooi	n hellem Encenhalit	ozoon cuniculi, Vittaforma corneae [No	
				isema corneumj)
Drug of choice:		Albendazole ⁷	400 mg bid	isema corneumj)
		Albendazole ⁷ plus fumagillin ^{79*}	400 mg bid	isema corneumj)
Intestinal (Ente		Albendazole ⁷ plus fumagillin ^{79*}		sema corneumj)
Intestinal (Ente E. bieneusi ⁸⁰		Albendazole ⁷ plus fumagillin ^{79*} on bieneusi, Encept	400 mg bid halitozoon [Septata] intestinalis)	isema corneumj)
Intestinal (Ente E. bieneusi ⁸⁰ Drug of choice:	rocytozo	Albendazole ⁷ plus fumagillin ^{79*}	400 mg bid	isema corneumj)
Intestinal (Ente E. bieneusi ⁸⁰	rocytozo	Albendazole ⁷ plus fumagillin ^{79*} on bieneusi, Encept	400 mg bid halitozoon [Septata] intestinalis) 60 mg/d PO x 14d	isema corneumj)
Intestinal (Ente E. bieneusi ⁸⁰ Drug of choice: E. intestinalis Drug of choice:	rocytozo	Albendazole ⁷ plus fumagillin ^{79*} on bieneusi, Encept Fumagillin* Albendazole ⁷	400 mg bid halitozoon [Septata] intestinalis)	
Intestinal (Ente E. bieneusi ⁸⁰ Drug of choice: E. intestinalis Drug of choice: Disseminated (Drug of choice: ⁸¹	E. heller	Albendazole ⁷ plus fumagillin ^{79*} on bieneusi, Encept Fumagillin* Albendazole ⁷	400 mg bid halitozoon [Septata] intestinalis) 60 mg/d PO x 14d 400 mg bid x 21d	
Intestinal (Ente E. bieneus ⁸⁰ Drug of choice: E. intestinalis Drug of choice: Disseminated (Drug of choice: ⁸¹ Mites, see SCAB	E. heller	Albendazole ⁷ plus fumagillin ⁷⁹ * <i>ion bieneusi, Encept</i> Fumagillin* Albendazole ⁷ <i>n, E. cuniculi, E. inte</i> Albendazole ⁷	400 mg bid halitozoon [Septata] intestinalis) 60 mg/d PO x 14d 400 mg bid x 21d stinalis, Pielstophora sp., Trachipleisto	
Intestinal (Ente E. bieneusl ⁸⁰ Drug of choice: E. intestinalis Drug of choice: Disseminated (Drug of choice: ⁸¹ dites, see SCAB	E. heller	Albendazole ⁷ plus fumagillin ⁷⁹ * <i>on bieneusi</i> , <i>Encept</i> Fumagillin* Albendazole ⁷ <i>m, E. cuniculi</i> , <i>E. inte</i> Albendazole ⁷ <i>mis</i> infection	400 mg bid halitozoon (Septata) intestinalis) 60 mg/d PO x 14d 400 mg bid x 21d stinalis, Pleistophora sp., Trachipleisto 400 mg bid	phora sp. and Brachiola vesicularum)
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Intestinal (Ente E. bieneus ⁸⁰ Drug of choice: E. intestinalis Drug of choice: Disseminated (Drug of choice: ⁸¹ Altes, see SCAB MONILIFORMIS Drug of choice:	E. hellen IIES monilifor	Albendazole ⁷ plus fumagillin ⁷⁹ * oon bieneusi, Encept Fumagillin* Albendazole ⁷ m, E. cuniculi, E. inte Albendazole ⁷ mis infection Pyrantel pamoate ⁷	400 mg bid halitozoon (Septata) intestinalis) 60 mg/d PO x 14d 400 mg bid x 21d stinalis, Pleistophora sp., Trachipleisto 400 mg bid	phora sp. and Brachiola vesicularum)
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Intestinal (Ente E. bieneus)® Drug of choice: E. Intestinali Diag of choice: Diag of choice: Diag of choice: Diag of choice: National Content of the choice of pregarary and of pregarary and the choice of the choice of the choice of pregarary and the choice of the choice of the choice of pregarary and the choice of the choice of the choice of the choice of the choice of the choice of the choice of the second of the choice of the choi	rocylozo	Albendazole ² plus (uraguillin ²⁺ on bieneus), Encept Furaguillin ⁴ Albendazole ² mis infection Pyranical paraolat ² mis infection Pyranical paraolat ² on page 190. regarding of the duals of sky but passed on deag mailles and patients with or cause gatorinestinal primaging for the duals of the advice physics and a patients with boot Agents Charada, kettragen of a kink of the basis of the duals of the duals primaging for the duals of a local charady set of the paraolation of the state of a local charady set of the primaging for the duals of the advice of the basis of the duals of the state of the duals of the duals of the duals the duals the duals the duals and the duals the duals of the duals the duals the duals of the duals the duals the duals the duals and the duals the duals the duals the duals and the duals the duals the duals the duals that the duals the duals the duals the duals the duals the duals the duals the duals the duals the duals the duals the duals the duals the duals that the duals the du	400 mg bid halitozoon (Saptata) intestinais) 60 mg/d PO x 14d 400 mg bid x 21d sistinais, Peisotophora sp., Trachipleisto 400 mg bid x 21d sistinais, Peisotophora sp., Trachipleisto 400 mg bid 11 mg/kg once, repeat twice, 2wks apart 10 mg/kg once, about 6 mg/kg once a was apart 10 mg/kg once, about 6 mg/kg once a was apart 10 mg/kg once, about 6 mg/kg once a was apart 10 mg/kg once a was apart 1	phora sp. and Brachiola vesicularum) 11 mg/kg once, repeat twice, 2wks apart 12 mg/kg once, repeat twice, 2wks apart 13 mg/kg once, repeat twice, 2wks apart 14 mg/kg once, repeat twice, 2wks apart 15 mg/kg once, 16 mg/kg 16 mg/kg once, 16 mg/kg 16 mg/kg

INFECTION	DRU	G	ADULT DOSAGE	PEDIATRIC DOSAGE
Naegleria species,	see AMEBIC ME	ININGOEN	CEPHALITIS, PRIMARY	
Necator americant	us, see HOOKWO	ORM infectio	n	
OESOPHAGOSTO	MUM bifurcum			
Drug of choice:	See footn	iote 82		
Onchocerca volvu				
Opisthorchis vive				
Paragonimus west			2	
Pediculus capitis,				
Pinworm, see ENT		rus pubis,	See LICE	
PNEUMOCYSTIS J		dy oorinii) n	aumonia (BCR)83	
Drug of choice:	Trimethop		MP 15 mg/kg/d, SMX 75 mg/kg/d,	TMP 15 mg/kg/d, SMX 75 mg/kg/d,
brug of onoico.	sulfame		PO or IV in 3 or 4 doses x 14-21d	
	azole			
Alternatives:	Primaquir		0 mg base PO daily x 21d	
	plus cline	damycin ⁷ 6	i00 mg IV q6h x 21d, or 300-	
			450 mg PO q6h x 21d	
	OR Trimethop		mg/kg tid x 21d	
	or plus daps OR Pentamid		00 mg daily x 21d I-4 mg/kg IV daily x 14-21d	3-4 mg/kg IV daily x 14-21d
	OR Atovaquo		'50 mg bid x 21d	1-3mos: 30 mg/kg/d
	On Alovaquo	ne /	50 mg blu x 2 m	4-24mos: 45 mg/kg/d
				>24mos: 30 mg/d
Primary and seco	ondary prophyla:	xis ⁸⁴		
Drug of Choice:	Trimethop		tab (single or double strength)	TMP 150 mg/m ² , SMX 750 mg/m ² ir
	sulfame	thox-	daily	2 doses on 3 consecutive days per
	azole			wk
Alternatives:85	Dapsone	/ 5	i0 mg bid, or 100 mg daily	2 mg/kg/d (max. 100 mg) or
				4 mg/kg (max. 200 mg) each wk
	OR Dapsone	7 5	0 mg daily or 200 mg each wk	
	plus pyrir		i0 mg or 75 mg each wk	
	amine ⁸⁶		io nig of 70 nig caon nit	
	OR Pentamid		00 mg inhaled monthly via	35yrs: 300 mg inhaled monthly via
	aerosol		Respirgard II nebulizer	Respirgard II nebulizer
	OR Atovaquo	ne ⁷ 1	500 mg daily	1-3mos: 30 mg/kg/d
				4-24mos: 45 mg/kg/d
				>24mos: 30 mg/kg/d
Roundworm, see A	SCARIASIS		CEPHALITIS, PRIMARY	
SCABIES (Sarcopt		ENINGOLI	CEFHALINS, FRIMARI	
Drug of choice:	5% Permethrin	т	opicallv ⁸⁷	Topically ⁸⁷
Alternatives:88	lvermectin7,89		00 mcg/kg once87	200 mcg/kg once87
	10% Crotamiton		opically once/daily x 2	Topically once/daily x 2
SCHISTOSOMIASI	S (Bilharziasis)			
S. haematobium				
Drug of choice:	Praziquar	ntel 4	0 mg/kg/d in 2 doses x 1d	40 mg/kg/d in 2 doses x 1d
Drug of choice: S. japonicum	Praziquar			
Drug of choice: <i>S. japonicum</i> Drug of choice:			0 mg/kg/d in 2 doses x 1d i0 mg/kg/d in 3 doses x 1d	40 mg/kg/d in 2 doses x 1d 60 mg/kg/d in 3 doses x 1d
Drug of choice: S. japonicum Drug of choice: S. mansoni	Praziquar Praziquar	ntel 6	i0 mg/kg/d in 3 doses x 1d	60 mg/kg/d in 3 doses x 1d
Drug of choice: <i>S. japonicum</i> Drug of choice:	Praziquar Praziquar Praziquar	ntel 6 ntel 4	0 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d
Drug of choice: <i>S. japonicum</i> Drug of choice: <i>S. mansoni</i> Drug of choice: Alternative:	Praziquar Praziquar	ntel 6 ntel 4	i0 mg/kg/d in 3 doses x 1d	60 mg/kg/d in 3 doses x 1d
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice:	Praziquar Praziquar Praziquar	ntel 6 ntel 4 uine ^{90*} 1	0 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice:	Praziquar Praziquar Praziquar Oxamniqu Praziquar	ntel 6 ntel 4 uine ^{90*} 1	i0 mg/kg/d in 3 doses x 1d i0 mg/kg/d in 2 doses x 1d 5 mg/kg once ⁹¹	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹
Drug of choice: <i>S. japonicum</i> Drug of choice: <i>S. mansoni</i> Drug of choice: Alternative: <i>S. mekongi</i> Drug of choice: · Availability problems. 32. Albendazole or pyrant	Praziquar Praziquar Praziquar Oxamniqu Praziquar See table on page 190. Iel pamoate may be effe	ntel 6 ntel 4 uine ^{go*} 1 ntel 6 ective (JB Ziem e	00 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d 5 mg/kg once ⁹¹ 10 mg/kg/d in 3 doses x 1d tal, Ann Trop Med Parasitol 2004; 98:385).	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: [•] Availability problems. 3. Abendazole or pyrant 3. Praeumografis has be	Praziquar Praziquar Praziquar Oxamniqu Praziquar See table on page 190. Iel pamoate may be effe reclassified as a fung	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 ctive (JB Ziem e gus. In severe di	00 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d 5 mg/kg/d once ⁹¹ 10 mg/kg/d in 3 doses x 1d tal, Am Trop Med Pansalo 2004; 98:385). sease with room air PO ₂₄ : 70 mm/s or A gradi	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: ^a Availability problems. ^a Availability problems. ^b (S dagnon et al, N Er (S dagnon et al, N Er	Praziquar Praziquar Praziquar Oxamniqu Praziquar See table on page 190. Iel pamoate may be effe en reclassified as a tung of J Med 1990; 323:144	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 ective (JB Ziem e gus. In severe dii 44; E Caumes et	00 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d 5 mg/kg once ⁹¹ 10 mg/kg/d in 3 doses x 1d tal, Ann Trop Med Parasitol 2004; 98:385).	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d errt <u>-</u> 35 mmHg, predrisone should also be used
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: ⁴ Availability problems. ² Ablendazote or pyrant ³ Aneumocystis has be (S Gagnon et al, N Er S. An alternative trimeth	Praziquar Praziquar Praziquar Oxamniqu Praziquar See table on page 190. I and 1909 232:144 optylaxis in patients with optylaxis in patients with optylaxis in patients with	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 ktive (JB Ziem e gus. In severe di 44; E Caumes et h HIV can be di HIV can be di	00 mg/kg/d in 3 doses x 1d 00 mg/kg/d in 2 doses x 1d 50 mg/kg.dei n2 doses x 1d 50 mg/kg.dei n3 doses x 1d 10 mg/kg/d in 3 doses x 1d 14 al. Am Top Med Paraelic 2004; 92:385). sase with room of PO ₂ < 70 mm/sg or As grad 1, Clin Med Di Burk 11:8319, isonthinude after CD4 court Intreases to >2002 x 16 16 ta 2d/w.Weeky Hengy with sultadore 5f 16 ta 2d/w.Weeky Hengy with sultadore 5f	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d ent a 35 mmHg, prednisone should also be used tr ⁶ /L for 3mos.
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: · Availabily problems. 22. Albendazole or pyrant S. Preumocystie has be (S. Gagnon et al, N.E. Primary'secondary pr 5. An alternative timeth was effective PCP pro	Praziquar Praziquar Praziquar Praziquar Oxamniqu Praziquar neclassifica as fung gl Med 1990; 323:44 1990; 323:44 neclassifica as fung pl/Med 1990; 323:44 neclassifica as fung pl/Med 1990; 323:44 neclassification primisultamethoxazole	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 tctive (JB Ziem e gus. In severe di t4: E Caumes et h HIV can be dis regimen is one ant patients (J Tr	00 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d 5 mg/kg once ⁹¹ 10 mg/kg/d in 3 doses x 1d tal. An Trop Med Parasitol 2004; 98:385). tases with room air PO ₂ x 70 mm/s or A gradi al. clin Inter Dis 1994; 18:319. continued after CD court Increases to >200 x 1	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d ent a 35 mmHg, prednisone should also be used tr ⁶ /L for 3mos.
Drug of choice: S. Japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: - Availability problems. 2. Altendace or pynnal 3. Aneumocystis has be (S Gagnon et al. N Er S. an alternative trimethy was effective PCP pro Plus lescoordin 25 mg	Praziquar Praziquar Praziquar Praziquar Oxamniqu Praziquar See tabio on gae 190. gl Med 1990; 323:144 ophyskas in patients wi gl Med 1990; 323:144 ophyskas in patients wi physikas in Iniver transpic uth sech dose of pyrir	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 ktive (JB Ziem e gus. In severe di t4; E Caumes et regimen is one ant patients (JT Come regimen is one) ant patients (JT Come tant	10 mg/kg/d in 3 doses x 1d 10 mg/kg/d in 2 doses x 1d 5 mg/kg.org.org. 15 mg/kg.org.org. 16 mg/kg.org.org. 17 mg/kg.org.org. 18 mg/kg.org.org. 10 mg/kg/d in 3 doses x 1d 11 al. mkm.tbl bit status 12 msigner 12 msigner status 12 msigner status 12 msigner	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d ent a 35 mmHg, prednisone should also be used tr ⁶ /L for 3mos.
Drug of choice: S. Japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: Austrative: Austrative: Austrative: Austrative: Austrative: S. Austrative: Gagono et al. NE Pila leucovini 25 m S. na lemané virneth was effective PCP pro S. na lemané virneth was effective PCP pro S. na lemané virneth was effective PCP pro S. na lemané virneth S. Lindane (rebrezené h	Praziquar Praziquar Praziquar Oxamniqu Praziquar e table on piae 190. el parnotar may be elfo gl J Med 1905, 323. Ho gl J Med 1905, 323. Ho gl J Med 1905, 323. Ho gl Med Los do pyri with sech dose of pyri met may need to be rep schloride, Kwelly sho.	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 kctive (JB Ziem e gus. In severe di 44; E Caumes et 44; E Caumes et 44; E Caumes et h HIV can be dir regimen is one ant patients (J Tr methamine. seated in 10-14 <i>d</i> uid be reserved <i>i</i>	00 mg/kg/d in 3 doses x 1d 00 mg/kg/d in 2 doses x 1d 50 mg/kg.do in 3 doses x 1d 10 mg/kg/d in 3 doses x 1d t al. Am Trop Med Panalol 2004;98:385). Deserve this one and PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and table PO ₂ x 70	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d ent 2 35 mm/s, prednione should also be used to ⁶ L for -3mos.
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekong j Drug of choice: Alternative: Alternative: Alternative: Alternative: Alternative: Alternative: Alternative: Alternative: S. makong j Drug of choice: S. makong j	Praziquar Praziquar Praziquar Oxamnig Praziquar necessitati a second praziquar necessitati a second gl J Med 1909. 323: 44 necessitati a se lung gl J Med 1909. 323: 44 necessitati a second gl attenta second primisultamethoxazela primisultamet	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 kctive (JB Ziem e gus. In severe di t4. E Caumes et h HIV can be di t4. E Caumes et h HIV can be di methamine. seated in 10-14 c uid be reserved 1 uid patients <50 i	00 mg/kg/d in 3 doses x 1d 00 mg/kg/d in 2 doses x 1d 5 mg/kg donce ⁹¹ 10 mg/kg/d in 3 doses x 1d 11 mg/kg/d in 3 doses x 1d 12 mg/kg/d in 3 doses x 1d 12 mg/kg/d in 3 doses x 1d 12 mg/kg/kg/kg/kg/kg/kg/kg/kg/kg/kg/kg/kg/kg	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d ent 2 35 mmlg, predrisone should also be used (o ⁶). for >3mos. 30 mg/sytmethamine 25 mg/leucovorin 25 mg led it should not be used for immunocompro-
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekongi Drug of choice: Analiabily proteima. Analiabily proteima. Promovješki sab te (S dagron et al, NE Primarylescondary pr S. Analiabil succentra Sin Primarylescondary pr S. Primarylescondary pr B. Primarylescondary pr B. Undare (chenzene h mised patients, rougo Determente, alter aldo	Praziquar Praziquar Praziquar Oxamniqu Praziquar Praziquar See table on page 190. el pamoate may be effo reflassificada sa fung gi J Med 1960; 323:141 en reflassificada sa fung optimularite necessaria gi atta sach das ed optim terr may need to be reg sachforder, Kwelly shou philidaren, he edderty, an e or in combination with	ntel 6 ntel 4 uine ^{90*} 1 ntel 6 disclive (JB Ziem e gus. In severe di 44; E Caumes et HIV can be di regimen is one in tatjentis (J Tc methamine. seated in 10-14 di be reserved i di be reserved i di patients <50 fc	00 mg/kg/d in 3 doses x 1d 00 mg/kg/d in 2 doses x 1d 50 mg/kg.do in 3 doses x 1d 10 mg/kg/d in 3 doses x 1d t al. Am Trop Med Panalol 2004;98:385). Deserve this one and PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and the table PO ₂ x 70 mHg or A grad and table PO ₂ x 70	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d eft 2 35 mm/g, predrisone should also be used to ⁶ /L for Jmos. 20 mg/symmethamine 25 mg/succount 25 mg fait should not be used for immunocompro- mmunocompromesed patients (P del Cludoe,
Drug of choice: S. japonicum Drug of choice: S. mansoni Drug of choice: Alternative: S. mekong j Drug of choice: Alternative: S. mekong j Drug of choice: Alternative of print B. Abendazok or print B. Abendazok or print B. Analernative terneth- S. makeng is excerned to the second S. na alternative terneth- S. makeng is excerned to the second S. na alternative terneth- S. na	Praziquar Praziquar Praziquar Oxamniqu Praziquar Banoste nu ye effe en reclassifi da s fung en not sen ye effe en reclassifi da s fung en vector sen ye effe en reclassifi da s fung en vector sen ye effe en reclassifi da s fung en vector sen ye en vector physias in patients with each of the off off each off off off each off off off off off each off off off off off off each off off off off off each off off off off off off off each off off off off off off off off off each off off off off off off off off off of	ntel 6 ntel 4 uine90° 1 ntel 6 etrive (JB Zieme nu uin. In severe di 44. E Caumes et h HIV can be dir 44. E Caumes et h HIV can be h HIV can be di	O mg/kg/d in 3 doses x 1d O mg/kg/d in 2 doses x 1d S mg/kg doses x 1d S mg/kg doses x 1d S mg/kg doses x 1d tal, Ann Trop Mad Paraselot 2004; 98:385), sease with room air PO ₂ x 70 mm/sg or As grad, al, Clin Intel® Dis 41:8319, continued after CD4 court Increases b >2002; X 1, dis down, Veeder Mergy with sublations 65 tis down, Veeder Mergy With sublations 65 sis down, Veeder Mergy With sublations 65 sis down, Veeder Mergy With sublations 65 g.	60 mg/kg/d in 3 doses x 1d 40 mg/kg/d in 2 doses x 1d 20 mg/kg/d in 2 doses x 1d ⁹¹ 60 mg/kg/d in 3 doses x 1d eft 2 35 mm/g, predrisone should also be used to ⁶ /L for 3mos. 20 mg/symmethamine 25 mg/succourin 25 mg fait should not be used for immunocompro- mmunocompromised patients (P del Cludee,

In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/d x 2d. Some experts recommend 40-60 mg/kg over 2-3d in all of Africa (KC Shekhar, Drugs 1991; 42:379).

NFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Bleeping sickness, see			
STRONGYLOIDIASIS (S			
Drug of choice:92	Ivermectin	200 mcg/kg/d x 2d	200 mcg/kg/d x 2d
Alternative:	Albendazole ⁷	400 mg bid x 7d	400 mg bid x 7d
OR	Thiabendazole	50 mg/kg/d in 2 doses x 2d (max 3g/d) ⁹³	50 mg/kg/d in 2 doses x 2d (max 3g/d) ⁹³
APEWORM infection		(max 3g/d)55	(max 3g/d)55
- Adult (intestinal st	age)		
		inata (beef), Taenia solium (pork), Dip	vlidium caninum (dog)
Drug of choice:	Praziguantel7	5-10 mg/kg once	5-10 mg/kg once
Alternative:	Niclosamide"	2 g once	50 mg/kg once
Hymenolepis nana (du	warf tapeworm)		
Drug of choice:	Praziguantel7	25 mg/kg once	25 mg/kg once
Alternative:	Nitazoxanide4,7	500 mg x 3d94	1-3yrs: 100 mg bid x 3d94
			4-11yrs: 200 mg bid x 3d94
- Larval (tissue stag	e)		
Echinococcus granul			
Drug of choice:95	Albendazole	400 mg bid x 1-6mos	15 mg/kg/d (max. 800 mg) x 1-6mos
Echinococcus multilo			
Freatment of choice:	See footnote 96		
Taenia solium (Cystice			
Treatment of choice:	See footnote 97		
Alternative:	Albendazole	400 mg bid x 8-30d; can be repeated	15 mg/kg/d (max. 800 mg) in 2 doses
		as necessary	x 8-30d; can be repeated as necessar
OR	Praziquantel ⁷	50-100 mg/kg/d in 3 doses x 30d	50-100 mg/kg/d in 3 doses x 30d
oxocariasis, see VISCE		NS	
OXOPLASMOSIS (Tox			
Drugs of choice: ^{99,100} Pyrin		25-100 mg/d x 3-4wks	2 mg/kg/d x 3d, then 1 mg/kg/d
	plus		(max. 25 mg/d) x 4wks102
	sulfadiazine	1-1.5 g qid 3-4wks	100-200 mg/kg/d x 3-4wks
RICHINELLOSIS (Trich			
Drugs of choice:	Steroids for sever	9	
	symptoms		
	plus		
	mebendazole ⁷	200-400 mg tid x 3d, then	200-400 mg tid x 3d, then
		400-500 mg tid x 10d	400-500 mg tid x 10d
Alternative:	Albendazole7	400-500 mg tid x 10d 400 mg bid x 8-14d	400-500 mg tid x 10d 400 mg bid x 8-14d
RICHOMONIASIS (Tric	homonas vaginalis)	400 mg bid x 8-14d	400 mg bid x 8-14d
RICHOMONIASIS (Tric Drug of choice: 103	<i>homonas vaginalis)</i> Metronidazole	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d	400 mg bid x 8-14d 15 mg/kg/d orally in 3 doses x 7d
RICHOMONIASIS (Tric	homonas vaginalis)	400 mg bid x 8-14d	400 mg bid x 8-14d
RICHOMONIASIS (Tric Drug of choice: 103 OR	<i>chomonas vaginalis)</i> Metronidazole Tinidazole ⁵	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d	400 mg bid x 8-14d 15 mg/kg/d orally in 3 doses x 7d
RICHOMONIASIS (Tric Drug of choice:103 OR Availability problems. See tat 2. In immunocompromised patie	homonas vaginalis) Metronidazole Tinidazole ⁵ ble on page 190. ents or disseminated disease	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d 2 g once .t may be necessary to prolong or repeat therapy, or to	400 mg bid x 8-14d 15 mg/kg/d orally in 3 doses x 7d 50 mg/kg once (max. 2 g) use other agents. Veterinary parenteral and
RICHOMONIASIS (Tric Drug of choice: ¹⁰³ OR Availability problems. See tat 2. In immunocompromised patie enems formulations of iverm	homonas vaginalis) Metronidazole Tinidazole ⁵ ble on page 190. ents or disseminated disease ectin have been used in seve	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d 2 g once , it may be necessary to prolong or repeat therapy, or to repli patients unable to take oral medicators (PC.tic)	400 mg bid x 8-14d 15 mg/kg/d orally in 3 doses x 7d 50 mg/kg once (max. 2 g) use other agents. Veterinary parenteral and
RICHOMONIASIS (Trice Drug of choice:103 OR Availability problems. See tal 2. In immunocompromised patii enema formulations of Iverm Clin Infect Dis 2003; 37:152;	chomonas vaginalis) Metronidazole Tinidazole ⁵ ble on page 190. ents or disseminated disease ectin have been used in seve PE Tarr Am J Trop Med Hyg	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d 2 g once , it may be necessary to prolong or repeat therapy, or to rep! it patents unable to take oral medications (PL Chic 2003; 68-453).	400 mg bid x 8-14d 15 mg/kg/d orally in 3 doses x 7d 50 mg/kg once (max. 2 g) use other agents. Veterinary parenteral and
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RICHOMONIASIS (Trim Drug of choice:103 CR Availability problems, See tai energy and choice of the second in Internuccomorsised patis- energy and the second second second of the second second second second in the second second second second second second second second second second second second second second second second second	homonas vaginalis): Mattonidazole Tinidazole5 Tinidazole5 Biel on page 190. en or diseminated disease exist have been used in seve the or diseminated disease exist have been used in seve of the seven of the seven of the seven of the seven of the seven of the seven paraton-injection-seapation of the seven of the seven of the seven paraton-injection-seven of the seven paraton-injection-seven of the seven of the seven of the seven of the seven paraton-injection of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven the seven of the seven of the seven of the seven the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven of the seven the seven of the seven of the seven of the seven of the seven the seven of the se	400 mg bid x 8-14d 2 g once or 500 mg bid x 7d 2 g once in any be necessary to prolong or repeat therapy, or to 2 g once in any be necessary to prolong or repeat therapy, or to 2 g once in a set of the set of	400 mg bid x 8-14d 15 mg/kg/ dorally in 3 doses x 7d 50 mg/kg once (max. 2 g) use other apents. Veterinary parentenal and din et al. Lancet 2000; 355:43; J Orem et al. yor in case of spillage of cyst contents dur- typ habe ene effective for management of binabacei or medendazoic can stabilize and anti-scizze medication. Treatment of 6.) Patients with the spenchymal cysts who science daily and an arti-scizzer medication use between tor tail least 30 (J/ Proto et al. dedisione d ongid may be given with sur- ogether with ablence of cyst contents and solutionaria. A science of the science of the science daily and an arti-scizzer medication used be treated for all least 30 (J/ Proto et al. dedisione d ongid may be given with sur- ogether with ablence of paragraphies (AC et al colaring dose of 200 mg) with sultidiazine ultinomade. Allowards and addresers. b, dime the first timester, if there is no doc- hengy with parinetamine and sulfabaliza- and scioul be used only. J Martinet for the first timester, if there is no doc- hengy with parinetamine and sulfabaliza- and scioul be used only after the first or about one year. (JS Remington and G tephicalisandex.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
TRICHOSTRONGY	LUS infection		
Drug of choice:	Pyrantel pamoate7	11 mg/kg base once (max. 1 g)	11 mg/kg once (max. 1 g)
Alternative:	Mebendazole ⁷	100 mg bid x 3d	100 mg bid x 3d
	OR Albendazole7	400 mg once	400 mg once
TRICHURIASIS (Tr	ichuris trichiura, whipworm	1)	
Drug of choice:	Mebendazole	100 mg bid x 3d or 500 mg once	100 mg bid x 3d or 500 mg once
Alternative:	Albendazole7	400 mg x 3d	400 mg x 3d
	Ivermectin ⁷	200 mcg/kg daily x 3d	200 mcg/kg daily x 3d
TRYPANOSOMIAS	IS ¹⁰⁴		
T. cruzi (American	n trypanosomiasis, Chagas	' disease)	
Drug of choice:	Benznidazole*	5-7 mg/kg/d in 2 divided doses x 30-90d	≤12yrs: 10 mg/kg/d in 2 doses x 30-90d
	OR Nifurtimox ^{105*}	8-10 mg/kg/d in 3-4 doses x 90-120d	1-10yrs: 15-20 mg/kg/d in 4 doses x 90d
			11-16yrs: 12.5-15 mg/kg/d in 4 doses x 90d
T. brucei gambie	nse (West African trypano:	somiasis, sleeping sickness)	
hemolymphatic			
Drug of choice:106	Pentamidine	4 mg/kg/d IM x 10d	4 mg/kg/d IM x 10d
	isethionate7	5 5 6	3 3 4
Alternative:	Suramin*	100-200 mg (test dose) IV, then 1 g IV on days 1,3,7,14 and 21	20 mg/kg on days 1,3,7,14 and 21
l ata disaasa wi	th CNS involvement	r g rr on dayo 1,0,7,77 and 21	
Drug of Choice:	Melarsoprol ¹⁰⁷	2.2 mg/kg/d x 10d	2.2 mg/kg/d x 10d
Brug of Offoldo.	OB Eflornithine ^{108*}	400 mg/kg/d in 4 doses x 14d	400 mg/kg/d in 4 doses x 14d
T h rhodesiense	(East African trypanosom		too nignigra in r acces x r ra
hemolymphatic		lable, electring electrices)	
Drug of choice:	Suramin*	100-200 mg (test dose) IV, then 1 g IV on days 1,3,7,14 and 21	20 mg/kg on days 1,3,7,14 and 21
l ate disease wi	th CNS involvement	rg re on days 1,0,7,11 and 21	
Drug of choice:	Melarsoprol ¹⁰⁷	2-3.6 ma/ka/d x 3d: after 7d	2-3.6 mg/kg/d x 3d; after 7d
Brug of onoice.	molaroopror	3.6 mg/kg/d x 3d; repeat again	3.6 mg/kg/d x 3d; repeat again
		after 7d	after 7d
VISCERAL LARVA	MIGRANS ¹⁰⁹ (Toxocarias	is)	
Drug of choice:	Albendazole ⁷	400 mg bid x 5d	400 mg bid x 5d
	Mebendazole ⁷	100-200 mg bid x 5d	100-200 mg bid x 5d
Whipworm, see TF		V	
	ofti, see FILARIASIS		
	a. See table on page 190.		
104. MP Barrett et al, La			
105. The addition of gam	ma interferon to nifurtimox for 20d in	experimental animals and in a limited number of patier	nts appears to shorten the acute phase of
	E McCabe et al, J Infect Dis 1991; 1		
		hin have equal efficacy but pentamidine is better tolerate the dose progressively. Pretreatment with suramin ha	
		e the dose progressively. Preteatment with suranii ha	
gambiense fail to re	spond to melarsoprol (MP Barrett, L	ancet 1999; 353:1113).	
		against T.b. rhodesiense infections. It is available in limit a Letter consultants would treat for 20d. For severe sym	
	tion.		presses and a second se

MANUFACTURERS OF DRUGS USED TO TREAT PARASITIC INFECTIONS

albendazole – *Albenza* (GlaxoSmithKline) *Albenza* (GlaxoSmithKline) – albendazole *Alinia* (Romark) – nitazoxanide amphotericin – *Fungizone* (Apothecon), and others *Ancobon* (ICN) – flucytosine

- § Antiminth (Pfizer) pyrantel pamoate
- *Aralen* (Sanofi) chloroquine HCl and chloroquine phosphate
- § artemether Artenam (Arenco, Belgium)
- § Artenam (Arenco, Belgium) artemether
- § artesunate (Guilin No. 1 Factory, People's Republic of China)
 - atovaquone *Mepron* (GlaxoSmithKline) atovaquone/proguanil – *Malarone* (GlaxoSmithKline) azithromycin – *Zithromax* (Pfizer)
- Bactrim (Roche) TMP/Sulfa
- § benznidazole Rochagan (Roche, Brazil) Biaxin (Abbott) – clarithromycin
- § Biltricide (Bayer) praziquantel
- † bithionol Bitin (Tanabe, Japan)
- † Bitin (Tanabe, Japan) bithionol
- § Brolene (Aventis, Canada) propamidine isethionate chloroquine HCl and chloroquine phosphate – Aralen (Sanofi), others
 - clarithromycin Biaxin (Abbott)
- Cleocin (Pfizer) clindamycin clindamycin – Cleocin (Pfizer), and others crotamiton – Eurax (Westwood-Squibb) dapsone – (Jacobus) Daraprim (GlaxoSmithKline) – pyrimethamine USP
- † diethylcarbamazine citrate USP Hetrazan
- Diflucan (Roerig) fluconazole
- § diloxanide furoate Furamide (Boots, United Kingdom) doxycycline – Vibramycin (Pfizer), and others
- † eflornithine (Difluoromethylornithine, DFMO) Ornidyl (Aventis)

· Also available generically.

^{*} Available in the US only from the manufacturer.

[§] Not available in the US; may be available through a compounding pharmacy.

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).

- § Egaten (Novartis) triclabendazole
- Elimite (Allergan) permethrin Ergamisol (Janssen) – levamisole Eurax (Westwood-Squibb) – crotamiton fluconazole – Diflucan (Roerig)
- Flagyl (Searle) metronidazole flucytosine – Ancobon (ICN)
- Fungizone (Apothecon) amphotericin
- § Furamide (Boots, United Kingdom) diloxanide furoate
- § furazolidone Furozone (Roberts)
- § Furozone (Roberts) furazolidone
- † Germanin (Bayer, Germany) suramin sodium
- § Glucantime (Aventis, France) meglumine antimonate
- † Hetrazan diethylcarbamazine citrate USP Humatin (Monarch) – paromomycin
- § Impavido (Zentaris, Germany) miltefosine iodoquinol – Yodoxin (Glenwood), and others itraconazole – Sporanox (Janssen-Ortho) ivermectin – Stromectol (Merck) ketoconazole – Nizoral (Janssen), and others
- † Lampit (Bayer, Germany) nifurtimox
- Lariam (Roche) mefloquine
- § Leshcutan (Teva, Israel) topical paromomycin levamisole – Ergamisol (Janssen) Malarone (GlaxoSmithKline) – atovaquone/proguanil malathion – Ovide (Medicis) mebendazole – Vermox (McNeil) mefloquine – Lariam (Roche)
- § meglumine antimonate *Glucantime* (Aventis, France)
- † melarsoprol Mel-B (Specia)
- † Mel-B (Specia) melarsoprol Mepron (GlaxoSmithKline) – atovaquone metronidazole – Flagyl (Searle), and others
- § miltefosine Impavido (Zentaris, Germany) NebuPent (Fujisawa) – pentamidine isethionate Neutrexin (US Bioscience) – trimetrexate
- § niclosamide Yomesan (Bayer, Germany)
- † nifurtimox Lampit (Bayer, Germany) nitazoxanide – Alinia (Romark)

· Also available generically.

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 Nizoral (Janssen) – ketoconazole Nix (GlaxoSmithKline) – permethrin § ornidazole – *Tiberal* (Roche, France) † Ornidyl (Aventis) – effornithine (Difluoromethylornithine, DFMO) Ovide (Medicis) - malathion § oxamniquine - Vansil (Pfizer) 8 Paludrine (Wyeth Ayerst, Canada; AstraZeneca, United Kingdom) - proguanil paromomycin - Humatin (Monarch); Leshcutan (Teva, Israel; (topical formulation not available in US) Pentam 300 (Fujisawa) – pentamidine isethionate pentamidine isethionate - Pentam 300 (Fujisawa), NebuPent (Fujisawa) † Pentostam (GlaxoSmithKline, United Kingdom) - sodium stibogluconate permethrin – Nix (GlaxoSmithKline), Elimite (Allergan) • praziquantel – *Biltricide* (Bayer) 8 primaguine phosphate USP 8 proguanil - Paludrine (Wyeth Averst, Canada: AstraZeneca, United Kingdom) proguanil/atovaquone – *Malarone* (GlaxoSmithKline) 8 propamidine isethionate – *Brolene* (Aventis, Canada) § pyrantel pamoate – Antiminth (Pfizer) pyrethrins and piperonyl butoxide - RID (Pfizer), and others pyrimethamine USP - Daraprim (GlaxoSmithKline) * quinidine gluconate (Eli Lilly) § quinine dihydrochloride quinine sulfate - many manufacturers • *RID* (Pfizer) – pyrethrins and piperonyl butoxide • *Rifadin* (Aventis) – rifampin rifampin - Rifadin (Aventis), and others § Rochagan (Roche, Brazil) – benznidazole Rovamycine (Aventis) – spiramycin † sodium stibogluconate - Pentostam (GlaxoSmithKline, United Kingdom) * spiramycin – *Rovamycine* (Aventis) Sporanox (Janssen-Ortho) – itraconazole Stromectol (Merck) - ivermectin sulfadiazine

· Also available generically.

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- † suramin sodium Germanin (Bayer, Germany)
- § Tiberal (Roche, France) ornidazole Tindamax (Presutti) – tinidazole tinidazole – Tindamax (Presutti) TMP/Sulfa – Bactrim (Roche), and others
- § triclabendazole Egaten (Novartis) trimetrexate – Neutrexin (US Bioscience)
- § Vansil (Pfizer) oxamniquine Vermox (McNeil) – mebendazole
- Vibramycin (Pfizer) doxycycline
- Yodoxin (Glenwood) iodoquinol
- § *Yomesan* (Bayer, Germany) niclosamide *Zithromax* (Pfizer) – azithromycin

§ Not available in the US; may be available through a compounding pharmacy.

^{*} Available in the US only from the manufacturer.

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[·] Also available generically.

| DRUGS FOR | Sexually Transmitted Infections

Original publication date - October 2004

Many infections can be transmitted during sexual contact. The text and tables that follow are limited to management of sexually transmitted infections (STIs) other than HIV, viral hepatitis and enteric infections. Guidelines are available from the US Centers for Disease Control and Prevention (CDC) with detailed recommendations for treatment of these diseases (MMWR Recomm Rep 2002; 51, RR-6:1). New guidelines are expected soon.

PARTNER TREATMENT — Complete treatment for STIs should include the sex partners of infected persons. Ideally, partners should be examined and tested for STIs, but that is often difficult to accomplish. Some clinicians and health departments, therefore, routinely treat sex partners without direct examination or counseling, either by prescription or by giving the medication for the partner to the index patient, a practice known as **expedited partner treatment** (EPT). Medical Letter consultants recommend using EPT when the partner is identifiable and treatment cannot otherwise be assured.

CHLAMYDIA — A single 1 g dose of azithromycin (*Zithromax*) or 7 days' treatment with a tetracycline are both effective for treatment of uncomplicated urethral or cervical infection caused by *Chlamydia trachomatis*. Taking azithromycin after a small snack (a few crackers or cookies) improves gastrointestinal (GI) tolerance. Seven days' treatment with generic doxycycline or another tetracycline costs less, but compliance may be a problem. Ofloxacin (*Floxin*, and others) or levofloxacin (*Levaquin*) for 7 days are effective but expensive alternatives; they are most useful when chlamydial infection cannot be distinguished clinically from bacterial urinary tract infection.

Drug	Dosage	Cost ¹
Azithromycin –	1 g PO once	
Zithromax (Pfizer)		\$24.43
Doxycycline –	100 mg PO bid x 7d	
average generic		15.68
Vibramycin (Pfizer)		66.36
Levofloxacin -	500 mg PO once x 7d	
Levaguin (Ortho-McNe	il)	73.50
Ofloxacin -	300 mg PO bid x 7d	
Floxin (Ortho-McNeil)		87.92
Amoxicillin ² –	500 mg PO tid x 7d	
average generic	0	9.24
Amoxil (GlaxoSmithKlin	ne)	11.55
	recent data (July 31, 2004) from NDCHealth, a healthcar	

In Pregnancy – Doxycycline, other tetracyclines and the fluoroquinolones generally should not be used during pregnancy. Azithromycin appears to be safe in pregnant women; most Medical Letter consultants consider it the treatment of choice (C Gardella, Curr Treat Opt Infect Dis 2003; 5:53). Amoxicillin (*Amoxil*, and others), an effective alternative, is also safe. Many patients, pregnant or not, cannot tolerate the GI effects of erythromycin, and erythromycin estolate is contraindicated in pregnancy. In general, treatment failure may be more common in pregnancy and repeat testing is recommended. Patients who fail treatment can usually be retreated with the same drug.

In Infancy – Children born to women with cervical *C. trachomatis* infection are at risk for conjunctivitis and pneumonia. Ophthalmic antibiotics used for gonococcal prophylaxis do not prevent ocular chlamydial infection in the newborn. For treatment of newborns with conjunctivitis or pneumonia caused by *C. trachomatis*, some clinicians have used systemic erythromycin for 14 days, but an association

Cost of Drugs for Gonorrhea					
Drug	Dosage	Cost [*]			
Cefixime – Suprax (Lupin)	400 mg PO once	\$8.41			
Cefpodoxime – Vantin (Pharmacia)	400 mg PO once	11.64			
Ceftriaxone – Rocephin (Roche)	125 mg IM once	16.58			
Ciprofloxacin – average generic	500 mg PO once	5.07			
Cipro (Bayer) Levofloxacin –	250 mg PO once	5.60			
Levaquin (Ortho-McNe Ofloxacin –	400 mg PO once	9.14			
Floxin (Ortho-McNeil) Spectinomycin –	2 g IM once	6.65			
Trobicin (Pharmacia) *Cost based on the most re					
macies nationwide availab tion services company.	ble from NDCHealth, a he	althcare informa-			

between hypertrophic pyloric stenosis and use of erythromycin has been reported (BE Mahon et al, J Pediatr 2001; 139:380). In one small study, a short course of oral azithromycin was effective for treatment of chlamydial conjunctivitis (MR Hammerschlag et al, Pediatr Infect Dis J 1998; 17:1049).

GONORRHEA — Single doses of cefixime (*Suprax*) orally or ceftriaxone (*Rocephin*) intramuscularly (IM) are highly effective for uncomplicated anogenital or pharyngeal infection, including infection with penicillin- and tetracycline-resistant strains of *Neisseria gonorrhoeae*. Cefpodoxime (*Vantin*) is another option for oral therapy, although experience is limited. Single-dose treatment with ciprofloxacin (*Cipro*, and others), ofloxacin or levofloxacin is highly effective when *N. gonorrhoeae* are susceptible, but strains with clinically significant fluoroquinolone resistance are common worldwide, especially in Asia and the Pacific Islands (including Hawaii), and are increasing in the western United States. Fluoroquinolone-resistant gonorrhea has been reported nationwide in the US in men who have sex with men (MMWR Morbid Mortal Wkly Rep 2004; 53:335). All patients with gonorrhea should also be treated for presumptive chlamydial infection (unless it is ruled out by diagnostic testing), usually with a single dose of azithromycin or 7 days of doxycycline (SB Lyss et al, Ann Intern Med 2003; 139:178).

Gonococcal ophthalmia, bacteremia, arthritis or meningitis in adults and all gonococcal infections in children are best treated with appropriate doses of a parenteral third-generation cephalosporin such as ceftriaxone.

In Pregnancy – Spectinomycin (*Trobicin*) can be used to treat pregnant women allergic to beta-lactam antibiotics, but is unreliable against pharyngeal gonococcal infection. Gentamicin (*Garamycin*, and others) is a possible alternative.

NONGONOCOCCAL NONCHLAMYDIAL URETHRITIS AND CERVICITIS — Nongonococcal urethritis (NGU) in men is often nonchlamydial as well. Possibly caused by *Ureaplasma urealyticum*, *Mycoplasma genitalium* or other (unknown) pathogens, it usually responds to azithromycin or doxycycline. NGU that does not resolve with azithromycin or doxycycline may respond to erythromycin or ofloxacin, or in some cases to treatment for trichomoniasis.

Mucopurulent cervicitis (MPC) has been characterized as the female counterpart of NGU in men (P Nyirjesy, Curr Infect Dis Rep 2001; 3:540). Like NGU, MPC generally responds to azithromycin or doxy-cycline. Empiric treatment for *N. gonorrhoeae* should also be given in areas with high prevalence.

FOLLOW-UP — Early rescreening, 3-4 weeks after treatment, to confirm cure is not recommended except for chlamydia in pregnant women

or when therapeutic compliance is in doubt. Late rescreening, 2-6 months after treatment, is indicated for all men and women with gonorrhea, for women with chlamydia, and probably for men with chlamydia to detect persistent infection or reinfection (P-A Mårdh and K Persson, Int J STD AIDS 2002; 13:363; CA Rietmeijer et al, Sex Transm Dis 2002; 29:65).

EPIDIDYMITIS — Acute epididymitis in men less than 35 years old is usually caused by *C. trachomatis* or, less frequently, *N. gonorrhoeae*. Older men or those who have had urinary tract instrumentation may have epididymitis due to enteric gram-negative bacilli or *Pseudomonas*. Gram-negative bacilli may also cause urethritis or epididymitis in men who practice insertive anal intercourse. When the organism is not known, epididymitis can be treated with ofloxacin or levofloxacin until microbiologic results are available.

PELVIC INFLAMMATORY DISEASE (PID) — *C. trachomatis* or *N. gonorrhoeae* cause about two thirds of cases of acute PID, but *Mycoplasma hominis* and various facultative and anaerobic bacteria may also be involved. Treatment regimens should include antimicrobial agents active against all of these pathogens. Parenteral regimens include either cefotetan (*Cefotan*) or cefoxitin (*Mefoxin*, and others), each plus doxycycline, or clindamycin (*Cleocin*, and others) plus an aminoglycoside. Parenteral therapy is continued until clinical improvement occurs, and then oral doxycycline is substituted to complete 14 days' total therapy. Recommended oral regimens are ofloxacin or levofloxacin, with or without metronidazole, or doxycycline after an initial IM dose of ceftriaxone (JD Ross, Curr Opin Infect Dis 2003; 16:37).

TRICHOMONIASIS — Oral metronidazole has been the treatment of choice for trichomoniasis. Tinidazole (*Tindamax* – Medical Letter 2004; 46:70), a nitroimidazole similar to metronidazole, was recently approved by the FDA for trichomoniasis; it is as effective as metronida-

Cost of Drugs for Trichomoniasis				
Drug	Dosage	Cost [*]		
Metronidazole –				
average generic	2 g PO once	\$2.36		
Flagyl (Pharmacia)		18.26		
Tinidazole –	2 g PO once			
Tindamax (Presutti)		14.48		
* Cost based on the most cies nationwide available ices company.				

zole and may be better tolerated. Intravaginal treatment with metronidazole is not effective. Sex partners must be treated simultaneously to prevent reinfection.

Treatment failures may be re-treated in both the patient and partner with a repeat single dose or with a longer course. Metronidazole-resistant strains of *T. vaginalis* can be treated with metronidazole 2 to 4 g/d for 7 to 14 days. A combination of tinidazole both orally (500 mg q.i.d.) and intravaginally (500 mg b.i.d.) for 14 days, or oral tinidazole alone 500 mg t.i.d. for 7 days also have been effective (JD Sobel et al, Clin Infect Dis 2001; 33:1341; WD Hager, Sex Transm Dis 2004; 31:343). An intravaginal tinidazole preparation is not commercially available, but can be compounded.

In pregnancy – Trichomoniasis in pregnancy has been associated with adverse pregnancy outcomes (D Soper, Am J Obstet Gynecol 2004; 190:281). Metronidazole is now believed to be safe during all stages of pregnancy and should be used to treat symptomatic trichomoniasis in pregnancy. However, in some placebo-controlled clinical trials among women with asymptomatic and symptomatic trichomoniasis, the frequency of preterm births has been higher in women treated with metron-

Infection in Pregnancy (Vibramycin') ² .3 OR Aztitromycin 1g oral OR Amoxicilin (Amoxi?) 300 mg Neonatal Ophthalmia or Pneumonia 20 mg/h Aztitromycin 2.3 100 mg EPIDIDYMITIS Oloxacin (Foxin') 300 mg OR Cevoltoxacin (Levaquin) 500 mg GONORRHEA ⁶ – Urethral, cervical, rectal or pharyngeal Cetiviaxone (Rocophin) 125 mg OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 2g IV q OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 2g IV q OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 2g IV q OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 2g IV q OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 2g IV q OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 00 mg OR Cetotatain (Cetotan) or cetoxitin (Metoxin') 2g IV q 00 mg OR Cetotatain (Metoxin') 2g IV q 00 mg 00 mg </th <th></th>	
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OR Celtrixine (<i>Cuprax</i>) 400 mg Celtrixaone (<i>Rocephin</i>) 125 mg ELVIC INFLAMMATORY DISEASE —parenteral Celotetan (<i>Celotan</i>) or 2g IV q celoxitin (<i>Meloxin</i> ') 2g IV plus doxycycline ³ 100 mg q12h, followed by doxy- cycline ³ 100 mg plus OR Clindamycin (<i>Cleocin</i> ') 900 mg plus gentamioin 2 mg/kg (<i>Garamycin</i> ') 1.5 mg until in	al once daily x10d
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Cetexitin (Metoxin*) 2g IV plus doxycycline ³ 100 mg q12h, followed by doxy- cycline ³ 100 mg plets OR Clindamycin (Cleccin*) 900 mg plus gentamioin 2 mg/kg (Garamycin*) 1.5 mg unti in	
cycline ³ 100 mg plete OR Clindamycin (<i>Cleccin'</i>) 900 mg plus gentamicin 2 mg/kg (<i>Garamycin'</i>) 1.5 mg until in	h levofloxacin ³ 500 mg IV once daily plus metronidazole 500 mg IV q8h 'or oral Ampicillin/sulbactam (<i>Unasyn</i>) 3g IV q til improved plus doxycycline ³ 100 mg orally
cycline ³ 100 mg plete OR Cilindamycin (<i>Cleccin'</i>) 900 mg plus gentamicin 2 mg/kg (<i>Garamycin'</i>) 1.5 mg until in	or IV q12h
OR Cilindamycin (<i>Cleocin'</i>) 900 mg plus gentamicin 2 mg/kg (<i>Garamycin'</i>) 1.5 mg until in	All continued until improved, then al bid to com- followed by doxycycline ³ 100 mg of bid to complete 14d ¹⁰
gentamicin 2 mg/kg (Garamycin*) 1.5 mg until in	
(Garamycin*) 1.5 mg until in	/ once, then
	g IV q8h ¹¹ ,
doxycycline ³ 100 mg 14d ¹⁰	al bid to complete
* Also available generically.	
 Related clinical syndromes include nonchlamydial nongonococcal urethritis and 2. Or oral tetracycline 500 mg qid. 	urvicitis.
3. Not recommended in pregnancy.	

All patients should also receive a ocurise of treatment effective for *Chlamydia*.
 Fluoroquinoles should not be used to treat genome-ta acquired in Alasi, Hawai, Israel or other areas where fluoroquinolone-resistant strains of *N genomhoese* are common.
 Recommended only for use during pregnancy in patients allergic to il-lactams. Not effective for pharyngeal infection.
 Some clinicates believe the addition of metroindizzole is not required.
 Or clinication: 450 mg coralig to complete 14 days.

11. A single daily dose of 3 mg/kg is likely to be effective, but has not been studied in pelvic inflammatory disease.

idazole (MA Klebanoff et al, N Engl J Med 2001; 345:487; JC Carey et al, Semin Perinatol 2003; 27:212; GG Kigozi et al, Am J Obstet Gynecol 2003; 189:1398).

VAGINAL INFECTIONS — Sulfonamide creams, other "broad-spectrum" vaginal preparations, and currently available preparations of *Lactobacillus* species or dairy products are not reliably effective for treatment or prevention of any vaginal infection. Douching is not effective for prevention or treatment of vaginal infection, may lead to upper genital tract infection, and should be discouraged.

BACTERIAL VAGINOSIS — The role of sexual transmission is unclear in bacterial vaginosis, in which normal H_2O_2 -producing *Lactobacillus* species are replaced by overgrowth with *Gardnerella* vaginalis, M. hominis, Mobiluncus and various anaerobes. Oral metronidazole for 7 days is usually effective for treatment. Single-dose oral metronidazole has similar short-term efficacy, but is followed by a higher rate of relapse. Vaginal metronidazole, or oral or vaginal clindamycin, are also effective. With any regimen, recurrence is common; re-treatment with the same agent is often effective. Treatment of sex partners does not reduce the frequency of recurrence.

In pregnancy – Bacterial vaginosis has been associated with premature labor and complications of delivery, and symptomatic bacterial vaginosis in pregnancy should be treated (CC Tebes et al, Infect Dis Obstet Gynecol 2003; 11:123). In controlled trials, however, treatment of asymptomatic bacterial vaginosis in pregnant women with oral metronidazole has not consistently reduced the frequency of adverse pregnancy outcomes, and vaginal clindamycin has not decreased the incidence of preterm delivery (JC Carey et al, N Engl J Med 2000; 342:534; M Kekki et al, Obstet Gynecol 2001; 97:643). Bacterial vaginosis has also been associated with an increased risk of

ype or Stage		Drugs of Choice	Dosage	Alternatives
PELVIC INFLAMMATOR	Y DISEAS	E (continued)		
-oral		Ofloxacin ³	400 mg oral bid x 14d	Cefoxitin 2g once
	OR	Levofloxacin ³	500 mg once daily x 14d	plus probenecid 1g
		+/- metronidazole9	500 mg oral bid x 14d	oral once followed by doxycycline ^{3,12} 100 mg oral bid x 14d
	OR	Ceftriaxone	250 mg IM once	
		followed by		
		doxycycline ^{3,12}	100 mg oral bid x 14d	
RICHOMONIASIS		Metronidazole (Flagyl*)	2g oral once	Metronidazole 375 or 500 mg oral bid x 7d
	OR	Tinidazole (Tindamax)	2g oral once	
BACTERIAL VAGINOSIS		Metronidazole	500 mg oral bid x 7d	Metronidazole 2g oral once ¹³ or Flagyl ER 750 mg once daily x 7d
	OR	Metronidazole gel 0.75% ¹⁴	5g intravaginally once or twice daily x 5d	Clindamycin 300 mg oral bid x 7d
	OR	Clindamycin 2% cream ¹⁴	5g intravaginally qhs x 3-7d	Clindamycin ovules ¹⁴ 100 mg intravaginally once daily x 3d
SYPHILIS				
Early (Primary, second	lary, or late			
		Penicillin G benzathine	2.4 MU IM once ¹⁵	Doxycycline ³ 100 mg oral bid x 14d
		Derizauline	Under-	
Late (more than one y	ear's durati	on, cardiovascular, gumma,	late-latent)	
		Penicillin G	2.4 MU IM	Doxycycline ³ 100 mg oral bid x 4wks
40		benzathine	wkly x 3wks	
Neurosyphilis ¹⁶		Penicillin G	3 to 4 MU IV q4h or 24 MU	Penicillin G procaine 2.4 million U IM daily plus probenecid 500 mg qid oral
			continuous IV infusion x 10-14d	both x 10-14d Ceftriaxone 2g IV once daily x
Congenital		Penicillin G	50,000 units/kg IV g8-12h	10-14d
Congenital		Pericilin G	for 10-14d	
	OB	Penicillin G	50,000 units/kg IM daily	
	OIT	procaine	for 10-14d	
				Ciprofloxacin ³ 500 mg
CHANCBOID ¹⁷		Azithromycin		
CHANCROID ¹⁷	OB	Azithromycin Ceftriaxone	1g oral once 250 mg IM once	
CHANCROID ¹⁷	OR	Azithromycin Ceftriaxone	250 mg IM once	oral bid x 3d
	OR	Ceftriaxone	250 mg IM once	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d
	OR	Ceftriaxone	•	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal
CHANCROID ¹⁷ GENITAL WARTS ¹⁸	OR	Ceftriaxone Trichloroacetic or bichloroacetic	250 mg IM once	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal Laser surgery
	OR	Ceftriaxone Trichloroacetic or bichloroacetic acid, or podophyllin ³	250 mg IM once	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal
	OR	Ceftriaxone Trichloroacetic or bichloroacetic acid, or podophyllin ³ or liquid nitrogen	250 mg IM once 1-2x/wk until resolved	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal Laser surgery
	OR	Ceftriaxone Trichloroacetic or bichloroacetic acid, or podophyllin ³ or liquid nitrogen Imiquimod 5% (Aldara) ³	250 mg IM once 1-2x/wk until resolved 3 3x/wk x 16wks	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal Laser surgery
	OR	Ceftriaxone Trichloroacetic or bichloroacetic acid, or podophyllin ³ or liquid nitrogen	250 mg IM once 1-2x/wk until resolved	oral bid x 3d Erythromycin ⁴ 500 mg oral qid x 7d Surgical removal Laser surgery

All regimens, especially single-dose cellrisxone, are less effective in HIV-inflected patients.
 Recommendations for external gentila warts. Eludi introger can also be used for varginal, urefbral, and oral warts. Podolfox or imiquimod can be used for urefbral meatus warts. Trichloroacetic or bichloroacetic acid can be used for anal warts.

pelvic inflammatory disease (JF Peipert et al, Am J Obstet Gynecol 1997; 177:1184).

VULVOVAGINAL CANDIDIASIS — Vulvovaginal candidiasis is not sexually transmitted, but is often found incidentally in women with STIs. Many remedies are available for vulvovaginal candidiasis. One-, 3- and 7-day regimens of intravaginal butoconazole, clotrimazole, miconazole, terconazole or tioconazole are effective for uncomplicated vulvovaginal candidiasis (Medical Letter 2001; 43:3). A single oral dose of fluconazole (*Diflucan*, and others) 150 mg is as effective as 7 days of clotrimazole or miconazole intravaginally and is preferred by many patients, but can cause GI symptoms; severe episodes may require a second oral dose of fluconazole 72 hours after the first (JD Sobel et al, Am J Obstet Gynecol 2001; 185:363).

Recurrences are common after all regimens. Six-month prophylactic regimens of oral fluconazole 150 mg once weekly, have been effective in most women with multiple culture-proven, recurrent infections (JD Sobel et al, N Engl J Med 2004; 351:876). Vulvovaginal candidiasis occasionally is caused by azole-resistant *Candida glabrata*, which in one study was treated successfully with 14-day courses of daily intravaginal boric acid 600 mg in a gelatin capsule or topical flucytosine cream (JD Sobel et al, Am J Obstet Gynecol 2003; 189:1297). It is unclear whether such cases are increasing in frequency (JD Sobel, Curr Infect Dis Rep 2001; 3:546).

SYPHILIS — Parenteral penicillin G remains the drug of choice for treating all stages of syphilis. Primary, secondary or latent syphilis known to be of less than one year's duration should be treated with an intramuscular injection of benzathine penicillin G, a repository formulation. Doxycycline is also usually effective if compliance is assured. A longer course of treatment, preferably with intramuscular penicillin G

		Dosage	
Acyc	lovir (Zovirax*)	400 mg oral tid x 7-10d	Acyclovir 200 mg oral 5x/d x 7-10d
R Famo	iclovir (Famvir)	250 mg oral tid x 7-10d	
R Valac	yclovir (Valtrex)	1g oral bid x 7-10d	
s)			
Acyc	lovir	5-10 mg/kg IV q8h x 5-7d	
ces ¹⁹			
Acyc	lovir	400 mg oral bid	Acyclovir 200 mg oral, 2-5x/d
R Famo	ciclovir	250 mg oral bid	
R Valad	cyclovir	500 mg-1g once daily ²⁰	
currences ²¹			
Acyc	lovir	800 mg oral tid x 2d or 400 mg oral tid x 3-5d ²	2
R Famo	ciclovir	125 mg oral bid x 3-5d ²²	
R Valar	cyclovir	500 mg oral bid x 3d	
	R Famo R Valac Is) Acyc Ices ¹⁹ Acyc R Famo R Valac Acyc R Famo R Valac Acyc R Famo R Valac	R Valacyclovir (Valtrax) (s) Acyclovir cces ¹⁹ Acyclovir R Famciclovir R Valacyclovir ccurrences ²¹ Acyclovir R Famciclovir R Famciclovir R Valacyclovir N Valacyclovir	x 7-10d R Famciclovir (<i>Famvin</i>) R Valacyclovir (<i>Valrex</i>) Acyclovir (<i>Valrex</i>) Acyclovir 400 mg oral bid R Famciclovir 250 mg oral bid R Valacyclovir 500 mg oral bid R Valacyclovir 500 mg oral bid R Valacyclovir 800 mg oral tid x 2d or 400 mg oral tid x 3-5d ²² R Famciclovir 125 mg oral bid x 3-5d ²²

benzathine, is required for late syphilis (more than one year's duration) other than neurosyphilis.

In small trials, a single dose of oral azithromycin (2 g) appeared promising for treatment of early syphilis (EW Hook III et al, Sex Transm Dis 2002; 29:486), but treatment failures have been reported in some populations particularly, men who have sex with men, and the prevalence of azithromycin-resistant strains of *Treponema pallidum* is high and may be rising (SA Lukehart et al, N Engl J Med 2004; 351:154). Until the results of larger trials are available, azithromycin should be used against syphilis with caution, if at all.

Neurosyphilis – Symptomatic neurosyphilis, including ophthalmic or otic infection, requires treatment with high doses of aqueous penicillin G IV or procaine penicillin G IM with probenecid.

Syphilis and HIV – Most clinicians treat HIV-infected patients with syphilis and normal CSF with standard penicillin doses for the stage of

syphilis, but some patients may need higher doses or longer treatment. Even high-dose IV therapy fails to cure neurosyphilis in up to 25% of HIV-infected patients. Controversy exists as to whether subclinical or asymptomatic neurosyphilis, which is common, regardless of the stage of infection, in patients with high titers (\geq 1:32) of non-treponemal sero-logical tests and in HIV-infected persons with CD4 lymphocyte counts \leq 350 cells/mm³, should be treated with high-dose penicillin in the same manner as symptomatic neurosyphilis (CM Marra et al, J Infect Dis 2004; 189:369).

Ceftriaxone for 10 days is probably as effective as IV penicillin for treatment of neurosyphilis in HIV-infected patients, but its efficacy for parynchymal or late forms of neurosyphilis has not been studied (CM Marra et al, Clin Infect Dis 2000; 30:540).

Syphilis in Pregnancy – Syphilis in pregnant women should be treated with penicillin in doses appropriate to the stage of the disease. When pregnant women with syphilis are allergic to penicillin, the US Public Health Service recommends hospitalization, desensitization and treatment with penicillin. Re-treatment in subsequent pregnancies is unnecessary in the absence of clinical or serological evidence of new or persistent infection.

Congenital Syphilis – A positive serological test for syphilis in a newborn without stigmata of syphilis may be due either to passive transfer of maternal antibodies or to prenatal infection. If there is no definite evidence of adequate treatment of the mother with penicillin during the pregnancy, Medical Letter consultants recommend prompt treatment of such infants rather than waiting 3 to 6 months to see if the antibody titer falls.

CHANCROID — Chancroid, caused by *Haemophilus ducreyi*, is rare in the US. A single dose of azithromycin or ceftriaxone is usually effective, but may be less effective in HIV-infected patients.

Cost of Drugs for Genital Herpes (initial episode)			
Drug	Dosage	Cost [*]	
Acyclovir –	400 mg PO tid x 7-10d		
average generic		\$38.01	
Zovirax (GSK)		66.57	
Famciclovir -	250 mg PO tid x 7-10d		
Famvir (Novartis)	0	87.15	
Valacyclovir -	1 g PO bid x 7-10d		
Valtrex (GSK)	•	115.64	
	nt based on the most recent data nationwide available from NDCH es company.		

PEDICULOSIS AND SCABIES — *Phthirus pubis* (pubic lice), which can be found on eyelashes, back, axillary and leg hairs as well as pubic areas, and *Sarcoptes scabiei* infestation (scabies) can both be transmitted sexually. The drug of choice for pubic lice is topical 1% permethrin, and for scabies is 5% permethrin. Oral ivermectin (*Stromectol*) (200 mcg/kg) is also effective as a single dose for treatment of lice, and has been used once daily for 3 days for resistant infections with scabies. Crusted scabies, a serious complication usually seen in patients with AIDS or other immunodeficiencies, should be treated with both permethrin and ivermectin (P del Giudice, Curr Opin Infect Dis 2002; 15:123).

GENITAL WARTS AND HUMAN PAPILLOMAVIRUS (HPV) INFECTION — External genital warts are caused by human papillomavirus, usually type 6 or 11; other types (16, 18 and others) cause dysplasia and neoplasia of the cervix, anus and genital skin. No form of HPV-specific treatment has been shown to eradicate the virus or to modify the risk of cervical dysplasia or cancer, and no single treatment is uniformly effective in removing warts or preventing recurrence. Trichloroacetic acid, podophyllin, and cryotherapy (with liquid nitrogen or a cryoprobe) remain the most widely used treatments for external genital warts, but the response rate is only 60% to 70%, and at least 20%

to 30% of responders will have a recurrence. Imiquimod 5% cream (*Aldara*), an immune modulator, and podofilox 0.5% solution or gel (*Condylox*) are no more effective, but they offer the advantage of self-application by patients at home.

No treatment is recommended for subclinical HPV infection in the absence of dysplasia or neoplasia. The short duration of most HPV infections in young women suggests that these infections and the low-grade cervical dysplasia often associated with them should both be treated conservatively as they often regress spontaneously (AB Moscicki et al, JAMA 2001; 285:2995). Vaccines to prevent HPV infection are in development and appear promising (LA Koutsky et al, N Engl J Med 2002; 347:1645).

In Pregnancy – Imiquimod, podofilox and podophyllin are not recommended for use during pregnancy. Topical trichloroacetic acid, cryotherapy, electrodesiccation and electrocauterization are options and can be used in pregnancy. Scissor excision or laser therapy are effective and well-tolerated if the clinician is properly trained.

GENITAL HERPES — Acyclovir (*Zovirax*, and others), famciclovir (*Famvir*) or valacyclovir (*Valtrex*) taken orally for 7-10 days shortens the duration of pain, viral shedding and systemic symptoms in initial herpes simplex virus genital infection. Continuous suppressive therapy with the same drugs decreases symptomatic recurrences and subclinical shedding without cumulative toxicity or apparent development of resistance in immunocompetent persons. Acyclovir-resistant strains of HSV have been reported, however, in previously treated HIV patients (M Reyes et al, Arch Intern Med 2003; 163:76).

Acyclovir, famciclovir or valacyclovir also speeds healing of symptomatic recurrent lesions if treatment is started early; treatment with 2

days of "high-dose" acyclovir (800 mg t.i.d.) or a 3-day course of valacyclovir appears to be as effective as longer regimens in healthy patients (A Wald et al, Clin Infect Dis 2002; 34:944; PA Leone et al, Clin Infect Dis 2002; 34:958). Most patients experience little improvement, however, and most Medical Letter consultants prefer continuous suppressive therapy to waiting for recurrences and treating them episodically.

In one study, valacyclovir 500 mg daily in heterosexual monogamous couples reduced the risk of sexual transmission of HSV (L Corey et al, N Engl J Med 2004; 350:11).

In pregnancy – Although acyclovir is not approved for treatment of pregnant women, its use during pregnancy has not been associated with an increased risk of congenital abnormalities, and many clinicians prescribe the drug for treatment of first episodes of genital herpes during pregnancy. Suppression of recurrent genital herpes in pregnant women near term reduces the need for cesarean sections to avoid neonatal herpes infections.

PROPHYLAXIS FOLLOWING SEXUAL ASSAULT — Many experts recommend that sexually assaulted adults and adolescents be given treatment to prevent sexually transmitted infections, including therapy for gonorrhea (cefixime, ciprofloxacin or ceftriaxone), chlamydial infection (azithromycin or doxycycline) and bacterial vaginosis and trichomoniasis (metronidazole or tinidazole). Prophylaxis is not routinely used for children. If not previously immunized, vaccination against hepatitis B (*Engerix-B, Recombivax HB*) should be initiated. Some experts also recommend post-exposure prophylaxis against HIV infection such as zidovudine (*Retrovir*) plus lamivudine (*Epivir*) with or without a protease inhibitor (Treatment Guidelines 2004; 2:1) in high risk situations such as multiple assailants or an assailant believed to be HIV-infected; treatment should be started within 72 hours.

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Patients planning to travel to other countries often ask physicians for advice about immunizations and prevention of diarrhea and malaria. More detailed advice for travelers is available from the Centers for Disease Control (CDC) at 877-FYI-TRIP (877-394-8747) or www.cdc.gov/travel. Recommendations for the treatment of parasitic diseases are available in the public reading room of The Medical Letter's web site (www.medicalletter.org).

MALARIA

Countries with a risk of malaria are listed on page 211. Some countries with both urban and rural malaria transmission may not have malaria in the most frequently visited major cities.

Prevention – Drugs for prevention of malaria are listed in the table on page 213. No drug for malaria prevention is 100% effective. Travelers to countries that have malaria should seek prompt medical attention for febrile illness while traveling and after return, especially in the first 2 months.

Chloroquine is the drug of choice for prevention of malaria in the few places that still have chloroquine-sensitive malaria: Central America west of the Panama Canal Zone, Paraguay, northern Argentina, Mexico, Haiti, the Dominican Republic and most of the Middle East (chloroquine resistance has been reported in Iran, Yemen, Oman, and Saudi Arabia). In rural areas of China where malaria occurs, it is generally chloroquine sensitive. Only Hainin and Yunnan provinces have chloroquine resistance.

For prevention of **chloroquine-resistant malaria**, 3 drugs with equal efficacy are available in the US. *Malarone*, a fixed-dose combination of atovaquone and proguanil taken once daily (Medical Letter 2000; 42:109) is generally the best tolerated (D Overbosch et al, Clin Infect Dis 2001; 33:1015; P Schlagenhauf et al, BMJ 2003; 327:1078). It can cause gastrointestinal disturbances, and was recently associated with a case of Stevens-Johnson syndrome (M Emberger et al, Clin Infect Dis 2003; 37:e5).

Mefloquine is taken once weekly, but recent reports of serious psychiatric adverse effects have prompted the manufacturer, along with the FDA, to strengthen the drug's contraindications and warnings. It is contraindicated in patients with a history of depression, anxiety, psychosis, schizophrenia or other major psychiatric disorder, seizures, or cardiac conduction abnormalities. Dizziness, headache, insomnia and disturbing dreams are the most common CNS adverse effects. If a patient develops anxiety, depression, restlessness or confusion while taking mefloquine, it should be stopped (www.fda.gov/medwatch/SAFETY/2002/safety02.htm#lariam). Adverse effects of mefloquine in children are similar to those in adults (TA Albright et al, J Travel Med 2002; 9:289).

Doxycycline, which frequently causes gastrointestinal disturbances and can cause photosensitivity and vaginitis, offers an inexpensive oncedaily alternative for travelers >8 years old who are not pregnant. Both doxycycline and atovaquone/proguanil are effective for prophylaxis against **mefloquine-resistant malaria**, which occurs in the border regions between Thailand and Myanmar and Thailand and Cambodia.

For prevention of malaria **after departure** from areas where *Plasmodium vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some Medical Letter consultants prescribe **primaquine phosphate** 15 mg base daily for adults in

AFRICA	Mauritania	Dominican Republic**	Indonesia**
Angola	Mauritius**	Ecuador**	Iran**
Benin	Mayotte	El Salvador**	Iraq**
Botswana	Mozambique	French Guiana	Korea, North**
Burkina Faso	Namibia	Guatemala**	Korea, South**
Burundi	Niger	Guyana	Kyrgystan**
Cameroon	Nigeria	Haiti	Laos**
Central African Republic	Rwanda	Honduras**	Malaysia**
Chad	São Tomé and Príncipe	Mexico**	Myanmar**
Comoros	Senegal	Nicaragua	Nepal**
Congo	Sierra Leone	Panama**	Pakistan
Côte d'Ivoire	Somalia	Paraguay**	Philippines**
Democratic Republic of	South Africa**	Peru**	Saudi Arabia**
the Congo	Sudan	Suriname**	Sri Lanka
Djibouti	Swaziland	Venezuela**	Syria**
Equatorial Guinea	Tanzania		Tajikistan
Eritrea**	Togo	ASIA	Thailand**
Ethiopia**	Uganda	Afghanistan	Turkey**
Gabon	Zambia	Armenia	Turkmenistan**
Gambia, The	Zimbabwe**	Azerbaijan**	Uzbekistan
Ghana		Bangladesh**	Viet Nam**
Guinea	AMERICAS	Bhutan**	Yemen**
Guinea-Bissau	Argentina**	Cambodia**	
Kenya	Belize**	China, People's	OCEANIA
Liberia	Bolivia**	Republic**	Papua New Guinea
Madagascar	Brazil	East Timor	Solomon Islands
Malawi	Colombia**	Georgia**	Vanuatu
Mali	Costa Rica**	India	

COUNTRIES WITH A RISK OF MALARIA*

Only includes countries for which prophylaxis is recommended. Seasonal and country-specific information is available at www.cdc.gov/travel and by phone for medical personnel from the Malaria Branch of the CDC at 770-488-7788.

** No malaria in major urban areas.

addition or, for children, 0.3 mg base/kg/d during the last two weeks of prophylaxis ("terminal prophylaxis"). Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases. Primaquine can cause hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, which is most common in African, Asian, and Mediterranean peoples. Travelers should be screened for G-6-PD deficiency before treatment. Primaquine should not be used during pregnancy. For patients unable to take other drugs, several studies have shown that daily primaquine beginning one day before departure from home and continued during travel until 2 days after leaving the malarious area can provide effective prophylaxis against chloro-

quine-resistant *P. falciparum* and *P. vivax* (JK Baird et al, Clin Infect Dis 2003; 37:1659).

Protection Against Insect Bites – To minimize insect bites, travelers should wear light-colored, long-sleeved shirts, pants and socks. The most effective topical insect repellent is N, N-diethyl-m-toluamide (DEET) (Medical Letter 2003; 45:41; MS Fradin and JF Day, N Engl J Med 2002; 347:13). Sprayed on exposed skin, DEET repels mosquitoes, ticks, chiggers, fleas, gnats and some flies. DEET is available in formulations of 5-40% and 100%. Higher concentrations do not improve efficacy, but usually protect longer; 30-35% DEET formulations are preferred by Medical Letter consultants. A long-acting DEET formulation originally developed for the US Armed Forces (US Army Extended Duration Topical Insect and Arthropod Repellent – EDTIAR) containing 25-33% DEET (*Ultrathon*) can provide protection for 6-12 hours.

Used as directed, DEET concentrations of up to 50% are probably safe in children and infants >2 months of age; it should not be used at all in infants <2 months old. One study found that applying DEET regularly during the second and third trimesters of pregnancy did not result in any adverse effects on the fetus (R McGready et al, Am J Trop Med Hyg 2001; 65:285). DEET may decrease the effectiveness of sunscreens; when they are used together, a sunscreen with a higher SPF should be used.

Permethrin (*Duranon, Permanone* and others) is an insecticide that is available in liquid and spray form for use on clothing, mosquito nets, tents and sleeping bags for protection against mosquitoes and ticks. It is more effective than DEET against ticks. After application to clothing, it remains active for several weeks through multiple launderings. If bednets or tents are immersed in the liquid, the effect can last for

Drug		Adult dosage	Pediatric dosage	Cost ¹
Chloro	quine-resistant areas:			
	Atovaquone/proguanil ² – <i>Malarone</i>	250 mg/100 mg (1 tablet) daily	11-20 kg: 62.5 mg/25 mg daily 21-30 kg: 125 mg/50 mg daily 31-40 kg: 187.5 mg/75 mg daily >40 kg: 250 mg/100 mg daily	\$108.24
OR	Mefloquine ³ – average generic price <i>Lariam</i>	250 mg (228 mg base) once/week	<5 kg: 5 mg/kg once/week 5-10 kg: 1/8 tablet once/week 11-20 kg: ½ tablet once/week 21-30 kg: ½ tablet once/week 31-45 kg: ¾ tablet once/week >45 kg: 1 tablet once/week	67.97 79.87
	Doxycycline hyclate ⁴ – average generic price <i>Vibramycin</i> quine-sensitive areas:	100 mg daily	2 mg/kg/day up to 100 mg/day	35.26 204.68
	Chloroquine phosphate ⁵ average generic price Aralen	500 mg (300 mg base) once/week	5 mg/kg base once/week, up to adult dose of 300 mg base	26.81 40.46
 wide p Begin in pre Eur J Begin appro trimes page betwe Begin 	provided by NDCHealth, a health of ning 1 to 2 days before travel and gnancy. There are case reports of Clin Pharmacol 2003; 59:545). ning 1 to 2 weeks before travel an ved for use during pregnancy. Ho ter of pregnancy and possibly duri 111; BL Smoak et al, J Infect Dis en Thailand and Myanmar and Th	are information services compani continuing daily for 1 week after atovaquone/proguanil being user d continuing weekly for 4 weeks wever, it has been reported to be ing early pregnancy as well (CDI 1997; 176:831). Resistance to mi alland and Cambodia. continuing daily for 4 weeks after	doses, according to data from retail phar yr, February 2004. leaving a malaria zone. It is not known w d to treat malaria in pregnant women (R I after leaving malaria zone. Melloquine ha safe for prophylactic use during the sac- y. Health Information for Infermational Tra stopping in a significant problem in the b leaving malaria zone. Use of tetracycline:	hether it is si McGready et as not been ond or third vel, 2003-200 order regions

about 6 months. It can also be used in combination with DEET for increased protection. Using permethrin-impregnated mosquito nets while sleeping can be helpful when rooms are not screened or air-conditioned.

A new product, picaridin (KBR3023; Bayrepel; *Autan Repel*, and others – SC Johnson), a piperidine derivative available in the US, Europe and Australia, may prove to be as effective as DEET. In a controlled field trial, 19.2% picaridin was as effective against mosquitoes (>95% protection for 8 hours) as US Army EDTIAR (SP Frances et al, J Med Entomol 2002; 39:541). [Since this article was published, *The Medical Letter* has reviewed picaridin. See page 235.]

TRAVELERS' DIARRHEA

The most common cause of travelers' diarrhea, usually a self-limited illness lasting several days, is infection with enterotoxigenic *Escherichia coli* (Z-D Jiang et al, J Infect Dis 2002; 185:497). *Campylobacter, Shigella, Salmonella, Aeromonas*, viruses and parasites are less common. Children tend to have more severe illness and are particularly susceptible to dehydration (WM Stauffer et al, J Travel Med 2002; 9:141). Travelers to areas where hygiene is poor should avoid raw vegetables, fruit they have not peeled themselves, unpasteurized dairy products, cooked food not served steaming hot, and tap water, including ice.

Prophylaxis – Medical Letter consultants generally do not prescribe antibiotic prophylaxis for travelers' diarrhea, but rather instruct the patient to begin self-treatment when symptoms are distressing or persistent. Some travelers, however, such as immunocompromised patients, might benefit from prophylaxis. In such patients, once-daily ciprofloxacin (*Cipro*) 500 mg, levofloxacin (*Levaquin*) 500 mg, ofloxacin (*Floxin*) 300 mg or norfloxacin (*Noroxin*) 400 mg can be given and are generally well tolerated. Bismuth subsalicylate (*Pepto-Bismol*, and others) can also prevent diarrhea in travelers who take 2 tablets 4 times/d, but it is less effective than antibiotics.

Treatment – Loperamide (*Imodium*, and others), an over-the-counter synthetic opioid (4-mg loading dose, then 2 mg orally after each loose stool to a maximum of 16 mg/d for adults), usually relieves symptoms of travelers' diarrhea in <24 hours. Loperamide is approved for use in children >2 years old.

If diarrhea is severe or associated with fever or bloody stools, self-treatment with a 3-day course of ciprofloxacin 500 mg b.i.d., levofloxacin 500

mg once daily, norfloxacin 400 mg b.i.d. or ofloxacin 300 mg b.i.d. is recommended. One- and two-day courses may also be effective (R Steffen et al, J Travel Med 2003; 10:38). Azithromycin (*Zithromax*) (1000 mg as a single dose or 500 mg/d x 3d) is an alternative (JA Adachi et al, Clin Infect Dis 2003; 37:1165) and is the drug of choice for travelers to areas with a high prevalence of fluoroquinolone-resistant *Campylobacter*, such as Thailand. It can also be used in other select groups, including pregnant women, children (10 mg/kg/d x 3d), and patients who do not respond to a fluoroquinolone in 48 hours.

[Rifaximin (*Xifaxan*), a non-absorbed oral antibiotic indicated for treatment of travelers' diarrhea caused by noninvasive strains of *E. coli.*, was approved by the FDA after publication of this article. *The Medical Letter* has reviewed rifaximin (*Xifaxan*). See page 232.]

Packets of **oral rehydration salts** mixed in potable water can help maintain electrolyte balance, particularly in children and the elderly. They are available from suppliers of travel-related products and in some pharmacies in the US, and from pharmacies overseas.

IMMUNIZATIONS

Immunocompromised or pregnant patients generally should not receive live virus vaccines, such as those for measles and yellow fever, although in some situations the benefit might outweigh the risk. Guidelines for pediatric and adult immunization have been published (Morbid Mortal Wkly Rep MMWR 2003; 52:965 and 2004; 53[1]:Q1). Pediatric travelers should be up to date on all routine immunizations in addition to receiving country-specific vaccines (HH Balkhy, Int J Antimicrob Agents 2003; 21:193; SM Mackell, Clin Infect Dis 2003; 37:1508).

Cholera – The risk of infection with cholera is very low in tourists. The parenteral vaccine licensed in the US is no longer available. One oral vaccine called *Dukoral* is available in some countries in Europe (Chiron) and in Canada (Aventis Pasteur). It is not currently recommended for routine use in travelers. Vaccination might be considered for travelers who plan to do relief work (refugee camps).

Haemophilus influenzae type b (Hib) – Hib is endemic worldwide. Previously unvaccinated infants <15 months of age should receive 2 doses of Hib vaccine (*ActHIB*, and others) at least 4 weeks apart before travel; children 15 months-5 years should receive a single Hib dose.

Hepatitis A – Hepatitis A vaccine (*Havrix* – GlaxoSmithKline; *Vaqta* – Merck) is recommended for all susceptible travelers going anywhere other than Canada, Australia, New Zealand, Japan or developed countries in Europe (AS Craig and W Schaffner, N Engl J Med 2004; 350:476). Prevaccination serologic testing is not recommended, except in select circumstances such as travelers who originally emigrated from high-risk areas or are members of high-risk populations such as men who have sex with men.

Hepatitis A vaccination for adults and children 2-18 years old usually consists of two IM doses separated by either 6-12 months (*Havrix*) or 6-18 months (*Vaqta*). Immunity after 2 doses of either vaccine lasts at least 20 years and perhaps longer (K Van Herck et al, J Med Virol 2001; 63:1; P Van Damme et al, Lancet 2003; 362:1065). Additional booster doses are not recommended. Second doses given up to 8 years after the first dose have produced protective antibody levels (S Iwarson et al, J Travel Med 2004; 11:120; S Iwarson, Vaccine 2002; 20:2017). Patients who received a first dose of one vaccine will respond to a second dose of the other. In Europe, *Vaqta* and *Havrix* are both approved for use in children \geq 1 year of age; a three-dose regimen has been used in infants (AE Fiore et al, Pediatr Infect Dis J 2003; 22:354; R Dagan et al, Pediatr Infect Dis J 2000; 19:1045).

Antibodies reach protective levels 2-4 weeks after the first dose. Even when exposure to the disease occurs sooner than 4 weeks after vaccination, the traveler is usually protected because of the relatively long incubation period of hepatitis A (average 28 days). According to the CDC, travelers who need full protection earlier than 4 weeks should also receive immunoglobulin (0.02 mL/kg IM) with the first dose of vaccine. Most Medical Letter consultants, however, no longer give immunoglobulin except to children <2 years of age and pregnant women.

Hepatitis B – Vaccination against hepatitis B (*Engerix-B* – GlaxoSmithKline; *Recombivax HB* – Merck) is now a routine pediatric immunization in the US. It is recommended for previously unvaccinated travelers going to highly or moderately endemic areas (Medical Letter 2001; 43:67) if they plan to stay for a long time, return frequently, live among the local population, receive medical or dental care, or undergo cosmetic needle punctures for tattoos or body-piercing. Risk areas include all of Africa and Asia, the Middle East, Southern Europe, the Southern and Western Pacific Islands, tropical South America and the Caribbean. People who might have unprotected sexual contact with new partners should be immunized against hepatitis B whether traveling or not.

Primary immunization usually consists of 3 doses given IM at 0, 1 and 6 months. An accelerated schedule of 3 doses given at 0, 1 and 2 months, followed by a fourth at 12 months, is approved for *Engerix-B* in the US. Accelerated schedules given at 0, 7 and 21 days plus a fourth dose 12 months after the first or 0, 7 and 14 days plus a fourth dose 6 months after the first can be used if necessary. A 2-dose schedule of *Recombivax* at 0 and 4-6 months is approved in the US for adolescents 11-15 years old. An interrupted hepatitis B vaccination series does not need to be restarted. A 3-dose series started with one vaccine may be completed with the other. Immunity is believed to be life-long

for most adults who have completed a primary immunization series, but about 3-5% of adults may not respond to the primary series.

Hepatitis A/B – A combination vaccine containing the same antigenic components as *Engerix-B* and pediatric *Havrix* (*Twinrix* – GlaxoSmithKline) is available for patients \geq 18 years old. It is given in 3 doses at 0, 1 and 6 months; at least 2 doses should be given before travel. Accelerated schedules of 0, 1 and 3 weeks with a fourth dose 12 months after the first, or 0, 1 and two weeks with a fourth dose at least 6 months after the first, can be given if necessary but are not FDA-approved (J Zuckerman, Drugs 2003; 63:1779). The combined vaccine can be used to complete an immunization series started with monovalent hepatitis A and B vaccines (B Kallinowski et al, Vaccine 2000; 19:16). *Twinrix Junior* is available in Canada and Europe for children 1-15 years old.

Influenza – Influenza may be a risk to travelers if the virus is circulating among the local population at the travel destination or when tourist groups include travelers from countries where seasonal influenza activity is occurring (TM Uyeki et al, Clin Infect Dis 2003; 36:1095). Influenza vaccine is sometimes available in the US until the end of June. High-risk patients (>65 years old or anyone ≥ 6 months old with certain chronic diseases) from the Northern Hemisphere who travel to the Southern Hemisphere during that region's influenza season (April-September) should consider being immunized on arrival.

Available influenza vaccines do not protect against the highly pathogenic strains of avian influenza A (H5N1) that have caused disease in humans in recent years. The CDC recommends that travelers to countries in Asia with documented outbreaks avoid live poultry markets, farms, and contact with surfaces that appear to be contaminated with poultry feces, and only eat poultry products that are well cooked (Morbid Mortal Wkly Rep MMWR 2004; 53:97). Travelers should wash their hands frequently with soap and water or use an alcoholbased hand rub.

Japanese encephalitis – Japanese encephalitis is an uncommon but potentially fatal mosquito-borne viral disease that occurs in rural Asia, especially near pig farms and rice paddies. The attack rate in travelers has been very low (DR Shlim and T Solomon, Clin Infect Dis 2002; 35:183). A vaccine is available in the US (*JE-Vax* – Aventis Pasteur) and should be considered for travelers >1 year old who expect a long stay (usually considered \geq 4 weeks) in rural areas or heavy exposure to mosquitoes (such as adventure travelers), particularly during the rainy season.

Three doses are given over 2 to (preferably) 4 weeks. Allergic reactions including urticaria and angioedema, local injection-site reactions, and mild systemic adverse effects such as fever, headache and myalgias occur in up to 20% of patients. The last dose should be given at least 10 days before departure due to the unpredictable allergic adverse effects. The duration of immunity is unknown; a booster can be given after 24 months.

Measles – Adults born after 1956 who have not received 2 doses of live measles vaccine (not the killed vaccine that was commonly used in the 1960s) after their first birthday and do not have a physician-documented history of infection or laboratory evidence of immunity should receive a single dose of measles or measles-mumps-rubella (MMR) vaccine before traveling. Both are attenuated live-virus vaccines.

Children \geq 12 months old should receive 2 doses of MMR vaccine at least 28 days apart before traveling to countries where measles is endemic. Children 6-11 months old should receive 1 dose before traveling, but will still need two subsequent doses for routine immunization, one at 12-15 months and one at 4-6 years.

Meningococcal disease – Meningococcal vaccine is recommended for adults and children >2 years old who are traveling to areas where epidemics are occurring, or to the "meningitis belt" (semi-arid areas of sub-Saharan Africa extending from Senegal and Guinea eastward to Ethiopia) from December to June (ZA Memish, Clin Infect Dis 2002; 34:84). Saudi Arabia requires a certificate of immunization for pilgrims during the Hajj. Immunization should also be considered for travelers who will be living in a dormitory or refugee camp, or working in a health care setting (A Wilder-Smith and Z Memish, Int J Antimicrob Agents 2003; 21:102).

A quadrivalent single-dose meningococcal polysaccharide vaccine (*Menomune* – Aventis Pasteur) is available against *Neisseria meningitidis* serogroups A, C, Y, and W135. The duration of immunity is at least 3 years; it may be shorter in children <4 years old. Conjugate vaccines against serogroups A and C available outside the US may be more effective in children <2 years old. [*Menactra*, a conjugated quadrivalent meningococcal vaccine was approved by the FDA after the publication of this article. *The Medical Letter* has reviewed *Menactra*. See page 227.]

Polio – Adults who have not previously been immunized against polio should receive a primary series of inactivated polio vaccine (IPV) if traveling to areas where polio is endemic (Africa and the Indian Subcontinent) or to areas with documented outbreaks. Previously unimmunized children should also receive a primary series of IPV. If protection is needed within 4 weeks, a single dose of IPV is recommended. Travelers to risk areas who have previously completed a primary series and have never had a booster should receive a booster dose of IPV.

Rabies – Rabies is highly prevalent in Africa, India, Asia and parts of Latin America, but the risk to travelers is low. Pre-exposure immunization

against rabies is recommended for travelers with an occupational risk of exposure, for those planning extended stays in endemic areas, especially children, and for outdoor-adventure travelers going to rural destinations in endemic areas (H Wilde et al, Clin Infect Dis 2003; 37:96). The 2 vaccines available in the US (*Imovax* – Aventis Pasteur; *RabAvert* – Chiron) are both given at 0, 7 and 21-28 days. After a bite or skin-penetrating scratch from a potentially rabid animal, patients should promptly receive 2 additional doses. Without preexposure immunization, treatment requires rabies immune globulin and 5 doses (over 28 days) of an approved vaccine, both frequently unavailable in developing countries.

Tetanus and Diphtheria – Everyone who has had a primary series as a child should receive a tetanus-diphtheria toxoid (Td) booster injection once every 10 years. Before traveling to areas with endemic diphtheria, children should complete a primary series (3 doses) of a diphtheria-tox-oid-containing vaccine.

Tick-Borne Encephalitis (TBE) – TBE occurs in Scandinavia, Western and Central Europe and countries of the former USSR, mainly in rural forested areas. Risk is greatest from April to August (U Dumpis et al, Clin Infect Dis 1999; 28:882). Immunization is recommended only for travelers who will spend extensive time outdoors in rural areas. The vaccine, which is not approved in the US, is usually given in 3 doses over 9-12 months, but can be given over as few as 2 or 3 weeks, and is available in Europe (*Encepur* – Chiron; *FSME-Immun Inject* – Baxter AG). It can be obtained in Canada through the Emergency Drug Release Program by contacting the Special Access Programme, Health Protection Branch (613-941-2108).

Typhoid – Typhoid vaccine is recommended for travelers to developing countries in Central and South America, Africa and Asia, especially if they plan a long stay or may be living in unhygienic conditions. A

purified capsular polysaccharide parenteral vaccine (*Typhim Vi* – Aventis Pasteur) for adults and children ≥ 2 years old is given as a single IM dose at least 2 weeks before departure. A booster is recommended every 2 years.

A live-attenuated oral vaccine (*Vivotif Berna* – Berna Products) is available for adults and children ≥ 6 years old. It is taken every other day as a single capsule (at least 1 hour before eating) for a total of 4 capsules, beginning no later than 2 weeks before departure; it protects for about 5 years. Gastrointestinal disturbance is common (EM Begier at al, Clin Infect Dis 2004; 38:771). Antibiotics should be avoided from the day before the first capsule until 2 days after the last.

Yellow Fever – Yellow fever vaccine, a single-dose attenuated live virus vaccine prepared in eggs, should be given at least 10 days before travel to endemic areas, which include much of tropical South America and sub-Saharan Africa between 15°N and 15°S (TP Monath and MS Cetron, Clin Infect Dis 2002; 34:1369). Some countries in Africa require an International Certificate of Vaccination against yellow fever from all entering travelers; other countries in Africa, South America and Asia require evidence of vaccination from travelers coming from or traveling through endemic or infected areas. The vaccine is available in the US only at centers certified by state health departments (directory available at www2.ncid.cdc.gov/travel/yellowfever). Boosters are given every 10 years, but immunity probably lasts much longer.

Yellow fever vaccine is contraindicated in travelers with egg allergy. Severe systemic illness, including fatal organ failure, has been associated rarely with the vaccine; the risk appears to be greater in first-time recipients, especially those >65 years old (MMWR Recomm Rep 2002; 51 RR-17:1; Morbid Mortal Weekly Rep MMWR 2002; 51:989). The vaccine should be avoided if possible in infants <9

months old and is contraindicated in infants <6 months old because of the risk of vaccine-induced encephalitis. If other live vaccines (measles, MMR) are not administered simultaneously with yellow fever vaccine, administration should be separated by one month to avoid a diminished immune response to the vaccines.

SOME OTHER INFECTIONS

Dengue – Dengue fever is a viral disease transmitted by mosquito bites that occurs worldwide in tropical and subtropical areas, including cities (RV Gibbons and DW Vaughn, BMJ 2002; 324:1563). Major epidemics have occurred in recent years in Southeast Asia, sub-Saharan Africa, and Central and South America. Travelers from the US and Europe have contracted the disease while vacationing at popular tourist destinations in the Caribbean, Mexico and Southern Asia (C Stephan et al, Infection 2002; 30:225). Prevention of mosquito bites during the day, particularly in early morning and late afternoon, is the only way to protect against dengue fever; no vaccine is currently available.

Leptospirosis – Leptospirosis, a bacterial disease that occurs in many domestic and wild animals, is endemic worldwide, but the highest incidence is in tropical and subtropical areas. Transmission to humans usually occurs through contact with water or damp soil contaminated by the urine of infected animals (AR Bharti et al, Lancet Infect Dis 2003; 3:757). Travelers at increased risk, such as those who engage in recreational water activities, hikers, bikers or adventure travelers should consider chemoprophylaxis with doxycycline 200 mg orally once a week, beginning 1-2 days before and continuing throughout the period of exposure. No human vaccine is available in the US.

SARS – After travelers' diarrhea, respiratory infection is the most common infectious disease affecting travelers (K Leder et al, Clin

Infect Dis 2003; 36:399). In the winter of 2003 a new coronavirus caused Severe Acute Respiratory Syndrome (SARS) and disrupted travel to much of Southeast Asia and Canada (F Fleck, Bull WHO 2003; 81:625). The CDC recommends that travelers to areas reporting current SARS cases avoid places where the disease is likely to be transmitted: health care settings and markets selling live animals (particularly civet cats). Travelers should also wash their hands frequently and monitor their health for 10 days after leaving a SARS area. If fever or respiratory illnesss develops, they should be seen by a physician, who should be alerted to a potential SARS exposure before the visit (www.cdc.gov/ncidod/sars/travel_advice.htm).

Sexually-transmitted diseases – Many travelers have new sexual contacts during their journeys and are at increased risk for acquiring sexually transmitted diseases including HIV, particularly when visiting developing countries with a high incidence of STDs in the local population (ZA Memish and AO Osoba, Int J Antimicrob Agents 2003; 21:131). Hepatitis B is the only STD for which a vaccine is available. Travelers should be aware of this risk and of safe sex practices for disease prevention; use of condoms should be emphasized.

NON-INFECTIOUS RISKS OF TRAVEL

Many non-infectious risks are associated with travel. Injuries, particularly **traffic accidents** and **drowning**, which account for the majority of travel-related deaths, and **sunburn** occur in many travelers.

Altitude – Rapid exposure to altitudes >10,000 feet (3000 meters) can cause acute mountain sickness (headache, fatigue, nausea, insomnia, dyspnea) in 30-40% of travelers; pulmonary and cerebral edema are less common (1%) (PW Barry and AJ Pollard, BMJ 2003; 326:915). Sleeping altitude appears to be especially important in determining whether symptoms

develop. The most effective preventive measure is acclimatization by a 2to 4-day stay at intermediate altitude (6000-8000 feet) and gradual ascent to higher elevations.

Acetazolamide (*Diamox*, and others), a carbonic anhydrase inhibitor, taken in a dosage of 125-250 mg b.i.d. (or 500 mg daily with the slow-release formulation *Diamox Sequels*) beginning 1-2 days before ascent and continuing at high altitude for 48 hours or longer, decreases the incidence and severity of acute mountain sickness (B Basnyat et al, High Alt Med Biol 2003; 4:45). The recommended dose for children is 5 mg/kg/d in 2 or 3 divided doses. Travelers who are allergic to sulfa drugs should not take acetazolamide. Symptoms can be treated after they occur by descent to a lower altitude or by giving supplemental oxygen, especially during sleep. When descent is impossible, dexamethasone (*Decadron*, and others) 4 mg q6h, acetazolamide 250-500 mg q12h, or the two together, may be helpful (P Hackett and RC Roach, N Engl J Med 2001; 345:107).

Venous Thromboembolism – Prolonged immobilization (>8 hours) increases the risk of lower extremity deep vein thrombosis (DVT), particularly in travelers with risk factors for thrombosis (T Schwarz et al, Arch Intern Med 2003; 163:2759; I Martinelli et al, Arch Intern Med 2003; 163:2771). Nevertheless, flight-related symptomatic pulmonary embolism is rare (E Perez-Rodriguez et al, Arch Intern Med 2003; 163:2766; SR Hertzberg et al, Vasc Med 2003; 8:21).To minimize the risk, travelers should be advised to walk around or exercise while sitting by flexing/extending ankles and knees, to drink plenty of fluids and to avoid alcohol. Compression stockings can decrease the risk of asymptomatic DVT (JH Scurr et al, Lancet 2001; 357:1485). One study found that giving a single dose of a low-molecular-weight heparin or aspirin as prophylaxis to travelers at high risk (past history of thrombosis, obesity, malignancy, increased platelets) reduced the incidence of DVT (MR Cesarone et al, Angiology 2002; 53:1), but there is little evidence supporting this approach.

Jet Lag – Disturbance of body and environmental rhythms resulting from a rapid change in time zones gives rise to jet lag, which is characterized by insomnia, decreased quality of sleep, loss of concentration, and irritability. It is usually more severe after eastward travel. A variety of interventions have been tried, but none is proven to be effective. Shifting daily activities to correspond to the time zone of the destination country before arrival, along with taking short naps, remaining well hydrated, avoiding alcohol and pursuing activities in sunlight on arrival, might help. The dietary supplement melatonin (5 mg started the night before travel and continued for 1-5 days after arrival) has been reported to facilitate the shift of the sleep- wake cycle and decrease symptoms in some patients (A Herxheimer and KJ Petrie, Cochrane Database Syst Rev 2002; 2:CD001520). As a dietary supplement in the US, however, its purity and potency are suspect (Medical Letter 2002; 44:84). Zolpidem (*Ambien*) started the first night after travel and taken for three nights may also be helpful (AO Jamieson et al, Sleep Med 2001; 2:423).

Motion Sickness – The pathogenesis of motion sickness is poorly understood. The prescription cholinergic blocker scopolamine in a patch or oral formulation can decrease symptoms. *Transderm Scop* is applied to the skin behind the ear 6-8 hours before exposure and changed every three days. The oral 8-hour tablet (*Scopace*) is taken 1 hour before exposure. Oral promethazine (*Phenergan*, and others) is a highly sedating alternative (CR Sherman, J Travel Med 2002; 9:251). Over-the-counter drugs such as dimenhydrinate (*Dramamine*, and others) or meclizine (*Bonine*, and others) are less effective, but may be helpful for milder symptoms.

Menactra: A Meningococcal Conjugate Vaccine

Menactra: A Meningococcal Conjugate Vaccine

Originally published in The Medical Letter - April 2005; 47:29

The FDA has approved a conjugated polysaccharide vaccine, *Menactra* (Sanofi-Pasteur), for protection against disease caused by *Neisseria meningitidis* in people 11-55 years old, and the manufacturer has applied for approval for use in children 2 to 10 years old. An unconjugated meningoccocal polysaccharide vaccine (*Menomune* – Sanofi-Pasteur) has been licensed in the US since 1981.

THE DISEASE — About 2000 cases of meningococcal disease occur in the US each year. The case fatality rate is more than 10% for meningitis and up to 40% for meningococcemia. Among survivors, about 20% are left with permanent disabilities such as hearing loss, neurological damage and limb amputations. Rates of meningococcal disease are highest in infancy, but a second peak occurs in adolescence and young adulthood. About 3% of cases occur in college students, especially freshmen living in dormitories.¹

SEROGROUPS — Five major serogroups of *N. meningitidis*, A, B, C, Y and W-135, cause most human infection. Serogroup A is the leading cause of disease in the "meningitis belt" across sub-Saharan Africa, but now occurs only rarely in the US. Serogroups B, C and Y are major causes of endemic disease in the US; serogroup B causes about one third of cases overall and more than half of cases in infants. In the US during the 1990s, the frequency of local outbreaks of meningococcal infection and the proportion of infection caused by serogroup C increased among 15 to 24 year olds, and these outbreaks were associated with a fatality rate of about 20%.² Serogroup W-135 is an uncommon cause of meningococcal disease in the US, but has caused outbreaks among pilgrims to Mecca during the Hajj and regional outbreaks throughout the world.^{3,4}

THE NEW VACCINE — *Menactra* contains 4 mcg of meningococcal polysaccharide from each of 4 serogroups (A, C, Y and W-135) conju-

Menactra: A Meningococcal Conjugate Vaccine

gated to diphtheria toxoid protein. Polysaccharides stimulate B-cells to produce antibodies, but optimal immune responses, particularly in young infants, require that the antigen be recognized by T-cells. Coupling polysaccharides to proteins provokes a T-cell dependent response that improves immunogenicity.⁵ Neither *Menactra* nor *Menomune* provides protection against serogroup B, which does not have an immunogenic polysaccharide capsule.

IMMUNOGENICITY — The safety and immunogenicity of the new vaccine was evaluated in two unpublished studies that are summarized in the package insert. Among 1280 adults (18-55 years old) and 423 adolescents (11-18 years old) who received *Menactra*, seroconversion rates for serogroups A, C, Y and W-135 measured by serum bactericidal antibody assay were 100%, 99%, 91% and 97% in the adults and 100%, 99%, 98% and 99% in the adolescents. These rates were about the same with *Menomune*. A study of US children 2-10 years old who received either *Menomune* or *Menactra* found that antibody titers were higher for all 4 serogroups in the children who received *Menactra*.⁶

EFFICACY — No controlled clinical trials have been conducted with *Menactra*. FDA approval was based on its immunogenicity and the effectiveness of other vaccines in preventing meningococcal disease. The meningococcal outbreaks that were once frequent in US military recruits have become rare since the military began routine immunization of recruits with meningococcal (unconjugated) vaccine. Unconjugated and conjugated (available in Europe) meningococcal vaccines have both been effective in preventing outbreaks caused by serogroup C.^{7,8} In the UK, after 80% of children less than 18 years old were vaccinated within 1 year, the annual number of deaths from serogroup C infection fell from 67 in 1999 to 5 in 2001; in the unvaccinated population >20 years old, there was no decrease in the number of deaths. Among younger children, the number of cases of disease declined even among the unvaccinated, suggesting that high antibody levels induced

by the vaccine led to decreased nasopharyngeal carriage and herd immunity.9-11

USE IN YOUNGER CHILDREN — Studies in children <3 years old who were immunized with *Menactra* have found inconsistent immunogenicity.^{12,13} Studies from the UK, where vaccination with a conjugated meningococcal serogroup C vaccine is routine at 2, 3 and 4 months of age, have found that children have little protective antibody left at age 4, but show a rapid response to a booster dose.^{14,15}

ADVERSE EFFECTS — The most common adverse reactions to *Menactra* include headache, fatigue and malaise, in addition to pain, redness and induration at the site of injection. The rates of these reactions are higher than with *Menomune*, but similar to those with tetanus toxoid. *Menactra* is contraindicated in persons with known hypersensitivity to any component of the vaccine or to latex, which is used in the vial stopper.

RECOMMENDATIONS — In February 2005, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination with *Menactra* for pre-adolescent children aged 11 or 12, and "catch-up" vaccination for previously unvaccinated teens entering high school and college freshmen.¹⁶ Other groups for whom the vaccine is recommended as a priority are microbiologists with frequent exposure to *N. meningitidis*, travelers to areas of the world where disease is hyperendemic, and persons with splenectomy or functional asplenia. The old unconjugated vaccine is effective and can still be used in all of these groups.¹ Revaccination could be considered for persons previously vaccinated with *Menomune*. Recommendations for use of the new vaccine are under review by the American Academy of Pediatrics and American Academy of Family Physicians.

DOSAGE, COST AND ADMINISTRATION — *Menactra* is given as a single intramuscular injection. The need for and timing of booster doses is unknown. According to the manufacturer, a single dose of the new vaccine

Menactra: A Meningococcal Conjugate Vaccine

will cost \$82.00, compared to \$86.10 for *Menomune*. An unpublished study summarized in the package insert found that when tetanus-diphtheria (Td) vaccine was given with *Menactra*, antibody responses to Td were similar and those to *Menactra* were higher than when the vaccines were given separately.

CONCLUSION — Based on immunogenicity studies and experience with other vaccines, the new meningococcal conjugate vaccine (*Menactra*) should be highly effective in preventing meningococcal disease in older children, adolescents and adults. The duration of protection with the new vaccine is unknown. Immunogenicity has been inconsistent in infants and toddlers.

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- 5. JU Ruggeberg and AJ Pollard. Meningococcal vaccines. Paediatr Drugs 2004; 6:251.
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- R Borrow et al. Antibody persistence and immunological memory at age 4 years after meningococcal group C conjugate vaccination in children in the United Kingdom. J Infect Dis 2002; 186:1353.
- CL Trotter et al. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004; 364:365.
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Rifaximin (Xifaxan) for Travelers' Diarrhea

Originally published in The Medical Letter - September 2004: 46:74

Rifaximin (Xifaxan - Salix), a non-absorbed oral antibiotic derived from rifampin (Rifadin, and others), has been approved by the FDA for treatment of travelers' diarrhea caused by noninvasive strains of Escherichia coli in patients 12 years of age or older. It has been available in Europe since 1987.

Drug class	Rifamycin antimicrobial
Mechanism of action	Inhibition of bacterial RNA synthesis
Formulation	200-mg tablets
Peak plasma levels	<0.4% absorbed from GI tract
Metabolism	Not metabolized
Excretion	97% excreted unchanged in feces

PHARMACOLOGY

TREATMENT OF TRAVELERS' DIARRHEA — The most common cause of travelers' diarrhea, usually a self-limited illness lasting several days, is infection with noninvasive enterotoxigenic (ETEC) or enteroaggregative (EAEC) strains of E. coli. Less common pathogens include Shigella, Salmonella, Campylobacter, Aeromonas, viruses and parasites.

For mild to moderate diarrhea, loperamide (Imodium, and others), an over-the-counter antiperistaltic agent, or bismuth subsalicylate (Pepto-Bismol, and others) usually relieves symptoms in less than 24 hours. Packets of oral rehydration salts mixed in potable water can help maintain electroyte balance.

When diarrhea is severe or associated with fever or bloody stools, selftreatment with a 3-day course of ciprofloxacin, levofloxacin, norfloxacin, or ofloxacin is usually recommended. One- and two-day courses may also be effective.¹ Azithromycin (*Zithromax*) is an alternative for travelers to areas with fluoroquinolone-resistant Campylobacter, such as Thailand, and for pregnant women, children and those who do not respond to a fluoroquinolone within 48 hours.

RUG	DOSAGE	COST ¹
zithromycin –	1000 mg once	\$31.24
Zithromax (Pfizer)	or 500 mg once/d x 3d	46.86
Ciprofloxacin –	500 mg bid x 3d	
average generic		30.42
Cipro (Bayer) sustained release		33.60
Cipro XR	1000 mg once/d x3d	28.17
evofloxacin –	500 mg once/d x 3d	
Levaquin		31.50
(Ortho-McNeil)		
Vorfloxacin – Noroxin (Merck)	400 mg bid x 3d	22.56
Ofloxacin – <i>Floxin</i> (Ortho-McNeil)	300 mg bid x 3d	37.68
Rifaximin – <i>Xifaxan</i> (Salix)	200 mg tid x 3d	32.76

ANTIBACTERIAL ACTIVITY — Rifaximin reaches high concentrations in the intestinal tract and is active *in vitro* against a broad range of enteropathogens, including ETEC, EAEC, *Shigella* spp. and *Salmonella* spp. It is much less active against *Campylobacter jejuni* and *Yersinia enterocolitica*.²

CLINICAL STUDIES — The 2 published clinical trials summarized in the table were conducted in travelers with diarrhea mostly caused by *E. coli*.^{3,4} One unpublished clinical trial summarized in the package insert found rifaximin ineffective for many patients with fever and/or blood in the stool, and for those who had *C. jejuni* isolated as the sole pathogen. Another unpublished study described in the package insert found that among 13 volunteers challenged with *Shigella flexneri* and treated with rifaximin after developing diarrhea, 8 required rescue treatment with ciprofloxacin because they did not respond, developed severe dysentery or relapsed. A study available only as an abstract that compared rifaximin 200 mg once, twice or 3 times a day to placebo for prevention of diarrhea in 209 travelers to Mexico found that 82%, 75% and 85% of travelers receiving rifaximin remained diarrhea-free after 2 weeks compared to 42% with placebo.⁵

ADVERSE EFFECTS — No severe adverse effects were observed in clinical trials with rifaximin. There have been a few postmarketing

Rifaximin (Xifaxan) for Travelers' Diarrhea

STUDY	DESIGN (N)	REGIMENS	RESULTS
R Steffen et al ³	Randomized, double-blind (380) placebo-controlled	Rifaximin 600 mg/d x3d	Median time to last unformed stool: rifaximin 32.5 hours; placebo 60 hours
HL DuPont ⁴	Randomized, double-blind (187)	Rifaximin 400 mg bid x3d versus ciprofloxacin 500 mg bid x3d	Median time to last unformed stool: rifaximin 25.7 hours; ciprofloxacin 25 hours; no statistically significant difference

reports of hypersensitivity reactions, including allergic dermatitis, rash, angioneurotic edema, urticaria and pruritus. The drug is contraindicated in patients who are allergic to rifamycins. It has not been studied in pregnant women, but was teratogenic when given orally to animals at doses 2 to 33 times the usual human oral dose adjusted for body surface area.

DRUG INTERACTIONS — Rifaximin can induce CYP3A4, but, unlike rifampin, has not caused clinically relevant interactions with drugs metabolized by CYP3A4 such as oral contraceptives and midazo-lam (*Versed*).

CONCLUSION — Rifaximin (*Xifaxan*), a non-absorbed oral antibiotic, was about as effective as ciprofloxacin for treatment of travelers' diarrhea, mostly caused by *E. coli*. It is not effective against infections associated with fever or blood in the stool or those caused by *Campylobacter jejuni*. Rifaximin has fewer adverse effects and drug interactions than systemic antibiotics, but should not be taken during pregnancy.

- R Steffen et al. Travelers' diarrhea in the new millennium: consensus among experts from German-speaking countries. J Travel Med 2003; 10:38.
- JM Sierra et al. In vitro activity of rifaximin against enteropathogens producing traveler's diarrhea. Antimicrob Agents Chemother 2001; 45:643.
- R Steffen et al. Therapy of travelers' diarrhea with rifaximin on various continents. Am J Gastroenterol 2003; 98:1073.
- HL DuPont et al. Rifaximin versus ciprofloxacin for the treatment of traveler's diarhea: a randomized, double-blind clinical trial. Clin Infect Dis 2001; 33:1807.
- HL DuPont et al. Rifaximin, a non-absorbed antibiotic prevents travelers' diarrhea. Presented at Digestive Disease Week, New Orleans, LA, May 2004; abstract 94.

Picaridin - A New Insect Repellent

Picaridin – A New Insect Repellent

Originally published in The Medical Letter - June 2005; 47:46

Picaridin (KBR 3023), which has been used as an insect repellent for years in Europe and Australia (*Autan Repel*, and others), is now available in the US in a 7% solution as *Cutter Advanced* (Spectrum Brands). The US Centers for Disease Control and Prevention (CDC) is recommending it as an alternative to DEET.

DEET — DEET is available in the US in many formulations with concentrations of 5%-40% and 100%; higher concentrations offer complete protection for a longer period of time, but the duration of effectiveness reaches a plateau at a 50% concentration. A long-acting DEET formulation, originally developed for the US Armed Forces (US Army Extended Duration Topical Insect and Arthropod Repellent, EDTIAR) is available in the US as *Ultrathon* (3M). *Ultrathon* contains 25% (in aerosol) or 33% (in cream) DEET in a polymer formulation, which prevents loss from the skin surface through absorption and evaporation. Studies have shown that it provides complete protection against mosquitoes for 6-12 hours.

Safety and Acceptability – Despite earlier concerns, toxic and allergic reactions to DEET have been uncommon, and serious adverse effects are rare.¹ Some patients dislike its odor and find it irritating or uncomfortably oily or sticky on the skin. DEET can damage clothes made from synthetic fibers such as spandex or rayon and can also damage leather and plastics on eyeglass frames and watch crystals.

PICARIDIN — Laboratory and field studies documenting the efficacy of picaridin are summarized in the table on page 236. No published data are available on the efficacy of the 7% solution now available in the US. Insect repellents are registered by the Environmental Protection Agency (EPA); they do not require FDA approval.

Picaridin – A New Insect Repellent

Some CEINICAE STODIES OF FICARIDIN					
STUDY	REPELLENT	DESIGN/VECTOR	RESULTS		
AM Pretorius et al (2003) ² South Africa	20% picaridin lotion vs. 20% DEET lotion	Laboratory tests/ticks: Amblyomma hebraeum (African tick bite fever)	Protection after 1,2,3 and 4 hours: Picaridin: >85%, 56%, 55%, 54% DEET: >85%, 84%, 68%, 71%		
A Badolo et al (2004) ³ Burkina Faso	Picaridin vs. DEET (varying concentrations)	Laboratory tests/mosquitoes: Aedes aegypti (yellow fever & dengue) Anopheles gambiae (malaria)	<u>Relative potency:</u> Picaridin at least as effective as DEET; both less effective against An. gambiae than Ae. aegypti		
SP Frances et al (2004) ⁴ Australia	19.2% picaridin vs. 20% DEET and 35% DEET	Field trial/mosquitoes: Culex annulirostris (arbovirus) Anopheles bancrofti and meraukensis (malaria)	>95% protection: Cx. annulirostris: Picaridin 5 hrs; DEET >7 hrs Anopheles spp: Picaridin 1 hr, 20% DEET <1h, 35% DEET 1 hr		
C Costantini et al (2004) ⁵ Burkina Faso	Picaridin vs. DEET (varying concentrations)	Field trial/mosquitoes: Anopheles spp. (98.5%) (malaria)	Relative potency after 10 hr: Picaridin similar to DEET		

SOME CLINICAL STUDIES OF PICARIDIN

Safety and Acceptability – In Australia and in Europe, no serious toxicity has been reported with picaridin. It has shown no evidence of dermal, organ or reproductive toxicity or carcinogenicity in animals, except for some hepatic toxicity in rats at extremely high doses.^{6,7} Unlike DEET, it is odorless, does not feel greasy or sticky, is less likely to irritate the skin, and does not damage plastics or fabrics.

DOSAGE AND COST — The manufacturer recommends spraying picaridin on the skin every 3 to 4 hours. *Cutter Advanced* (with 7% picaridin) is the only formulation available commercially in the US; a 6-ounce pump-spray bottle can be purchased over the counter for about \$4.

CONCLUSION — The 7% picaridin formulation currently sold in the US might be as effective in repelling mosquitoes as low concentrations of DEET, but no data are available. Higher strength products sold in Europe (with 20% picaridin) protect against mosquitoes for up to 8 hours and against ticks for a shorter period of time. If higher concentrations become available in the US, picaridin could replace DEET due to its superior tolerability, but its long-term safety is less well established.

^{1.} Insect Repellents. Med Lett Drugs Ther 2003; 45:41.

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- A Badolo et al. Evaluation of the sensitivity of Aedes aegypti and Anopheles gambiae complex mosquitoes to two insect repellents: DEET and KBR 3023. Trop Med Int Health 2004; 9:330.
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PRINCIPAL ADVERSE EFFECTS OF ANTIMICROBIAL DRUGS

Adverse effects of antimicrobial drugs vary with dosage, duration of administration, concomitant therapy, renal and hepatic function, immune competence, and the age of the patient. The principal adverse effects of antimicrobial agents are listed in the following table. The designation of adverse effects as "frequent," "occasional" or "rare" is based on published reports and on the experience of Medical Letter consultants. Information about adverse interactions between drugs, including probable mechanisms and recommendations for clinical management, are available in the Medical Letter Adverse Drug Interactions Program.

ABACAVIR (Ziagen)

Frequent: hypersensitivity reaction with fever, GI or respiratory symptoms and rash Occasional: arthralgias; anemia; lactic acidosis Rare: anaphylaxis; pancreatitis; hyperglycemia

ACYCLOVIR (Zovirax, others)

Frequent: local irritation at infusion site

Occasional: local reactions with topical use; headache, rash, nausea, diarrhea, vertigo, and arthralgias with oral use; decreased renal function sometimes progressing to renal failure; metabolic encephalopathy; bone marrow depression; abnormal hepatic function in immunocompromised patients

Rare: lethargy or agitation; tremor, disorientation; hallucinations; transient hemiparesthesia

ADEFOVIR (Hepsera)

Frequent: asthenia; headache; abdominal pain

Occasional: hepatitis exacerbation after drug discontinuation

Rare: increased serum creatinine; renal tubular dysfunction with high doses (>60 mg/d)

ALBENDAZOLE (Albenza)

Occasional: abdominal pain; reversible alopecia; increased serum transaminases **Rare:** leukopenia; rash; renal toxicity

AMANTADINE (Symmetrel, others)

Frequent: livedo reticularis and ankle edema; insomnia; dizziness; lethargy Occasional: depression; psychosis; confusion; slurred speech; congestive heart failure; orthostatic hypotension; urinary retention; GI disturbance; rash; visual disturbance; sudden loss of vision; increased seizures in epilepsy **Rare:** convulsions; leukopenia; neutropenia; eczematoid dermatitis; oculogyric episodes; photosensitivity

AMIKACIN (Amikin)

Occasional: vestibular damage; renal damage; fever; rash Rare: auditory damage; CNS reactions; blurred vision; nausea; vomit ing; neuromuscular blockade and

apnea, may be reversible with calcium salts; paresthesias; hypotension

AMINOSALICYLIC ACID (Paser)

Frequent: GI disturbance Occasional: allergic reactions; liver damage; renal irritation; blood dyscrasias; thyroid enlargement; malabsorption syndrome

Rare: acidosis; hypokalemia; encephalopathy; vasculitis; hypoglycemia in diabetics

AMOXICILLIN — See Penicillins

AMOXICILLIN/CLAVULANIC ACID — See Penicillins

AMPHOTERICIN B DEOXYCHOLATE

(Fungizone, others) Frequent: renal damage; hypokalemia; thrombophlebitis at site of peripheral vein infusion; anorexia; headache; nausea; weight loss: bone marrow suppression with reversible decline in hematocrit: chills, fever, vomiting during infusion, possibly with delirium, hypotension or hypertension, wheezing, and hypoxemia, especially in cardiac or pulmonary diease Occasional: hypomagnesemia; normocytic, normochromic anemia Rare: hemorrhagic gastroenteritis; blood dyscrasias; rash; blurred vision peripheral neuropathy; convulsions; anaphylaxis: arrhythmias: acute liver failure: reversible nephrogenic diabetes insipidus: hearing loss; acute pulmonary edema; spinal cord damage with intrathecal use

AMPHOTERICIN B LIPID FORMU-

LATIONS (Ambisone, Abelcet, Amphotec) — See page 121.

AMPICILLIN- See Penicillins

AMPICILLIN/SULBACTAM — See Penicillins

AMPRENAVIR (Agenerase)

Frequent: GI disturbance; oral and perioral paresthesias; rash; hypersensitivity with fever Occasional: hyperglycemia; increased aminotransferase activity; hyperlipidemia; abnormal fat distribution Rare: severe rash including Stevens-Johnson syndrome; hemolytic anemia

ARTEMETHER (Artenam)

Occasional: neurological toxicity; possible increase in length of coma;

increased convulsions; prolongation of QTc interval

ARTESUNATE

Occasional: ataxia; slurred speech; neurological toxicity; possible increase in length of coma; increased convulsions; prolongation of QTc interval

ATAZANAVIR (Reyataz)

Frequent: hyperbilirubinemia; rash; nausea

Occasional: increased cholesterol and triglycerides; depression; dizziness; fatigue; fever; headache **Rare:** insomnia; peripheral neuropathy; PR prolongation, heart block; angioedema; alopecia; Stevens-Johnson syndrome; gout; myasthenia, hepatitis; diabetes; pancreatitis

ATOVAQUONE (Mepron, Malarone

[with *proguanil*]) **Frequent:** rash; nausea **Occasional:** diarrhea; increased aminotransferases; cholestasis

AZITHROMYCIN (Zithromax)

Occasional: nausea; diarrhea; abdominal pain; headache; dizziness; vaginitis Rare: angioedema; cholestatic jaundice; photosensitivity; reversible doserelated hearing loss

AZT - See Zidovudine

AZTREONAM (Azactam)

Occasional: local reaction at injection site; rash; diarrhea; nausea; vomiting; increased aminotransferases Rare: thrombocytopenia; pseudomembranous colitis

BACITRACIN — many manufacturers Frequent: nephrotoxicity; GI disturbance Occasional: rash; blood dyscrasias Rare: anaphylaxis

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BENZNIDAZOLE (Rochagan)

Frequent: allergic rash; dose-dependent polyneuropathy; GI disturbance; psychic disturbances

BITHIONOL (Bitin)

Frequent: photosensitivity reactions; vomiting; diarrhea; abdominal pain; urticaria Rare: leukopenia; toxic hepatitis

CAPREOMYCIN (Capastat)

Occasional: renal damage; eighth nerve damage; hypokalemia and other electrolyte abnormalities; pain, induration, excessive bleeding, sterile abscess at injection site **Rare:** allergic reactions; leukocytosis, leukopenia; neuromuscular blockade and apnea with large IV doses, reversed by neostigmine

CARBENICILLIN - See Penicillins

CASPOFUNGIN (Cancidas)

Occasional: fever; rash; increased aminotransferases; GI disturbance; facial flushing Rare: anaphylaxis

CEPHALOSPORINS

(cefaclor - Ceclor; cefadroxil - Duricef, others: cefamandole - Mandol: cefazolin - Ancef, others; cefdinir - Omnicef; cefditoren pivoxil - Spectracef; cefepime - Maxipime; cefixime -Suprax; cefonicid - Monocid; cefoperazone - Cefobid; cefotaxime -Claforan; cefotetan - Cefotan; cefoxitin - Mefoxin; cefpodoxime -Vantin; cefprozil - Cefzil; ceftazidime -Fortaz, Tazidime, Tazicef, Ceptaz: ceftibuten - Cedax; ceftizoxime -Cefizox; ceftriaxone - Rocephin; cefuroxime - Kefurox, Zinacef; cefuroxime axetil - Ceftin; cephalexin -Keflex, others; cephapirin - Cefadyl, others; cephradine - Velosef, others; loracarbef - Lorabid Frequent: thrombophlebitis with IV use: serum-sickness-like reaction with

prolonged parenteral administration; moderate to severe diarrhea, especially with cefoperazone and cefixime **Occasional:** allergic reactions, rarely anaphylactic; pain at injection site; GI disturbance; hypoprothrombinemia, hemorrhage with cefamandole, cefoperazone or cefotetan; rash and arthritis ("serum-sickness") with cefaclor or cefprozil, especially in children; cholelithiasis with ceftriaxone; vaginal candidiasis (especially with cefdinir); carmitine deficiency with prolonged use of cefditoren

Rare: hemolytic anemia; hepatic dysfunction; blood dyscrasias; renal damage; acute interstitial nephritis; pseudomembranous colitis; seizures; toxic epidermal necrolysis

CHLORAMPHENICOL

(Chloromycetin, others) Occasional: blood dyscrasias; gray syndrome (cardiovascular collapse); GI disturbance

Rare: fatal aplastic anemia, even with eye drops or ointment; allergic and febrile reactions; peripheral neuropathy; optic neuritis and other CNS injury; pseudomembranous colitis

CHLOROQUINE HCL and CHLORO-

QUINE PHOSPHATE (Aralen, others) Occasional: pruritus; vomiting; headache; confusion; depigmentation of hair; skin eruptions; corneal opacity; weight loss; partial alopecia; extraocular muscle palsies; exacerbation of psoriasis, eczema, and other exfoliative dermatoses; myalgias; photophobia **Rare:** irreversible retinal injury (especially when total dosage exceeds 100 grams); discoloration of nails and mucus membranes; nerve-type deafness; peripheral neuropathy and myopathy; heart block; blood dyscrasias; hematemesis

CIDOFOVIR (Vistide)

Frequent: nephrotoxicity; ocular hypotony; neutropenia

Occasional: metabolic acidosis; uveitis; Fanconi syndrome

CINOXACIN (*Cinobac*, others) — Probably same as nalidixic acid

CIPROFLOXACIN (Cipro) — See Fluoroquinolones

CLARITHROMYCIN (Biaxin)

Occasional: nausea; diarrhea; abdominal pain; abnormal taste; headache; dizziness

Rare: reversible dose-related hearing loss; pseudomembranous colitis; pancreatitis; torsades de pointes

CLINDAMYCIN (Cleocin, others)

Frequent: diarrhea; allergic reactions Occasional: pseudomembranous colitis, sometimes severe, can occur even with topical use

Rare: blood dyscrasias; esophageal ulceration; hepatotoxicity; arrhythmia due to QTc prolongation

CLOFAZIMINE (Lamprene)

Frequent: ichthyosis; pigmentation of skin, cornea and retina; urine discoloration; dryness and irritation of eyes; GI disturbance

Occasional: headache; retinal degeneration

Rare: splenic infarction, bowel obstruction, and GI bleeding with high doses

CLOXACILLIN - See Penicillins

COLISTIMETHATE — See Polymyxins

CROTAMITON (Eurax) Occasional: rash

CYCLOSERINE (Seromycin, others) Frequent: anxiety; depression; confusion; disorientation; paranoia; hallucinations; somnolence; headache Occasional: peripheral neuropathy; liver damage; malabsorption syndrome; folate deficiency Rare: suicide; seizures; coma

DAPSONE

Frequent: rash; transient headache; GI irritation: anorexia: infectious mononucleosis-like syndrome Occasional: cyanosis due to methemoglobinemia and sulfhemoglobinemia; other blood dyscrasias, including hemolytic anemia; nephrotic syndrome; liver damage; peripheral neuropathy; hypersensitivity reactions; increased risk of lepra reactions: insomnia: irritability; uncoordinated speech; agitation; acute psychosis Rare: renal papillary necrosis: severe hypoalbuminemia; epidermal necrolysis; optic atrophy; agranulocytosis; neonatal hyperbilirubinemia after use in pregnancy

DAPTOMYCIN (Cubicin)

Occasional: GI disturbances; rash, injection site reaction; fever; headache; insomnia; dizziness Rare: increased CPK; eosinophilia

DELAVIRDINE (*Rescriptor*) — Similar to nevirapine, but rash may be less severe and hepatotoxicity is less common

DEMECLOCYCLINE — See Tetracyclines

DICLOXACILLIN- See Penicillins

DIDANOSINE (ddI; Videx)

Frequent: peripheral neuropathy; diarrhea; nausea; vomiting; abdominal pain Occasional: pancreatitis; hyperuricemia; increased aminotransferases; hypokalemia; headache; constipation; loss of taste; fever; rash; lactic acidosis; retinal depigmentation Rare: hepatic failure; retinal atrophy in children

DIETHYLCARBAMAZINE

CITRATE (*Hetrazan*) **Frequent:** severe allergic or febrile reactions in patients with microfilaria in the blood or the skin; GI disturbance **Rare:** encephalopathy

DILOXANIDE FUROATE (Furamide)

Frequent: flatulence Occasional: nausea; vomiting; diarrhea Rare: diplopia; dizziness; urticaria; pruritus

DIRITHROMYCIN (Dynabac) — Similar to erythromycin

DOXYCYCLINE — See Tetracyclines

EFAVIRENZ (Sustiva)

Frequent: dizziness; headache; inability to concentrate; insomnia and somnolence; rash

Occasional: vivid dreams; nightmares; hallucinations; hypersensitivity reaction with fever, GI or respiratory symptoms and rash; Stevens-Johnson syndrome in children; increased cholesterol and triglycerides

Rare: pancreatitis; peripheral neuropathy; psychiatric symptoms; photosensitivity reactions; gynecomastia

EFLORNITHINE

(Difluoromethylornithine, DFMO, Ornidyl) Frequent: anemia; leukopenia Occasional: diarrhea; thrombocytopenia; seizures Rare: hearing loss

EMTRICITABINE (FTC, Emtriva)

Frequent: headache; dizziness; insomnia; rash; GI disburbance; weakness; increased CPK

Occasional: dream disturbances; increased triglycerides; hyperpigmentation of palms and soles; lactic acidosis; hepatomegaly with fatty liver; exacerbation of hepatitis B with drug discontinuation

ENFUVIRTIDE (Fuzeon)

Frequent: injection site reactions; insomnia; depression; increased triglycerides; neuropathy Occasional: rash; eosinophilia Rare: hypersensitivity reactions; increased bacterial pneumonias

ENOXACIN- See Fluoroquinolones

ENTECAVIR (Baraclude)

Occasional: headache; fatigue; nausea; dizziness; hepatitis exacerbation after drug discontinuation

ERTAPENEM (Invanz)

Occasional: phlebitis; nausea; vomiting; diarrhea Rare: seizures

ERYTHROMYCIN (*Ery-Tab*, others) Frequent: GI disturbance

Occasional: stomatitis; cholestatic hepatitis especially with erythromycin estolate in adults

Rare: allergic reactions, including severe respiratory distress; pseudomembranous colitis; hemolytic anemia; hepatotoxicity; transient hearing loss with high doses, prolonged use, or in patients with renal insufficiency; ventricular arrhythmias including torsades de pointes with IV infusion; aggravation of myasthenia gravis; hypothermia; pancreatitis; hypertrophic pyloric stenosis following treatment of infants

ETHAMBUTOL (Myambutol)

Occasional: optic neuritis; allergic reactions; GI disturbance; mental confusion; precipitation of acute gout Rare: peripheral neuritis; possible renal damage; thrombocytopenia; toxic epidermal necrolysis; lichenoid skin eruption

ETHIONAMIDE (Trecator-SC)

Frequent: GI disturbance Occasional: liver damage; CNS disturbance, including peripheral neuropathy; allergic reactions; gynecomastia; depres-

sion; myalgias; hypotension **Rare:** hypothyroidism; optic neuritis; arthritis; impotence

FAMCICLOVIR (Famvir) Occasional: headache: nausea: diarrhea

FLUCONAZOLE (Diflucan)

Occasional: nausea; vomiting; diarrhea; abdominal pain; headache; rash; increased aminotransferases Rare: severe hepatic toxicity; exfoliative dermatitis; anaphylaxis; Stevens-Johnson syndrome; toxic epidermal necrolysis; hair loss

FLUCYTOSINE (Ancobon)

Frequent: blood dyscrasias, including pancytopenia and fatal agranulocytosis; GI disturbance, including severe diarrhea and ulcerative colitis; rash; hepatic dysfunction

Occasional: confusion; hallucinations Rare: anaphylaxis

FLUOROQUINOLONES

(ciprofloxacin - Cipro; enoxacin Penetrex; gatifloxacin - Tequin; gemifloxacin - Factive: levofloxacin -Levaquin: lomefloxacin - Maxaquin: moxifloxacin - Avelox: norfloxacin -Noroxin; ofloxacin - Floxin) Occasional: nausea; vomiting; abdominal pain; dizziness; headache; tremors; restlessness; confusion; rash; Candida infections of the pharynx and vagina; eosinophilia: neutropenia: increased hepatic enzymes; increased serum creatinine concentration; insomnia; diarrhea: leukopenia: photosensitivity reactions, especially with lomefloxacin; prolongation of OTc interval Rare: hallucinations; delirium; psychosis: vertigo; paresthesias; blurred vision and photophobia; severe hepatitis; hypoglycemia; seizures; pseudomembranous colitis; interstitial nephritis; vasculitis; possible exacerbation of myasthenia gravis; serum-sickness-like reaction; anaphylaxis; toxic epidermal necrolysis; anemia; tendinitis or tendon rupture; ventricular tachycardia and torsades de pointes; rhabdomyolysis with ofloxacin

FOSAMPRENAVIR (Lexiva)

Frequent: headache; fatigue; rash; GI disturbance

Occasional: depression; increased triglycerides; increased lipase and aminotransferases; perioral numbness or tingling Rare: neutropenia; Stevens-Johnson syndrome

FOSCARNET (Foscavir)

Frequent: renal dysfunction; anemia; nausea; disturbances of Ca, P, Mg, and K metabolism Occasional: headache; vomiting; fatigue; genital ulceration; seizures; neuropathy Rare: Nephrogenic diabetes insipidus; cardiac arrhythmias; hypertension

FOSFOMYCIN (Monurol)

Frequent: diarrhea Occasional: vaginitis

FURAZOLIDONE (Furoxone)

Frequent: nausea; vomiting Occasional: allergic reactions, including pulmonary infiltration; hypotension; urticaria; fever; vesicular rash; hypoglycemia; headache Rare: hemolytic anemia in G-6-PD deficiency and neonates; disulfiramlike reaction with alcohol; MAOinhibitor interactions; polyneuritis

GANCICLOVIR (Cytovene)

Frequent: neutropenia; thrombocytopenia Occasional: anemia; fever; rash; abnormal liver function; neurological toxicity; phlebitis

Rare: hypertension; cardiac arrhythmias; nausea; vomiting; abdominal pain; diarrhea; eosinophilia; hypoglycemia; alopecia; pruritus; urticaria; renal toxicity; psychiatric disturbances; seizures

GATIFLOXACIN- See Fluoroquinolones

GEMIFLOXACIN - See Fluoroquinolones

GENTAMICIN (Garamycin, others) Occasional: vestibular damage; renal damage; rash Rare: auditory damage; neuromuscular blockade and apnea, reversible with calcium or neostigmine; disturbed mental function; polyneuropathy; anaphylaxis

GRISEOFULVIN (*Fulvicin-U/F*, others) Occasional: GI disturbance; allergic and photosensitivity reactions **Rare:** proteinuria; blood dyscrasias; mental confusion; paresthesias; exacerbation of lupus; fixed-drug eruption; reversible liver damage; lymphadenopathy; exacerbation of leprosy

HALOFANTRINE (Halfan)

Occasional: diarrhea; abdominal pain; pruritus; prolongation of QTc and PR interval Rare: fatal cardiac arrhythmias

IMIPENEM-CILASTATIN (Primaxin)

Occasional: phlebitis; pain at injection site; fever; urticaria; rash; pruritus; nausea, vomiting and transient hypotension during intravenous infusion; diarrhea **Rare:** seizures; pseudomembranous colitis

IMIQUIMOD (Aldara)

Frequent: local erythema, erosion and excoriation **Occasional:** itching, burning and pain

INDINAVIR (Crixivan)

Frequent: hyperbilirubinemia; dysuria; kidney stones; flank pain; hematuria; crystalluria

Occasional: pyuria; interstitial nephritis; hemolytic anemia; increased aminotransferases; GI disturbance; reflux esophagitis; glucose intolerance; hyperlipidemia; abnormal fat distribution; increased bleeding in hemophiliacs; paronychia; alopecia; dry skin and mucous membranes **Rare**: rash: hyperprolactinemia;

cholelithiasis

INTERFERON ALFA (Alferon N, Infergen,

Intron A, Roferon-A, Rebetron with ribavirin; Pegylated interferon alfa 2b – Peg-Intron)

Frequent: Transient flu-like syndrome; fatigue; anorexia; nausea; diarrhea; rash; dry skin or pruritus; weight loss; change in taste; bone marrow suppression; increased aminotransferases; depression; anxiety; insomnia Occasional: Paresthesias; alopecia; diaphoresis; reactivation of herpes labialis; hypo- and hyperthyroidism; tinnitus; activation of autoimmune diseases, including diabetes Rare: Visual disturbance and retinopathy; hypertension; cardiac arrhythmias; renal failure; nephrotic syndrome; hearing loss; capillary leak syndrome with mono-

IODOQUINOL (Yodoxin, others) Occasional: rash; acne; slight enlargement of the thyroid gland; nausea; diarrhea; cramps; anal pruritus **Rare:** optic neuritis, atrophy and loss of vision; peripheral neuropathy after prolonged use in high dosage (for months); iodine sensitivity

ISONIAZID (Nydrazid, others)

clonal gammopathy

Occasional: peripheral neuropathy; liver damage, potentially fatal, particularly in patients more than 35 years old; glossitis and GI disturbance; allergic reactions; fever

Rare: blood dyscrasias; red cell aplasia; depression; agitation; auditory and visual hallucinations; paranoia; optic neuritis; hyperglycemia; folate and vitamin B6 deficiency; pellagra-like rash; keratitis; lupus erythematosus-like syndrome; chronic liver injury; cirrhosis; Stevens-Johnson syndrome

ITRACONAZOLE (Sporanox)

Occasional: nausea; epigastric pain; headache; dizziness; edema; hypokalemia; rash; hepatic toxicity Rare: congestive heart failure

IVERMECTIN (Stromectol)

Occasional: Mazzotti-type reaction seen in onchocerciasis, including fever, pruritus, tender lymph nodes, headache, and joint and bone pain Rare: hypotension

KANAMYCIN (*Kantrex*, others) Occasional: eighth-nerve damage affecting mainly hearing that may be irreversible and may not be detected until after therapy has been stopped (most likely with renal impairment); renal damage

Rare: rash; fever; peripheral neuritis; parenteral or intraperitoneal administration may produce neuromuscular blockade and apnea, not reversed by neostigmine or calcium gluconate

KETOCONAZOLE (Nizoral)

Frequent: nausea; vomiting Occasional: decreased testosterone synthesis; gynecomastia; oligospermia and impotence in men; abdominal pain; rash; hepatitis; pruritus; dizziness; constipation; diarrhea; fever and chills; photophobia; headache **Rare:** fatal hepatic necrosis; liver injury with jaundice; transient elevated transaminase; severe epigastric burning and pain; may interfere with adrenal function; anaphylaxis

LAMIVUDINE (3TC; Epivir)

Rare: headache; nausea; dizziness; nasal symptoms; rash; pancreatitis in children; neuropathy; lactic acidosis

LEVOFLOXACIN- See Fluoroquinolones

LINCOMYCIN (*Lincocin*, others) Frequent: diarrhea, sometimes progressing to severe pseudomembranous colitis **Occasional:** allergic reactions, rarely anaphylactic **Rare:** blood dyscrasias; hypotension with rapid IV injection

LINEZOLID (Zyvox)

Frequent: GI disturbance; thrombocytopenia particularly with treatment greater than 10 days; anemia; myelosuppression; increased aminotransferases Rare: peripheral nerve and optic neuropathy; bradycardia

LOMEFLOXACIN — See Fluoroquinolones

LOPINAVIR/RITONAVIR (Kaletra)

Similar to ritonavir, but less common; nephrotoxicity has not been reported **Rare:** pancreatitis, may be fatal; bradyarrhythmia

LORACARBEF - See Cephalosporins

MALATHION (Ovide)

Occasional: local irritation

MEBENDAZOLE (Vermox)

Occasional: diarrhea; abdominal pain Rare: leukopenia; agranulocytosis; hypospermia

MEFLOQUINE (Lariam)

Frequent: vertigo; lightheadedness; nausea, other GI disturbances; nightmares; visual disturbances; headache; insomnia Occasional: confusion Rare: psychosis; hypotension; convulsions; coma; paresthesias

MEGLUMINEANTIMONIATE

(Glucantime) — Similar to sodium stibogluconate

MELARSOPROL (Mel B)

Frequent: myocardial damage; albuminuria; hypertension; colic; Herxheimer-type reaction; encephalopa-

thy; vomiting; peripheral neuropathy **Rare:** shock

MEROPENEM (*Merrem*)— Similar to imipenem, but may be less likely to cause seizures

METHENAMINE MANDELATE (Mandelamine, others) and METHENAMINE HIPPURATE (Hiprex, Urex) Occasional: Gl disturbance; dysuria; allergic reactions

METHICILLIN— See Penicillins

METRONIDAZOLE (*Flagyl*, others) Frequent: nausea; headache; anorexia; metallic taste Occasional: vomiting; diarrhea; insomnia; weakness; dry mouth; stomatitis; vertigo; tinnitus; paresthesias; rash; dark urine; urethral burning; disulfiram-like reaction with alcohol; candidiasis Rare: pseudomembranous colitis; leukopenia; pancreatitis; seizures; peripheral neuropathy; encephalopathy; cerebellar syndrome with ataxia, dysarthria and MRI abnormalities

MICAFUNGIN (Mycamine)

Occasional: fever; headache; GI disturbance; leukopenia; phlebitis at injection site; increased aminotransferases Rare: rash; pruritus; facial swelling; anaphylaxis; hemolysis

MICONAZOLE (Monistat)

Occasional: phlebitis; thrombocytosis; chills; intense, persistent pruritus; rash; vomiting; hyperlipidemia; dizziness; blurred vision; local burning and irritation with topical use **Rare:** anemia; thrombocytopenia; hyponatremia; renal insufficiency; anaphylaxis; cardiac and respiratory arrest with initial dose

MINOCYCLINE— See Tetracyclines

MOXIFLOXACIN— See Fluoroquinolones

NAFCILLIN- See Penicillins

NALIDIXIC ACID (NegGram, others) Frequent: GI disturbance; rash; visual disturbance Occasional: CNS disturbance; acute intracranial hypertension in young children and rarely in adults; photosensitivity reactions, sometimes persistent; convulsions; hyperglycemia Rare: cholestatic jaundice; blood dyscrasias; fatal immune hemolytic anemia; arthralgia or arthritis; lupus-like syndrome; confusion, depression, excitement. visual hallucinations

NELFINAVIR (Viracept)

Frequent: mild to moderate diarrhea Occasional: increased aminotransferases; rash; nausea; glucose intolerance; increased bleeding in hemophiliacs; hyperlipidemia; abnormal fat distribution

NEOMYCIN

Occasional: eighth-nerve and renal damage, same as with kanamycin but hearing loss may be more frequent and severe and may occur with oral, intraarticular, irrigant, or topical use; GI disturbance; malabsorption with oral use; contact dermatitis with topical use **Rare:** neuromuscular blockade and apnea that may be reversed by intravenous neostigmine or calcium gluconate; pseudomembranous colitis

NEVIRAPINE (Viramune)

Frequent: rash, can progress to Stevens-Johnson syndrome Occasional: fever; nausea; headache; hepatotoxicity, which can be fatal; vivid dreams

NICLOSAMIDE (Niclocide)

Occasional: nausea; abdominal pain

NIFURTIMOX (Lampit)

Frequent: anorexia; vomiting; weight loss; loss of memory; sleep disorders; tremor; paresthesias; weakness; polyneuritis Rare: convulsions; fever; pulmonary infiltrates and pleural effusion

NITAZOXANIDE (Alinia)

Occasional: GI disturbance; headache Rare: yellow discoloration of sclera; allergic reactions; increased creatinine; dizziness; flatulence; malaise; salivary gland enlargement

NITROFURANTOIN (Macrodantin, others) Frequent: GI disturbance; allergic reactions, including pulmonary infiltrates Occasional: lupus-like syndrome; blood dyscrasias; hemolytic anemia; peripheral neuropathy, sometimes severe; pulmonary fibrosis Rare: cholestatic jaundice; chronic active hepatitis, sometimes fatal; focal nodular hyperplasia of liver; pancreatitis; trigeminal neuralgia; crystalluria; increased intracranial pressure; lactic acidosis; parotitis; severe hemolytic anemia in G-6-PD deficiency

NORFLOXACIN- See Fluoroquinolones

NYSTATIN (*Mycostatin*, others) Occasional: allergic reactions; fixed drug eruption; GI disturbance

OFLOXACIN- See Fluoroquinolones

ORNIDAZOLE (Tiberal) Occasional: dizziness; headache; GI disturbance Rare: reversible peripheral neuropathy

OSELTAMIVIR PHOSPHATE (*TamiFlu*) **Occasional:** nausea; vomiting; headache

OXACILLIN— See Penicillins

OXAMNIQUINE (Vansil) Occasional: headache; fever; dizziness; somnolence and insomnia; nausea; diarrhea; rash; increased aminotransferases; ECG changes; EEG changes; orange-red discoloration of urine

Rare: seizures; neuropsychiatric disturbances

OXYTETRACYCLINE — See Tetracyclines

PARA-AMINOSALICYLIC ACID — See Aminosalicylic acid

PAROMOMYCIN (aminosidine; *Humatin*) Frequent: GI disturbance with oral use Rare: eighth-nerve damage (mainly auditory) and renal damage when aminosidine is given IV; vertigo; pancreatitis

PENICILLINS

(amoxicillin - Amoxil, others: amoxicillin/clavulanic acid - Augmentin; ampicillin - Principen, others; ampicillin/sulbactam - Unasyn: carbenicillin indanyl - Geocillin: cloxacillin; dicloxacillin - Dycill, others; methicillin: mezlocillin - Mezlin: nafcillin - Nafcil, others; oxacillin; penicillin G; penicillin V; piperacillin - Pipracil; piperacillin/ tazobactam -Zosvn; ticarcillin - Ticar; ticarcillin/ clavulanic acid - Timentin) Frequent: allergic reactions, rarely anaphylaxis, erythema multiforme or Stevens Johnson syndrome; rash (more common with ampicillin and amoxicillin than with other penicillins); diarrhea (most common with ampicillin and amoxicillin/clavulanic acid); nausea and vomiting with amoxicillin/clavulanic acid

Occasional: hemolytic anemia; neutropenia; pseudomembranous colitis; platelet dysfunction with high doses of piperacillin, ticarcillin, nafcillin, or methicillin; cholestatic hepatitis with amoxicillin/clavulanic acid

Rare: hepatic damage with semisynthetic penicillins; granulocytopenia or agranulocytosis with semisynthetic penicillins;

renal damage with semisynthetic penicillins and penicillin G; muscle irritability and seizures, usually after high doses in patients with impaired renal function: hyperkalemia and arrhythmias with IV potassium penicillin G given rapidly; bleeding diathesis; Henoch-Schönlein purpura with ampicillin; thrombocytopenia with methicillin and mezlocillin; terror, hallucinations, disorientation, agitation, bizarre behavior and neurological reactions with high doses of procaine penicillin G, oxacillin, or ticarcillin; hypokalemic alkalosis and/or sodium overload with high doses of ticarcillin or nafcillin; hemorrhagic cystitis with methicillin; GI bleeding with dicloxacillin; tissue damage with extravasation of nafcillin

PENTAMIDINE ISETHIONATE (Pentam

300, NebuPent, others)

Frequent: hypotension; hypoglycemia often followed by diabetes mellitus; vomiting; blood dyscrasias; renal damage; pain at injection site; GI disturbance Occasional: may aggravate diabetes; shock; hypocalcemia; liver damage; cardiotoxicity; delirium; rash Rare: Herxheimer-type reaction; anaphylaxis; acute pancreatitis; hyperkalemia

PERMETHRIN (Nix others) Occasional: burning; stinging; numbness; increased pruritus; pain;

edema; erythema; rash

PIPERACILLIN — See Penicillins

PIPERACILLIN/TAZOBACTAM — See Penicillins

POLYMYXINS

(colistimethate – *Coly-Mycin*, polymyxin B – generic)

Occasional: renal damage; peripheral neuropathy; thrombophlebitis at IV injection site with polymyxin B Rare: allergic reactions; neuromuscular blockade and apnea with parenteral administration, not reversed by neostigmine but may be by IV calcium chloride

PRAZIQUANTEL (Biltricide)

Frequent: abdominal pain; diarrhea; malaise; headache; dizziness Occasional: sedation; fever; sweating; nausea; eosinophilia Rare: pruritus; rash; edema; hiccups

PRIMAQUINE PHOSPHATE

Frequent: hemolytic anemia in G-6-PD deficiency Occasional: neutropenia; GI disturbance; methemoglobinemia Rare: CNS symptoms; hypertension; arrhythmias

PROGUANIL (Paludrine; Malarone

[with atovaquone]) Occasional: oral ulceration; hair loss; scaling of palms and soles; urticaria Rare: hematuria (with large doses); vomiting; abdominal pain; diarrhea (with large doses); thrombocytopenia

PYRANTEL PAMOATE (Antiminth,

others) Occasional: GI disturbance; headache; dizziness; rash; fever

PYRAZINAMIDE

Frequent: arthralgia; hyperuricemia Occasional: liver damage; GI disturbance; acute gouty arthritis; rash Rare: photosensitivity reactions; acute hypertension

PYRETHRINS with PIPERONYL BUTOXIDE (*RID*, others) Occasional: allergic reactions

PYRIMETHAMINE (Daraprim)

Occasional: blood dyscrasias; folic acid deficiency Rare: rash; vomiting; convulsions; shock; possibly pulmonary eosinophilia;

fatal cutaneous reactions with pyrimethamine-sulfadoxine (Fansidar)

QUINACRINE

Frequent: disulfiram-like reaction with alcohol; nausea and vomiting; colors skin and urine yellow Occasional: headache; dizziness Rare: rash; fever; psychosis; extensive exfoliative dermatitis in patients with psoriasis

QUININE SULFATE — See Quinine dihydrochloride

QUININE DIHYDROCHLORIDE

Frequent: cinchonism (tinnitus, headache, nausea, abdominal pain, visual disturbance)

Occasional: deafness; hemolytic anemia; other blood dyscrasias; photosensitivity reactions; hypoglycemia; arrhythmias; hypotension; fever **Rare:** blindness; sudden death if injected too rapidly; hypersensitivity reaction with TTP-HUS

QUINUPRISTIN/DALFOPRISTIN

(Synercid)

Frequent: local irritation and thrombophlebitis with peripheral IV administration; arthralgias; myalgias; increase in conjugated bilirubin Occasional: nausea; rash: increased

aminotransferases

RIBAVIRIN (Copegus, Rebetol, Virazole, Rebetron with interferon alfa) Occasional: anemia; headache; abdominal cramps and nausea; fatigue; elevation of bilirubin; teratogenic and embryo-lethal in animals and mutagenic in mammalian cells; rash; conjunctivitis; bronchospasm with aerosol use; hyperuricemia; depression **RIFABUTIN** (*Mycobutin*) — Similar to rifampin; also iritis, uveitis, leukopenia, arthralgia

RIFAMPIN (*Rifadin, Rimactane*) Frequent: colors urine, tears, saliva, CSF, contact lenses, and lens implants red-orange Occasional: liver damage; GI disturbance; allergic reactions Rare: flu-like syndrome, sometimes with thrombocytopenia, hemolytic anemia, shock, and renal failure, particularly with intermittent therapy; acute organic brain syndrome; acute adrenal crisis in patients with adrenal insufficiency; renal damage; severe proximal myopathy

RIFAMPIN-ISONIAZID (*Rifamate*) — See individual drugs

RIFAMPIN-ISONIAZID-PYRAZI-

NAMIDE (*Rifater*) — See individual drugs

RIFAPENTINE (*Priftin*) — Similar to rifampin; higher rate of hyperuricemia

RIFAXIMIN (Xifaxan)

Occasional: headache **Rare:** abnormal dreams; allergic dermatitis; hypersensitivity reactions; photosensitivity; motion sickness

RIMANTADINE (*Flumadine*) — Similar to amantadine, but lower risk of CNS effects

RITONAVIR (Norvir)

Frequent: nausea; diarrhea; vomiting; asthenia; elevated serum triglycerides, cholesterol

Occasional: abdominal pain; anorexia; dyspepsia; circumoral and peripheral paresthesias; rash; altered taste; increased aminotransferase activity; cholestasis; glucose intolerance; abnormal fat distribution; increased bleeding in hemophiliacs **Rare:** nephrotoxicity; hyperprolactinemia

SAQUINAVIR (Invirase; Fortovase) Occasional: diarrhea; abdominal discomfort; nausea; glucose intolerance; hyperlipidemia; abnormal fat distribution; increased aminotransferase activity; increased bleeding in hemophiliacs Rare: rash; hyperprolactinemia

SODIUM STIBOGLUCONATE

(Pentostam)

Frequent: muscle and joint pain; fatigue; nausea; increased aminotransferase activity; T-wave flattening or inversion; pancreatitis

Occasional: weakness; abdominal pain; liver damage; bradycardia; leukopenia; thrombocytopenia; rash; vomiting **Rare**: diarrhea; pruritus; myocardial damage; hemolytic anemia; renal damage; shock; sudden death

SPECTINOMYCIN (Trobicin)

Occasional: soreness at injection site; urticaria; dizziness; nausea; chills; fever; insomnia; decreased urine output; allergic reactions

SPIRAMYCIN (Rovamycine)

Occasional: GI disturbance Rare: allergic reactions

STAVUDINE (D4T; Zerit)

Frequent: peripheral neuropathy Occasional: increased aminotransferases; lactic acidosis; loss of subcutaneous fat Rare: rash; pancreatitis

STREPTOMYCIN

Frequent: eighth-nerve damage (mainly vestibular), sometimes permanent; paresthesias; rash; fever; eosinophilia Occasional: pruritus; anaphylaxis; renal damage Rare: blood dyscrasias; neuromuscular blockade and apnea with parenteral administration, usually reversed by

neostigmine; optic neuritis; hepatic necrosis; myocarditis; hemolytic anemia; renal-failure; pseudomembranous colitis; toxic erythema; Stevens-Johnson syndrome

SULFONAMIDES

Frequent: allergic reactions (rash, photosensitivity, drug fever) Occasional: kernicterus in newborn; renal damage; liver damage; Stevens-Johnson syndrome (particularly with long-acting sulfonamides); hemolytic anemia; other blood dyscrasias; vasculitis Rare: transient acute myopia; pseudomembranous colitis; reversible infertility in men with sulfasalazine; CNS toxicity with trimethoprim-sulfamethoxazole in patients with AIDS

SURAMIN SODIUM

Frequent: vomiting; pruritus; urticaria; paresthesias; hyperesthesia of hands and feet; peripheral neuropathy; photophobia Occasional: kidney damage; blood dyscrasias; shock; optic atrophy

TELITHROMYCIN (Ketek)

Frequent: GI disturbance; headache; dizziness

Occasional: visual disturbances including blurred vision, diplopia; difficulty focus-ing; rash

Rare: exacerbation of myasthemia; hepatitis; increased aminotransferases; anaphylaxis; edema; muscle cramps; QT prolongation

TENOFOVIR (Viread)

Occasional: diarrhea; nausea; vomiting; flatulence

TERBINAFINE (Lamisil)

Frequent: headache; GI disturbance Occasional: Taste disturbance; rash; pruritus; urticaria; toxic epidermal necrolysis; erythema multiforme; increased aminotransferases Rare: serious hepatic injury; anaphylaxis; pancytopenia; agranulocytosis; severe neutropenia; changes in ocular lens and retina; parotid swelling; congestive heart failure

TETRACYCLINES

(demeclocycline - Declomycin; doxycycline - Vibramycin, others; minocycline - Minocin, others; oxytetracycline - Terramycin, others; tetracycline hydrochloride - Sumycin, others) Frequent: GI disturbance; bone lesions and staining and deformity of teeth in children up to 8 years old, and in the newborn when given to pregnant women after the fourth month of pregnancy Occasional: malabsorption: enterocolitis: photosensitivity reactions (most frequent with demeclocycline); vestibular toxicity with minocycline; increased azotemia with renal insufficiency (except doxycycline, but exacerbation of renal failure with doxycycline has been reported); renal insufficiency with demeclocycline in cirrhotic patients; hepatic injury; parenteral doses may cause serious liver damage, especially in pregnant women and patients with renal disease receiving 1 gram or more daily; esophageal ulcerations; cutaneous and mucosal hyperpigmentation, tooth discoloration in adults with minocycline

Rare: allergic reactions, including serum sickness and anaphylaxis; pseudomembranous colitis; blood dyscrasias; drug-induced lupus with minocycline; autoimmune hepatitis; increased intracranial pressure; fixed-drug eruptions; diabetes insipidus with demeclocycline; transient acute myopia; blurred vision, diplopia, papilledema; photoonycholysis and onycholysis; acute interstitial nephritis with minocycline; aggravation of myasthenic symptoms with IV injection, reversed with calcium; possibly transient neuropathy; hemolytic anemia

THIABENDAZOLE (Mintezol)

Frequent: nausea; vomiting; vertigo; headache; drowsiness; pruritus Occasional: leukopenia; crystalluria; rash; hallucinations and other psychiatric reactions; visual and olfactory disturbance; erythema multiforme **Rare:** shock; tinnitus; intrahepatic cholestasis; convulsions; angioneurotic edema; Stevens-Johnson syndrome

TICARCILLIN - See Penicillins

TICARCILLIN/CLAVULANIC ACID — See Penicillins

TIGECYCLINE (*Tygacil*) — See also Tetracyclines

Frequent: nausea; vomiting; diarrhea; abdominal pain; permanent discoloration of teeth when given during tooth development (last half of pregnancy, infancy, and childhood to age 8 yrs)

Occasional: photosensitivity; pseudotumor cerebri; pancreatitis; injection site reactions

Rare: pseudomembranous colitis

TINIDAZOLE (Tindamax)

Occasional: metallic taste; GI symptoms; rash

Rare: weakness

TIPRANAVIR (*Aptivus*)/ RITONAVIR — See also Ritonavir Frequent: diarrhea; nausea; elevated

serum triglycerides, cholesterol; increased aminotransferases

Occasional: fatigue; vomiting; abdominal pain; dyspepsia; anorexia; hyperglycemia; rash; abnormal fat distribution; increased bleeding in hemophiliacs

Rare: hepatitis; hepatic failure; nephrotoxicity

TOBRAMYCIN (*Nebcin*, others) — Similar to gentamicin Rare: delirium

TRIFLURIDINE (Viroptic)

Occasional: burning or stinging; palpebral edema Rare: epithelial keratopathy; hypersensitivity reactions

TRIMETHOPRIM (*Proloprim*, others) Frequent: nausea, vomiting with high doses

Occasional: megaloblastic anemia; thrombocytopenia; neutropenia; rash; fixed drug eruption **Rare:** pancytopenia; hyperkalemia

TRIMETHOPRIM/SULFAMETHOXA-

ZOLE (*Bactrim, Septra*, others) **Frequent:** rash; fever; nausea and vomiting

Occasional: hemolysis in G-6-PD deficiency; acute megaloblastic anemia; granulocytopenia; thrombocytopenia; pseudomembranous colitis; kernicterus in newborn; hyperkalemia

Rare: agranulocytosis; aplastic anemia; hepatotoxicity; Stevens-Johnson syndrome; aseptic meningitis; fever; confusion; depression; hallucinations; deterioration in renal disease; intrahepatic cholestasis; methemoglobinemia; pancreatitis; ataxia; CNS toxicity in patients with AIDS; renal tubular acidosis; hyperkalemia

TRIMETREXATE (Neutrexin; with

"leucovorin rescue") Occasional: rash; peripheral neuropathy; bone marrow depression; increased serum aminotransferases

TROLEANDOMYCIN (TAO)

Occasional: stomatitis; GI disturbance; cholestatic jaundice **Rare:** allergic reactions

VALACYCLOVIR (Valtrex) — Generally same as acyclovir **Rare:** thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in severely immunocompromised patients treated with high doses

VALGANCICLOVIR (Valcyte) — Generally same as ganciclovir

VANCOMYCIN (Vancocin, others) Frequent: thrombophlebitis; fever, chills Occasional: eighth-nerve damage (mainly hearing) especially with large or continued doses (more than 10 days), in presence of renal damage, and in the elderly; neutropenia; renal damage; allergic reactions; rash; "redman" syndrome **Rare:** peripheral neuropathy; hypotension with rapid IV administration; exfoliative dermatitis

VORICONAZOLE (Vfend)

Frequent: transient visual disturbances Occasional: rash; increased aminotransferases

Rare: photosensitivity with prolonged use

ZALCITABINE (ddC; Hivid)

Frequent: peripheral neuropathy Occasional: stomatitis; esophageal ulceration; nausea; headache; fever; fatigue; abdominal pain; diarrhea; rash Rare: pancreatitis; hypersensitivity reaction with fever, GI or respiratory symptoms and rash

ZANAMIVIR (Relenza)

Occasional: nasal and throat discomfort; headache; cough; broncospasm in patients with asthma

ZIDOVUDINE (Retrovir)

Frequent: anemia; granulocytopenia; nail pigment changes; nausea; fatigue Occasional: headache; insomnia; confusion; diarrhea; rash; fever; myalgias; myopathy; light-headedness; lactic acidosis Rare: seizures; Wernicke's encephalopathy; cholestatic hepatitis; transient ataxia and nystagmus with acute large overdosage

DOSAGE OF ANTIMICROBIAL AGENTS

In choosing the dosage of an antimicrobial drug, the physician must consider the site of infection, the identity and antimicrobial susceptibility of the infecting organism, the possible toxicity of the drug of choice, and the condition of the patient, with special attention to renal function. This article and the table that follows on page 256 offer some guidelines for determining antimicrobial dosage, but dosage recommendations taken out of context of the clinical situation may be misleading.

RENAL INSUFFICIENCY — Antimicrobial drugs excreted through the urinary tract may be toxic for patients with renal insufficiency if they are given in usual therapeutic doses, because serum concentrations in these patients may become dangerously high. Nephrotoxic and ototoxic drugs such as gentamicin or other aminoglycosides may damage the kidney, further decreasing the excretion of these drugs, leading to higher blood concentrations that may be ototoxic and may cause additional renal damage. In patients with renal insufficiency, therefore, an antimicrobial drug with minimal nephrotoxicity, such as a beta-lactam, is preferred. When nephrotoxic drugs must be used, renal function should be monitored. Measurements of serum creatinine or blood urea nitrogen (BUN) concentrations are useful as indices of renal function, but are not as accurate as measurements of creatinine clearance; serum creatinine and BUN concentrations may be normal even with significant loss of renal function.

In renal insufficiency, control of serum concentrations of potentially toxic drugs can be achieved either by varying the dose or by varying the interval between doses. Serum antimicrobial concentrations should be measured whenever possible; rigid adherence to any dosage regimen can result in either inadequate or toxic serum concentrations in patients with renal insufficiency, particularly when renal function is changing rapidly.

CHILDREN'S DOSAGE — Many antimicrobial drugs have such a broad therapeutic index that it makes no difference in practice if children's dosage is based on weight or on surface area. Where dosage considerations are important in preventing severe toxic effects, as with the aminoglycosides, recommendations for safe usage are derived primarily from experience with dosage based on weight.

ONCE-DAILY AMINOGLYCOSIDES — In certain categories of patients once-daily doses of gentamicin, tobramycin and amikacin are as effective for many indications as multiple daily doses and are equally or less nephrotoxic. Monitoring 24-hour trough drug levels is recommended to minimize the risk of toxicity. Once-daily doses of aminogly-cosides are not recommended for treatment of endocarditis and should be used cautiously in the elderly, immunocompromised patients and those with renal insufficiency.

THE TABLE — **Dosage** – The recommendations in the table that follows are based on the judgment of Medical Letter consultants. In some cases they differ from the manufacturer's recommendations, partly because clinical experience reported after the labeling is approved is not always reflected by an appropriate change in the manufacturer's recommendations. The range of dosage specified for some drugs may not include relatively rare indications. In general, lower doses are sufficient for treatment of urinary tract infection, and higher doses are recommended for such severe infections as meningitis, endocarditis and the sepsis syndrome. **Interval** – More than one interval between doses is recommended for some drugs. In general, the longer intervals should be used for infections of the urinary tract and for intramuscular administration. Recommendations are made in hours, but many oral drugs can be given three or four times during the daytime for convenience. For maximum absorption, which is often not necessary, most oral antibiotics should be given at least 30 minutes before or two hours after a meal.

Antimicrobial Drug Dosage[†]

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Abacavir	300 mg q12h or 600 mg q24h		8 mg/kg q12h		
Abacavir/ lamivudine	600 mg/300 mg q24h				
Acyclovir	200 mg 5x/d or 400 mg q8h ¹	5-15 mg/kg q8h	20 mg/kg q6h	5-20 mg/kg q8h	
Adefovir	10 mg q24h				
Albendazole	400 mg q12-24h		10-15 mg/kg/d		
Amantadine	100 mg q12-24h		4.4 mg/kg q12-24h		
Amikacin		5 mg/kg q8h, 7.5 mg/kg q12h or 15 mg/kg q24h ³		5 mg/kg q8h or 7.5 mg/kg q12h ³	
Aminosalicylic acid	8-12 g div q12-8h		200-300 mg/kg div q12-6h		
Amoxicillin	250-500 mg q8h or 500-875 mg q12h ⁴		6.6-13.3 mg/kg q8h or 15 mg/kg q12h'	1	
Amoxicillin/ clavulanic acid	250-500 mg⁵ q8h or 500-875 mg⁵ q12 or 2000 mg⁵ q12h	2h	6.6-13.3 mg/kg ^t or 12.5-45 mg/k q12h		
Amphotericin B		0.3-1.0 mg/kg ⁶ q24h		0.3-1.0 mg/kg ⁶ q24h	
Ampho B chole sulfate comple (Amphotec)		3-4 mg/kg q24h		3-4 mg/kg q24h	
Ampho B lipid complex (Abe	lcet)	5 mg/kg q24h		5 mg/kg q24h	
Ampho B liposo (AmBisome)	omal	3-5 mg/kg q24h		3-5 mg/kg q24h	
Ampicillin	500 mg q6h	1-2 g q4-6h	12.5-25 mg/kg q6h	25-50 mg/kg q6h ⁸	
Ampicillin/ sulbactam		1.5-3 g ⁹ q6h		50 mg/kg ⁹ q6h	
Amprenavir ¹⁰	1200 mg q12h		20 mg/kg q12h or 15 mg/kg q8		

† Dosage recommendations are also included in some articles within this handbook. Certain factors, such as site of infection, susceptibility of infecting organism and concomitant use of interacting drugs, need to be considered when dosing antimicrobial drugs.

1. For treatment of initial genital herpes. For suppression of genital herpes, 400 mg q12h is used. For treatment of varicella, 800 mg q6h and for zoster, 800 mg 5 times daily every 4 hours are recommended. 2. For patients on hemodialysis, dose is 10 mg q7 days, given after hemodialysis.

3. For information on once-daily dosing, see page 254. For renal failure give full dose once, then monitor levels.

4. Doses up to 4 g/d (80-90 mg/kg/d, divided q12h in children) are sometimes used for infections with intermediately-resistant pneumococcus.

Usual Maximum	Daga	For Cr	sage in Rena eatinine Clea (mL/min)		Extra Dose After
Dose/Day 600 mg	Dose	80-50	50-10 Change not requi		Hemodialysis
ooo mg			nange not requ	leu	110
600 mg/ 300 mg		No change	Not recomme	nded	
4 g oral 45 mg/kg IV	10 mg/kg	q8h	q12-24h	2.5 mg/kg q24h	yes
10 mg	10 mg	q24h	q48-72h	unknown	yes ²
800 mg		C	Change not requi	red	no
200 mg		100 mg q24h	100-200 mg q24-48h	200 mg q7d	no
1.5 g	5 mg/kg	q12h	q24-36h	see foot- note 3	yes
12 g		Unknown	Unknown	Not recom- mended	
3 g ⁴	250- 500 mg	q8h	q12h	q24h	yes
1.5 g		No change	250-500 mg⁵ q12h	250-500 mg⁵ q24h	yes
1 mg/kg ⁶		C	Change not requi	red ⁷	no
4mg/kg			Unknown		
5 mg/kg			Unknown		
5 mg/kg			Unknown		
14 g	0.5-2 g	q6h	q8h	q12h	yes
12 g	1.5-3 g ⁹	No change	q8-12h	q24h	yes
2400 mg		C	Change not requi	red	

 Dosage based on amoxicillin content. In order to ensure the proper amount of clavulanic acid, the use of half or multiple tablets is not recommended (unless using *Augmentin XR*).

6. Or up to 1.5 mg/kg given every other day. Given IV, over a period of two to four hours.

7. A pre- and post-dose IV bolus of 500 mL normal saline may decrease renal toxicity.

 For meningitis in children caused by ampicillin-sensitive *H. influenzae* type b, Medical Letter consultants recommend up to 400 mg/kg/d. Meningitis should be treated q4h.

 Combination formulation: 1.5-g vial contains 1 g ampicillin/500 mg sulbactam; 3-g vial contains 2 g ampicillin/1 g sulbactam.

10. Dosage adjustment may be necessary in patients with hepatic dysfunction.

11. Using capsules. Also available in solution: 22.5 mg/kg q12h or 17 mg/kg q8h (max. 2800 mg/d).

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Atazanavir	400 mg q24h ¹²				
Atovaquone	750 mg q12h ¹³		30 mg/kg q24h ¹⁴		
Atovaquone/ proguanil	1000 mg/400 mg q24h ¹⁵		See foot- note 16		
Azithromycin	250-1000 mg ¹⁷ q24h or 2 g once ¹⁷	500 mg q24h	5-12 mg/kg ¹⁷ q24h		
Aztreonam ¹⁰		1-2 g q6-8h		30 mg/kg q6-8h	
Capreomycin		15 mg/kg q24h		15-30 mg/kg q24h	
Carbenicillin indanyl sodium	1-2 tabs ¹⁸ n q6h		7.5-12.5 mg/kg q12h		
Caspofungin ¹⁰		70 mg day 1, then 50 mg q24h ^{19,20}		See foot- note 21	
Cefaclor	250-500 mg q8h or 375-500 mg q12l	n	6.6-13.3 mg/kg q8h		
Cefadroxil	1 g q12-24h		15 mg/kg q12h		
Cefamandole		500 mg-2 g q4-8h		50-150 mg/kg/d, div q4-8h	
Cefazolin		500 mg-2 g q6-8h		25-100 mg/kg/d, div q6-8h	
Cefdinir	300 mg q12h or 600 mg q24h		7 mg/kg q12h or 14 mg/kg q24	4h	
Cefditoren	200-400 mg q12h		See foot- note 22		
Cefepime		1-2 g q8-12h		50 mg/kg q8-12h	
Cefixime	200 mg q12h or 400 mg q24h		4 mg/kg q12h or 8 mg/kg q24	h	

12. For treatment-experienced patients or those taking efavirenz or tenofovir, the recommended dose is 300 mg taken once daily with 100 mg of ritonavir.

 For treatment of *Pneumocystis jiroveci* pneumonia (PCP). The dose for prevention of PCP is 1500 mg once daily.

14. For infants 1-3 months and children older than 24 months of age. The recommended dose for children 4-24 months of age is 45 mg/kg once daily.

 Dosage for treatment of malaria. For prevention of malaria, dose is 250 mg/100 mg once daily. Each adult tablet contains 250 mg atovaquone/100 mg proguanil.

16. For pediatric dosing, see Drugs for Parasitic Infections (Malaria) page 184.

Usual Maximum		For C	osage in Rena reatinine Clea (mL/min)	rance	Extra Dose After
Dose/Day	Dose	80-50	50-10	<10	Hemodialysis
400 mg			Change not requ	ired	
1500 mg		(Change not requ	ired	
1000 mg/ 400 mg		No change	Unknown	Unknown	no
500 mg			Change not requ	ired	
8 g		500 mg- 1 g q8h	500-750 mg q8h	250-500 mg q8h	yes
1 g		No change	7.5 mg/kg q24-48h	7.5 mg/kg q72h	
3 g		:	See package ins	ert	
50 mg		(Change not requ	ired	no
4 g		(Change not requ	ired	yes
2 g	500 mg	q12-24h	q12-24h	q36h	yes
12 g		1-2 g q6h	1-2 g q8h	0.5-1 g q8-12h	yes
6 g		1 g q8h	1 g q8-12h	1 g q24h	yes
600 mg	300 mg	No change	q24h	q24h	yes
800 mg	200- 400 mg	No change	200 mg q12-24h	Unknown	
6 g	2 g	q12h	1-2 g q24h	500 mg q24h	yes
400 mg	200- 400 mg	q24h	q24h	200 mg q24h	no

17. For adults: 500 mg on day 1 and 250 mg/d on days 2-5; urethritis and cervicitis: 14 g once for C. trachomatis, 2 g once for N. gonorrhoeae; MAC prophylaxis: 1200 mg once/week; MAC treatment: 600 mg once daily (with ethambutol). For children: pharyngitis/tonsilittis: 12 mg/kg once a day for 5 days; acute otitis media: 10 mg/kg on day 1 and 5 mg/kg on days 2 to 5 or single-dose 30 mg/kg or 10 mg/kg once daily for 3 days. Extended-release oral suspension (*Zmax*) is given as 2 g once for treatment of adults with acute bacterial sinusitis or mild-moderate CAP.

18. Tablets contain 382 mg of carbenicillin.

19. Loading dose not needed for treatment of esophageal candidiasis.

20. For patients with moderate hepatic insufficiency (Child-Pugh score 7-9) the daily dose should be reduced to 35 mg following the standard 70 mg loading dose on day 1.

21. Not approved for use in children. Limited experience in clinical trials with 1 mg/kg q24h.

22. Has not been studied in children. Use adult dosage in adolescents ≥12 years of age.

Adults			Children		
	Oral	Parenteral	Oral	Parenteral	
Cefonicid		500 mg-2 g q24h		20-40 mg/kg q24h ²³	
Cefoperazone ¹	0	500 mg-4 g q6-12h		25-100 mg/kg q12h	
Cefotaxime		1-2 g q4-12h		50-180 mg/kg/d, div q4-6h	
Cefotetan		500 mg-3 g q12h		20-40 mg/kg q12h ²³	
Cefoxitin		1-3 g q4-6h		80-160 mg/kg/d, div q4-6h	
Cefpodoxime	100-400 mg q12h		10 mg/kg q24h or 5 mg/kg q12	h	
Cefprozil	250-500 mg q12h		15 mg/kg q12h		
Ceftazidime		250-2 g q8-12h		30-50 mg/kg q8h	
Ceftibuten	400 mg q24h		9 mg/kg q24h		
Ceftizoxime		500 mg-4 g q8-12h		50 mg/kg q6-8h	
Ceftriaxone		1-2 g q12-24h		50-100 mg/kg/d, div q12-24h	
Cefuroxime		750 mg-1.5 g q8h		50-150 mg/kg/d, div q6-8h	
Cefuroxime axetil	125-500 mg q12h		10-15 mg/kg q12h		
Cephalexin	250 mg-1 g q6h		6.25-25 mg/kg q6h		
Cephradine	250 mg-1 g q6h or 500 mg-1 g q12h	500 mg-2 g q6h	6.25-25 mg/kg q6h or 12.5- 50 mg/kg q12h	12.5-25 mg/kg q6h	
Chloram- phenicol ¹⁰	12.5-25 mg/kg q6h	12.5-25 mg/kg ²⁴ q6h	12.5-25 mg/kg q6h	12.5-25 mg/kg ²⁴ q6h	
Chloroquine	See foot- note 25		See foot- note 25		
Cidofovir		5 mg/kg once/wk x2, then 5 mg/kg every other wk			
23. Not approved	for use in children. Dos	age recommended by the	Committee on Infect	ious Diseases of	

23. Not approved for use in children. Dosage recommended by the Committee on Infectious Diseases of the American Academy of Pediatrics.

IV administration; doságe should be adjusted according to serum concentration.
 For specific dosing information, see Drugs for Parasitic Infections (Malaria), page 184.

Usual Maximum Dose/Day	Dose		sage in Rena eatinine Clea (mL/min) 50-10		Extra Dose After Hemodialysis
2 g		0.5-1.5 g q24h	0.25-1 g q24-48h	0.25-1 g q3-5d	no
12 g		C	Change not requ	ired	no*
12 g	1-2 g	No change	q6-12h	q12-24h	yes
6 g	1-3 g	q12h	q12-24h	q48h	yes
12 g		1-2 g q8h	1-2 g q12h	0.5-1 g q12-24h	yes
800 mg	200- 400 mg	q12h	q24h	q24h	yes
1000 mg	250- 500 mg	No change	q24h	q24h	yes
6 g		0.5-2 g q8-12h	1 g q12-24h	0.5 g q24-48h	yes
400 mg		No change	100-200 mg q24h	100 mg q24h	no*
12 g		0.5-1.5 g q8h	0.25-1 g q12h	0.25-1 g q24-48h	yes
4 g		C	Change not requ	ired	no
9 g	0.75-1.5 g	q8h	q8-12h	q24h	yes
1 g		Change no	t required	250 mg q24h	yes
4 g	0.25-1 g	No change	q8-12h	q12-24h	yes
8 g	1-2 g	q6h	q8h	q12-72h	yes
4 g		C	Change not requ	ired	no*
		No change	No change	50% of usual dose	no
		S	ee footnote 26		

 ^{*} But give usual dose after dialysis.
 26. For CMV. Initiation of therapy contraindicated in patients with serum creatinine >1.5 mg/dL, creatinine clearance ≤55 mL/min or urine protein ≥100 mg/dL. If serum creatinine increases by 0.3-0.4 mg/dL above baseline, decrease dose to 3 mg/kg. Discontinue for increases ≥0.5 mg/dL.

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Cinoxacin	250 mg q6h or 500 mg q12h				
Ciprofloxacin	250-750 mg q12h or 1000 mg q24h ²⁷	200-400 mg q8-12h	10-20 mg/kg q12h	6-10 mg/kg ²⁸ q8-12h	
Clarithromycin	250-500 mg q12h		7.5 mg/kg q12h		
Clindamycin ¹⁰	150-450 mg q6h	150-900 mg q6-8h	2-8 mg/kg q6-8h	2.5-10 mg/kg q6h	
Colistin (colistimethate sodium)	2	2.5-5 mg/kg/d, div in 2-4 doses		2.5-5 mg/kg/d, div in 2-4 doses	
Cycloserine ³⁰	250-500 mg q12h		5-10 mg/kg q12h		
Dapsone ³¹	100 mg q24h		2 mg/kg q24h		
Daptomycin		4 mg/kg q24h			
Delavirdine	400 mg tid				
Dicloxacillin	125-500 mg q6h		3.125-6.25 mg q6h	/kg	
Didanosine ³²	>60 kg: 200 mg q12 or 400 mg q24h ³² <60 kg: 125 mg q12 or 250 mg q24h ³²		90-120 mg/m ² q12h ³²		
Dirithromycin	500 mg q24h		≥12 yrs: 500 mg q24h		
Doxycycline	100 mg q12-24h	100 mg q12-24h	2.2 mg/kg ³³ q12-24h	2.2 mg/kg ³³ q12-24h	
Efavirenz	600 mg q24h		200-400 mg q24h		
Emtricitabine	200 mg q24h				
Emtricitabine/ tenofovir	200 mg/300 mg q24h				
Enfuvirtide		90 mg SC q12h		≥6 yrs: 2 mg/kg	

27. Extended-release formulation for treatment of UTI.

 For PEP of inhalation anthrax oral dose is 15 mg/kg (max 500 mg) and IV dose is 10 mg/kg (max 400 mg).

29. Based on serum creatinine: 1.3-1.5 mg/dL, dose 2.5-3.8 mg/kg/d divided q12h; 1.6-2.5 mg/dL, dose 2.5 mg/kg/d q24h; 2.6-4 mg/dL, dose 1.5 mg/kg q36h.

2 mg/kg SC q12h

30. Monitor concentrations, toxicity increases markedly above 30 mcg/mL.

31. Dosage for prophylaxis of *Pneumocystis jiroveci* pneumonia (PCP). Adult dosage can be changed to 50 mg daily or 200 mg weekly if given with weekly pyrimethamine and leucovorin.

Usual Maximum Dose/Day	Dose		osage in Rena Creatinine Clea (mL/min) 50-10		Extra Dose After Hemodialysis
1 g		250 mg q8h	250 mg q12-24h	250 mg q24h	no
1.5 g		No change	250-500 mg q12-18h	250-500 mg q24h	no*
1 g		No change	q24h	Unknown	
4.8 mg			Change not requi	ired	no
5 mg/kg			See footnote 29		
1 g		No change	250 mg q12-24h	250 mg q24-48h	
100 mg		No change	No change	Unknown	
		No change	CrCl<30 mL/n 4 mg/kg q48h		no*
1.2 g			Change not requi	ired	no
4 g			Change not requ	ired	no
400 mg		No change	100-200 mg q24h	75-100 mg q24h	yes
500 mg			Change not requi	ired	no
200 mg			Change not requi	ired	no
600 mg			Change not requi	ired	
200 mg		No change	200 mg q48-72h	200 mg q24h	no*
200 mg/ 300 mg	200 mg/ 300 mg	No change	CrCl 30-4 CrCl <30 recomme	not	
180 mg		No change	Unknown fo CrCl <35 mL/		

* But give usual dose after dialysis.

32. Refers to chewable, dispersible tablets. For adults and children more than one year old, each dose Set. Here's to thereade, dispersione tablets. For additis and cliniter infore trian one year ob, each observation of the state of th

	Adults	Adults Childre		
	Oral	Parenteral	Oral	Parenteral
Entecavir	0.5 mg q24h ³⁴			
Ertapenem		1 g q24h		15 mg/kg q12h ²³
Erythromycin	250-500 mg q6h	250 mg-1 g IV ³⁶ q6h	7.5-12.5 mg/kg q6h	3.75-12.5 mg/kg IV ³⁶ q6h
Ethambutol	15-25 mg/kg q24h or 50 mg/kg 2-3x/wk		15-25 mg/kg q24h ³⁷ or 50 mg/kg 2x/wł	(
Ethionamide	250-500 mg q12h		7.5-10 mg/kg q12h	
Famciclovir	500 mg q8h ³⁸			
Fluconazole	50-400 mg q24h	100-400 mg q24h	3-12 mg/kg q24h	3-12 mg/kg q24h
Flucytosine	12.5-37.5 mg q6h		12.5-37.5 mg/k q6h	g
Fosampren avir ¹⁰	1400 mg q12h ⁴⁰			
Foscarnet		60 mg/kg q8h or 90 mg/kg q12h ⁴¹		
Fosfomycin	3 g once			
Furazolidone	100 mg q6h		6 mg/kg/d div q6h	
Ganciclovir	1 g q8h	5 mg/kg ⁴² q12h		5 mg/kg ⁴² q12h
Gatifloxacin	200-400 mg q24h	200-400 mg q24h	See foot- note 43	
Gemifloxacin	320 mg q24h		See foot- note 43	
Gentamicin		1-2.5 mg/kg q8h or 5-7 mg/kg q24h ³		1-2.5 mg/kg q8h ³

34. Dose for nucleoside-naive patients <u>></u>16 years old. For patients refractory to lamivudine, regular dosage is 1 mg once daily and dosage in renal failure is CrCl 50-10: 0.3-0.5 mg q24h; CrCl <10: 0.1 mg q24h.</p>

35. If the 500-mg dose is given within 6 hours prior to HD, a supplemental dose of 150 mg is recommended after HD. If the 500-mg dose is given >6 hours before HD, no supplemental dose is needed.

36. By slow infusion to minimize thrombophlebitis.

37. Not recommended in children whose visual acuity cannot be monitored (<6 years old).

38. For herpes zoster. For first episode genital herpes, the dosage is 250 mg q8h. For genital herpes recurrence, it is 125 mg q12h. For suppression of genital herpes, it is 250 mg q12h.

 If treatment is essential, begin with 15-25 mg/kg q24h and adjust daily dose to maintain the plasma concentration between 50 and 75 mcg/mL.

Usual Maximum Dose/Day	Dose		age in Renal atinine Clea (mL/min) 50-10		Extra Dose After Hemodialysis
0.5 mg		No change	0.15-0.25 mg ³⁴ q24h	0.05 mg ³⁴ q24h	no*
1 g		No change	CrCl <30: 500 mg q24h	500 mg q24h	yes ³⁵
4 g		Change not	required		no
2.5 g	20 mg/kg	No change	q24-36h	q48h	no*
1 g		No change	No change	500 mg q24h	no
1.5 g	500 mg	q12h	q24h	Not recom- mended	yes
400 mg	100- 400 mg	No change	q48h	q72h	yes
150 mg/kg	12.5-37.5 mg/kg	No change	q12-24h	Not recom- mended ³⁹	yes
2.8 g		Cł	nange not requi	red	
		Se	ee package inse	ert	
3 g		Cł	nange not requi	red	
		Ur	nknown		
10 mg/kg	IV	2.5 mg/kg ⁴² q12h	1.25-2.5 mg/kg ⁴² q24h	1.25 mg/kg ⁴² 3x/wk	no*
3g	PO	0.5-1 g tid	0.5-1 g q24h	500 mg 3x/wk	no*
400 mg		No change	400 mg once then 200 mg q24h	400 mg once then 200 mg q24h	e no*
320 mg		No change	160 mg q24h	160 mg q24h	no*
	1.5 mg/kg	q8-12h	q12-24h	See foot- note 3	yes

* But give usual dose after dialysis.

40. For therapy-naive patients. May also be given as 1,400 mg once daily with ritonavir 200 mg once daily or 700 mg twice daily with ritonavir 100 mg twice daily. The dose for protease inhibitor-experienced patients is 700 mg bid with ritonavir 100 mg bid.

41. For induction therapy of CMV, given over at least one hour; for maintenance, 90-120 mg/kg daily over two hours. For HSV or VZV, 40 mg/kg q8h.

42. Dosage for GMV induction (give IV at constant rate over one hour); for IV maintenance without renal failure: 5 mg/kg once daily 7 days/week or 6 mg/kg once daily 5 days/week; for IV maintenance with renal failure: induction dose is reduced by half.

43. According to The American Academy of Pediatrics, although fluoroquinolones are generally contraindicated in children <18 years old, their use may be justified in special circumstances, such as when no other oral agent is available.

	Adults		Childr	en
	Oral	Parenteral	Oral	Parenteral
Griseofulvin microsize Ultra-	500-1000 mg q24h		11 mg/kg q24h	
microsize	330-660 mg q24h		7.25 mg/kg q24h	
Imipenem/ cilastin		250 mg-1 g q6-8h		15-25 mg/kg q6h
Indinavir	800 mg q8h ⁴⁴		350 mg/m ² q8h	
Interferon alfa-2a, 2b pegylated, alfa-2b		3 MIU 3x/wk SC or IM ⁴⁵ 1 mcg/kg SC g wk		See foot- note 45
pegylated, alfa-2a		180 mcg SC q wk		
Isoniazid ¹⁰	300 mg q24h		10-20 mg/kg q24h	
Itraconazole	100-200 mg q12-24h	200 mg q12h x 4 then 200 mg q24h	5 mg/kg q24h	
Ivermectin	200 mcg/kg q24h		200 mcg/kg q24h	
Kanamycin		5 mg/kg q8h or 7.5 mg/kg q12h		5 mg/kg q8h or 7.5 mg/kg q12h
Ketoconazole	200-400 mg q12-24h		3.3-6.6 mg/kg q24h	
Lamivudine ⁴⁶	150 mg q12h or 300 mg q24h		4 mg/kg q12h	
Levofloxacin	250-750 mg q24h	250-750 mg q24h	See foot- note 43	
Lincomycin	500 mg q6-8h	600 mg-1g ⁴⁷ q8-24h	30-60 mg/kg/d, div q6-8h	10-20 mg/kg/d, div q8-12h
Linezolid	400-600 mg q12h	600 mg q12h	10 mg/kg ⁴⁸ q8h	10 mg/kg ⁴⁸ q8h
Lomefloxacin	400 mg q24h			

44. Dose adjustment is necessary when administered with other drugs including delavirdine, efavirenz, lopinavir/ritonavir and ritonavir.

45. For chronic hepatitis C in adults. For acute hepatitis C in adults the dosage is 5 MIU 24h x 3 weeks, then TIW. For chronic hepatitis B the dosage of interferon alfa-2b is 5 MIU 24h or 10 MIU TIW for adults and for children it is 3-6 MIU/m² TIW.

Usual Maximum Dose/Day	Dose		Oosage in Renal Creatinine Clear (mL/min) 50-10		Extra Dose After Hemodialysis
1 g			Change not requi	red	
660 mg			Change not requi	red	
4 g	250- 500 mg	q6-8h	q8-12h	q12h	yes
			Change not requi	red	
3 MIU			Change not requi	red	
		No change	Use cauti	on	
		No change	Use cauti	on	
300 mg			Change not requi	red	no*
400 mg			Change not request but IV not recommendation for CrCl <30	nended	
			Unknown		
1.5 g	5-7.5 mg/k	g q24h	q24-72h	See foot- note 3	yes
400 mg			Change not requi	red	
300 mg		No change	150 mg once then 100-150 mg/d	once then	no
750 mg	500 mg	No change	500 mg once then 250 mg q24h	500 mg once then 250 mg q48h	no
8 g		No change	Severe renal in 25%-30% us		
1200 mg			Change not requi	red	no*
400 mg		No change	400 mg once then 200 mg q24h	Unknown	no

* But give usual dose after dialysis. 46. For treatment of HIV. For treatment of hepatitis B, the dose of lamivudine is 100 mg/d in patients with normal renal function and dosage in renal failure is CrCl 50-15: 100 mg x 1, then 25-50 mg/d; CrCl <15: 47. For hilder up to 11 years of age. Pediatric patients ≥12 years should receive 600 mg q12h.

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Lopinavir/ ritonavir	400 mg/ 100 mg q12h ⁴⁹ or 800 mg/ 200 mg q24h ⁵⁰		7-15 kg: 12/3 mg/kg q12h ⁴⁹ 15-40 kg: 10/2.5 mg/kg q12h ⁴ >40 kg or 12 yrs: 400/100 mg q12h ⁴⁵		
Loracarbef	200-400 mg q12h		7.5 mg/kg q12h		
Mebendazole	100-200 mg q12h		100-200 mg q12h		
Mefloquine	1250 mg once ⁵¹		15 mg/kg once ⁵¹		
Meropenem		1-2 g q8h		20-40 mg/kg q8h	
Methenamine hippurate	1 g q12h		12.5-25 mg/kg q12h		
Methenamine mandelate	1 g q6h		12.5-18.75 mg/ q6h	kg	
Metroni- dazole ¹⁰	500 mg q6-8h ⁵²	500 mg q8h ⁵²	7.5 mg/kg q6-8h ⁵²	7.5 mg/kg q6-8h ⁵²	
Micafungin		150 mg q24h ⁵³			
Miconazole ⁵⁴		600 mg-1.2 g q8h		6.6-13.3 mg/kg q8h	
Minocycline	200 mg x1, then 100 mg q12h	200 mg x1, then 100 mg q12h	4 mg/kg x1, 2 mg/kg q12h ³³	4 mg/kg x1, 2 mg/kg q12h ³³	
Moxifloxacin ¹⁰	400 mg q24h	400 mg q24h	See foot- note 43		
Nafcillin		500 mg-2 g q4-6h		25-50 mg/kg q6h	
Nalidixic acid	1 g q6h		Not recom- mended		
Nelfinavir ¹⁰	750 mg q8h or 1250 mg q12h		25-30 mg/kg q8h		
Nevirapine	200 mg/d x14, followed by 200 mg bid		<8 yrs: 4 mg/kd/d x14 followed by 7 mg/kg ≥8 yrs: 4 mg/kd/d x14 followed by 4 mg/kg	bid 1,	

49. A dose increase is necessary if coadministered with nevirapine or efavirenz in treatment-experienced patients when reduced susceptibility to lopinavir is suspected.

 For treatment-naive patients. Should not be administered as once/d regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

51. Dosage for treatment of malaria; given as 750 mg followed 12 hrs later by 500 mg for adults and 15 mg/kg followed 12 hrs later by 10 mg/kg for children. Dosage for once/wk prophylaxis of malaria; adults, 250 mg; children , 5 mg/kg (<5 kg), 1/8 tab (5-10 kg), 1/4 tab (11-20 kg), 1/2 tab (21-30 kg), 3/4 tab (31-45 kg).</p>

Usual Maximum Dose/Day	Adult Dosage in Renal Failure For Creatinine Clearance (mL/min) Dose 80-50 50-10 <10				Extra Dose After Hemodialysis
800 mg/ 200 mg			Change not requ	ired	
800 mg		No change	200-400 mg q24h	200-400 mg q3-5 days	yes
400 mg			Unknown		
1250 mg			Unknown		
6 g		No change	0.5-1 g q12h	0.5 g q24h	no*
4 g		No change	Not recomm	ended	
4 g		No change	Not recomm	ended	
4 g			Change not requ	ired	no*
			Change not requ	ired	
3.6 g			Change not requ	ired	no
200 mg			Change not requ	ired	
400 mg			Change not requ	ired	
12 g			Change not requ	ired	no
4 g		No change	No change	Not recom- mended	
2.5 g		•	Change not requ	ired	
400 mg	lose after dialysis		Change not requ	ired	

* But give usual dose after dialysis.
 52. Dosage for anaerobic bacterial infections. For antiparasitic dosages, see Drugs for Parasitic Infections, page 179.
 55. For treatment of esophageal candidiasis. The dose for prophylaxis of *Candida* infections in HSCT is

50 mg/d. 54. The manufacturer recommends an initial test dose of 200 mg.

	Adults		Children	
	Oral	Parenteral	Oral	Parenteral
Nitazoxanide	500 mg q12h		1-3 yrs: 100 mg q12h 4-11 yrs: 200 mg q12	
Nitrofurantoin	50-100 mg q6h		1.25-1.75 mg/kg q6h	9
Norfloxacin	400 mg q12h		See foot- note 43	
Ofloxacin	200-400 mg q12h	200-400 mg q12h	See foot- note 43	
Oseltamavir	75 mg q12h ⁵⁵		≤15 kg: 30 mg q12h 16-23 kg: 45 mg q12h 24-40 kg: 60 mg q12h >40 kg: 75 mg q12h	
Oxacillin	500 mg-1 g q6h	500 mg-2 g q4-6h	12.5-25 mg/kg q6h	25-50 mg/kg q6h
Paromomycin	25-35 mg/kg/d div q8h		25-35 mg/kg/d div q8h	
Penicillin G	250-500 mg q6h	1.2-24 million U/d, div q2-12h ⁵⁶	6.25-12.5 mg/kg q6h	100,000- 250,000 U/d, div q2-12h ⁵⁶
Penicillin V	250-500 mg q6h		6.25-12.5 mg/kg q6h	9
Pentamidine		4 mg/kg ⁵⁸ q24h		4 mg/kg ⁵⁸ q24h
Piperacillin		3-4 g q4-6h		200-300 mg/kg/d, div q4-6h
Piperacillin/ tazobactam59		3.375 g q4-6h or 4.5 g q6-8h		240 mg/kg/d piperacillin div q8h
Polymyxin B		15-20,000 U/kg/d IV, div q12h		15-20,000 U/kg/d IV, div q12h ⁶⁰
Praziquantel	20-25 mg/kg q8-12h		20-25 mg/kg q8-12h	
Primaquine	30 mg base q24h		0.6 mg base/kg q24h	
Pyrantel pamoate	11 mg/kg		11 mg/kg	

 For treatment of influenza. Dosage may be given once daily for influenza prophylaxis.
 The interval between parenteral doses can be as short as 2 hours for initial intravenous treatment of meningococcemia, or as long as 12 hours between intramuscular doses of penicillin G procaine.

57. Patients with severe renal insufficiency should be given no more than one third to one half the maximum daily dosage, i.e., instead of giving 24 million units per day, 10 million units could be given. Patients on lower doses usually tolerate full dosage even with severe renal insufficiency.

Usual Maximum Dose/Day	Dose		osage in Renal reatinine Clea (mL/min) 50-10		Extra Dose After Hemodialysis
1 g			Use with caution		
400 mg		No change	Not recomme	ended	
800 mg	400 mg	No change	No change	q12-24h	no
800 mg		No change	200-400 mg q24h	100-200 mg q24h	no
150 mg	75 mg	No change	q24h	Not recom- mended	
12 g	Change not required				no
	Unknown				
24 million units	Change not required See foot- note 57				yes
4 g			Change not requi	red	
	4 mg/kg	q24h	q24-36h	q48h	no
24 g	3-4 g	No change	q6-8h	q8-12h	yes
		No change	2.25-3.375 g q6h	2.25 g q6-8h	yes
		No change	50%-100% usual dose	15%-50% usual dose	
			Change not requi	red	
30 mg base			Change not requi	red	
1 g			Unknown		

58. For treatment of PCP. For prophylaxis of PCP, the dosage for adults and children ≥5 years is 300 mg inhaled monthly via nebulizer.

59. Combination formulation: A 2.25-g vial contains 2 g piperacillin/250 mg tazobactam; a 3.375-g vial contains 3 g piperacillin/375 mg tazobactam; a 4.5-g vial contains 4 g piperacillin/500 mg tazobactam. 60. For children ≥2 years old. Infants can receive up to 40,000 U/kg/d.

	Adults		Children	
	Oral	Parenteral	Oral	Parenteral
Pyrazinamide	15-30 mg/kg q24h		15-30 mg/kg q24h	
Pyrimethamine	25-100 mg ⁶¹ q24h		0.5-1 mg/kg ⁶¹ q12h	
Pyrimethamine/ sulfadoxine	75/1500 mg once		See foot- note 62	
Quinidine gluconate		10 mg/kg then ⁶³ 0.02 mg/kg/min		10 mg/kg then ⁶³ 0.02 mg/kg/min
Quinine sulfate	650 mg q8h		10 mg/kg q8h	
Quinupristin/ dalfopristin		7.5 mg/kg q8-12h		7.5 mg/kg q8-12h
Ribavirin	75 kg: 400 mg q AM and 600 mg q PM >75 kg: 600 mg bid			
Rifabutin	150 mg q12h or 300 mg q24h		5-20 mg/kg/d	
Rifampin ¹⁰	600 mg q24h ⁶⁴	600 mg q24h	10-20 mg/kg q24h ⁶⁴	10-20 mg/kg q24h
Rifampin/ _isoniazid ⁶⁵	600/300 mg ⁶⁵ q24h			
Rifampin/ isoniazid/pyra- zinamide ⁶⁵	≤44 kg: 4 tabs ⁶⁶ 45-54 kg: 5 tabs 55-90 kg: 6 tabs			
Rifapentine	600 mg once wkly			
Rifaximin	200 mg q8h		≥12 yrs: 200 m q8h	g
Rimantadine ¹⁰	100 mg once or q12h		5 mg/kg once	
Ritonavir ¹⁰	600 mg q12h ⁶⁷		400 mg/m ² q12h	
Saquinavir ⁶⁸	1200 mg q8h			
Spectinomycin		2 g once		40 mg/kg once
Stavudine ¹⁰	≥60 kg: 40 mg q12h <60 kg: 30 mg q12h		≥30 kg: 30 mg <30 kg: 1 mg/k	

61. For treatment of toxoplasmosis. Leucovorin should be administered with pyrimethamine.

 Each tablet contains 25 mg pyrimethamine/500 mg sulfadoxine. Pediatric dose: <1 yr: 1/4 tab; 1-3 yrs: 1/2 tab; 4-8 yrs: 1 tab; 9-14 yrs: 2 tabs.

63. Loading dose should be decreased or omitted in patients who have received quinine or mefloquine. If >48 hours IV treatment required, dose should be reduced by 30-50%.

64. For meningococcal carriers, dosage is 600 mg bid x 2 days for adults, 10 mg/kg q12h x 2 days for children more than one month old, and 5 mg/kg q12h x 2 days for infants less than one month old.

Usual Maximum Dose/Day	Dose		Oosage in Rena Creatinine Clea (mL/min) 50-10		Extra Dose After Hemodialysis
2 g			Change not requ	uired	
100 mg			Change not requ	uired	no
75/1500 mg			Use with caution	1	
600 mg		No change	No change	75% of usual dose	yes
	650 mg	No change	q8-12h	q24h	no*
Unknown			Change not requ	uired	
1200 mg		No change	Not recom	mended	
300 mg			Change not requ	uired	no
600 mg			Change not requ	uired	
600/300 mg			Change not requ	uired	
			Change not requ	uired	
600 mg			Change not requ	uired	
600 mg			Change not requ	uired	
200 mg			Change not requ	uired	no
1200 mg			Change not requ	uired	no
3600 mg			Change not requ	uired	
		No change	Not recom	mended	
80 mg		No change	20 mg q12-24h 15 mg q12-24h		-

^{*} But give usual dose after dialysis. 65. Pyridoxine 10-25 mg should be added to prevent neuropathy in malnourished or pregnant patients

and those with HIV infection, alcoholism or diabetes. 66. Each tablet contains rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg. For patients >90 kg -6 tabs plus additional pyrazinamide to achieve total of 20-25 mg/kg/d.

^{67.} When used in combination with other protease inhibitors the ritonavir dose is 100-400 mg PO b.i.d. 68. Soft gelatin capsules.

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Streptomycin		15 mg/kg q24h ⁶⁹ or 25-30 mg/kg 2-3x/wk		20-40 mg/kg q24h ⁶⁹	
Sulfadiazine ⁷⁰	1-1.5 g q6h		25-50 mg/kg q6h		
Sulfisoxazole	500 mg-1 g q6h	25 mg/kg q6h	150 mg/kg/d div q4-6h	100 mg/kg/d div q6-8h	
Telithromycin	800 mg q24h				
Tenofovir	300 mg q24h				
Terbinafine	250 mg q24h				
Tetracy- cline ⁷²	250-500 mg q6h		6.25-12.5 mg q6h ³³	g/kg	
Thiabendazole	50 mg/kg/d div q12h		50 mg/kg/d div q12h		
Ticarcillin		200-300 mg/kg/d div q4-6h		200-300 mg/kg/d div q4-6h	
Ticarcillin/ _clavulanic acio	173	3.1 g q4-6h		200-300 mg/kg/d div q4-6h	
Tigecycline ¹⁰		100 mg x1, then 50 mg q12h		See foot- note 33	
Tinidazole74	2 g q24h		50 mg/kg q24h		
Tipranavir/ ritonavir	500/200 mg q12h				
Tobramycin		1-2.5 mg/kg q8h or 5-7 mg/kg q24h ³		1-2.5 mg/kg q8h ³	
Trimethoprim	100 mg q12h or 200 mg q24h		2 mg/kg q12h		
Trimethoprim- sulfamethox- azole (TMP-SMX)	1 SS tab ⁷⁵ q6h or 2 SS tabs q12h ⁷⁵	4-5 mg/kg (TMP) q6-12h	4-5 mg/kg (TMP) q6h	4-5 mg/kg (TMP) q6-12h	
Valacyclovir	1 g q8h ⁷⁷				

69. Given IM for tuberculosis. Dose for endocarditis: 500 mg-1 g q12h.

70. Given in conjunction with pyrimethamine for toxoplasmosis. 71. AUC increased 1.9 fold in pateints with CrCl <30 mL/min.

72. Tetracycline or oxytetracycline. The oral dose of demeclocycline for adults is 600 mg daily in two to four divided doses.

73. Combination formulation: a 3.1-g vial contains 3 g ticarcillin/100 mg clavulanic acid.

74. For 3-5 days for amebiasis. For treatment of giardiasis and trichomoniasis, the dose is 2 g once.

Usual Maximum Dose/Day	Dose		osage in Ren Creatinine Cle (mL/min) 50-10		Extra Dose After Hemodialysis
1-2 g		q24h	q24-72h	q72-96h	yes
6 g			Unknown		
8 g	0.5-1 g	q6-8h	q8-12h	q12-24h	yes
800 mg		No change	Unknow	/n ⁷¹	
300 mg		No change	Not recomm	mended	
250 mg		No change	Not recomm	mended	
2 g			Not recommend	led	
3 g		Unl	known; use with c	aution	
24-30 g	2-3 g	q4-6h	q6-8h	2 g q12h	yes
18 g		No change	2 g q4-8h	2 g q12h	yes
			Change not req	uired	
2 g			Change not req	uired	yes
1 g/400 mg			Change not req	uired	
	1.5 mg/kg	q8-12h	q12-24h	See foot- note 3	yes
200 mg	100 mg	No change	q18h	q24h	yes
See foot- note 76	4-5 mg/kg (TMP)	q12h	q18h	Not recom- mended	yes
3 g		1 g q8h	1 g q12-24h	500 mg q24h	

75. Each SS tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole. Double-strength tablets are also available; the usual dosage of these is 1 tablet q12h. Suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole per 5 mL.

76. The usual maximum daily dose is 4 tablets orally or 1200 mg trimethoprim with 6000 mg sulfamethoxazole IV.

77. For herpes zoster. For a first episode of genital herpes, the dosage is 1 g q12h. For recurrence of genital herpes, it is 500 mg q12h. For suppression of genital herpes, it is 1 g q24h.

	Adults		Children		
	Oral	Parenteral	Oral	Parenteral	
Valganciclovir	Induction: 900 mg q12h Maintenance: 900 mg q24h		See foot- note 22		
Vancomycin ⁷⁸	125-500 mg q6h ⁷⁹	1 g IV q12h	12.5 mg/kg q6h ⁷⁹	10 mg/kg IV q6h ⁸⁰	
Voriconazole	≥40 kg: 200 mg bid ⁸¹ <40 kg: 100 mg bid ⁸¹	Loading: 6 mg/kg q12h x2 Maintenance: 4 mg/kg q12h ⁸²	See fo		
Zalcitabine (ddC)	0.375-0.75 mg q8h		0.005 to 0.01 mg/kg q8	3h	
Zanamivir	10 mg q12h by inhalation		>7 yrs: 10 n q12h by inhal		
Zidovudine ¹⁰ (AZT)	200 mg q8h or 300 mg q12h		90-180 mg/m ² q6-8h	2	
Zidovudine/ lamivudine	300/150 mg q12h		>12 yrs: 300/ 150 mg q12h		
Zidovudine/ lamivudine/ abacavir	300/150/300 mg q12h				

78. Vancomycin should be infused over a period of at least 60 minutes.

79. Only for treatment of pseudomembranous colitis.

80. Sixty mg/kg/d may be needed for staphylococcal central-nervous-system infections.

81. IV loading dose of 6 mg/kg q12h x 2 doses is recommended prior to oral maintenance. Dose may be increased to 300 mg q12h (if ≥40 kg) and 150 mg q12h (if <40 kg).</p>

Usual Maximum	Adult Dosage in Renal Failure For Creatinine Clearance (mL/min)			Extra Dose After	
Dose/Day	Dose	80-50	50-10	<10	Hemodialysis
1800 mg		Induction: No change	450 mg q12-48h	Not recom- mended	
		Maintenance: No change	450 mg q24h-2 wks	Not recom- mended	
	1 g	q12-24h	q24h	Full dose x1, then per leve	
		Change not required	Change not re voricon	equired for oral azole ⁸⁴	
2.25 mg	0.75 mg	No change	q12h	q24h	
20 mg		Cł	nange not requi	ired	
600 mg		No change	No change	100 mg q6-8h	no*
600/ 300 mg	300/ 150 mg	No change	Not recomm	nended	
600/300/ 600 mg	300/150 300 mg	No change	Not recomm	nended	

* But give usual dose after dialysis.

82. In patients also taking phenytoin, maintenance dose should be increased to 5 mg/kg/q12h IV or 400 mg q12h PO.

83. Not approved for use in children <12 yrs. Adult dosage has been effective in children (TJ Walsh et al, Pediatr Infect Dis J 2002; 21:240). 84. Cyclodextrin (IV vehicle) accumulates in patients with CrCl <50 mL/min. Oral voriconazole is recom-

mended in these patients.

SAFETY OF ANTIMICROBIAL DRUGS IN PREGNANCY

Use of antimicrobial drugs during pregnancy is a frequent cause for concern. The table that follows summarizes the known prenatal risks of many antimicrobials, but the teratogenic potential of many agents remains unknown. The recommendations in the table are based on published data, the opinions of Medical Letter consultants, and on the importance of the drug and the availability of alternatives. Adverse effects not particularly related to pregnancy are not included here; they are summarized in the chapter beginning on page 238. Serum levels of some renally excreted drugs (e.g. ß-lactams, aminoglycosides) are decreased by 10% to 50% in late pregnancy. For serious infections, maximal recommended doses should be used and serum levels may need to be monitored (OM Korzeniowski, Infect Dis Clin North Am 1995; 9:639).

Drug	Toxicity in Pregnancy	Recommendation
Antibacterial		
Amikacin (Amikin)	Possible 8th-nerve toxicity in fetus	Caution*
Azithromycin (Zithromax)	None known	Probably safe
Aztreonam (Azactam)	None known	Probably safe
Cephalosporins ¹	None known	Probably safe
Chloramphenicol (<i>Chloro-</i> <i>mycetin</i> , and others)	Unknown – gray syndrome in newborn	Caution*, especially at term
Cinoxacin (Cinobac, and others)	Arthropathy in immature animals	Contraindicated
Clarithromycin (Biaxin)	Teratogenic in animals	Contraindicated
Clindamycin (<i>Cleocin</i> , and others)	None known	Caution*
Dapsone	None known; carcinogenic in rats and mice; hemolytic reactions in neonates	Caution*, especially at term
Daptomycin (Cubicin)	None known	Caution*
Dirithromycin (Dynabac)	Retarded fetal development in rodents with high doses	Caution*

SOME ANTIMICROBIAL AGENTS IN PREGNANCY

* Use only for strong clinical indication in absence of suitable alternative.

 Cefaclor (*Ceclor*, others), cefadroxil (*Duricef*, others), cefamandole (*Mandol*), cefazolin (*Ancef*, others), cefepime (*Maxipime*), cefdinir (*Omnicef*), cefditoren (*Spectracef*), cefixime (*Suprax*), cefonicid (*Monocid*), cefoperazone (*Cefobid*), cefotaxime (*Claforan*), cefotetan (*Cefotan*), cefoxitin (*Mefoxin*), cefpodoxime (*Vantin*), cefprozil (*Cefzil*), ceftazidime (*Fortaz*, others), ceftibuten (*Cedax*), ceftizoxime (*Vantin*), cefprozil (*Cefzil*), ceftazidime (*Fortaz*, others), ceftibuten (*Cedax*), ceftizoxime (*Cefizox*), ceftriaxone (*Rocephin*), cefuroxime (*Kefurox*, *Zinacef*), cefuroxime axetil (*Cefin*), cephalexin (*Keflex*, others), cephapirin (*Cefady*], others), cephradine (*Velosef*, others), loracarbef (*Lorabid*). Experience with newer agents is limited.

Drug	Toxicity in Pregnancy	Recommendation
Ertapenam (Invanz) Erythromycin estolate (Ilosone, and others)	Decreased total weight in animals Risk of cholestatic hepatitis appears to be increased in pregnant women	Caution* Contraindicated
Erythromycin (<i>Ery-Tab</i> , and others)	None known; neonatal use has been associated with pyloric stenosis	Probably safe
Fosfomycin (Monurol)	Fetal toxicity in rabbits with maternally toxic doses	Caution*
Fluoroquinolones ²	Arthropathy in immature animals	Caution*
Gentamicin (Garamycin, and others)	Possible 8th-nerve toxicity in fetus	Caution*
Imipenem-cilastatin (Primaxin)	Toxic in some pregnant animals	Caution*
Kanamycin (<i>Kantrex</i> , and others)	Possible 8th-nerve toxicity in fetus	Caution*
Linezolid (Zyvox)	Decreased fetal survival in rats	Caution*
Meropenem (<i>Merrem</i>) Methenamine mandelate (<i>Mandelamine</i> , and others)	Unknown Unknown	Caution* Probably safe
Metronidazole (<i>Flagyl</i> , and others)	None known – carcinogenic in rats and mice	Caution*
Nalidixic acid (<i>NegGram</i> , and others)	Arthropathy in immature animals; increased intracranial pressure in newborn	Contraindicated
Nitrofurantoin (<i>Macrodantin</i> , and others)	Hemolytic anemia in newborn	Caution*; contra- indicated at term
Penicillins ³ Quinupristin/dalfopristin (Synercid)	None known Unknown	Probably safe Caution*
Rifaximin (Xifaxan)	Teratogenic in animals Unknown	Caution* Probably safe
Spectinomycin (Trobicin) Streptomycin	Possible 8th-nerve toxicity in fetus	Caution*
Sulfonamides	Teratogenic in some animal studies; hemolysis in new- born with G-6-PD deficiency; increased risk of kernicterus in newborn	Caution*; contra- indicated at term
Telithromycin (Ketek)	None known	Caution*

* Use only for strong clinical indication in absence of suitable alternative.

2. Ciprofloxacin (*Cipro*, and others), enoxacin (*Penetrex*), gatifloxacin (*Tequin*), gemifloxacin (*Factive*), levofloxacin (*Levaquin*), lomefloxacin (*Maxaquin*), moxifloxacin (*Avelox*), norfloxacin (*Noroxin*), ofloxacin (*Floxin*). The older quinolones (ciprofloxacin, ofloxacin, norfloxacin) appear to be safe (R Loebstein et al, Antimicrob Agents Chemother 1998; 42:1336) and could be used for serious infection when there is no alternative.

Drug	Toxicity in Pregnancy	Recommendation
Tetracyclines ⁴	Tooth discoloration and dys- plasia, inhibition of bone growth in fetus; hepatic toxicity and azotemia with IV use in pregnant patients with decreased renal function or with overdosage	Contraindicated
Tigecycline (Tygacil)	Decreased fetal weight and delays in bone ossification in animals	Caution*
Tobramycin (<i>Nebcin</i> , and others)	Possible 8th-nerve toxicity in fetus	Caution*
Trimethoprim (<i>Proloprim</i> , and others)	Folate antagonism; teratogenic in rats	Caution*
Trimethoprim-sulfa- methoxazole (<i>Bactrim</i> , and others)	Same as sulfonamides and trimethoprim	Caution*; contra- indicated at term
Vancomycin (Vancocin, and others)	Unknown – possible auditory and renal toxicity in fetus	Caution*
Antifungal		
Amphotericin B (Fungizone, and others)	None known	Caution*
Caspofungin (<i>Cancidas</i>) Fluconazole (<i>Diflucan</i>)	Embryotoxic in animals Teratogenic	Contraindicated Contraindicated for high-dose; caution* for single dose
Flucytosine (Ancobon) Griseofulvin (Fulvicin U/F, and others)	Teratogenic in rats Embryotoxic and teratogenic in animals; carcinogenic in rodents	Contraindicated Contraindicated
Itraconazole (Sporanox)	Teratogenic and embryotoxic in rats	Caution*
Ketoconazole (Nizoral)	Teratogenic and embryotoxic in rats	Contraindicated; topical probably safe
Micafungin (Mycamine)	Teratogenic and embryocidal in rabbits	Caution*
Miconazole (Monistat i.v.)	None known	Caution*; topical probably safe
Nystatin (<i>Mycostatin</i> , and others)	None known	Probably safe
Voriconazole (Vfend)	Teratogenic and embryotoxic in animals	Contraindicated

* Use only for strong clinical indication in absence of suitable alternative.

3. Amoxicillin (Amoxil, and others), amoxicillin/clavulanic acid (Augmentin), ampicillin (Principen, and others), ampicillin/sulbactam (Unasyn), carbenicillin indanyl (Geocillin), cloxacillin, dicloxacillin (Dycill, and others), nafcillin (Nafcil, and others), oxacillin, penicillin G, penicillin V, piperacillin (Princil), piperacillin/tazobactam (Zosyn), ticarcillin (Ticar), ticarcillin/clavulanic acid (Timentin). Experience with newer agents is limited.

4. Doxycycline (*Vibramycin*, and others), minocycline (*Minocin*, and others), oxytetracycline (*Terramycin*), demeclocycline (*Declomycin*), tetracycline hydrochloride (*Sumycin*, and others).

Drug	Toxicity in Pregnancy	Recommendation
Antiparasitic		
Albendazole (Albenza)	Teratogenic and embryotoxic in animals	Caution*
Atovaquone (Mepron)	Maternal and fetal toxicity in animals	Caution*
Atovaquone/proguanil (Malarone)	Maternal and fetal toxicity in animals	Caution*
Chloroquine (Aralen, and others)	None known with doses recommended for malaria prophylaxis	Probably safe in low doses
Crotamiton (Eurax)	Unknown	Caution*
Diloxanide (Furamide)	Safety not established	Caution*
Furazolidone (Furoxone)	None known; carcinogenic in rodents; hemolysis with G-6-PD deficiency in newborn	Caution*; contra- indicated at term
Hydroxychloroquine (Plaquenil)	None known with doses recommended for malaria prophylaxis	Probably safe in low doses
Iodoquinol (<i>Yodoxin</i> , and others)	Unknown	Caution*
Ivermectin (Stromectol)	Teratogenic in animals	Contraindicated
Lindane	Absorbed from the skin; potential CNS toxicity in fetus	Contraindicated
Malathion, topical (Ovide)	None known	Probably safe
Mebendazole (Vernox)	Teratogenic and embryo- toxic in rats	Caution*
Mefloquine (Lariam)5	Teratogenic in animals	Caution*
Metronidazole (<i>Flagyl</i> , and others)	None known – carcinogenic in rats and mice	Caution*
Niclosamide (Niclocide)	Not absorbed; no known toxicity in fetus	Probably safe
Nitazoxanide (Alinia)	None known	Caution*
Oxamniquine (Vansil) Paromomycin (Humatin)	Embryocidal in animals Poorly absorbed; toxicity in fetus unknown	Contraindicated Probably safe
Pentamidine (<i>Pentam 300</i> , <i>NebuPent</i> , and others)	Safety not established	Caution*
Permethrin (Nix, and others)	Poorly absorbed; no known toxicity in fetus	Probably safe
Piperazine (<i>Antepar</i> , and others)	Unknown	Caution*
Praziquantel (Biltricide)	Not known	Probably safe
Primaquine	Hemolysis in G-6-PD deficiency	Contraindicated
Pyrantel pamoate (<i>Antiminth</i> , and others)	Absorbed in small amounts; no known toxicity in fetus	Probably safe

* Use only for strong clinical indication in absence of suitable alternative.5. See page 184, footnote 61 and page 186, footnote 74.

Drug	Toxicity in Pregnancy	Recommendation
Pyrethrins and piperonyl butoxide (<i>RID</i> , and others)	Poorly absorbed; no known toxicity in fetus	Probably safe
Pyrimethamine (Daraprim) Pyrimethamine-sulfadoxine (Fansidar)	Teratogenic in animals Teratogenic in animals; increased risk of kernicterus in newborn	Caution* Caution*; especially at term
Quinacrine (Atabrine)	Safety not established	Caution*
Quinine	Large doses can cause abortion; auditory nerve hypoplasia, deafness in fetus; visual changes, limb anomalies, visceral defects also reported	Caution*
Suramin sodium (Germanin)	Teratogenic in mice	Caution*
Thiabendazole (Mintezol)	None known	Caution*
Tinidazole (Tindamax)	Increased fetal mortality in rats	Caution*
Antituberculosis		
Capreomycin (Capastat)	None known	Caution*
Cycloserine (Seromycin, and others)	Unknown	Caution*
Ethambutol (Myambutol)	None known – teratogenic in animals	Caution*
Ethionamide (Trecator-SC)	Teratogenic in animals	Caution*
Isoniazid (Nydrazid, and others)		Probably safe
Pyrazinamide	Unknown	Caution*
Rifabutin (Mycobutin)	Unknown	Caution*
Rifampin (<i>Rifadin, Rimac-</i> tane)	Teratogenic in animals	Probably safe
Rifapentine (Priftin)	Teratogenic in animals	Caution*
Streptomycin	Possible 8th-nerve toxicity in fetus	Contraindicated
Antiviral		
Abacavir (Ziagen)	Teratogenic in animals	Caution*
Acyclovir (Zovirax, and others)		Caution*
Amantadine (<i>Symmetrel</i> , and others)	Teratogenic and embryotoxic in rats	Contraindicated
Amprenavir (Agenerase)	Teratogenic in animals	Caution*
Atazanavir (Reyataz)	None known	Caution*
Cidofovir (Vistide)	Embryotoxic in rats and rabbits	Caution*
Delavirdine (Rescriptor)	Teratogenic in rats	Caution*
Didanosine (ddl; Videx)	None known	Caution*
Efavirenz (Sustiva)	Neural tube defects	Contraindicated
Emtricitabine (Emtriva)	None known	Caution*
Famciclovir (Famvir)	Animal toxicity	Contraindicated
Foscarnet (Foscavir)	Animal toxicity	Caution*
Ganciclovir (Cytovene;	Teratogenic and embryotoxic	Caution*
Vitrasert)	in animals	

* Use only for strong clinical indication in absence of suitable alternative.

Drug	Toxicity in Pregnancy	Recommendation
Indinavir (Crixivan)	None known	Caution*
Interferon alfa (Intron A,	Large doses cause abortions	Caution*
and others)	in animals	
Pegylated interferon	As above	As above
(PEG-Intron, Pegasys)		
Lamivudine (3TC; Epivir)	Unknown	Caution*
Lopinavir/ritonavir (Kaletra)	Animal toxicity	Caution*
Nelfinavir (Viracept)	No fetal toxicity in animals	Caution*
Nevirapine (Viramune)	Decrease in fetal weight in rats	Caution*,6
Oseltamivir (Tamiflu)	Some minor skeletal abnormal- ities in animals	Caution*
Ribavirin (Virazole, Rebetol)	Mutagenic, teratogenic, embryo- lethal in nearly all species, and possibly carcinogenic in animals	Contraindicated
Rimantadine (Flumadine)	Embryotoxic in rats	Contraindicated
Ritonavir (Norvir)	Animal toxicity	Caution*
Saquinavir (Invirase; Fortovase)	None known	Caution*
Stavudine (d4T; Zerit)	Animal toxicity with high doses	Caution*
Tenofovir (Viread)	None in animals	Caution*
Tipranavir (Aptivus)	Fetal toxicity in animals	Caution*
Valacyclovir (Valtrex)	None known	Caution*
Valganciclovir (Valcyte)	Teratogenic and embryo- toxic in animals	Caution*
Vidarabine (Vira-A)	Teratogenic in rats and rabbits	Caution*
Zalcitabine (ddC; Hivid)	Teratogenic and embryo- toxic in mice	Caution*
Zanamivir (Relenza)	None in animals	Caution*
Zidovudine (AZT; <i>Retrovir</i>)	Mutagenic in vitro	Indicated to prevent HIV infection of fetus

* Use only for strong clinical indication in absence of suitable alternative.
6. Shown to be safe and effective for HIV-infected women at single 200 mg PO dose at start of labor.

Drug Trade Names

A

abacavir - Ziagen (GlaxoSmithKline) abacavir-lamivudine-zidovudine – Trizivir (GlaxoSmithKline) Abelcet (Elan) – amphotericin B lipid complex Actisite (Proctor & Gamble) – tetracycline HCl * acyclovir – Zovirax (GlaxoSmithKline) adefovir - Hepsera (Gilead) Aftate (Schering) - tolnaftate Agenerase (GlaxoSmithKline) - amprenavir Ala-Tet (Del-Ray) - tetracycline HCl alatrofloxacin - Trovan IV (Pfizer) albendazole – *Albenza* (GlaxoSmithKline) Alferon N (Interferon Sciences) – interferon alfa-n3 * amantadine - Symmetrel (Du Pont), others AmBisome (Fujisawa) – amphotericin B liposomal amikacin – Amikin (Bristol-Myers Squibb) Amikin (Bristol-Myers Squibb) - amikacin * aminosalicylic acid – Paser (Jacobus) * amoxicillin - Amoxil (GlaxoSmithKline), others amoxicillin/clavulanic acid – Augmentin (GlaxoSmithKline) Amoxil (GlaxoSmithKline) – amoxicillin Amphotec (Sequus) – amphotericin B cholesteryl sulfate complex * amphotericin B - Fungizone (Bristol-Myers Squibb), others amphotericin B cholesteryl sulfate complex - Amphotec (Sequus) amphotericin B lipid complex - Abelcet (Elan) amphotericin B liposomal – AmBisome (Fujisawa) * ampicillin - Principen (Bristol-Myers Squibb), others ampicillin/sulbactam - Unasyn (Pfizer) amprenavir - Agenerase (GlaxoSmithKline) Ancef (GlaxoSmithKline) - cefazolin Ancobon (Roche) - flucytosine

^{*} Also available generically.

[§] Not commercially available in the US.

* Antiminth (Pfizer) – pyrantel pamoate
Aptivus (Boehringer Ingelheim) – tipranavir
Aralen (Sanofi) – chloroquine
§ Arsobal (Aventis, France) – melarsoprol
artemether – Artenam (Arenco, Belgium)
atazanavir – Reyataz (Bristol-Myers Squib b)
atovaquone – Mepron (GlaxoSmithKline)
atovaquone/proguanil – Malarone (GlaxoSmithKline)
Augmentin (GlaxoSmithKline) – amoxicillin/clavulanic acid
Avelox (Bayer) – moxifloxacin
Azactam (Bristol-Myers Squibb) – aztreonam
AZT – see zidovudine
azithromycin – Zithromax (Pfizer), Zmax (Pfizer)
aztreonam – Azactam (Bristol-Myers Squibb)

B

Bactrim (Roche) – trimethoprim-sulfamethoxazoleBaraclude (Bristol-Myers Squibb) – entecavirBeepen-VK (GlaxoSmithKline) – penicillin V§ benznidazole – Rochagan (Roche, Brazil)Biaxin (Abbott) – clarithromycinBicillin LA (Wyeth-Ayerst) – penicillin G benzathineBiltricide (Bayer) – praziquantelBio-cef (Intl Ethic Lab) – cephalexin§ bithionol – Bitin (Tanabe, Japan)§ Bitin – bithionol (Tanabe, Japan)Brodspec (Truxton) – tetracycline HClbutoconazole – Femstat (Bayer), Gynazole (Ther-Rx)

^{*} Also available generically.

[§] Not commercially available in the US.

Drugs Trade Names

С

Cancidas (Merck) - caspofungin Capastat (Dura) – capreomycin carbenicillin – *Geocillin* (Pfizer) caspofungin - Cancidas (Merck) Ceclor (Lilly) - cefaclor cefaclor - Ceclor (Lilly) Cedax (Biovail) - ceftibuten * cefadroxil - Duricef (Bristol-Myers Squibb), others Cefadyl (Bristol-Myers Squibb) - cephapirin cefamandole - Mandol (Lilly) * cefazolin - Ancef (GlaxoSmithKline), others cefdinir - Omnicef (Abbott) cefditoren – Spectracef (TAP) cefepime - Maxipime (Elan) cefixime - Suprax (Lederle) Cefizox (Fujisawa) - ceftizoxime Cefobid (Pfizer) - cefoperazone cefonicid – *Monocid* (GlaxoSmithKline) cefoperazone - Cefobid (Pfizer) Cefotan (AstraZeneca) - cefotetan cefotaxime - Claforan (Aventis) cefotetan – Cefotan (Zeneca) cefoxitin - Mefoxin (Merck) cefpodoxime - Vantin (Pharmacia) cefprozil - Cefzil (Bristol-Myers Squibb) ceftazidime - Fortaz, Ceptaz, Tazicef (GlaxoSmithKline), Tazidime (Lilly) ceftibuten - Cedax (Biovail)

* Also available generically.

§ Not commercially available in the US.

Ceftin (GlaxoSmithKline) - cefuroxime axetil ceftizoxime – *Cefizox* (Fujisawa) * ceftriaxone – Rocephin (Roche), others cefuroxime - Kefurox (Lilly), Zinacef (GlaxoSmithKline) cefuroxime axetil - Ceftin (GlaxoSmithKline) Cefzil (Bristol-Myers Squibb) - cefprozil * cephalexin - Keflex (Dista), others cephapirin - Cefadyl (Bristol-Myers Squibb) * cephradine - Velosef (Bristol-Myers Squibb), others Ceptaz (GlaxoSmithKline) - ceftazidime * chloramphenicol - Chloromycetin (Parke-Davis), others Chloromycetin (Parke-Davis) - chloramphenicol * chloroquine - Aralen (Sanofi), others cidofovir - Vistide (Gilead) Cinobac (Oclassen) – cinoxacin * cinoxacin - Cinobac (Oclassen), others Cipro (Bayer) - ciprofloxacin * ciprofloxacin - Cipro (Bayer), others Claforan (Aventis) - cefotaxime clarithromycin – *Biaxin* (Abbott) Cleocin (Pharmacia) - clindamycin * clindamycin - Cleocin (Pharmacia), others clofazimine - Lamprene (Novartis) clotrimazole – Mycelex (Bayer) * cloxacillin - generic Cofatrim Fort (Ampharco) - trimethoprim-sulfamethoxazole colistimethate - Coly-Mycin (Parke-Davis) Coly-Mycin (Parke-Davis) - colistimethate Combivir (GlaxoSmithKline) - lamivudine-zidovudine Cotrim (Teva) - trimethoprim-sulfamethoxazole crotamiton – Eurax (Westwood-Squibb)

* Also available generically.

§ Not commercially available in the US.

Drugs Trade Names

Crixivan (Merck) – indinavir *Cubicin* (Cubist) – daptomycin * cycloserine – *Seromycin* (Dura), others *Cytovene* (Roche) – ganciclovir

D

ddC - see didanosine ddI – see zalcitabine * dapsone – generic (Jacobus) daptomycin - Cubicin (Cubist) Daraprim (GlaxoSmithKline) – pyrimethamine Declomycin (Lederle) – demeclocycline delavirdine - Rescriptor (Pharmacia) demeclocycline – *Declomycin* (Lederle) Denavir (Novartis) - penciclovir * dicloxacillin - Dycill (GlaxoSmithKline), others didanosine - Videx (Bristol-Myers Squibb) diethylcarbamazine - Hetrazan (Lederle) Diflucan (Pfizer) – fluconazole § diloxanide furoate - Furamide (Knoll, U.K.) dirithromycin – *Dynabac* (Muro) Doryx (Warner Chilcott) – doxycycline * doxycycline - Vibramycin (Pfizer), others Duricef (Bristol-Myers Squibb) - cefadroxil Dycill (GlaxoSmithKline) – dicloxacillin Dvnabac (Muro) – dirithromvcin Dynapen (Bristol-Myers Squibb) - dicloxacillin

^{*} Also available generically.

[§] Not commercially available in the US.

E

E.E.S. (Abbott) – ervthromvcin efavirenz – Sustiva (DuPont) § Egaten (Novartis) – triclabendazole § eflornithine – Ornidyl (Aventis) Elimite (Allergan) - permethrin emitricitabine – Emtriva (Gilead) Emtet-500 (EconoMed) - tetracycline HCl *E-Mycin* (Knoll) – erythromycin enfuvirtide – *Fuzeon* (Trimeris-Roche) enoxacin - Penetrex (Aventis) entecavir – *Baraclude* (Bristol-Myers Squibb) Epivir (GlaxoSmithKline) - lamivudine Epzicom (GlaxoSmithKline) - abacavir-lamivudine ertapenem – *Invanz* (Merck) *Ery-Tab* (Abbott) – erythromycin ERYC (Parke-Davis) - erythromycin Erythrocin (Abbott) - erythromycin * erythromycin – *Erythrocin* (Abbott), others * erythromycin-sulfisoxazole - Pediazole (Ross/Abbott), others *Eryzole* (Alra) – erythromycinsulfisoxazole ethambutol – Myambutol (Lederle) ethionamide - Trecator-SC (Wyeth-Ayerst) Eurax (Westwood-Squibb) - crotamiton Exelderm (Westwood-Squibb) - sulconazole

F

Factive (Oscient) – gemifloxacin famciclovir – *Famvir* (GlaxoSmithKline)

^{*} Also available generically.

[§] Not commercially available in the US.

Famvir (GlaxoSmithKline) - famciclovir Fansidar (Roche) - pyrimethamine-sulfadoxine Femstat (Bayer) - butoconazole Flagyl (Searle) - metronidazole Floxin (Ortho-McNeil) - ofloxacin * fluconazole - Diflucan (Pfizer) flucytosine - Ancobon (Roche) Flumadine (Forest) - rimantadine fomivirsen - Vitravene (Novartis) Fortaz (GlaxoSmithKline) - ceftazidime Fortovase (Roche) - saquinavir fosamprenavir – Lexiva (GlaxoSmithKline) foscarnet – Foscavir (AstraZeneca) Foscavir (AstraZeneca) – foscarnet fosfomycin – *Monurol* (Forest) Fulvicin P/G (Schering) – griseofulvin Fulvicin U/F (Schering) – griseofulvin Fungizone (Bristol-Myers Squibb) – amphotericin B Furacin (Roberts) - nitrofurazone Furadantin (Dura) - nitrofurantoin § Furamide (Knoll, U.K.) – diloxanide furoate furazolidone – Furoxone (Roberts) Furoxone (Roberts) – furazolidone

G

ganciclovir – *Cytovene* (Roche); *Vitrasert* (Bauch & Lomb) *Gantrisin* (Roche) – sulfisoxazole *Garamycin* (Schering) – gentamicin gatifloxacin – *Tequin* (Bristol-Myers Squibb)

^{*} Also available generically.

[§] Not commercially available in the US.

gemifloxacin – Factive (Oscient) * gentamicin – Garamycin (Schering), others Geocillin (Pfizer) – carbenicillin § Glucantime (Aventis, France) – meglumine antimoniate G-Mycin (Bolan) – gentamicin Grifulvin V (Ortho) – griseofulvin Grisactin (Wyeth-Ayerst) – griseofulvin * griseofulvin – Fulvicin U/F (Schering), others Gris-PEG (Allergan) – griseofulvin Gynazole (Ther-Rx) – butoconazole

Н

§ Halfan (GlaxoSmithKline) – halofantrine § halofantrine – Halfan (GlaxoSmithKline) Hetrazan (Lederle) – diethylcarbamazine Hiprex (Aventis) – methenamine hippurate Hivid (Roche) – zalcitabine Humatin (Parke-Davis) – paromomycin hydroxychloroquine – Plaquenil (Sanofi-Synthelabo)

I

llosone (Dista) – erythromycin estolate imipenem-cilastatin – *Primaxin* (Merck) imiquimod – *Aldara* (3M) indinavir – *Crixivan* (Merck) *Invanz* (Merck) – ertapenem *Infergen* (Amgen) – interferon alfacon-1 interferon alfa-2a – *Roferon-A* (Roche) interferon alfa-2a, pegylated – *Pegasys* (Roche)

^{*} Also available generically.

[§] Not commercially available in the US.

interferon alfa-2b - Intron A (Schering) interferon alfa-2b, pegylated - PEG-Intron (Schering) interferon alfa-n3 - Alferon N (Interferon Sciences) interferon alfacon-1 - Infergen (Amgen) Intron A (Schering) - interferon alfa-2b Invirase (Roche) - saquinavir * iodoquinol - Yodoxin (Glenwood), others * isoniazid - Nydrazid (Bristol-Myers Squibb) itraconazole - Sporanox (Janssen) ivermectin - Stromectol (Merck)

K

Kaletra (Abbott) – lopinavir/ritonavir * kanamycin – Kantrex (Bristol-Myers Squibb), others Kantrex (Bristol-Myers Squibb) – kanamycin Keflex (Dista) – cephalexin Keftab (Dista) – cephalexin Kefurox (Lilly) – cefuroxime Kefzol (Lilly) – cefazolin Ketek (Aventis) – telithromycin ketoconazole – Nizoral (Janssen)

L

lamivudine – *Epivir, Epivir HBV* (GlaxoSmithKline) lamivudine-zidovudine – *Combivir* (GlaxoSmithKline) lamivudine-zidovudine-abacavir – *Trizivir* (GlaxoSmithKline) § *Lampit* (Bayer, Germany) – nifurtimox *Lamprene* (Novartis) – clofazimine

* Also available generically.

Lariam (Roche) – mefloquine Ledercillin VK (Lederle) – penicillin V levofloxacin – Levaquin (Ortho-McNeil) Lincocin (Pharmacia) – lincomycin * lincomycin – Lincocin (Pharmacia) Lincorex (Hyrex) – lincomycin linezolid – Zyvox (Pharmacia) lomefloxacin – Maxaquin (Searle) lopinavir/ritonavir – Kaletra (Abbott) Lorabid (Lilly) – loracarbef loracarbef – Lorabid (Lilly) Lyphocin (Lypho-Med) – vancomycin

Μ

Macrobid (Proctor & Gamble) – nitrofurantoin Macrodantin (Proctor & Gamble) – nitrofurantoin Malarone (GlaxoSmithKline) – atovaquone/proguanil malathion – Ovide (Medicis) Mandelamine (Warner Chilcott) – methenamine mandelate Mandol (Lilly) – cefamandole Marcillin (Marnel) – ampicillin Maxaquin (Searle) – lomefloxacin Maxipime (Elan) – cefepime mebendazole – Vermox (Janssen) mefloquine – Lariam (Roche) Mefoxin (Merck) – cefoxitin § meglumine antimoniate – Glucantime (Aventis, France) § melarsoprol – Arsobal (Aventis, France) meropenem – Merrem (AstraZeneca)

^{*} Also available generically.

[§] Not commercially available in the US.

Merrem (AstraZeneca) – meropenem methenamine hippurate - Hiprex (Aventis), Urex (3M) * methenamine mandelate - Mandelamine (Warner Chilcott), others * metronidazole – *Flagyl* (Searle), others micafungin – Mycamine (Astellas) * miconazole - Monistat (Ortho-McNeil), others § miltefosine – Imparido (Zentaris, Geranay) Minocin (Wyeth) - minocycline * minocycline - Minocin (Wyeth), others Mintezol (Merck) - thiabendazole Monistat (Ortho-McNeil) – miconazole Monodox (Oclassen) - doxycycline Monurol (Forest) - fosfomycin moxifloxacin – Avelox (Bayer) Myambutol (Lederle) – ethambutol Mycamine (Astellas) - micafungin Mycelex (Bayer) - clotrimazole Mycobutin (Pharmacia) - rifabutin Mycostatin (Bristol-Myers Squibb) - nystatin My-E (Seneca) – erythromycin

Ν

nafcillin – Unipen (Wyeth-Ayerst) * nalidixic acid – NegGram (Sanofi), others Nallpen (Baxter) – nafcillin Natacyn (Alcon) – natamycin natamycin – Natacyn (Alcon) Nebcin (Lilly) – tobramycin NebuPent (Fujisawa) – pentamidine

* Also available generically.

NegGram (Sanofi) - nalidixic acid nelfinavir - Viracept (Pfizer) * neomycin - many manufacturers Neutrexin (US Bioscience) - trimetrexate nevirapine - Viramune (Boehringer Ingelheim) § niclosamide – Yomesan (Bayer, Germany) § nifurtimox – *Lampit* (Bayer, Germany) Nilstat (Lederle) - nystatin nitazoxanide – Alinia (Romark) § nitazoxanide – Cryptaz (Romark) * nitrofurantoin - Macrodantin (Proctor & Gamble), others * nitrofurazone - Furacin (Roberts), others Nix (GlaxoSmithKline) – permethrin Nizoral (Janssen) - ketoconazole norfloxacin - Noroxin (Merck) Noroxin (Merck) - norfloxacin Norvir (Abbott) - ritonavir Nydrazid (Bristol-Myers Squibb) - isoniazid * nystatin - Mycostatin (Bristol-Myers Squibb), others Nystex (Savage) - nystatin

0

ofloxacin – *Floxin* (Ortho-McNeil) *Omnicef* (Abbott) – cefdinir *Omnipen* (Wyeth-Ayerst) – ampicillin § ornidazole – *Tiberal* (Hoffmann LaRoche, Switzerland) § *Ornidyl* (Aventis) – eflornithine oseltamivir – *Tamiflu* (Roche/Gilead) *Ovide* (Medicis) – malathion

^{*} Also available generically.

[§] Not commercially available in the US.

* oxacillin – generic oxamniquine – Vansil (Pfizer) oxytetracycline – Terramycin (Pfizer)

Р

§ Paludrine (Ayerst, Canada, ICI, U.K.) – proguanil Panmycin (Pharmacia) - tetracycline HCl paromomycin - Humatin (Parke-Davis) Paser (Jacobus) - aminosalicylic acid Pediazole (Ross/Abbott) - erythromycin-sulfisoxazole Pegasys (Roche) – pegylated interferon alfa 2a *PEG-Intron* (Schering) – pegylated interferon alfa 2b penciclovir - Denavir (Novartis) Penetrex (Aventis) - enoxacin * penicillin G - many manufacturers penicillin G benzathine - Bicillin LA (Wyeth-Ayerst), Permapen (Pfizer) * penicillin G procaine - many manufacturers * penicillin V - many manufacturers Pentam 300 (Fujisawa) – pentamidine * pentamidine isethionate - Pentam 300 (Fujisawa), NebuPent (Fujisawa), others § Pentostam (GlaxoSmithKline, U.K.) - sodium stibogluconate Pen-V (Zenith Goldline) – penicillin V Permapen (Pfizer) - penicillin G benzathine * permethrin – *Elimite* (Allergan), *Nix* (GlaxoSmithKline) piperacillin - Pipracil (Wyeth) piperacillin/tazobactam - Zosyn (Wyeth) Pipracil (Wyeth) - piperacillin Plaquenil (Sanofi-Synthelabo) - hydroxychloroquine

* Also available generically.

* polymyxin B – generic praziquantel – *Biltricide* (Bayer) Priftin (Aventis) - rifapentine primaquine phosphate (Sanofi) - generic Primaxin (Merck) - imipenemcilastatin sodium Principen (Bristol-Myers Squibb) - ampicillin § proguanil – Paludrine (Ayerst, Canada; ICI, U.K.) proguanil/atovaquone – *Malarone* (GlaxoSmithKline) Proloprim (GlaxoSmithKline) - trimethoprim Pronto (Del) - pyrethrins with piperonyl butoxide Protostat (Ortho-McNeil) - metronidazole * pyrantel pamoate - Antiminth (Pfizer), others * pyrazinamide - generic * pyrethrins with piperonyl butoxide- RID (Pfizer), others pyrimethamine – *Daraprim* (GlaxoSmithKline) pyrimethamine-sulfadoxine - Fansidar (Roche)

Q

* quinidine gluconate - many manufacturers

§ quinine dihydrochloride

* quinine sulfate - many manufacturers

quinupristin-dalfopristin - Synercid (Aventis)

R

Rebetol (Schering) – ribavirin Rebetron (Schering) – ribavirin-interferon alfa-2b Relenza (GlaxoSmithKline) – zanamivir

^{*} Also available generically.

Rescriptor (Pharmacia) - delavirdine Retrovir (GlaxoSmithKline) - zidovudine ribavirin - Virazole (ICN); Rebetol (Schering) ribavirin-interferon alfa-2b - Rebetron (Schering) *RID* (Pfizer) – pyrethrins with piperonyl butoxide rifabutin – Mycobutin (Pharmacia) Rifadin (Aventis) - rifampin Rifamate (Aventis) - rifampin-isoniazid rifamaxin - Xifaxan (Salix) rifampin - Rimactane (Novartis), Rifadin (Aventis) rifampin-isoniazid - Rifamate (Aventis) rifapentine - Priftin (Aventis) Rifater (Aventis) - rifampin, isoniazid and pyrazinamide *Rimactane* (Novartis) – rifampin rimantadine - Flumadine (Forest) ritonavir – Norvir (Abbott) ritonavir/lopinavir - Kaletra (Abbott) Rocephin (Roche) - ceftriaxone § Rochagan (Roche, Brazil) – benznidazole Roferon-A (Roche) – interferon alfa-2a § Rovamycine (Aventis) – spiramycin

S

saquinavir – Fortovase; Invirase (Roche) Septra (GlaxoSmithKline) – trimethoprim-sulfamethoxazole Seromycin (Lilly) – cycloserine Sertaconazole – Ertaczo (Ortho Neutrogena) § sodium stibogluconate – Pentostam (GlaxoSmithKline, U.K.) Soxa (Vita Elixir) – sulfisoxazole

* Also available generically.

spectinomycin – *Trobicin* (Pharmacia) Spectracef (TAP) - cefditoren § spiramycin – *Rovamycine* (Aventis) Sporanox (Janssen) - itraconazole stavudine – Zerit (Bristol-Myers Squibb) * streptomycin – generic Stromectol (Merck) - ivermectin sulconazole - Exelderm (Westwood-Squibb) Sulfatrim - trimethoprim-sulfamethoxazole * sulfisoxazole – *Gantrisin* (Roche), others Sumycin (Bristol-Myers Squibb) – tetracycline HCl Suprax (Lederle) - cefixime § suramin – (Bayer, Germany) Suspen (Circle) – penicillin V Sustiva (DuPont) – efavirenz Symmetrel (Du Pont) - amantadine Synercid (Aventis) – quinupristin-dalfopristin

Т

Tamiflu (Roche/Gilead) – oseltamivir TAO (Pfizer) – troleandomycin Tazicef (GlaxoSmithKline) – ceftazidime Tazidime (Lilly) – ceftazidime telithromycin – Ketek (Aventis) tenofovir – Viread (Gilead) Tequin (Bristol-Myers Squibb) – gatifloxacin Terramycin (Pfizer) – oxytetracycline Tetracap (Circle) – tetracycline HCl

^{*} Also available generically.

[§] Not commercially available in the US.

Tetracon (Consolidated Midland) - tetracycline HCl * tetracycline HCl - Sumycin (Bristol-Myers Squibb), others thiabendazole – *Mintezol* (Merck) § Tiberal (Hoffmann LaRoche, Switzerland) - ornidazole Ticar (GlaxoSmithKline) - ticarcillin ticarcillin – *Ticar* (GlaxoSmithKline) ticarcillin/clavulanic acid - Timentin (GlaxoSmithKline) tigecycline – *Tygacil* (Wyeth) Timentin (GlaxoSmithKline) - ticarcillin/clavulanic acid *Tindamax* (Presutti) – tinidazole tinidazole - Tindamax (Presutti) tioconazole - Vagistat (Bristol-Myers Squibb) tipranavir - Aptivus (Boehringer Ingelheim) * tobramycin - Nebcin (Lilly), others * tolnaftate - Aftate (Schering), others Trecator-SC (Wyeth-Ayerst) - ethionamide § triclabendazole – Egaten (Novartis) trifluridine - Viroptic (GlaxoSmithKline) * trimethoprim - Proloprim (GlaxoSmithKline), others * trimethoprim-sulfamethoxazole - Bactrim (Roche), Septra (GlaxoSmithKline), others trimetrexate - Neutrexin (US Bioscience) Trimox (Bristol-Myers Squibb) - amoxicillin Trimpex (Roche) - trimethoprim * trisulfapyrimidines - Triple Sulfa (Allscripts), others Trizivir (GlaxoSmithKline) – abacavir, lamivudine, zidovudine Trobicin (Pharmacia) – spectinomycin troleandomycin – TAO (Pfizer) trovafloxacin - Trovan (Pfizer)

^{*} Also available generically.

[§] Not commercially available in the US.

Trovan (Pfizer) - trovafloxacin *Truvada* (Gilead) – emitricitabine-tenofovir *Truxazole* (Truxton) – sulfisoxazole *Truxcillin VK* (Truxton) – penicillin V *Tygacil* (Wyeth) – tigecycline

U

Unasyn (Pfizer) – ampicillin/sulbactam *Unipen* (Wyeth-Ayerst) – nafcillin *Urex* (Virco) – methenamine hippurate

V

Vagistat (Bristol-Myers Squibb) – tioconazole valacyclovir – Valtrex (GlaxoSmithKline) valganciclovir – Valcyte (Roche) Valcyte (Roche) - valganciclovir Valtrex (GlaxoSmithKline) - valacyclovir Vancocin (Lilly) - vancomycin Vancoled (Lederle) - vancomycin * vancomycin – Vancocin (Lilly), others Vansil (Pfizer) - oxamniquine *Vantin* (Pharmacia) – cefpodoxime V-cillin K (Lilly) – penicillin Veetids (Bristol-Myers Squibb) - penicillin V Velosef (Bristol-Myers Squibb) - cephradine *Vermox* (Janssen) – mebendazole Vfend (Pfizer) - voriconazole Vibramycin (Pfizer) - doxycycline

^{*} Also available generically.

Vibra-Tabs (Pfizer) – doxycycline vidarabine – Vira-A (Parke-Davis) Videx (Bristol-Myers Squibb) – didanosine Vira-A (Parke-Davis) – vidarabine Viracept (Pfizer) – nelfinavir Viramune (Boehringer Ingelheim) – nevirapine Virazole (ICN) – ribavirin Viread (Gilead) – tenofovir Viroptic (GlaxoSmithKline) – trifluridine Vistide (Gilead) – cidofovir Vitrasert (Bausch & Lomb) – ganciclovir Vitravene (Novartis) – fomivirsen voriconazole – Vfend (Pfizer)

W

Wesmycin (Wesley) – tetracycline HCl Wycillin (Wyeth-Ayerst) – penicillin G Wymox (Wyeth-Ayerst) – amoxicillin

Х

Xifaxan (Salix) - Rifamaxin

Y

Yodoxin (Glenwood) – iodoquinol § Yomesan (Bayer, Germany) – niclosamide

^{*} Also available generically.

Z

zalcitabine – Hivid (Roche) zanamivir – Relenza (GlaxoSmithKline) Zerit (Bristol-Myers Squibb) – stavudine Ziagen (GlaxoSmithKline) – abacavir zidovudine – Retrovir (GlaxoSmithKline) zidovudine-lamivudine – Combivir (GlaxoSmithKline) zidovudine-lamivudine-abacavir – Trizivir (GlaxoSmithKline) Zinacef (GlaxoSmithKline) – cefuroxime Zithromax (Pfizer) – azithromycin Zmax (Pfizer) – azithromycin Zosyn (Wyeth) – piperacillin/tazobactam Zovirax (GlaxoSmithKline) – acyclovir Zyvox (Pharmacia) – linezolid

^{*} Also available generically.

[§] Not commercially available in the US.

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