Pocket Guide to

Antimicrobial Therapy

in

Otolaryngology—Head and Neck Surgery

13th Edition

DAVID N.F. FAIRBANKS, M.D.

The American Academy of Otolaryngology—Head and Neck Surgery Foundation

EMPIRIC DRUG CHOICES FOR COMMON INFECTIONS OF THE EARS, NOSE, THROAT, HEAD AND NECK (see page 26 ff for microbiology, rationale, and more options)

OTOLOGY (page 26 ff)	**Primary Choice**	**Some Alternatives**
Acute otitis media (See pages 26-27, 46-48)	high dose amoxicillin +/- clavulanate	ceftriaxone, resp quinolones cefpodoxime or cefdinir
Acute mastoiditis	vancomycin + ceftriaxone	resp quinolones, etc. (p. 28)
Chr suppurative otitis media	ciprofloxacin otic	ofloxacin otic, etc. (p. 28)
Acute otitis externa (ototopicals p. 55)	alcohol/acid	neo/polymyx, ciproflox, etc.
Otomycosis (ototopicals p. 55)	alcohol/acid	ketoconazole, etc. (p. 30)
Necrotizing otitis externa (p. 30)	ciprofloxacin otic/IV plus: meropenem or ceftazidime	piperacillin/tazobactam plus gentamicin, etc.

RHINOLOGY (page 30 ff)		
Acute rhinosinusitis	high dose amoxicillin +/- clavulanate	levofloxacin, moxifloxacin cefpodoxime, etc.
Orbital/CNS extended (p. 32)	ceftriaxone IV, or resp quinolone IV, or vancomycin + rifampin	
Chr rhinosinusitis	amox/clav or clindamycin	ceph + metronidazole
Pseudomonal	ciprofloxacin or levofloxacin	topicals: ceftazidime, gentamicin, etc. (p. 33)
Fungal	voriconazole	itraconazole (pp. 22, 33)

PHARYNX, HEAD, NECK (p. 34 ff)	
Tonsillo-adenoiditis	1st/2nd gen ceph +/- metronidazole, clindamycin, amox/clav
Acute pharyngitis (p. 36)	erythro-clarithromycin, penicillin, amox, 1st/2nd gen cephs
Diphtheria (p. 37)	erythromycin, or clindamycin, or penicillin (all plus antitoxin)
Necrotizing stomatitis (p. 37)	clindamycin, or amox/clav, or ampi/sulbac, or penicillin + metronidazole
Aphthous stomatitis and herpangina	(canker-sore mixture p. 38)
Thrush (fungal stomatitis) (p. 38)	topicals: nystatin or clotrimazole or fluconazole
Tracheobronchitis, subacute (p. 39)	erythromycins, doxycycline, resp quinolones
Epiglottitis, acute (p. 39)	ceftriaxone IV, ampicillin/sulbactam IV, resp quinolone IV
Croup (p. 40)	ampicillin/sulbactam IV, ceftriaxone IV
Deep neck abscess (p. 40)	clindamycin or linezolid/vancomycin + metronidazole
Necrotizing fasciitis (p. 41)	clindamycin or meropenem + vancomycin +/- metronidazole
Sialadenitis (p. 41)	amox/clav or clindamycin or 1st gen ceph +/- metronidazole

For other infections, see pages 42-45.
For choices according to bacteria, see pages 81-85.

Abbreviations: amox/clav = amoxicillin/clavulanate (Augmentin, Augmentin ES, Augmentin XR)
Ampi/sulbac = ampicillin/sulbactam (Unasyn)
1st gen ceph = cephalexin (Keflex), cefazolin (Ancef, Kefzol), etc.
2nd gen/equiv ceph = cefuroxime (Ceftin), cefpodoxime (Vantin), cefdinir (Omnicef), etc.
Resp quinolones = levofloxacin (Levaquin), moxifloxacin (Avelox)

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ANTIMICROBIAL THERAPY

in

OTOLARYNGOLOGY--

HEAD AND NECK SURGERY

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PREFACE

Of the historical events that have shaped the character of the specialty dealing with ear, nose, throat, head, and neck disorders, probably none has carried the impact as did the appearance of antimicrobial agents for clinical use. It is a story that continues to unfold even today with the appearance of new antibiotics every year and the continuing emergence of new strains of resistant bacteria. Such change gives our knowledge a short half-life, and perhaps in no other clinical discipline is reeducation as important as in the use of antimicrobials.

One-fourth of all Americans who seek medical care do so because of an infectious disease, and over 150 million courses of antibiotics are prescribed each year. The five symptoms most commonly treated are cough, sore throat, fever, nasal congestion, and earache, which suggests that the physician who deals with the upper respiratory tract must be especially current in his understanding of the uses and costs of antimicrobials.

With the objectives of improvement in patient care, curtailment of unnecessary or inappropriate prescribing (to lessen emergence of resistant bacteria), and containment of costs, this monograph is provided to the profession by the American Academy of Otolaryngology--Head and Neck Surgery Foundation in consultation with various of the Academy's Committees and members (especially Drs. Michael Benninger, Berrylin J. Ferguson, James Hadley, Michael D. Poole). Geraldine Hahn Ely has edited, prepared, and maintained the manuscripts of this monograph.

This publication is offered as a concise, practical guide to the practicing physician dealing with the usual or average patient. No recommendations for antimicrobial therapy can be absolute, and the good clinician will modify them according to special circumstances in his patient or community. The recommendations contained herein are not to be considered as any official position of the Academy, but, rather, the opinions of the author, the members of the committees, and other consultants at the time of publication; they are subject to change as new developments occur. It is anticipated that this guide will be revised and updated biennially. (It is now in its thirteenth edition with more than 1.25 million copies printed since 1981.)

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Appreciation is offered to my wife, Sylvia, whose patience and understanding are exercised at the writing of each revision.

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SECTION I

OVERVIEW OF ANTIMICROBIALS BY CATEGORY

Section I.A–Penicillins (Beta Lactams)

Section I.A.l--Penicillin G and V

	(Brand name)
Penicillin G IM, IV:	(Bicillin L-A) IM
Penicillin V oral	

Penicillin is the traditional drug of choice for treatment of pneumococcal and streptococcal infections; it is also active against actinomycosis and about half of the usual anaerobic organisms of the oral and upper-respiratory tract.

Penicillin has a very wide margin of safety; parenteral high doses are tolerated well. Since penicillin is excreted by the kidneys, renal impairment may lead to high concentrations, and neurotoxicity can develop from high concentrations in the cerebrospinal fluid. Penicillins cross the blood-brain barrier satisfactorily for therapeutic purposes, at least when the meninges are inflamed.

DISADVANTAGES:

Gastric acid destroys penicillin; therefore, oral preparations should be administered one-half hour before or 2 hours after meals.

Penicillin is associated with hypersensitivity reactions in approximately 5 percent of patients. Rashes (maculopapular, measles-like, nonurticarial) are the most common reactions. They could be treated with antihistamines, but the usual practice is to discontinue the drug. The rash unpredictably recurs on only half of subsequent administrations of penicillin. In serious infections when there is no other better choice, penicillin has been given safely to patients with previous nonurticarial rash reactions. The serious penicillin reaction is urticaria/angioedema/asthma/anaphylaxis. See page 63. Its prevalence is up to 0.05 percent of administrations, of which some are fatal. It is often not predictable. It does not necessarily occur in a patient with previous history of a reaction. Fatalities are much more likely to follow parenteral administration; therefore, oral preparations are preferred for outpatient management. Cross-allergenicity exists between all types of penicillins, as listed in this section.

Penicillin is inactivated by the beta-lactamases, enzymes that attack the beta-lactam molecular ring in the penicillins and many cephalosporins. Beta-lactamases are produced by *Hemophilus influenzae, M. catarrhalis,* many anaerobes, various other gram negative organisms, and nearly all *Staphylococcus aureus* (which produces its own specific beta-lactamase: penicillinase). The emerging resistance of *Strep. pneumoniae* (over 30 percent of strains in U.S.A.) is mediated entirely differently--by alterations in penicillin binding proteins, which reduce (but do not prevent) the binding of penicillins to the proteins. (See Sections III.A, B, and C, pages 46-50.)

Section I.A.2--Antistaphylococcal (Penicillinase Resistant) Penicillins

Methicillin; Oxacillin IV, IM; Cloxacillin oral; Dicloxacillin oral; Nafcillin IV

Methicillin was the first penicillin that resisted hydrolysis by penicillinase. Its name is often applied to this category of drugs. Oxacillin, cloxacillin, and dicloxacillin were subsequently developed for oral use (distasteful). Nafcillin is for parenteral use. These agents are more effective than methicillin against staphylococci, but none of them offers any advantages over penicillin vs. streptococci or pneumococci. Oral administration should be in the fasting state, and dicloxacillin achieves the highest serum levels. Prolonged (over 21 days) therapy with nafcillin may cause a reversible neutropenia. The indication for use of these drugs is penicillin-resistant staphylococcal infection (see Section III.C, page 49).

Methicillin-resistant *Staph. aureus* ("MRSA") refers to increasingly prevalent strains that are resistant to this entire group plus all the beta-lactam antibiotics (all the penicillins and all generations of cephalosporins and carbapenems). See page 49.

Section I.A.3--Amino-Penicillins

	(Brand name)
Ampicillin IV, oral	
Amoxicillin oral:	(Amoxil, Trimox)

The amino-penicillins are active (more so than penicillin) against streptococci and pneumococci (except for "high-level" penicillin resistant strains). They also have increased activity against many gram-negative organisms, notably *Hemophilus influenzae*, *Proteus mirabilis*, and many E. coli, but not *Pseudomonas aeruginosa*. Gastric acid destroys ampicillin, but amoxicillin is best administered at mealtime; serum levels and middle ear fluid levels are considerably higher than those attained with ampicillin.

Amino-penicillins generate more rash-type reactions (approximately 7 percent) than do other penicillins; this is particularly true when ampicillin is given to a patient who has infectious mononucleosis (65-90 percent). Since exudative tonsillitis is so often the first sign of infectious mononucleosis--even in young children–agents other than amino-penicillins are preferred for acute tonsillitis with exudate.

Ampicillin-resistant strains of *Hemophilus influenzae* show an average prevalence of 40 percent in the U.S.A. and 20 percent worldwide. Furthermore, ampicillin-resistant strains of *M. catarrhalis* approach 90 percent in the U.S.A. Alternative drugs are discussed in Section III.B (see page 48). Resistance is induced by beta-lactamase production from hemophilus, *M. catarrhalis*, and a variety of other aerobic and anaerobic bacteria. Staphylococcal resistance is induced by penicillinase.

Section I.A.4--Augmented Amino-Penicillins

	(Brand name)
Amoxicillin plus potassium clavulanate (amox/clav):	(Augmentin, Augmentin ES, Augmentin XR) PO
Ampicillin plus sulbactam (ampi/sulbac):	(Unasyn) IV

To combat resistant bacteria, beta-lactamase inhibiting compounds such as clavulanic acid, sulbactam, and tazobactam have been developed. These agents exhibit little antimicrobial activity by themselves, but they have the capacity to bind irreversibly the beta-lactamase enzymes that give certain bacteria resistance against beta-lactam antibiotics (penicillins and cephalosporins). When used in combination, clavulanic acid restores antimicrobial activity to amoxicillin against such otherwise resistant bacteria *as Hemophilus influenzae, Moraxella catarrhalis, Staph. aureus* (except MRSA), *B. fragilis*, and other anaerobes. Therefore, the combination has proven to be very effective in treatment of acute otitis media and sinusitis, even when such bacteria were demonstrated to be resistant to amoxicillin alone. Unfortunately, these compounds do not influence pneumococcal resistance to penicillins, because it is not beta-lactamase mediated. But amoxicillin enhanced doses in amox/clav (ES and XR formulations) often retain activity against pneumococci with reduced susceptibility to penicillin (see Section III.A, page 46).

Gastrointestinal side effects (nausea, vomiting, diarrhea) are drawbacks to oral usage, but they can be minimized if the drugs are taken at mealtime and the meal is followed by a lactobacillus preparation (Lactinex, Bacid) or yogurt.

The parenteral (IV) equivalent of amoxicillin/clavulanate is ampicillin/sulbactam. These combinations are useful in a very broad spectrum of head and neck infections, since they are active against the bacterial species listed below.

GRAM-POSITIVE BACTERIA		GRAM-NEGATIVE BACTERIA	
Aerobes:	Anaerobes:	Aerobes:	Anaerobes:
S. aureus (except MRSA)	Clostridium	*H. influenzae*	Bacteroides sp.,
S. epidermidis	Peptostreptococcus	*M. catarrhalis*	incl. *B. fragilis*
S. pneumoniae, most	Peptococcus	*E. coli*	
S. pyogenes		Klebsiella	
S. viridans		Enterobacter	
Enterococcus		Proteus	
		N. gonorrhoeae	

Notably absent from the above list is *Pseudomonas aeruginosa*. The combination of ticarcillin with clavulanic acid (Timentin) or the more potent piperacillin with tazobactam (Zosyn) adds pseudomonas to the spectrum above and creates a combination that is useful especially when pseudomonas is presumed to be mixed with Staph. aureus (except MRSA), *Bacteroides fragilis,* and other anaerobes.

Section I.A.5--Antipseudomonas Penicillins

(Brand name)

Ticarcillin: (Ticar) IM/IV

Ticarcillin plus potassium clavulanate (ticar/clav): (Timentin) IV

Piperacillin: (Pipracil) IM/IV

Piperacillin plus tazobactam (pip/taz): (Zosyn) IV

These agents are effective against most strains of *Pseudomonas aeruginosa* as well as proteus, *E. coli,* klebsiella, enterobacter, serratia, and *B. fragilis*. They are less active than the amino-penicillins against the usual gram-positive upper-respiratory pathogens. They are inactivated by the beta-lactamases, including penicillinase from *Staph. aureus*, which is why beta-lactamase inhibitors are added (to make

Timentin and Zosyn). The combination greatly expands their spectrum of activity to include *Staph. aureus* (except MRSA), anaerobes, etc. (as above). For infections of the head and neck, they can be administered only by the parenteral route. Ticarcillin may cause prolonged bleeding times, and occasional anemia/neutropenia has been caused by drugs in this class. Piperacillin with tazobactam is the most active of these agents against pseudomonas, with the fewest number of strains resistant.

These drugs are of value in the treatment of "malignant" or necrotizing otitis externa and other invasive pseudomonas infections, especially when intracranial spread is threatening. For serious infections, they are usually combined with an aminoglycoside such as amikacin, tobramycin, or gentamicin since a synergistic phenomenon occurs against pseudomonas, and resistance is less likely to emerge (See Section III.D, page 50).

Section I.B--Cephalosporins (Beta-Lactams)

Cephalosporins can be used as penicillin substitutes to treat staphylococcal (except MRSA), streptococcal, and penicillin-sensitive pneumococcal infections when the additional cost is justified; cephalosporins are often used as alternatives to penicillin in patients who have experienced a mild rash reaction to penicillin. However, in patients who have a history of urticaria, angioedema, asthma, or anaphylactic reactions to penicillin, cephalosporin use is usually avoided. See page 63, Section III.L.

The broad spectrum activity of cephalosporins sometimes leads to overgrowth of yeast/fungi (e.g., mucocutaneous candidiasis) or bacteria (i.e., *Clostridium difficile*, that leads to pseudomembranous enterocolitis. See discussion on page 12, Section I.E.) Diarrhea is more troublesome with second and third generation agents. These drugs are categorized as first, second, third, or fourth generation according to certain molecular configurations that affect their spectrum of antimicrobial activity. Pneumococcal resistance (or reduced susceptibility) to penicillin implies resistance (more or less) to all cephalosporins by the same process (altered penicillin binding proteins).

FIRST-GENERATION cephalosporins are active against most gram-positive cocci; i.e., *Strep. pyogenes* (group A beta-hemolytic strep. or GABHS), *Strep. pneumoniae* (except for penicillin-resistant strains) and *Staph. aureus* (except for methicillin-resistant strains, which are resistant to all the beta-lactams including all generations of cephalosporins.) The treatment and prevention of *Staphylococcus aureus* infections (see page 49, Section III.C) account for the greatest usage of these agents in otolaryngology--head and neck surgery. Prophylaxis against surgical infections is a well established indication (see page 66, Section IV). Many strains of gram-negative bacilli are also sensitive to these first-generation drugs, particularly E. coli, Proteus mirabilis, and klebsiella. They are not effective against serratia, enterobacter, and enterococcus species, *Pseudomonas aeruginosa, Bacteroides fragilis, Hemophilus influenzae, or M. catarrhalis*.

CEPHAMYCINS include cefoxitin (Mefoxin) and cefotetan (Cefotan). This is a subset of cephalosporins that is grouped with the second-generation agents, but more by chronology of origin than by activity. They are active against anaerobes, particularly *B. fragilis*.

SECOND-GENERATION cephalosporins (except for the cephamycins) are useful in the treatment of *Hemophilus influenzae* infections (acute otitis media and sinusitis, epiglottitis, etc., see page 48, Section III.B). They are also active against *Streptococcus pyogenes*. They are somewhat less active than is

amoxicillin vs. pneumococci, especially strains with reduced susceptibility to penicillin (intermediate-level resistance), and they are inactive vs. fully resistant strains. Also, they may be somewhat less active than the first generation drugs vs. *Staph. aureus*.

Cefuroxime is both an oral (Ceftin) and parenteral (Zinacef) agent that is active against most *Hemophilus influenzae,* including ampicillin-resistant strains. It is also effective against penicillin-sensitive pneumococcus and against most *M. catarrhalis*. Cefprozil (Cefzil) is less potent vs. pneumococci and hemophilus; *M. catarrhalis* strains are resistant. Cefaclor (Ceclor) is the least potent oral agent in this category; almost all *M. catarrhalis* and hemophilus strains are resistant to it. Serum sickness has been reported following cefaclor usage. Loracarbef (Lorabid), technically a carbacephem, is a derivative of cefaclor; it exhibits a similar lack of potency but does not cause serum sickness. Nausea and diarrhea can accompany use of these agents. Cefuroxime is best absorbed when taken with meals, followed by yogurt or Lactinex (to prevent diarrhea).

Cefuroxime is the only second generation cephalosporin with good CSF penetration, but some CNS infection treatment failures are reported. Both cefuroxime and cefoxitin are active against penicillinase-producing *N. gonorrhoeae*.

SECOND-GENERATION EQUIVALENTS. Cefpodoxime is the most active of the oral cephalosporins for treatment of acute otitis media and sinusitis. Technically, cefpodoxime (Vantin caps, susp) and cefdinir (Omnicef caps, susp) and cefditoren (Spectracef caps only) are third-generation cephalosporins. But their antimicrobial activity is more like the second-generation agent cefuroxime (Ceftin). Likewise, they are orally administered twice daily (cefdinir once daily) with meals for all the same indications; they may cause diarrhea (use yogurt to prevent). The choice between these agents (or vs. amoxicillin/clavulanate) can be made on the basis of cost, convenience, or tolerability.

THIRD-GENERATION cephalosporins (as compared to first-generation agents) are more active against gram negative bacilli and cocci (such as *Hemophilus influenzae, M.. catarrhalis, N. gonorrhoeae,* and *N. meningitidis*), but they are generally less active against gram positive cocci (such as staphylococci, streptococci, and pneumococci) and the anaerobes. This is especially so for the oral agents cefixime and ceftibuten (Cedax) which are useful in treatment of acute otitis media or sinusitis only when pneumococci are absent or have been treated.

The parenteral (IM or IV) agents ceftriaxone (Rocephin) and cefotaxime (Claforan), however, do exhibit effective antipneumococcal activity even against the penicillin-resistant strains at "intermediate" and sometimes "highly" resistant levels. Since they are also highly active against *Hemophilus influenzae* and *N. meningitidis*, and since they penetrate so well into the CSF (across the "blood brain barrier"), they are the agents most commonly employed for treatment of meningitis. Ceftriaxone IV may be combined with vancomycin IV treatment if high-level, multi-drug resistant pneumococcal (MDRSP) infection is suspected. Ceftriaxone is more potent than cefotaxime against gram-positive pathogens, and it needs only once daily dosing.

Intramuscular injection of ceftriaxone (Rocephin) is effective treatment for many stubborn cases of otitis media (3 alternate-day doses) and for gonococcal infections (one dose), especially for unreliable patients.

Ceftazidime (Fortaz, Tazicef) and FOURTH-GENERATION cefepime (Maxipime) have the best activity against *Pseudomonas aeruginosa* of the cephalosporins. They are non-ototoxic, non-

nephrotoxic alternatives to the aminoglycosides for treatment of that organism, or they may be combined with other antipseudomonas agents (gentamicin, et al.) to pre-empt resistance. See Section III.D, page 50. Cefepime also has activity vs. staph. and pneumococci.

COMPARISON OF CEPHALOSPORINS

AGENT	ROUTE/ ADMINIS-TRATION	ADVANTAGES	DISADVANTAGES
FIRST-GENERATION CEPHALOSPORINS			
Cefazolin (Ancef, Kefzol, *et al*.)	IV, IM	Prolonged serum levels Active vs. staph.,* strep, pneumo.,** *E. coli,* proteus	Less active vs. klebsiella *H. influenzae* and *B. fragilis* and pseudomonas resistance
Cephalexin (Keflex)	Oral	*Active vs. staph.,* strep. and* pneumo.,** *E. coli,* proteus, klebsiella	*H. influenzae and* B. fragilis and pseudomonas resistance also
Cefadroxil (Duricef)	Oral		Not active vs. penicillin-resistant pneumococci or MRSA
CEPHAMYCINS			
Cefoxitin (Mefoxin) Cefotetan (Cefotan)	IV, IM	Very active vs. *B. fragilis,* anaerobes, and *N. gonorrhoeae* (includes penicillin-resistant strains)	Not active vs. enterococci and *pseudomonas* Limited vs. gram positive and hemophilus Some bleeding.
SECOND-GENERATION CEPHALOSPORINS			
Cefaclor (Ceclor) Loracarbef (Lorabid)	Oral Oral	Somewhat active vs. *Hemophilus influenzae,* staph.,* strep., pneumo.,** *E. coli,* klebsiella, proteus	Much *M. catarrhalis* and *H. influenzae* resistance Inactive vs. *B. fragilis* Serum-sickness like reactions (cefaclor)
Cefprozil (Cefzil)	Oral bid	Active vs. *Staph. aureus,** *S. pyogenes*. Somewhat active vs. *H. influenzae, M. catarrhalis*, and *S. pneumoniae***	*Not active vs. B. fragilis or* pseudomonas or penicillin-resistant pneumococci
Cefuroxime (Zinacef, Kefurox) (Ceftin)	IV, IM IV, IM Oral (bid with meals)	Active vs. *H. influenzae, N. gonorrhoeae, Staph. aureus,** *S. pneumoniae,*** *S. pyogenes,* and most *M. catarrhalis* Good CSF penetration	Not active vs. *B. fragilis* or pseudomonas or penicillin-resistant pneumococci

SECOND-GENERATION EQUIVALENT, THIRD GENERATION CEPHALOSPORINS			
Cefpodoxime (Vantin) Cefdinir (Omnicef) Cefditoren (Spectracef)	Oral (bid with meals) Oral once daily with meals Oral bid with meals	Active vs. *H. influenzae, N. gonorrhoeae, S. pyogenes, Staph. aureus** (except cefpodoxime), most *S. pneumoniae*,** *M. catarrhalis*	Not active vs. *B. fragilis* or pseudomonas or penicillin-resistant pneumococci or MRSA
THIRD/FOURTH-GENERATION CEPHALOSPORINS			
Cefixime (Suprax) Ceftibuten (Cedax)	Oral susp. Oral	Active vs. *hemophilus, M. catarrhalis, N. gonorrhoeae, E. coli,* klebsiella, etc. gram negative bacteria Once daily dosage	Not active vs. pseudomonas, *Staph. aureus*, or *B. fragilis* Weak vs. strep. and pneumococci
Cefotaxime (Claforan)	*IV, IM*	*Very active vs*. H. influenzae and *N. gonorrhoeae* Active vs. pneumococci High CSF penetration	Poor vs. pseudomonas and *Staph. aureus* Serious infections require multiple doses/day
Ceftazidime (Fortaz, Tazicef)	IV, IM	Very active vs. pseudomonas, proteus, serratia, *E. coli, H. influenzae*, and *N. gonorrhoeae* High CSF penetration	Inactive vs. *B. fragilis* Poor vs. *S. aureus*
Cefepime (Maxipime)	IV, IM	Very active vs. pseudomonas Active vs. Staph. aureus (except meth. resistant), S. pneumoniae, Strep. *pyogenes* High CSF penetration	
Ceftizoxime (Cefizox)	IV, IM	Very active vs. *H. influenzae* and *N. gonorrhoeae* tid dosage	Poor vs. gram-positive cocci and pseudomonas

Ceftriaxone (Rocephin) BEST CHOICE FOR MENINGITIS AND ORAL GONORRHEA	IV, IM	Very active vs. *H. influenzae, S. pneumoniae,*** *N. meningitidis*, and *N. gonorrhoeae* High CSF penetration Once daily dosage	Poor vs. anaerobes, pseudomonas, and staph.

*Except for methicillin-resistant staph. (MRSA), which is resistant to all cephalosporins.
**Except for penicillin-resistant pneumococci, all levels.
***Including intermediate-level penicillin-resistant pneumococci.

Section I.C--Other Beta Lactam Agents

CARBEPENEMS:

Ertapenem; (Invanz) IM, IV
Imipenem-Cilastatin: (Primaxin) IM, IV
Meropenem: (Merrem) IV

These agents possess a very broad spectrum of antimicrobial activity. They are active against *Staph. aureus* (except methicillin-resistant strains) and against streptococci (*S. pyogenes* and most *S. pneumoniae*). Gram-negative organisms against which they are effective include *Neisseria gonorrhoeae*, *Hemophilus influenzae*, proteus species, most *Pseudomonas aeruginosa* (but not ertapenem), klebsiella, *Bacteroides fragilis*, and almost all anaerobes (but not *C. difficile*). Meropenem is more active vs. *Hemophilus influenzae* and *Pseudomonas aeruginosa*; imipenem is more active vs. highly resistant pneumococci. Methicillin-resistant staphylococci vary in their susceptibility. Ertapenem is not active vs. methicillin-resistant staph. or penicillin-resistant pneumococci.

INDICATIONS:

Meropenem or imipenem is useful for treatment of serious hospital-acquired or mixed infections in which aerobic and anaerobic gram-negative bacilli plus *Staph. aureus* (not MRSA) might be involved. They could be logical single-agent choices to initiate treatment of serious or unidentified infections (except when the CNS is involved) in immunocompromised neutropenic patients. Generally, however, they are used when initial therapy with cephalosporins or penicillins has proven ineffective.

DISADVANTAGES:

Patients allergic to penicillin should be considered allergic to agents in this class. These drugs can be administered only by the parenteral route. Seizures may accompany imipenem overdose or use in patients who are at increased risk for convulsions. Dosages should be corrected for small body weight and reduced for patients with renal impairment or in children treated for meningitis. Meropenem, however, has shown some promise in treatment for meningitis, and it is not associated with adverse CNS effects.

Because resistance can develop during treatment, serious pseudomonas infections should not be treated with imipenem alone, but rather combined with an aminoglycoside (see page 14, Section I.H, and page

50, Section III.D) such as gentamicin. Mycoplasma and chlamydia are resistant.

MONOBACTAMS:
Aztreonam: (Azactam) IM, IV

Aztreonam is for parenteral treatment of aerobic gram-negative infections, as a safer substitute for aminoglycosides. It has little cross-allergenicity with penicillins or cephalosporins, even in patients with a history of penicillin anaphylaxis.

ADVANTAGES:

Aztreonam is highly active against *Hemophilus influenzae* and *N. gonorrhoea*e (penicillinase producers). It is also active against *E. coli,* klebsiella, serratia, proteus, and *Pseudomonas aeruginosa* (more active than antipseudomonas penicillin but slightly less active than imipenem or ceftazidime). Ototoxicity and nephrotoxicity have not been reported.

DISADVANTAGES:

The drug is so highly specific against gram-negative infections that gram-positive colonization and superinfection is common (20-30 percent). The combination of aztreonam with clindamycin or vancomycin is safe and effective in expanding the antimicrobial spectrum. Experience in treatment of CNS infections is limited.

Section I.D--Macrolides, Ketolides, Azalides

Macrolides-Erythromycins:

This group of antibiotics includes erythromycins, dirithromycin, and clarithromycin. These agents are useful alternatives to the beta-lactam antibiotics (penicillins and cephalosporins) since they effectively treat many of the same infections but there is no crossover allergenicity between the two groups.

Erythromycins

	(Brand name)
Erythromycin:	(ERYC, Ery-Tab, PCE, EES, EryPed)
Combination--Erythromycin and sulfisoxazole:	(Pediazole)
Clarithromycin:	(Biaxin, Biaxin XL)

INDICATIONS:

Erythromycins are almost as effective against streptococci and pneumococci as is penicillin, but pneumococci that are resistant to penicillin (even at intermediate levels) are fully resistant to macrolides and the prevalence of pneumococcal resistance is higher.

Moraxella catarrhalis may be effectively treated with erythromycins, but most strains of *Hemophilus influenzae* are resistant; so erythromycins alone, as a treatment for otitis media, are often disappointing. However, the combination of erythromycin with a sulfonamide is generally effective against hemophilus, but the combined side-effects profile is troublesome (page 20).

Erythromycins are also effective against infections caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila* (the "atypical" or intracellular pathogens), and *B. pertussis* ("whooping cough"). These organisms cause respiratory disease sometimes mistaken as viral infections. For example, what used to be called "primary atypical pneumonia" (the "walking pneumonia" of young adults), with a protracted course and prolonged productive cough, is often due to such organisms, which are important (common) causes of cough in adults that persists several weeks after "the flu." See page 39 (Tracheobronchitis).

Erythromycins are also recommended for treatment of chlamydia or mycoplasma pharyngitis (which is common). For diphtheria, and the carrier state of *Corynebacterium diphtheriae*, erythromycin is the drug of choice.

Dirithromycin need be taken only once daily, but low serum levels are achieved. Clarithromycin is given twice daily (once daily with the "XL" prep), with meals; its metabolite exhibits some activity vs. *Hemophilus influenzae*, but combination with a sulfonamide (i.e., TMP/SMX) would assure better coverage.

DISADVANTAGES:

Erythromycins are effective against many strains of staphylococci, but not methicillin-resistant strains. Furthermore, resistance to erythromycin can emerge quickly. So the drug is not recommended for serious *S. aureus* infections. Resistance of *S. pneumoniae* and *H. influenzae* is also prevalent.

Some 10 to 15 percent of patients refuse to complete the prescribed course of erythromycin because of gastrointestinal distress. This is a side effect of all erythromycins and may be minimized by administration at mealtime except that the base and stearate preparations (which are usually dispensed when "generic" erythromycin is prescribed) would not be well absorbed. Enteric-coated preparations (Ery-Tab, ERYC) and particle tablets (PCE) are less subject to this problem. And absorption of the ethylsuccinate (EES) is even enhanced by food.

Hearing loss has been reported in patients receiving high doses of intravenous (not oral) erythromycin (e.g., 1 Gm q 6 hours). But the ototoxicity is reversible after the drug is discontinued.

All members of this class minimally prolong the electrocardiographic QT-interval. They should be used with caution in patients with arrhythmias, uncorrected hypokalemia, and with other drugs which may prolong the QT-interval, such as quinidine, sotalol, or procainamide.

Erythromycins are oxidized by the cytochrome P-450 isoenzymes to form a stable metabolite complex. This inhibits metabolism of other drugs that are oxidized by P-450. Interactions by this mechanism result in increased concentrations (sometimes toxic) of a wide variety of drugs (see page 77, Section VI), most importantly:

anti-arrhythmic agents: quinidine, disopyramide
lovastatin (Mevacor)
simvastatin (Zocor)
atorvastatin (Lipitor)
sildenafil (Viagra)–dosage needs reduction
theophylline* (Theo-Dur, et al.)–dosage needs reduction
cyclosporine

warfarin
carbamazepine (Tegretol)
benzodiazepines
    triazolam (Halcion)
    alprazolam (Xanax)
    midazolam (Versed)
alfentanil
digoxin and digitoxin
methylprednisolone
dopamine agonists (antipsychotics: bromocriptine, pimozide-Orap)

Contraindicated is concomitant use with pimozide, cisapride, astemizole, and terfenadine which may not be available in the U.S.A., but from abroad.

*No adverse interactions with dirithromycin or azithromycin.

Ketolide-Telithromycin (Ketek) oral:

This agent is a derivative of erythromycin/clarithromycin, and it shares many of their properties. Telithromycin exerts activity (similar to the erythromycins) against the "atypical" respiratory pathogens (mycoplasma, legionella, chlamydia), *B. pertussis,* and erythromycin-susceptible strains of *M. catarrhalis, Staph. aureus,* and streptococci. Hemophilus coverage is questionable. Its distinguishing feature is its good (in vitro) activity against pneumococci, including penicillin/erythromycin-resistant strains.

It is administered orally, once daily, two 400 mg tablets with meals.

DISADVANTAGES:

Blurred vision or difficulty focusing (slowed ability to accommodate or release accommodation) occur in 1-2 percent of users (beware night driving). GI disturbances are similar to the erythromycins. Q-T prolongation is a potential but unobserved effect. Exacerbation of myasthenia gravis has been noted, so other drugs are better used. Drug interactions encountered with erythromycins (as listed above) apply to telithromycin. It is a potent inhibitor of cytochrome P-450 isoenzymes and can cause potentially dangerous increases in serum concentrations of the "statin" drugs (Zocor, Mevacor, Lipitor, etc.), which should be suspended during telithromycin therapy.

Caution is recommended with simultaneous use of telithromycin and benzodiazepines, likewise with metoprolol (Lopressor, Toprol) in patients with heart failure. Co-administration of theophylline and telithromycin increases gastrointestinal side effects. They are better administered an hour apart. Reports of serious hepatic toxicity are troublesome.

Azalide-Azithromycin (Zithromax, Z-PAK):

This relative of macrolides exerts antimicrobial activities similar to the erythromycins (as above) except that it is somewhat less active vs. staph., strep., and pneumococci, and resistances have become common. It is useful against *M. catarrhalis* as well as the "atypical" respiratory pathogens. It does not interact adversely with drugs oxidized by cytochrome P-450 listed above.

It is extremely long acting and needs once daily dosing (on an empty stomach) for only 5 days to accomplish 10 days of therapy. A loading dose (double) is taken on the first day.

Section I.E--Clindamycin

Clindamycin (Cleocin), oral, IV, IM, suppresses bacterial protein synthesis.

INDICATIONS:

Clindamycin is effective against all streptococci, most pneumococci, and most penicillin-resistant (but not methicillin-resistant) staphylococci. It is concentrated in respiratory tissues, mucus, saliva, and bone. It is the drug of choice for the treatment of osteomyelitis. It is also important for its activity against anaerobic infections, particularly against *Bacteroides fragilis* (see Section III.E, page 51).

Bacteroides fragilis is a cause of deep tissue abscess and gram-negative septicemia with shock. Since *B. fragilis* usually comes from lower colon (fecal) contamination, it would be suspected in contaminated neck wounds and chronic draining ears. Clindamycin is especially useful against polymicrobial-mixed infections of bacteroides species and other oral anaerobes that are prevalent in chronic tonsillitis and deep neck abscess of dental or oral origin (Brook: *Laryngoscope* 1986; 96:1385). Clindamycin is superior to penicillin for eradication of streptococci in tonsillo-pharyngitis, probably because the polymicrobial flora (producing beta-lactamases) of such infections renders penicillin ineffective.

For prophylaxis against infections in surgery, clindamycin is as effective as any other regimen. The combination of clindamycin with gentamicin covers the three main contaminating infections of head and neck surgery: staph., anaerobes, and pseudomonas (see Prophylaxis, page 66, Section IV).

DISADVANTAGES:

Oral clindamycin can cause nausea/vomiting, and taken at bedtime it can cause esophagitis from reflux. It is best given with meals and with the evening dose given with a substantial snack an hour before bedtime. Yogurt (or Lactinex) taken after the meal/snack may also be helpful.

Oral (and rarely intravenous) use of clindamycin has been followed by gastroenteritis and diarrhea, the worst manifestation of which is pseudomembranous colitis (see page 17, Section I.J, and page 62, Section III.K), an uncommon disorder characterized by severe diarrhea, megacolon, dehydration, and sometimes death. If diarrhea occurs with use of this drug, it should be discontinued promptly, and either oral metronidazole or oral vancomycin should be initiated promptly. Some clinicians pre-treat with metronidazole a few days before initiating clindamycin.

Clindamycin is not useful in intracranial infections because of poor penetration of the blood-brain barrier. It has no activity against pseudomonas, mycoplasma, or hemophilus organisms. Penicillin-resistant pneumococci are increasingly resistant to clindamycin. Intravenous infusions should be slowly administered (10-60 minutes) to avoid cardiopulmonary arrest. They prolong action of muscle relaxants.

Although clindamycin, erythromycin, and chloramphenicol are not structurally related, they all bind at the identical site on the ribosome, so that the effect of one inhibits the action of another if they are (mistakenly) used concurrently.

Section I.F--Tetracyclines

	(Brand name)
Tetracyclines:	(Declomycin, Sumycin) oral
Long-acting tetracyclines:	Minocycline (Dynacin) oral
	Doxycycline (Doryx, Monodox, et al.) oral, IV

INDICATIONS:

Tetracyclines enjoy popularity for the treatment of acne, for prevention of traveler's diarrhea, and for nonspecific treatment of "flu" (presumably to treat mycoplasma, chlamydia, legionella, or other secondary bacterial infections). Minocycline needs to be taken only twice daily, and doxycycline only once daily. Doxycycline is the only tetracycline acceptable for use in renal failure patients. Minocycline is more effective than others for treatment of acne, for *Staph. aureus*, and for meningococcal prophylaxis.

Doxycycline is useful against *Mycoplasma pneumoniae,* chlamydia, legionella, various rickettsiae (e.g., Rocky Mountain spotted fever), and the spirochete: *Borrelia burgdorferi* (Lyme disease). See page 44.

Tetracycline suspension is empirically used in a topical mixture (mouthwash, gargle, and swallow) to relieve the pain of aphthous stomatitis and other mouth infections (e.g., Vincent's angina), which may be caused by invasion of various oral microorganisms (see page 38).

DISADVANTAGES:

Many streptococcus and pneumococcus strains have become resistant to tetracyclines. Likewise, some *Staph. aureus* (including some MRSA), most bacteroides, some mycoplasma, and all *Pseudomonas aeruginosa* strains are resistant.

Calcium, magnesium, iron, and aluminum ions interfere with absorption of orally administered tetracyclines. Therefore, they should not be administered simultaneously with antacid preparations or at the time of a meal containing milk products. Doxycycline and minocycline, however, are not affected by these interactions.

Tetracyclines may cause grayish-brown discoloration of the teeth if they are taken during the time of enamel formation. Therefore, they should not be given to nursing mothers or to children in the first 8-10 years of life (which would stain the child's permanent teeth) or to the mother during the last half of pregnancy (which would stain the deciduous teeth). Furthermore, they are contraindicated in pregnancy because of fetal bone growth inhibition, congenital limb abnormalities, and cataracts (see page 52, Section III.F).

Tetracyclines predispose users to sunburn. Minocycline use is often associated with vertigo, ataxia, and nausea (all transient). Esophagitis can occur with many acidic medications (such as tetracyclines) taken at bedtime, either from incomplete swallowing or from reflux; doxycycline is the most frequently incriminated agent.

Tigecycline IV

Tigecycline (Tygacil IV) is a derivitive of minocycline; but it is not affected by the major mechanisms that cause tetracycline resistance.

INDICATIONS:

Tigecycline is useful in skin-structure infections caused by *Strep. pyogenes* and *Staph. aureus* including MRSA. It is also active against penicillin resistant *S. pneumoniae*, anaerobes (including *B. fragilis* and clostridia), and many "atypical bacteria."

DISADVANTAGES:

Like tetracyclines, tygecycline causes photosensitivity and should not be used in children ≤ 8 years old or during pregnancy. It is not effective against *Pseudomonas aeruginosa*. It is available for IV use only.

Section I.G–Chloramphenicol

(Brand name)
Chloramphenicol: (Chloromycetin) IV Oral chloramphenicol is no longer available in the U.S.A., but it is sold over the counter in other countries. Intramuscular therapy is ineffective.

INDICATIONS:

Chloramphenicol is a broad-spectrum antibiotic that crosses the "blood-brain barrier" well. If safer alternatives were not available, it could be used in treatment vs. streptococci, pneumococci (except for penicillin-resistant strains), staphylococci, *Hemophilus influenzae,* and anaerobic bacteria in polymicrobial infections and abscesses.

DISADVANTAGES:

Penicillin-resistant strains of pneumococcus are fully resistant to chloramphenicol. Chloramphenicol is reserved for life-threatening infections that pose a greater risk than that inherent in the use of the drug itself. Aplastic anemia caused by chloramphenicol can be irreversible and fatal. It is idiosyncratic; it is not dose related; it can occur after a single dose and can appear several months after the course of therapy has been completed. The incidence of aplastic anemia following chloramphenicol usage has been estimated between 1/20,000 and 1/40,000. Chloramphenicol is also hazardous to the fetus and the neonate causing the so-called "gray baby syndrome," which can be fatal.

Section I.H–Aminoglycosides

These antibiotics are of special interest to otolaryngologists because they can be ototoxic. Aminoglycosides bind to the ribosomes in the same manner as tetracyclines.

INDICATIONS:

STREPTOMYCIN is thought of primarily as an antituberculous drug, although it is also useful in treatment of bacterial endocarditis.

KANAMYCIN offers no advantages that outweigh its toxicity risk.

NEOMYCIN is widely used as a topical agent against a broad spectrum of gram-positive and negative organisms (see Ototopical Therapy, page 54, Section III.H). *Pseudomonas aeruginosa is* often resistant.

GENTAMICIN is indicated in serious invasive infections caused by most *Pseudomonas aeruginosa* strains, klebsiella-enterobacter-serratia species, and some proteus species, which are the usual hospital-acquired infections. Gentamicin could also be used effectively against proteus, *E. coli*, and most staphylococcal infections, but less toxic agents are available in the penicillin and cephalosporin categories. Generic gentamicin is the least expensive antipseudomonas antibiotic, but in many U.S. hospitals some 30 percent of pseudomonas strains have become resistant. It is useful against intranasal pseudomonas as a nasal spray (80 mg in 45 ml saline) or a nasal irrigation (80 mg in 500 ml saline).

(NOTE: The correct spelling of gentamicin is with an "i" where the "y" would be usually expected.)

TOBRAMYCIN (Nebcin) has activity similar to gentamicin but with less pseudomonas resistance. It has been used in nasal irrigations (20 mg in 50 ml saline) vs. pseudomonas in cystic fibrosis patients (Davidson: *Laryngoscope* 1995; 105:354).

AMIKACIN (Amikin) is a semisynthetic derivative of kanamycin. It is active against the same range of gram-negative species as gentamicin and tobramycin. Its major advantage is that strains resistant to gentamicin or tobramycin are often still susceptible to amikacin (see page 50, Section III.D).

Against pseudomonas infections, drugs of this class (gentamicin, tobramycin, or amikacin) are often used in combination with ticarcillin or piperacillin for a synergistic effect and to deter emergence of resistant strains. Aminoglycosides are often included in combination antibiotic regimens for polymicrobial infections and for prophylaxis in surgery (clindamycin plus gentamicin, *et al*.)

DISADVANTAGES:

All aminoglycoside antibiotics are ototoxic and nephrotoxic, but they can be used safely if dosages and renal function are monitored (see Section V on Ototoxicity, page 73). Furthermore, many infections in the head and neck, such as acute and chronic sinusitis, acute otitis media, deep neck infections, and some infected cholesteatoma, are due to bacteria that are resistant to this class of drugs, notably pneumococci, streptococci, non-aeruginosa pseudomonas, many *Staphylococcus aureus*, and all anaerobic bacteria (including *B. fragilis*). These drugs are not well absorbed after oral administration, and they cross the blood-brain barrier poorly.

Section I.I--Quinolones (Fluoroquinolones)

The fluoroquinolones are broad spectrum antibiotics that play an increasingly important role in treatment of multi-drug resistant bacterial infections. And since they are unrelated to other classes of antibiotics, they may also be used in patients that are allergic to (or intolerant of) the penicillins, cephalosporins, sulfonamides, erythromycins, etc.

"Antipseudomonas quinolones": Ciprofloxacin (Cipro) oral, IV
Ofloxacin (Floxin) oral, IV
Levofloxacin (Levaquin) oral, IV

INDICATIONS:

These agents are important because they are effective as ORALLY administered treatments for *Pseudomonas aeruginosa* infections of skin, bone, and respiratory mucosa. Ciprofloxacin and levofloxacin are more potent than ofloxacin, and they cause fewer side effects. These agents also provide effective oral treatment of pseudomonas pneumonia and bronchitis in cystic fibrosis patients.

By inference, they may be useful in treatment of pseudomonas sinusitis (polyposis). Necrotizing ("malignant") otitis externa can be treated (intravenously in the acute stage, then orally on an outpatient basis in the convalescent stage) with ciprofloxacin. Unlike the aminoglycosides, quinolones are not ototoxic. For treatment of serious pseudomonas infections, and to deter emergence of resistance, antipseudomonas quinolones should be combined with other antipseudomonals such as piperacillin/tazobactam, ceftazidime, aztreonam, or an aminoglycoside (gentamicin, *et al*.) See Section III.D, page 50.

Topical ciprofloxacin is superior to parenteral gentamicin in treatment of pseudomonas suppurative otomastoiditis (*Arch*. *Otolaryng*. 1992; 118:842 and 1995; 121:880). As topicals, ciprofloxacin (Cipro otic, Ciloxan ophth.) and ofloxacin (Floxin otic) create no ototoxic risk for application through a tympanostomy tube or a tympanic membrane perforation. Drug levels in the middle ear are superior.

Ciprofloxacin might also be used against other gram-negative organisms (e.g., *Hemophilus influenzae* or *M*. *catarrhalis* against which it is very active), but its use in ordinary ear, sinus, or throat infections is considered inappropriate since the usual pathogens (*Streptococcus pyogenes* and *pneumoniae*) are generally resistant to it (*JAMA* 1990; 264:1438), and widespread use encourages pseudomonas resistance (*JAMA* 2003; 289:885) which has exceeded 30 percent in many U.S. hospitals.

"Respiratory quinolones"

Levofloxacin (Levaquin) oral/IV
Gatifloxacin (Tequin) oral/IV
Moxifloxacin (Avelox) oral/IV
Gemifloxacin (Factive) oral

INDICATIONS:

These agents are useful in treatment of respiratory and pharyngeal infections because of their expanded activity which includes gram-positive organisms such as *Streptococcus pyogenes* (beta hemolytic), *Streptococcus pneumoniae* (including penicillin and macrolide-resistant strains), and *Staphylococcus aureus* (not methicillin-resistant strains). Furthermore, they retain their activity vs. *Hemophilus influenzae* and *M*. *catarrhalis* (even beta-lactamase producing strains). And they are also active against the "atypical" pathogens: mycoplasma, chlamydia, legionella, and pertussis. Therefore, these drugs should be very useful for treatment of acute otitis media, sinusitis, pharyngitis, tracheobronchitis, epiglottitis (probably), etc. (in adults). Except for levofloxacin, respiratory quinolones retain little activity vs. pseudomonas. The mild anaerobic activity of moxifloxacin is of limited clinical importance (other than its adverse effect on intestinal microflora). So if anaerobic infection requires therapy, metronidazole can be combined with any of these quinolones.

Orally administered they are well absorbed and widely distributed through body tissues, and they are long acting, which allows the advantage of once-a-day dosing. They may be taken with meals, even with milk products.

The "respiratory quinolones" are currently the most effective ORALLY administered antibiotics available to treat multi-drug/highly (penicillin) resistant pneumococcal infections. In their parenteral forms they are as potent against these organisms as is ceftriaxone and perhaps vancomycin. Furthermore, they cover *H*. *influenzae* well, and they penetrate inflamed meninges well enough (neither of which does vancomycin) that they may be effective treatment for meningitis (*J*. *Antimic*. *Chemoth*. 1997; 39:Suppl B), although this use has not been fully studied.

Since antimicrobial efficacy for each of the respiratory quinolones is equivalent at recommended doses (see below), selection between agents should be based on safety issues.

DISADVANTAGES:

Rashes have been troublesome with gemifloxacin use (3 percent), more especially in women under age 40 and postmenopausal women taking replacement hormones (approaching 30 percent). Gatifloxacin has been associated with unexpected alterations in blood sugar, especially in elderly patients or those taking oral medications for diabetes.

Neurological symptoms such as headache, dizziness, restlessness, stimulation, and insomnia are the most commonly experienced side effects. With ciprofloxacin these are aggravated by concomitant use of nicotine, caffeine, and nonsteroidal anti-inflammatory drugs. Quinolones are used with caution in patients with suspected CNS disorders or other factors that lower the seizure threshold. Theophylline elimination time is prolonged by ciprofloxacin, so dosage adjustments of theophylline are required. Achilles tendon rupture has been associated with quinolone use.

Quinolones are listed among the drugs that prolong the electro cardiographic Q-T interval. Others include erythromycins, clarithromycin, ketoconazole, fluconazole, etc. It is prudent to avoid combination-use of quinolones with the other listed agents or with antiarrhythmic agents or use in patients with bradycardia, hypokalemia, or acute myocardial ischemia. (FDA--Levofloxacin: "precaution," moxifloxacin: "warning.") Doses above those recommended (levofloxacin 750 mg/day, moxifloxacin 400 mg/day) increase the hazard of Q-T prolongation. Levofloxacin risk is less.

Bioavailability of all quinolones is impaired by di- and trivalent cations in the stomach: Al^{+++}, Ca^{++}, Mg^{++}, Fe^{++}, Zn^{++}, as in vitamins with zinc or iron, antacids, sucralfate (Carafate), and buffering in didanosine (Videx). Therefore, manufacturers have recommended the following:

Cipro: Take 2 hours before or 6 hours after Levaquin: Take 2 hours before or 2 hours after Tequin: Take 4 hours before or 4 hours after Avelox: Take 4 hours before or 8 hours after Factive: Take 2 hours before or 3 hours after	Antacids or vitamins with minerals (Zn, Fe) or iron supplements, or calcium or iron enriched juices and cereals

For simplicity, the patient could take the quinolone at breakfast and the antacids and/or supplements at suppertime, or visa versa. Conversely, quinolone absorption is not impaired by H2 antagonists or dietary milk products. Ciprofloxacin, levofloxacin, and ofloxacin may interact with cimetidine (Tagamet), cyclosporine, probenecid, warfarin (bleeding), and NSAIDS (ibuprofen *et al*., lowering seizure thresholds). (See Section VI, page 77.)

In animal studies, ciprofloxacin impaired bone growth. For this reason, quinolones are not FDA-approved for use in children. But several studies of cystic fibrosis children and neonates suggest this is not a risk in humans (*Arch. Otolaryng*. 1995; 121:880, *Pediatr. Inf. Dis. J*. 1997; 16:127).

Pneumococcal resistance to respiratory quinolones remains low (<1 percent) in the U.S.A. despite 8 years of use. Some investigators fear that if use of quinolones as first-line agents for common/minor infections (especially in children) becomes a common practice, their unique role as the only available oral-agents for highly resistant pneumococcal infections will be compromised (*Current Inf. Dis. Reports* 2000; 2:115).

Section I.J–Vancomycin

Vancomycin is of interest to otolaryngologists because it has ototoxic potential and because its use is increasing generally (for treatment of methicillin-resistant staph. and penicillin-resistant pneumococci–in combination with third-generation cephalosporins). It is unrelated to any other class of antibiotic, and therefore there is no cross resistance or allergy with other antibiotics.

INDICATIONS:

With few exceptions, the activity of vancomycin is limited to gram-positive bacteria. It is valuable in serious gram-positive coccal infections as a penicillin substitute for allergic patients and/or against resistant organisms. It is bactericidal against almost all staphylococci, streptococci (aerobic and anaerobic), and pneumococci (including "high-level" multi-drug resistant strains), and against clostridium species and enterococci (i.e., endocarditis). It is active vs. *Staphylococcus epidermidis* (coag -) and *Staphylococcus aureus* (coag. +) even when they are resistant to antistaphylococcal penicillins (MRSA) and cephalosporins (see Section III.C, page 49). It is also used orally against antibiotic-induced pseudomembranous enterocolitis (see page 62, Section III.K), but such usage is thought to be a factor inducing vancomycin-resistant enterococci in the U.S.A. Therefore, most such cases should be primarily treated with metronidazole (below).

DISADVANTAGES:

Vancomycin is not absorbed from the gastrointestinal tract, and it is too painful for intramuscular administration. It may create chills, fever, rash and flushing ("red-man" syndrome), and phlebitis on intravenous administration, but slow injection and prophylactic use of antihistamines minimize these side effects. Hearing loss has been reported when it is used in patients concurrently being treated with aminoglycosides (gentamicin, *et al*.). Probably vancomycin potentiates the ototoxicity of other known ototoxic agents. Anecdotal reports of vancomycin (alone) ototoxicity (sensori-neural hearing loss) suggest that it is rare and may be reversible. Treatment failures are reported with vancomycin used alone for pneumococcal meningitis. It does not cross the "blood-brain-barrier" well.

The drug should be used for the shortest period possible; and when doses over 2 Gm/day are used, serum levels should be monitored, and renal function should be assessed twice weekly.

Section I.K–Daptomycin

Daptomycin (Cubicin) IV is a once daily bactericidal alternative to vancomycin for treatment of methicillin-resistant *Staph. aureus* (MRSA) and *Staph. epidermidis* (MRSE). Its activity vs. *Strep. pyogenes* and *pneumoniae* (including multi-drug highly resistant strains) is similar to vancomycin's. It is unrelated to any other category of antibiotics, sharing no allergenicities. It may elevate creatine phophokinase levels (leading to muscle discomfort/weakness). Thus, consideration is given to stopping "statin" drugs (Lipitor, etc.) during treatment with daptomycin. It should be administered slowly IV (over a 30-minute period).

Section I.L–Linezolid

Linezolid (Zyvox), IV and oral, is an alternative to vancomycin for treatment of methicillin-resistant *Staph. aureus* (MRSA), even vancomycin-resistant strains, and for vancomycin-resistant enterococci infections. It is especially important because it can be given orally (which vancomycin cannot), but at present it is extremely expensive.

It is also active against other gram-positive bacteria, such as S. pneumoniae (but penicillin-susceptible strains only, against which other traditional antibiotics are effective and preferred and much less costly).

It tends to raise blood pressure in patients taking oral decongestants (pseudoephedrine, ephedrine, phenylephrine) and may cause or aggravate thrombocytopenia. Platelet counts are needed if 2 weeks or longer of therapy is required.

Section I.M--Metronidazole

Metronidazole (Flagyl oral, IV) is active against various protozoa, oral spirochetes, and almost all obligate anaerobes including bacteroides species (e.g., *B. fragilis*), prevotella (formerly *B. melaninogenicus)*, fusobacterium species, peptostreptococcus (anaerobic strep.), and clostridium species (e.g., *C. difficile*). Metronidazole promptly relieves the pain of the multiple pharyngeal and tonsillar ulcers of Vincent's angina; it also may exert a favorable effect on tonsillitis of infectious mononucleosis, which suggests that anaerobic micro-organisms are associated with these conditions.

Unfortunately, it is useless against all aerobic and micro-aerophilic bacteria (including gram + cocci, hemophilus, and pseudomonas), but it can be effectively used in combination with penicillins, cephalosporins (cephalexin, cefazolin, ceftazidime, etc.), quinolones (levofloxacin, ciprofloxacin), or aminoglycosides for treatment of mixed infections such as tonsillitis, sinusitis, infected cholesteatoma, wound infections, odontogenic disease, or deep-neck abscesses. Since it penetrates the blood-brain barrier well, it may be useful against brain abscess from chronic otitis or cholesteatoma.

It is the primary therapy for antibiotic-induced diarrhea or pseudomembranous enterocolitis (see page 62, Section III.K), and it is much less expensive than vancomycin for a course of therapy. It may also be used to pretreat a patient who will be receiving clindamycin. Metronidazole is administered either orally or intravenously; it is long acting and can be effectively dosed at 1-2 Gm once daily. It has a long safety record for use in adults; it is not well studied in children. Patients taking metronidazole should avoid alcohol consumption during therapy and for 48 hours thereafter, because of an Antabuse-like interaction.

Section I.N--Rifampin

Rifampin (Rifadin oral, IV) is a potent antibiotic against *Staph. aureus* and *epidermidis* (including methicillin-resistant strains), pneumococci, *Neisseria (gonorrhoeae* and *meningitidis*), *Hemophilus influenzae*, legionella, anaerobes (including *B. fragilis*), many mycobacterium species, and most streptococci. However, resistance to rifampin occurs rapidly under therapy, which is why the drug should not be used alone to treat established infections. But for prophylaxis, it is used as a single agent. Rifampin has the ability to concentrate in nasopharyngeal secretions and to enter white cells which may be harboring bacteria. It is, therefore, useful in treatment of nasopharyngeal carriers of Neisseria meningitidis and *H. influenzae* for prophylaxis vs. meningitis and epiglottitis (see page 66, Section IV). For the *Staph. aureus* carrier state in the nares, a combination of oral rifampin and topical mupirocin (Bactroban) ointment (with or without trimethoprim/sulfamethoxazole) is helpful.

Rifampin potentiates cytochrome P-450 metabolic activity and, thus, lowers serum levels (and effectiveness) of many substances, such as corticosteroids, beta blockers, oral antifungals, anticoagulants, contraceptives, methadone, cyclosporine, etc. (See Section VI, page 77.) Hepatic or renal dysfunction may be induced by rifampin. These are rare and are reversible if recognized.

Dosage: Adults: 300 mg cap 1-2 caps bid 1 hour ac
Children: 10-20 mg/kg bid 1 hour ac (make suspension from capsules)

Section I.O--Mupirocin

Mupirocin (Bactroban) is unrelated to any other antibiotic, and thus the potential for cross resistance (of bacteria) or allergy (of patients) with any others is eliminated. It is a topical antibiotic with activity against *Staph. aureus* (including methicillin resistant and beta-lactamase producing strains), *Staph. epidermidis,* and aerobic *Strep. pyogenes* (beta hemolytic). It is approved for treatment of impetigo as an ointment applied twice daily. It is effective (applied inside the nares) for treatment of staph. infections (including the carrier state) in the nostrils (Scully, *Arch. Intern. Med.* 1992; 152:353). When provided to health care workers, it is valuable for staphylococcal infection control in hospitals and surgical care facilities. For applications deeper in the nose, some clinicians prescribe the ointment mixed into a saline spray (Bactroban 5 Gm in 45 ml "Ocean" nasal spray). Bactroban ointment is available in both dermatologic and nasal preparations; a cream is for dermatologic use: infected skin injuries.

Section I.P--Sulfonamides (Folate inhibitors)

INDICATIONS:

Sulfonamides have antimicrobial activity against most strains (75 percent) of *Hemophilus influenzae*. But as single agents they are not reliable against *M. catarrhalis,* pneumococci, streptococci, anaerobes, or pseudomonas.

Combined therapy improves the potency of sulfonamides used alone. The combination of a sulfonamide and an erythromycin (Pediazole susp.) is a traditional treatment for acute otitis media and purulent rhinosinusitis, targeting hemophilus and pneumococci. Sulfonamides may also be combined with penicillin, cephalosporins, or clindamycin with the same objective. However, emerging resistances may render these combinations ineffective: pneumococcal resistance to sulfonamides, erythromycins, and cephalosporins currently exceeds 30 percent, and 15-25 percent of hemophilus strains are resistant to sulfonamides, as are most *M. catarrhalis* strains.

Trimethoprim (TMP) is marketed in combination with sulfamethoxazole (SMX) as Septra, *et al*. Trimethoprim is an antibacterial like a sulfonamide, but the two drugs attack the chain of bacterial protein synthesis at different sites, and their combined actions are synergistic. This increases their potency but not necessarily their spectrum of antimicrobial activity. TMP/SMX is quite active against *Staph. aureus*, including methicillin-resistant strains.

TMP/SMX has also proven effective as an adjuvant to immunosuppressive drugs in treatment (and prevention of relapse) of Wegener's granulomatosis (McRae: *Arch. Otolaryng.* 1993; 119:103). Furthermore, it is effective in treatment or prophylaxis for most patients with *Pneumocystis carinii* infection (lungs, middle ear/mastoid, esophagus, etc.) as a complication of AIDS (HIV infection).

DISADVANTAGES:

Skin eruptions of any type can occur from sulfonamides, most commonly morbilliform rashes, hives, and photodermatitis. Sulfonamide allergy is life-long (rashes will recur with every subsequent use). Erythema multiforme (Stevens-Johnson syndrome) and aplastic anemia are serious but rare reactions

associated with sulfonamides. AIDS patients are especially likely (up to 80 percent) to suffer from rashes, neutropenia, or thrombocytopenia from TMP/SMX. Because of the risk of blood dyscrasias (agranulocytosis, thrombocytopenia) following prolonged TMP/SMX usage (and the need for repetitive blood testing), its use for otitis media prophylaxis is to be discouraged. Sulfonamides interact adversely with phenytoin (Dilantin), rifampin, warfarin, oral hypoglycemics, methotrexate, and cyclosporine.

The main disadvantage of sulfonamides is their relative lack of potency when used as single agents. Also, many bacterial strains are resistant to sulfonamides; i.e., most streptococci, all pseudomonas, about 30 percent of pneumococci, and increasing numbers of hemophilus. Furthermore, laboratory sensitivity studies often do not predict accurately what the clinical response to the sulfonamides may be.

Section I.Q--Antifungals

AMPHOTERICIN B (Fungizone IV) is effective vs. most systemic mycotic infections. Its broad spectrum includes candida, aspergillus, and mucor species, which can infect the nasal and sinus cavities and become invasive in patients with an immunodeficient state caused by advanced age, debility, diabetes, the AIDS virus, corticosteroid use, or tumor chemotherapy. Amphotericin B is administered intravenously, or intrathecally in cases of intracranial infection. Fever, rigors, nausea/vomiting, hypotension, and tachypnea follow IV infusion. Its most important toxicity is renal damage, which is usually dose related and reversible. It is diminished if the lipid formulations are used (Abelcet, Amphotec, AmBisome). (*Med. Letter* 1997; 39:86) Anemia is also commonly seen, but it is reversible. Topically it has been used with variable success vs. fungal sinusitis as a nasal rinse: Amphotericin B as 250 micrograms per ml sterile water (not saline or dextrose): 20 ml washed/irrigated into each nostril bid *(J. Allergy* and *Clinical Immunol*. 2005; 115:123-131).

FLUCYTOSINE (Ancobon) has a narrower spectrum than amphotericin B, but it is better tolerated and can be given orally. It may be effective for treatment of candidiasis, cryptococcosis, or with amphotericin B vs. aspergillosis. In general, it has been disappointing when used alone. Resistant organisms emerge frequently during therapy. Its major side effect is bone marrow suppression, usually reversible.

KETOCONAZOLE (Nizoral) is an oral drug to treat chronic mucocutaneous candidiasis (thrush). It should not be relied upon for life-threatening candidiasis. Mucor organisms are resistant to ketoconazole. Aspergillus strains are sometimes susceptible, as are some dermatophytes (tenia infections). Because it requires gastric acidity for absorption, it is administered orally with meals (Coca-Cola improves absorption) but not with antacids or gastric acid suppressants (e.g., Tagamet, Zantac, Prilosec) or Carafate. It is distributed poorly into CSF, eye, or saliva but accumulates in skin and nails. Adverse interactions are reported when used concurrently with anticoagulants, oral hypoglycemics, corticosteroids, alcohol, phenytoin (Dilantin), triazolam (Halcion), theophylline, rifampin, etc. See Section VI, page 77. Mild hepatic toxicity is fairly common with ketoconazole, but serious liver damage is uncommon. If jaundice or hepatitis symptoms appear, the drug should be discontinued (potentially fatal). Dose: 400 mg PO daily.

FLUCONAZOLE (Diflucan) is the preferred oral and intravenous antifungal to treat oropharyngeal, esophageal, and vaginal candidiasis, and also cryptococcal meningitis. It differs from ketoconazole and itraconazole in that oral absorption is excellent (not requiring gastric acid), and it distributes well into all body fluids, including cerebral spinal fluid, brain tissue, eye, and saliva. It may be used concomitantly with oral amphotericin or clotrimazole or nystatin for refractory candida infections. Drug interactions are fewer but similar to ketoconazole (as above and Section VI, page 79). Its long

serum half-life allows once daily dosing. First day: 150-200 mg; subsequent days, 100 mg/day. One 150 mg dose may suffice for antibiotic-induced vaginal candidiasis.

VORICONAZOLE (Vfend) is the preferred oral and intravenous antifungal to treat invasive aspergillosis (including invasive fungal sinusitis) and significant infections with *Scedosporium* and *Fusarium* species. It also has activity against the majority of (but not all) fluconazole resistant *Candida* strains. It achieves good penetration into the cerebrospinal fluid (CSF). It is not active in vitro against mucormycosis. Intravenous voriconazole preparation contains a cyclodextrin vehicle which accumulates in renal insufficiency so intravenous voriconazole is contraindicated in patients with a creatinine clearance of less than 50 ml/minute. Voriconazole-related visual disturbances are common (30 percent altered visual perception, blurred vision, color vision changes and/or photophobia occur, usually mild and transient.) Rare cases of hepatic failure leading to death have been reported. Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Voriconazole is metabolized by the cytochrome P-450 enzymes, so coadministration with pimozide, quinidine, sirolimus, rifampin, carbamazepine, and ergot alkaloids is contraindicated. Coadministration of voriconazole with cyclosporine or tacrolimus will likely lead to increased levels of these immunosuppressive agents, but coadministration is not contraindicated. See page 79.

Intravenous voriconazole is administered with a loading dose of 6 mg/kg every 12 hours for two doses, followed by a maintenance dose of 4 mg/kg every 12 hours. In view of the good bioavailability of the film-coated tablets and the expense of the intravenous preparation, therapy should be switched to voriconazole tablets (200 mg every 12 hours) as soon as possible. See *Medical Letter* 2002; 44:63.

ITRACONAZOLE (Sporanox), like voriconazole (but unlike ketoconazole and fluconazole) is active against *Aspergillus* species, many dematiaceous species (i.e., *Alternaria, Curvularia,* and *Bipolaris*), as well as *Candida* species. Itraconazole has many drug-drug interactions (p. 79), and penetrates poorly into the CSF.

It is available in three formulations–capsules, an orally administrable solution, and an intravenous preparation. The capsules (take with food & cola) may be poorly absorbed in some patient populations, the solution has an unpleasant gasoline-like taste (but is better absorbed—take fasting). Dose: Intravenous preparation 200 mg every 12 hours for 4 doses, then 200 mg once daily. Capsules 100-200 mg every 12 hours. For "allergic fungal sinusitis," a 3-month course has been advocated, beginning at 200 mg bid then tapered to 100 mg daily (Ferguson; *Arch. Otolaryng*. 1998: 124:1174). Orally administered solution: 200 mg once daily.

POSACONAZOLE (Noxafil oral) is active against most *Candida* (including some fluconazole-resistant strains), *Aspergillus*, dermatophytes, *Histoplasma*, *Blastomyces*, *Coccidioides*, *Scedosporium*, etc. And—unlike other azoles and echinocandins (cancidas)—it has good activity against *Zygomycetes* (Mucor). For treatment of refractory invasive mucormycosis, posaconazole is reported to be more effective than Amphotericin B (not yet FDA-approved). But it is available in oral preparation only, and should be taken with a full meal or liquid nutritional supplement (*Medical Letter* 2006; 48;94). Posaconazole shares the adverse-effects of other -azole antifungals (see ketoconazole, voriconazole).

CASPOFUNGIN (Cancidas) is the first of a new class of remarkably non-toxic antifungal drugs, the echinocandins. They are available in intravenous forms only. Caspofungin has activity against *Aspergillus* and *Candida* species, including fluconazole-resistant *Candida* strains. The drug is indicated in therapy of refractory invasive aspergillosis. It has proven to be effective in esophageal candidiasis, in candidemia. Occasional patients develop fever, facial flushing, or skin rash during infusion. Studies of

caspofungin coadministration with cyclosporine showed a significant risk of hepatotoxicity. Other drug-drug interactions require dose adjustments (p. 79). The dose is 70 mg as a loading dose, followed by 50 mg once per day.

NYSTATIN (Mycostatin susp. and lozenges) has fungistatic activity clinically limited to candidiasis (moniliasis, thrush). It is poorly absorbed across any surface but is effective against cutaneous, oropharyngeal, and vaginal candidiasis that occasionally complicates broad-spectrum antibiotic therapy. No side effects or drug interactions occur. Dose: 1 tsp (5 ml) qid pc. Swish in mouth, gargle, swallow.

MICONAZOLE (Monistat cream) is useful as a skin or vaginal cream for candidal infections that may accompany broad-spectrum antibiotic therapy. It is available over the counter.

GRISEOFULVIN (Fulvicin, etc.) provides systemic therapy against superficial dermatophyte infections of skin and hair; e.g., "ringworm." Do not use in pophyria patients.

CLOTRIMAZOLE (Lotrimin, et al.) is for treatment of dermatological infections of tenia and candida types. Some cases of otomycosis may respond to use of the solution as ear drops. For treatment of oropharyngeal candidiasis, it is available (without prescription) as a troche (Mycelex). Dose: dissolve in mouth 5 times daily. No adverse events or drug interactions occur.

TERBINAFINE (Lamisil) is an oral antifungal for treatment of dermatophyte infections of the toenails or fingernails. Such infections have been thought to cause a secondary, allergic otitis externa in some patients. Improvement has been reported with prolonged oral administration of this agent: one 250 mg tablet daily for 6-12 weeks (*Oto. Clin. N.A.* 1998; 31:157). Hepatotoxic potential makes pretreatment screening advisable.

Section I.R–Antivirals (for ENT, H&N Infections)

ACYCLOVIR (Zovirax) ointment is effective in the treatment of mucocutaneous *Herpes simplex* infections in immunocompromised patients. Intravenously or orally, it is effective against both localized and disseminated *Herpes simplex* and *zoster* infections (i.e., *Herpes zoster* oticus).[2] Orally it has suppressed or prevented symptomatic attacks of mucocutaneous *Herpes simplex* virus during the course of drug therapy (e.g., 400 mg bid for 4 months). Unfortunately, herpes viruses persist in a latent form for prolonged periods (e.g., neural cells of ganglia for *Herpes simplex* and *zoster*). Currently available herpes drugs require actively multiplying virus to be effective. Since none are active against latent virus, active infections can be expected to recur. Topical acyclovir is effective against *Herpes simplex labialis*, keratitis, and primary genital herpes. Renal dysfunction is encountered rarely (with IV therapy); it is reversible. Dosage for *Herpes zoster*: 800 mg q 4 hrs, 5 times daily for 7-10 days. For chicken pox (adults and children over 40 kg): 800 mg qid for 5 days decreases severity of varicella if initiated within 24 hours of the rash. For *Herpes simplex labialis*: 400mg po 5 times daily (q 4 hr while awake) X 5 days.

VALACYCLOVIR (Valtrex, oral) administered orally is rapidly converted into acyclovir at substantially higher serum levels. It has proven effective for shortening the course and discomfort of *Herpes simplex labialis* if it is initiated within 2 hours of symptom onset (tingling, itching, burning). Dosage: 2 Gm po q 12 hr x 1 day (optional additional 2 Gm po once on day 2). Dosage for *Herpes zoster*: begin within 48 hours of rash, give 1 Gm tid for 7 days. For recurring *Herpes simplex* (genital), begin within 48 hours of onset, 500 mg bid for 5 days.

FAMCICLOVIR (Famvir) is useful against *Herpes zoster* infections. When given within 72 hours of rash onset (500 mg q 8-12 hrs for 7 days), it can shorten the recovery time. For Herpes simplex recurrences: 125-500 mg bid for 5 days; for HIV patients: 500 mg bid for 7 days (genital or orolabial).

Some clinicians treat "Bell's Palsy" with antivirals such as above on the supposition of a viral etiology (*Lancet* 2001; 357:1513).

PENCICLOVIR (Denavir), as a 1 percent topical cream (q 2 hr x 4 days) shortens healing time for recurrent orolabial *Herpes simplex* virus. DOCOSANOL (Abreva) is a similarly helpful cream (10 percent, 2 Gm) when applied 5 times daily until healed. It is available without prescription and is the least expensive treatment.

AMANTADINE (Symmetrel) is useful against influenza type A infections for both active therapy as well as prophylaxis (for 6-8 weeks through exposure period). During known influenza type A epidemics, amantadine can be recommended for patients with clinical influenza when initiated within the first 48 hours of symptom onset. Dose: 100 mg capsule bid or preferably 200 mg q a.m. with breakfast; for 5 days. Reduced doses are mandated in patients over age 65 (not over 100 mg daily) and in those with renal insufficiency. Side effects include nausea, dry mouth, anorexia, nervousness, light headedness, anxiety, confusion, and insomnia. The drug is contraindicated in pregnancy. Patients with seizure disorders are at greater risk for neurologic side effects. Resistant influenza A strains were noted in 2005-6.

RIMANTADINE (Flumadine) is indicated in the same circumstances as its predecessor, amantadine, and it is prescribed in the same dosages. CNS side effects are reduced with rimantadine, as is dry mouth, but nausea may be more. Rimantadine is acceptable at full doses in renal insufficiency until the creatinine clearance falls below 10 ml/min. Resistant influenza A strains were noted in 2005-6.

OSELTAMIVIR (Tamiflu) decreases severity and duration of symptoms caused by either A or B influenza if treatment is initiated within 36 hours of symptom onset. It also decreases respiratory complications that require an antibiotic. Prophylaxis of influenza with this drug may be considered for familial-exposed persons or for nursing home occupants during an outbreak. Side effects (nausea, vomiting, headache) are minimized if the drug is taken with meals. It is excreted entirely by the kidneys, so interactions with other drugs are unlikely. Dose: one 75 mg capsule twice daily, begin within 2-3 days of "flu" symptoms (once daily for prevention).

ZANAMIVIR (Relenza) likewise diminishes symptom severity and duration (and complications) of both A and B influenza if treatment is started within 36-48 hours of symptom onset. It requires oral inhalation of a dry powder. Side effects (irritated nose and mouth, bronchospasm in asthmatics) are uncommon. Dose: Two inhalations (5 mg each) twice daily for 5 days for treatment or once daily (X 5 days) for 42 days for prevention.

ANTIRETROVIRAL (HIV) AGENTS: The treatment of human immunodeficiency virus (HIV) infection is a subject that exceeds the scope of this Pocket Guide. Readers are referred to the *Sanford Guide to HIV/AIDS Therapy*; *JAMA* 2004; 292:251-268. Ever increasing numbers of drugs are available, listed in three categories. Some exhibit drug interactions with a number of antimicrobials that are used for associated secondary infections in the ears, nose, pharynx, and neck.[3]

Category and Name	**Interactions with Antimicrobials**[5]
Nucleoside reverse-transcriptase inhibitors ("NRTI's" or "nukes")	
Zidovudine, ZDV, AZT (Retrovir)	Fluconazole, clarithromycin, rifampin, TMP/SMX
Stavudine, d4T (Zerit)	
Didanosine, ddI (Videx)	Quinolones, azole-antifungals, rifampin, TMP, metronidazole
Zalcitabine, ddC (Hivid)	Metronidazole
Lamivudine 3TC (Epivir)	
Abacavir (Ziagen)	
Lamivudine/Zidovudine (Combivir)	(as for Zidovudine, above)
Emtricitabine (Emtriva)	
Tenofovir	
Non-nucleoside reverse-transcriptase inhibitors ("NNRTI's" or "non-nukes")	
Nevirapine (Viramune)	Rifampin, –azole antifungales (ketoconazole, etc.)
Delavirdine (Rescriptor)	Clarithromycin, rifampin, –azole antifungals
Efavirenz (Sustiva)	Clarithromycin, rifampin, –azole antifungals
Tenofovir (Viread)	
Protease inhibitors ("PI's")	
Saquinavir (Invirase, Fortavase)	Erythro/clarithro, rifampin, –azole antifungals
Indinavir (Crixivan)	Erythro/clarithro, rifampin, –azole antifungals
Ritonavir (Norvir) with Lopinavir (Kaletra)	Metronidazole, erythro/clarithro, rifampin, and –azole antifungals
Nelfinavir (Viracept)	Erythro/clarithro, rifampin, –azole antifungals
Amprenavir (Agenerase)	Erythro/clarithro, rifampin, –azole antifungals
Fosamprenavir (Lexiva)	Erythro/clarithro, rifampin, –azole antifungals
Atazanavir (Reyataz)	Erythro/clarithro, rifampin
Tipranavir (Aptivus)	Metronidazole, rifampin, –azole antifungals

Note: for interactions with other drugs see Sanford guides.[3]

REFS:

1. Drugs for Non-HIV Virus Infections, *Med. Letter* 2003; 44:9.
2. Dickens: Herpes Zoster Oticus: Treatment with IV Acyclovir, *Laryngoscope* 1988; 98:776, and *Med. Letter* 1999; 41:113.
3. Gilbert, *et al*.: *The Sanford Guide to Antimicrobial Therapy*.

For Sanford Guides, see page 106.

SECTION II

MICROBIOLOGY AND DRUG SELECTIONS FOR TREATMENT OF INFECTIONS IN THE EAR, NOSE, THROAT, HEAD, AND NECK

Rational antimicrobial therapy requires an understanding of the microbiology of infectious diseases. Ideally, antimicrobial therapy should be based on results of cultures from specific infections. However, in some instances culture studies may be impractical or the clinical condition too threatening for treatment to await the reporting of results. Empirical therapy is then instituted, based on probabilities of the etiological organism for the clinical infection, as reviewed below.

ACUTE OTITIS MEDIA.

Microbiology: *Streptococcus pneumoniae* and non-typable *Hemophilus influenzae* account for over half of pathogens. *Moraxella catarrhalis*, a smaller percent. Viruses, low-virulence organisms, and occasional *Streptococcus pyogenes* or *Staphylococcus aureus* account for the rest.

Streptococcus pneumoniae	25-50%
Hemophilus influenzae	15-30%
Moraxella catarrhalis	320%
Streptococcus pyogenes (gr. A)	2%
Staphylococcus aureus	1%
Viruses	45-70%
No microorganisms	16-25%

Summary of numerous studies.[1]

Over half of acute otitis media cases will resolve spontaneously (without antibiotic therapy), which explains why almost any drug tried will appear to bring success in the majority of patients.[2] This fact also has prompted some authorities to withhold all antibiotics in patients with only mild symptoms who can readily be reevaluated (and treated if not well) in 2-3 days.[1] But relief of pain and prevention of hearing loss are attainable therapeutic objectives with antibiotics. Furthermore, antibiotics may prevent mastoiditis, which occurs in approximately 1 in 400 untreated children with acute otitis media.[2]

Pathogenicity varies with the infecting microorganism. Over 75 percent of infections caused by *M. catarrhalis* will resolve without treatment since it is a low-virulence pathogen. But spontaneous resolution occurs in only 50 percent of *H. influenzae* infections and, worse, in only 10-19 percent of *S. pneumoniae* infections. Pneumococcus is the invasive pathogen that is most likely to progress to mastoiditis and otitic meningitis.

Drug choices: Most authorities continue to recommend amoxicillin (in high doses) as the initial treatment choice for first-time, untreated, uncomplicated acute otitis media, despite the prevalence of resistant strains among the common pathogens: 30-40 percent of hemophilus are resistant to amoxicillin, as are over 90 percent of *M. catarrhalis* and an ever increasing number of *S. pneumoniae* (see page 46, Section III.A). The low cost of amoxicillin and its effectiveness in yet the majority of infections (including those that would have spontaneously resolved) are arguments in its favor.[1,2]

For penicillin-allergic patients, the traditional combination of erythromycin or clindamycin (vs. pneumococci) plus a sulfonamide (vs. hemophilus) is a low-cost choice even though most hemophilus strains are resistant to erythromycin, and some are resistant to sulfonamides. Furthermore, pneumococcus is usually resistant to sulfonamides, and its penicillin-resistant strains are resistant to erythromycin. So, for penicillin allergic adults, a respiratory quinolone would be preferred; e.g., levofloxacin (Levaquin), moxifloxacin (Avelox). If a child's "allergy" is of the mild-rash-only type, better choices would be a 3rd generation cephalosporin, such as cefpodoxime (Vantin) orally, or ceftriaxone (Rocephin) intramuscularly.

Drug choices: (American Academy of Pediatrics . . . *Pediatrics* 2004; 113:1451-1465)

Primary:
Amoxicillin high dose, or high-dose amox/clav (Augmentin ES, XR)

Alternatives:
Cefpodoxime (Vantin), cefdinir (Omnicef),
Ceftriaxone (Rocephin) IM
one injection daily (or every day) x3
Levo-or-moxifloxacin (Adults)* See page 15, Section I.I

For children under age 2, or patients with a frequent otitis media history, or patients with antibiotic use within 3 months, or patients who appear seriously ill, it is prudent to proceed directly to (high-dose) amoxicillin/clavulanate (Augmentin ES-extra strength, pediatric, or XR-extended release, adult), or intramuscular ceftriaxone. Pneumococcal strains with reduced susceptibility to penicillin are usually susceptible to an enhanced (doubled) amoxicillin dosage, to which can be added the clavulanate (for hemophilus and *M. cat.)*

Infections that fail treatment with the above medications are probably due to highly penicillin-resistant (multi-drug-resistant) pneumococcal strains. Culture-directed therapy (from myringotomy) is advantageous. For high-level penicillin-resistant pneumococci: (See Section III.A, page 46)

Ceftriaxone (Rocephin) IM or IV
Levo-or-moxifloxacin oral
See page 15, Section I.I*
Vancomycin IV
with or without rifampin

*Quinolones are not available in oral pediatric suspensions. See page 15, Section I.I, regarding their use in children.

Many other agents have been successfully used in treatment of acute otitis media, but current resistance patterns make treatment failures possible. For example, pneumococcus (the most important pathogen) is increasingly resistant to sulfonamides (e.g., trimethoprim/sulfa), to macrolides (e.g., erythromycins, azithromycin, clarithromycin), to the cephalosporins, and somewhat to clindamycin.

Length of treatment has become a controversial issue since some authorities are recommending shortened courses to avoid excessive or unnecessary antibiotic usage.[3] Nevertheless, small children (under age 3 years) require a minimum of 10 days of treatment to prevent recurrence. For an older child with a mild case (without a prior otitis media history) who responds promptly, 5 days of treatment may suffice. However, a patient whose pain and inflammation fails to respond to 48-72 hours of amoxicillin should be switched to one of the alternative agents (vs. resistant bacteria) for a 10-day course. Ceftriaxone (Rocephin) IM is given to children at 50 mg/kg once daily (or every other day) for 3 doses.

ACUTE BULLOUS MYRINGITIS and ACUTE SUPPURATIVE OTITIS MEDIA (in the absence of prior tympanic membrane perforation or cholesteatoma) are variants of acute otitis media. They are caused by the same organisms and are treated with the same agents.

PERSISTENT OTITIS MEDIA WITH EFFUSION. This is the subacute or incompletely resolved stage of acute otitis media. Even when acute otitis media has been adequately treated, the serous effusion in children often requires several weeks for its complete resolution.[1] Aspirates can be sterile or exhibit low-virulence bacteria, or be resistant strains of the same bacteria as in acute otitis media. If pain and

inflammation are absent or if hearing loss is not troublesome, antibiotics are not necessarily required. If these symptoms are present (or they recur), one of the alternative agents (as above) would be employed.

CHRONIC OTITIS MEDIA WITH EFFUSION. This sequela of acute otitis media exhibits a thick mucoid middle ear fluid that lasts for months after the inciting infection. The pathogens present (either by culture or gram stain) are the same as in acute otitis media, but their prevalence is diminished or altered, presumably by antimicrobial treatment which exerts selective pressure for resistant organisms to remain. Antimicrobial choice should be directed against those strains, i.e., the alternative agents, as above, but usually they do not exert a long-term efficacy. The effusion can take several months to resolve by itself. Hearing loss dictates the urgency of therapy. Myringotomy, fluid aspiration, and insertion of tympanostomy tubes reduce the resolution time and thus the amount of antimicrobial usage. See Clinical Practice Guidelines, Otitis Media with Effusion, *Otolaryng., Head, Neck Surg*. May 2004; 130:Suppl S95-S118.

OTITIS MEDIA of NASOTRACHEAL INTUBATION
About half of patients with a nasotracheal tube in place for over 48 hours will have an otitis media with affusion. Organisms isolated have included pseudomonas, klebsiella and enterobacter species. Ceftazadine, meropenem or levofloxacin are logical therapeutic choices.

ACUTE MASTOIDITIS as an invasive complication of acute otitis media.

Microbiology: *S. pneumoniae*, group A beta-hemolytic streptococci (*Strep. pyogenes*), *Staph. aureus*, and coag-neg. staph. are the predominant pathogens. Hemophilus, proteus, pseudomonas, and bacteroides species are also reported.[4] (*Otolaryngol Head Neck Surgery* 2006; 135: 106)

Drug choices: Culture and gram-stain-directed therapy is optimal. Penicillin resistant pneumococci should be anticipated, as also the potential for intracranial extension.[5]

Primary:	Alternatives:
Vancomycin IV plus Ceftriaxone (Rocephin) IV with or without rifampin	Levofloxacin (Levaquin), moxifloxacin (Avelox) IV Clindamycin IV plus rifampin or ceftriaxone IV Ampicillin/sulbactam (Unasyn) IV plus rifampin

An acute exacerbation of chronic tympanomastoiditis can also include the pathogens of chronic suppurative otitis media (see following), and other drug selections would apply.

CHRONIC SUPPURATIVE OTITIS MEDIA (CHRONIC TYMPANOMASTOIDITIS) with tympanic membrane perforation, with or without cholesteatoma.

Microbiology: Most chronic ear drainage results from mixed infections with both aerobic and anaerobic pathogens. Aerobic *Pseudomonas aeruginosa*, *Staph. aureus* and e*pidermidis*, proteus species, klebsiella, and *E. coli* are isolated, as are prevotella and porphyromonas anaerobes.

Draining ears, especially if cholesteatoma (keratoma) is present, often produce foul-smelling pus which is characteristic of anaerobic streptococci. From two-thirds of infected cholesteatomas, various anaerobes can be recovered including *Bacteroides fragilis*.

Drug choices: Ototopical therapy (see Section III.H, page 54.)

Primary:	Alternatives:
Ofloxacin (Floxin otic) Or ciprofloxacin (Cipro HC otic, Ciloxan ophthalmic, Ciprodex)	Povidone-iodine (Betadine) Boric acid/iodine powder *et al*. antiseptics

Oral therapy alone is usually not very effective unless the culture or gram-stain studies show a pure staphylococcus, pneumococcus, or hemophilus infection (such as in an acute infection in a "chronic" ear). Adjunctive systemic therapy is sometimes required:

Oral/parenteral therapy:

Primary:	Alternatives:
Ciprofloxacin (Cipro) or levofloxacin (Levaquin) in adults with or without clindamycin IV piperacillin/tazobactam (Zosyn)	IV ceftazidime (Fortaz) or cefepime (Maxipime), with or without clindamycin IV meropenem with or without clindamycin or metronidazole

ACUTE (DIFFUSE) OTITIS EXTERNA ("Swimmer's Ear")

Microbiology: *Pseudomonas aeruginosa* is the predominant pathogen. *Staph. aureus* is also prevalent. Other organisms may be causative (e.g., strep. and other staph. species, proteus, klebsiella, and other gram-negative species), but they will respond to treatment choices for staph. and pseudomonas.

Drug choices: See Section III.H, page 54.

Primary:	Alternatives:
Alcohol/acid (acetic or boric) mixtures (Domeboro, VõSol HC, *et al.)* Or neomycin/polymyxin/hydrocortisone (Cortisporin, *et al.)*	Ofloxacin otic (Floxin) Ciprofloxacin (Cipro HC, Ciprodex, Ciloxan) Gentamicin ophthalmic Tobramycin ophthalmic (Tobradex) Antiseptics (see page 54, Section III.H)

Diabetics (to prevent necrotizing otitis) or patients with severe or spreading infection (cellulitis, lymphadenitis) require added oral/IV therapy vs. pseudomonas (e.g., ciprofloxacin or levofloxacin) or vs. *Staph. aureus* (choice based on culture & sensitivities).

ACUTE LOCALIZED OTITIS EXTERNA (FURUNCULOSIS OF THE EAR CANAL).

Microbiology: *Staph. aureus*, or occasionally other staph./strep. species.

Drug choices for oral therapy:

Primary:	Alternatives:
Cephalexin	Clindamycin, dicloxacillin, TMP/SMX

OTOMYCOSIS ("FUNGUS-EAR," "JUNGLE-EAR").

Microbiology: Aspergillus species predominate. *Aspergillus niger* (black), *Aspergillus flavus* (yellow), *Aspergillus fumigatus* (gray), *Candida albicans* (white), and various other fungi can be causative. Cleansing of the ear canal is a prerequisite to successful therapy.

Drug choices: See Section III.H, page 54—re: ototopical therapy

Primary:	Alternatives:
2% acetic acid (otic Domeboro) or Acetic/citric acids in alcohol (VõSol) or 3% boric or 2% acetic acid in 70% isopropyl alcohol or Ketoconazole cream	Aqueous merthiolate Povidone-iodine (Betadine) Gentian violet 2% in 95% alcohol M-cresyl acetate (Cresylate) Boric acid/iodine powder

CHRONIC (RECURRING) OTITIS EXTERNA (ECZEMATOUS, SEBORRHEIC, ATOPIC, ALLERGIC, PSORIATIC, etc. OTITIS EXTERNA).

Microbiology: During active infections, pathogens may be those of otomycosis or acute otitis externa. Treatment then would be as listed above. Prevention/control needs dandruff shampoos such as selenium sulfide (Selsun) or ketoconazole (Nizoral) shampoo and nightly applications of topical corticosteroids (VõSol HC or cortisporin ointment). See also Terbinafine, page 23, Section I.Q.

NECROTIZING ("MALIGNANT") OTITIS EXTERNA.

Microbiology: *Pseudomonas aeruginosa* (in diabetic patients).
Consider hyperbaric oxygen.
Drug choices: Topical plus oral plus IV/IM antipseudomonals (see pages 50-51).

Topical ciprofloxacin (Cipro HC) or topical ofloxacin (Floxin otic) PLUS oral or IV levofloxacin or meropenem IV	PLUS	Added intravenous antipseudomonals: Piperacillin/tazobactam (Zosyn) plus: gentamicin or tobramycin or amikacin Ceftazidime (Fortaz) or cefepime (Maxipime)

ACUTE BACTERIAL RHINOSINUSITIS is an infection equivalent to acute otitis media but in a different complex of air spaces in the skull. Similarly, many clinically suggestive cases are not bacterial infections at all but are virus infections, "colds," allergies, headaches from other causes, etc. The accompanying table refers to only culture-positive studies.

	Children	Adults
S. pneumoniae	35-42%	20-43%
H. influenzae	21-28%	22-35%
M. catarrhalis	21-28%	2-10%
Strep. species	3-7%	3-9%
Anaerobes	3-7%	0-9%
Staph. aureus		0-8%

Microbiology: The causative organisms are similar to acute otitis media: About 75 percent of cultures obtained from antral puncture in patients with acute

maxillary sinusitis contain either *S. pneumoniae* or non-typable strains of *Hemophilus influenzae* (both beta-lactamase + and -).[6] *Moraxella catarrhalis* is an occasional isolate (?pathogen) in adults, but in children it rivals *H. influenzae*. Viruses are also prevalent. They mimic bacterial infections and ofttimes (like allergy attacks) predispose to secondary bacterial infections of the usual pathogens. *Staph. aureus* is frequently found in nasal cultures (even 30 percent of normal people) but rarely in antral puncture cultures, which suggests it is probably a contaminant. However, in the hospitalized or immunosuppressed patient, the pathogenicity of *Staph. aureus* is more likely. Anaerobic organisms in acute rhinosinusitis suggest dental disease as the source.

Drug choices: (see Guidelines for Acute Bacterial Rhinosinusitis, *Otolaryng., Head, Neck Surg.* 2004;130:Suppl S34 ff.[6,7]) The likelihood of spontaneous resolution (without antibiotic therapy) of acute rhinosinusitis is similar to that of acute otitis media (half or more of uncomplicated mild cases), which suggests that antibiotics should be reserved for patients with moderate to severe symptoms and those that are progressively worsening (for more than the 5-7 days of a "common-cold"). Inexpensive amoxicillin (high-dose) is widely recommended as the first choice antibiotic for previously untreated, mildly symptomatic, uncomplicated adult cases. For penicillin-allergic patients, the combination of erythromycin and a sulfonamide is inexpensive but troubled with side effects and bacterial resistances; doxycycline is an inexpensive option for adults.

Primary for mild, no prior treatment, low-resistance risk cases:
Amoxicillin (high-dose) with or without clavulanate (Augmentin ES/XR)
Doxycycline (adults)
Cefpodoxime (Vantin),
or cefdinir (Omnicef)

Resistances to amoxicillin and other commonly used antibiotics are prevalent, as is illustrated in the accompanying table. For a) treatment failures, or for b) patients in whom a treatment failure is unacceptable, or for c) moderately to severely ill patients (especially frontal or sphenoid sinusitis), or for d) patients who have recently taken a penicillin or cephalosporin drug, or e) in circumstances where resistance is prevalent, the alternative options (below) are recommended.

Susceptibility of Isolates at PK/PD Breakpoints [6]
Percentage of Strains Susceptible

Agent	*S. pneumoniae*	*H. influenzae*	*M. catarrhalis*
Amox/clav	92	98	100
Amoxicillin	92	70	7
Cefixime	66	100	100
Cefpodoxime	75	100	85
Cefdinir	76	100	85
Ceftriaxone	96	100	94
Cefuroxime	73	83	50
Erythro-clarithromycin	72	0	100
Telithromycin	84	?	100
Azithromycin	71	2	100
Clindamycin	90	0	0
Doxycycline	80	25	96
Resp. quinolones	99	100	100
TMP/SMX	64	78	19

Alternative agents are selected for their activity against amoxicillin-resistant hemophilus and *M. catarrhalis* organisms and against pneumococcal strains that are sensitive to penicillin or resistant at the intermediate level (reduced susceptibility), which are generally susceptible to an enhanced (doubled) amoxicillin dosage (90 mg/kg/day for children, or 3-4 Gm/day for adults, in divided doses): amoxicillin/clavulanate (Augmentin ES, XR) or other agents listed on the following page. (For treatment of high-level, multi-drug resistant pneumococci, see Section III.A, page 46.)

Length of treatment: The usual recommendation for 10 days of antibiotic therapy is an empiricism. Several recent studies, aimed at reducing antibiotic usage, have shown courses of 3, 4, 5, and 8 days that yield similar cure rates as do 10-day courses, at least in early disease in adults with mild symptoms. [3] This should be expected since acute, uncomplicated rhinosinusitis (like acute otitis media) has a high probability of spontaneous resolution from nonvirulent bacteria and from nonbacterial (i.e., viral) pathogenesis. Even after a bacterial cure, mild symptoms persist for several days.

Alternatives for moderate-severe or prior treated cases or probably-resistant bacterias:
Amoxicillin/clavulanate (Augmentin ES, XR)
"Respiratory Quinolones" (adults)*
Levofloxacin (Levaquin),
or Moxifloxacin (Avelox), *et al*.
Ceftriaxone (Rocephin) IV, IM
Clindamycin plus rifampin /or/ TMP/SMX
Cefpodoxime or Doxycycline (adult)
*Quinolones are not available for pediatrics.
See p.46 for high-level pneumococcal resistance.

So it is probable that 5 days of an appropriate agent (as above) may be sufficient therapy for new, mild, uncomplicated cases of acute sinusitis, previously untreated, with mild symptoms that respond promptly. However, nonresponders (in 2-5 days) will need to be switched to one of the alternative agents (vs. virulent or resistant bacteria) for 7-10 days, or more with even a third agent.

ACUTE ORBITAL CELLULITIS and/or SUBPERIORBITAL ABSCESS are most commonly the extension of acute rhinosinusitis; Risk: impending rhinogenic meningitis, etc.

Ceftriaxone (Rocephin) IV +/- metronidazole
Ampicillin/sulbactam (Unasyn) IV with or without rifampin IV
Levofloxacin +/- metronidazole
(see page 15, Section I.I, re: use in children)
Any of above with or without vancomycin IV

Microbiology: *Strep. milleri* group, other *strep.*, oral anaerobes, *S. pneumoniae*, *Staph. aureus*, etc. species (*Otol HNS* 2005;133:32 & 2006;134:738)

Drug choices: Agents should treat oral anaerobes & resistant pneumocci and should penetrate into the CSF to pre-empt meningitis.

CHRONIC RHINOSINUSITIS during an acute symptomatic exacerbation may be due to the same organisms as acute rhinosinusitis. In quiescent stages, chronic sinus disease is due to inadequate mucociliary function or obstructed drainage, so antimicrobial therapy alone is often disappointing. Cultures generally show a polymicrobial synergistic flora: pathogenic organisms mingled with various nonvirulent or opportunistic or beta-lactamase producing organisms, and a high percentage of anaerobes,[8] the significance of which is controversial. (See Chronic Rhinosinusitis Task Force, *Otolaryng., Head, Neck Surg*. 2003; 129:Suppl S1-S32.) Typically anaerobes yield "no growth" on routine culture. They require strict anaerobic sampling techniques to reveal their true identity. *Staph. aureus* is also more likely in chronic than acute sinusitis, and various fungi may be isolated from patients who have been treated with multiple antibiotic courses or who have advanced mucosal disease ("allergic fungal sinusitis"). In patients with polyps (including cystic fibrosis and "triad asthma syndrome", *Pseudomonas aeruginosa* is prevelent, as are *Staph. aureus* strains which produce exotoxins. (*Laryngoscope* 2005;115:1580)

Chronic Rhinosinusitis Microbiology

Aerobic		Anaerobic	
Staphylococcus aureus	4%	Peptostreptococcus sp.	22%
Other staph. (coag. neg.)	common	Prevotella sp.	15%
Streptococci		Bacteroides sp.	8%
Hemolytic (alpha)	6%	Propionibacterium sp.	7%
Pyogenes (B-hemo)	3%	Fusobacterium sp.	5%
Pneumoniae	2%	Etc. various others	
Other	4%		
Hemophilus species	4%	Fungal	
M. catarrhalis	4%	*Aspergillus flavus, fumigatus*	
Klebsiella pneum. etc. various others		*Bipolaris specifera*	
Pseudomonas (in polyps and cystic fibrosis)		*Exserohilum rostratum*	
		Curvularia lunata	
Modified from Frederick, Brook, and others.[8]		Alternaria species	
See *Oto. Clin. N.A.* 2004; 37:253.		See *Oto. Clin. N.A.* 2004; 37:301	

Patients who have undergone prior nasal/sinus surgery who suffer persistent or recurring sinusitis most commonly yield cultures of pseudomonas or *Staph. aureus* (including MRSA). A variety of other bacteria may be implicated. Agents (or combinations) active vs. staph. (MRSA strains) and pseudomonas will usually be active vs. the other bacteria. (see pages 49-51)

Drug choices: For acute exacerbation of chronic sinusitis: (culture/sensitivity studies are preferable) consider likelihood of beta-lactamase producing anaerobes and *Hemophilus influenzae*, plus pen-resistant *S. pneumoniae* (Arch Otolaryng. Head Neck Surg 2006; 132: 1099)

Primary:	Alternatives:
Amoxicillin/clavulanate (Augmentin ES, XR)	Metronidazole plus levofloxacin or Clindamycin plus rifampin /or/ TMP/SMX

For chronic (indolent) rhinosinusitis (if/when antimicrobials seem indicated):

For *Staph. aureus* and anaerobes:		
Clindamycin	or	Amox/clav (Augmentin ES, XR)
	or	TMP/SMX-or-doxycycline plus metronidazole
If pseudomonas:		
Levofloxacin or ciprofloxacin plus metronidazole		Irrigation or nebulization with: Ceftazidime (Fortaz) or Aminoglycoside (page 14) or ciprofloxacin

If fungi: Voriconazole (Vfend) or Itraconazole (Sporanox) or amphotericin B irrigation.

Children with CHRONIC rhinosinusitis are less likely than adults to exhibit anaerobes and saprophytic organisms. They are more likely to have the common pathogens of ACUTE rhinosinusitis, and they would be treated accordingly (except for cystic fibrosis patients).

Rhinosinusitis in HIV Patients

Pseudomonas aeruginosa	48%
Klebsiella pneumoniae	28%
Enterobacter species	28%
Proteus mirabilis	20%
Escherichia coli	12%
Staphylococcus aureus	4%
B-hemolytic Strep. (not gr. A)	12%
Bacteroides species	8%

Staphylococcus epidermidis, serratia, etc.

As many as 70 percent of HIV (AIDS) patients may develop sinusitis in the course of their disease. In addition to the common pathogens, they are often infected with unusual and/or opportunistic bacteria, viruses, and fungi (e.g., pseudomonas, *Staph. epidermidis*, mycobacteria, cytomegalovirus, cryptococcus, alternaria, aspergillus, and *Pseudallescheria boydii*). Drug choices should be culture/sensitivity directed.

NOSOCOMIAL (hospital-acquired) SINUSITIS, associated with nasotracheal or nasogastric tubes or nasal packing, is mostly due to gram-negative bacilli and is often mixed.[9] Treatment requires removal of the offending foreign material plus antibiotics active against acinetobacter, pseudomonas, staphylococci, and anaerobes.[5]

Drug choices:

Primary:
Levofloxacin or ciprofloxacin
plus metronidazole
or imipenem IV or meropenem IV
or piperacillin/tazobactam (Zosyn) IV

Alternatives:
Ceftazidime (Fortaz) IV or cefepime
(Maxipime) IV plus
clindamycin or vancomycin or linezolid
Or an aminoglycoside (gentamicin,
tobramycin, or amikacin) IV or IM plus
clindamycin or vancomycin or linezolid

CHRONIC RHINITIS/NASOPHARYNGITIS: THE NONSYMPTOMATIC CARRIER STATE.

Hemophilus influenzae is a prevalent inhabitant of adenoids in the nasopharynx of children, especially those with recurring otitis media and/or sinusitis. If adenoidectomy is not an option, then rifampin (Rifadin) may be used. Nasopharyngeal carriers of *Neisseria meningitidis* are similarly treated.

Staph. aureus may be cultured from the nares of a third of normal, healthy persons with no nasal symptoms (except if they pull out their vibrissae and become infected). Attempts at eradication of their staph. are often futile and are unnecessary except among personnel who work around ill patients and patients with open wounds.

Drug choices:

Mupirocin ointment (Bactroban)
Plus rifampin (Rifadin)
Plus TMP/SMX or cephalexin or clindamycin or doxycycline

TONSILLO-ADENOIDITIS: *Streptococcus pyogenes* (group A beta-hemolytic streptococcus) is considered the most important treatable pathogen responsible for acute tonsillitis, but culture studies show wide variability, depending on patient age and chronicity of the disease. Unfortunately, cultures of tonsillar surfaces may not reliably predict pathogenic bacteria that exist in the core of the tonsils.

Streptococcus viridans, Staph. aureus, and various hemophilus species (especially *H. influenzae* in children) are commonly cultured from the core of tonsils and adenoids removed for either size (obstruction) or recurring infections. Actinomycosis is also not uncommon.

Brook studied chronic infected adult tonsils and showed mixed aerobic and anaerobic growth in all specimens. In more than three-fourths of patients, beta-lactamase producing organisms (co-pathogens) would render penicillin ineffective in treatment of these mixed infections, even if the principal pathogen (i.e., strep.) were otherwise penicillin sensitive. Clindamycin was required for strep. eradication. Likewise, amoxicillin/clavulanate (Augmentin) or cefpodoxime eliminate streptococci in the asymptomatic carrier more consistently than does penicillin.

Aerobic:	Anaerobic:	
*Strep. pyogenes** (gr. A beta-hemolytic)	Bacteroides sp.	Veillonella
Strep. pneumoniae	Peptococcus sp.	Fusobacteria
*Strep. viridans** and other strep.	Peptostreptococcus	Prevotella sp., etc.
M. catarrhalis	Viruses:	
*Staphylococcus aureus**	Epstein-Barr	Cytomegalovirus
Diphtheroids*	Adenovirus	
Hemophilus influenzae, *et al.* species*	Yeast:	Candida
Neisseria sp.* etc.	Other:	
	Toxoplasma	*F. tularensis*

*These are often cultured from tonsils/adenoids removed for airway obstruction (not infections), which suggests a carrier state is prevalent.

Adapted from Brook and De Dio.[10]

In an acute tonsillitis, the clinical finding of exudate on the tonsil often suggests streptococcal infection. However, an exuberant growth of exudate is more likely from E-B virus (infectious mononucleosis). Such a possibility is often overlooked in little children, when in fact it occurs quite commonly. Other mononucleosis like illnesses producing exudative tonsillitis include toxoplasmosis, tularemia, and cytomegalovirus infections.

Acute peritonsillar abscess aspirates most commonly yield multiple organisms (including various streptococcal species (alpha and beta-hemolytic strep., *Strep. viridans*, etc.) neisseria species, various anaerobic and gram-negative bacteria, plus, sometimes, no growth (which might suggest prior antibiotic therapy or failure to culture anaerobes). See Deep Neck Abscesses, page 40, for drug choices.

Drug choices for acute tonsillitis: Agents that treat co-pathogens and resist beta-lactamases are superior to traditionally recommended penicillin.

Primary:
Cefuroxime (Ceftin) or cefpodoxime (Vantin) or cefdinir (Omnicef) or cefditoren (Spectracef) all with or without metronidazole

Alternatives:
Clindamycin (Cleocin)
Amoxicillin/clavulanate (if mononucleosis has been ruled out)
Cephalexin (Keflex) or other first generation cephalosporin with or without metronidazole (Flagyl)

Length of treatment: Since 1951, a 10-day course of penicillin has been the standard treatment for streptococcal tonsillopharyngitis. However, more potent agents (as above) may allow shorter courses in acute, uncomplicated cases that respond promptly. For example, the U.S. Food and Drug Administration has approved a 5-day regimen of twice daily cefpodoxime (Vantin) for streptococcal tonsillopharyngitis, based on bacterial eradication rates superior to treatment with 10 days of penicillin.[3] (See Brock: Bacterial Interference, *Otolaryngol Head Neck Surg*. 2005;133:139)

Bacterial	(approx.) 30%
Strep. pyogenes(gr. A beta hemolytic)	15-30%
Group C beta-hemolytic strep.	5%
Mycoplasma pneumoniae	?%
Chlamydia species	?%
N. gonorrhoeae	1-2%
Viral	(approx.) 40%
Other	(approx.) 30%

PHARYNGITIS (ACUTE): *Streptococcus pyogenes* (group A beta-hemolytic) is the most prevalent bacterial cause of pharyngitis and the organism of most concern to clinicians because of the risk of rheumatic fever. But additional risks include contagion, scarlet fever, toxic shock syndrome, necrotizing fasciitis, deep neck-space abscess, glomerulonephritis, and certain pediatric autoimmune neuropsychiatric disorders with streptococcal infections (PANDAS) such as obsessive-compulsive behavior, tics, hyperactivity, attention difficulties, emotional lability, etc. (*Laryngoscope* 2001; 111:1515). Culture results in patients with sore throats vary with the age of the patient, symptoms, signs, and the season of the year. November through May are peak months for streptococcal pharyngitis in North America (25 to 30 percent of cultures in children with sore throats are positive for *Strep. pyogenes* during those months as opposed to 12 percent in July through September.[11] The prevalence in adults is about half that of children.)

SEVERE PAIN LASTING MORE THAN A FEW DAYS (IN THE ABSENCE OF CORYZA, COUGH, OR HOARSENESS), FEVER, MARKED ERYTHEMA, PHARYNGEAL EXUDATE, TENDER CERVICAL ADENOPATHY, AND RECENT EXPOSURE TO STREPTOCOCCAL INFECTION ARE FACTORS FAVORING STREPTOCOCCAL INFECTION. (But rapid progression within hours, extreme pain on swallowing, drooling, and a muffled voice should raise concern for acute epiglottitis instead. See below). When the diagnosis is obvious (by the presence of several of the above factors), empiric therapy (without culture) is acceptable and cost effective. But clinical judgment is only 55-75 percent accurate as a detector of streptococcal infection. "Rapid strep. tests" are very specific (accurate if positive), but false negative results (10-20 percent) are misleading.[12] Conventional throat cultures are more sensitive (closer to 5 percent false negative[13]); so in high risk seasons or patients, both tests may be advisable if the rapid-test screen is negative.[12]

Traditional teaching has held that *S. pyogenes* infections are the only sore throats deserving treatment and that, since a treatment delay of several days (awaiting culture results) did not increase the risk of rheumatic fever, withholding of penicillin was an acceptable idea. Such a practice may have limited overutilization of medications, but it did so often at the expense of needless prolongation of fever and sore throat. Contrarily, early treatment of streptococcal pharyngitis with penicillin has been shown to eliminate fever, sore throat, and positive culture within 24 hours, allowing early return to school and work and reducing the contagious potential.[14,15] Furthermore, there may be other bacteria, not generally considered pathogenic, that cause symptoms: *Staph. aureus*, *S. pneumoniae*, *M. catarrhalis*, *Hemophilus influenzae*, and group C or G beta-hemolytic streptococci.[16,17] Many authorities dismiss these as inconsequential in the throat, not requiring treatment. But patients may welcome the relief of symptoms that their treatment brings.

Even when *Strep. pyogenes* is the pathogen to be treated, co-pathogens (as above) may induce penicillin resistance. This explains why amoxicillin/clavulanate, cephalosporins (1st, 2nd gen.), erythromycin, or clindamycin are often more effective in pharyngitis treatment than is penicillin.[18]

Any of the following pharyngitis-causing bacterial infections will yield negative "strep cultures," but they are treatable with antibiotics:

1. *Mycoplasma pneumoniae* and chlamydia species may account for up to 30 percent of clinical pharyngitis in adults,[17] but their prevalence is not generally appreciated because they do not grow on routine throat cultures. These infections respond promptly to macrolides (erythromycin, azithromycin, clarithromycin) or tetracycline. The "respiratory" quinolones (levo-, gati-, or moxifloxacin) are also effective, but their use for minor sore throats ought to be avoided (to prevent emergence of resistance).
2. Diphtheria is rarely seen in the United States, and identification of the *Corynebacterium diphtheriae* organism may be difficult. This anaerobic organism produces a white (progressing to grey to patchy, black necrotic) adherent membrane and emits an odor similar to mouse feces--or a "wet mouse."[19] Lymphadenitis is pronounced ("bull neck"), and the airway is at risk. Culture requires Loeffler's or tellurite sensitive media. *Corynebacterium hemolyticum* pharyngotonsillitis may produce a scarlatina-form rash. See treatment under Diphtheria, below.
3. Gonococcal pharyngitis, gingivitis, and tonsillitis account for 1-2 percent of adult sore throats, primarily in patients with orogenital sexual activity. Diagnosis requires culture on selective Thayer-Martin medium and confirmatory studies to distinguish it from moraxella species. Pharyngeal gonococcus co-exists with chlamydia in almost half of cases. See page 60, Section III.I, for treatment recommendations.

For all types of pharyngitis, the accuracy of throat cultures is improved if the swab is vigorously rubbed and scrubbed over the infected area and, in the case of tonsillitis, deep into the tonsillar crypts.

Drug choices: Early, mild cases may be viruses not requiring therapy.

Primary: (vs. strep. and mycoplasma, etc.)
Erythromycin or clarithromycin (Biaxin)

Alternatives: (vs. streptococci)
Penicillin V or benzathine penicillin G, IM
Amoxicillin with or without clavulanate
1st gen. ceph.: cephalexin (Keflex)
2nd gen. ceph. or equivalent: cefuroxime (Ceftin), cefpodoxime (Vantin), cefdinir (Omnicef), cefditoren (Spectracef)

Length of treatment: *Strep. pyogenes* (causing pharyngitis/tonsillitis) requires 10 days of penicillin therapy for eradication. But shorter courses (5-7 days) are sufficient with the more potent alternatives such as 1st and 2nd generation cephalosporins, and possibly amoxicillin.[3]

DIPHTHERIA (See pharyngitis, above)

Microbiology: *Corynebacterium diphtheriae* plus *Strep. pyogenes* in 30 percent of cases.

Drug choices: **All cases require antitoxin** 40,000-100,000 U IV plus antibiotics as follows:[5]

Primary:	Alternatives:
Erythromycin or penicillin	Clindamycin or rifampin

VINCENT'S ANGINA ("trench mouth"), as found in debilitated patients with poor oral hygiene. (ACUTE NECROTIZING ULCERATIVE GINGIVO-STOMATITIS)

Microbiology: A mixed infection of spirochetes (*Treponema vincenti*), fusiforms, and anaerobes. These same organisms cause gangrenous stomatitis or noma or cancrum oris in malnourished, dehydrated children.

Drug choices: (Adjunctive hydrogen peroxide mouthwash, debridement, and antibiotic oral suspensions)

Primary:	Alternatives:
Clindamycin (Cleocin) oral or IV (especially if osteomyelitis)	Ampicillin/sulbactam (Unasyn) IV or amoxicillin/clavulanate (Augmentin) oral Penicillin IV plus metronidazole (Flagyl)

STOMATITIS–"THRUSH"[4]
(MONILIASIS, MUCOCUTANEOUS CANDIDIASIS).

Microbiology: *Candida albicans*

Drug choices:

Primary:	Alternatives for severe or HIV patients:
Nystatin (Mycostatin) susp. or lozenges Clotrimazole (Mycelex) oral troches	Fluconazole (Diflucan) oral tablets Itraconazole (Sporanox) oral tablets

APHTHOUS STOMATITIS is probably an auto-immune or allergic disorder with ulcerations that become secondarily invaded by normal oral flora: coag neg staph., alpha strep., *Neisseria*, *H. pylori* (*Arch Oto Head Neck Surg* 2005;131:804) They appear anywhere in the mouth, palate, pharynx, or tongue. Curative treatment is of yet unproven. Various topical preparations are helpful. The author's favorite is a mixture that gives symptomatic relief and may shorten the healing time.

Canker sore mixture:

Diphenhydramine (Benadryl) liquid	100 ml
Dexamethasone 0.5 mg/5 ml elixir	20 ml
Nystatin suspension	60 ml
Tetracycline (from capsules)	1500 mg
Sig: One tsp. 6 times daily (after and in-between each meal and at bedtime) for canker sore pain. Swish in mouth, gargle, and swallow.	

For children's use, the tetracycline should be omitted and replaced by amoxicillin/clavulanate 125, 75 ml. or erythromycin suspension.

HERPANGINA is caused by type A Coxsackie viruses (not herpes). Multiple aphthae-like ulcers appear on the tonsillar pillars, soft palate, and uvula. It is usually seen in children. The mixture for aphthous ulcers might be helpful (in preventing secondary infections), if modified for children as above.

HAND, FOOT, and MOUTH DISEASE is another type A Coxsackie virus infection in young children. Maculopapular lesions (which vesiculate) develop on the hands, soles of the feet, cheeks, palate, tongue, tonsillar fauces, and buccal mucosa. It lasts several days before spontaneous recovery.

CHANCRE: Primary oral syphilis produces a painless punched out ulceration (chancre) most commonly on the lip, but also on the tongue, tonsil, or palate. Chancres are teeming with spirochetes of *Treponema pallidum*, but on dark field exam they are difficult to distinguish from *Treponema microdentium*, a common inhabitant of the oral cavity. Secondary oral syphilis demonstrates an oval red papule or mucus patch in any location of the oral cavity. (For treatment, see Section III.I, page 60.)

LARYNGITIS (ACUTE) is usually caused by a virus. However, if hoarseness persists for longer than the typical few days, one might consider the possibility of secondary bacterial invasion by respiratory pathogens, predominantly *M. catarrhalis* and *H. influenzae*.[20]

Usually: rhinoviruses, adenoviruses, Respiratory syncytial virus

Bacteria::
Moraxella catarrhalis 50%
Hemophilus 15%
Pneumococcus, streptococcus, staphylococcus, mycoplasma, pertussis

Drug choices:

Primary:
Supportive care for viral illness

Alternatives:
Azithromycin (Zithromax)
Doxycycline
Levo- or gati- or moxifloxacin

TRACHEOBRONCHITIS (ACUTE and SUBACUTE).

The acute cough accompanying a "flu" or "cold" may be viral infection, which should not last beyond 2 weeks. Cough that persists longer is likely due to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *B. pertussis*, or Legionella infection, and each of these responds to macrolides, tetracyclines, or "respiratory" quinolones. Pertussis is an important cause of paroxysmal cough after a "flu-like" illness (in 10-20 percent of such adults), and it is increasingly prevalent in the U.S.A.[21,22] "Whooping" is not an obvious feature of pertussis-cough in adults.

Drug choices:

Primary:
Supportive care for virus illness

Alternatives:
Erythromycin or clarithromycin (Biaxin) or azithromycin (Zithromax) with or without sulfonamide (TMP/SMX)
Levofloxacin or moxifloxacin
Doxycycline

EPIGLOTTITIS (supraglottic croup) is predominantly an infection by the *Hemophilus influenzae* type b organism (of which 36 percent may be resistant to ampicillin). Other hemophilus species, pneumococcus, *Strep. pyogenes* and staph. are occasional offenders.

A less dangerous condition is UVULITIS, which may or may not accompany epiglottitis. The microbiology and therapeutic choices are the same, except oral equivalents of them may be used for outpatient treatment of uvulitis alone.

Predominately:
Hemophilus influenzae type b
Strep. pyogenes (esp. adults)
Occasionally:
Streptococcus pneumoniae
Staphylococcus aureus
Other hemophilus species

Drug choices (after airway is secured):

Primary:
Ceftriaxone (Rocephin) IV or
Cefotaxime (Claforan) IV

Alternatives:
Ampicillin/sulbactam (Unasyn) IV
Levofloxacin or moxifloxacin IV
(if penicillin anaphylaxis history)

LARYNGOTRACHEOBRONCHITIS (subglottic croup) is predominantly a viral infection. However, superinfection with *Staph. aureus*, streptococcus, or *H. influenzae* can occur, causing a membranous form of the disease (*Otolaryng., Head, Neck Surg.* 2004; 131:871). In one children's hospital[23] the incidence of bacterial infection was 15 percent of subglottic croup patients.

Usually viruses:
Parainfluenza virus
Influenza A virus
Respiratory syncytial virus

Secondary invaders:
Staphylococcus aureus
Strep. pyogenes (gr. A beta hemolytic)
Hemophilus influenzae, *M. catarrhalis*
S. pneumoniae

Drug choices: For viral stage, airway protection with corticosteroids.

For membranous (bacterial super-infection) stage:

Primary:
Ampicillin/sulbactam (Unasyn) IV

Alternatives:
Ceftriaxone (Rocephin) IV (or cefotaxime)
Levofloxacin or moxifloxacin IV (if penicillin anaphylaxis history)

DEEP NECK SPACE ABSCESSES are complications/extensions of dental or pharyngeal infections. They are typically polymicrobial,[4] including various oral aerobes and anaerobes, with occasional respiratory or skin pathogens (incl. MRSA). (*Otolaryng. Head Neck Surg.* 2006;135:894)

Staphylococcus, various aerobic, anaerobic, incl. MRSA
Streptococcus, various aerobic and anaerobic
Fusobacterium necrophorum
Bacteroides species (incl. *B. fragilis*)
Pneumococcus, Hemophilus species
Klebsiella, *E. coli*, et al. coliforms
Enterobacter, Enterococcus, Neissaria
Eikenella corrodens
Prevotella (*B. melaninogenicus*)

Accurate culturing of anaerobic organisms requires adherence to strict anaerobic sampling techniques. Even under ideal circumstances, anaerobes may take 4 to 5 days to grow so that smears for gram stain yield more immediate practical clinical information.

Drug choices:

Primary:	Alternatives:
Clindamycin (Cleocin) IV, oral	Linezolid or Vancomycin plus metronidazole

ACUTE SUPPURATIVE THYROIDITIS.[4]

Microbiology: *Staph. aureus*, *Strep. pyogenes*, *pneumoniae, et al*., streptococcal species, *E. coli*, klebsiella, various facultative aerobes and anaerobes. Rarely: mycobacteria, actinomyces, salmonella, treponema, and a great variety of others.

Drug choices: Same as for "Deep Neck Space Abscesses" as above until gram stain dictates otherwise.

NECROTIZING CELLULITIS/FASCIITIS (a virulent subcutaneous and fascial space infection usually of oral or dental origin, sometimes injury or wound contamination).

Microbiology: Mixed anaerobic/aerobic synergistic, "flesh-eating" bacteria. Organisms of odontogenic infections (see below) often *Strep. pyogenes*, *Strep. viridans*, peptostreptococcus, *Staph. aureus* (MRSA), *Hemophilus influenzae*, clostridia (gas gangrene), enterobacteriaceae, etc.[4] (*Laryngoscope* 1997;107:1071).

Drug choices (as dictated by gram stain to differentiate clostridia vs. strep., staph., etc.):[5]

If strep. or clostridia	If polymicrobial:
Clindamycin IV plus Penicillin IV	Meropenem IV plus Vancomycin with or without metronidazole Or others as dictated by gram stain

PAROTITIS and SIALADENITIS.

The most common infection is viral mumps. Less common are cytomegalovirus, Coxsackie virus, and Epstein-Barr virus infections. Corticosteroids are occasionally required for these.

Bacterial sialadenitis is usually a coagulase positive *Staph. aureus* infection. Others, less common, include *S. pneumoniae*, *E. coli*, *Hemophilus influenzae*, and oral anaerobes (bacteroides species and peptostreptococcus).

Drug choices for bacterial sialadenitis:

Primary:	Alternatives:
Amoxicillin/clavulanate (Augmentin) oral Or ampicillin/sulbactam (Unasyn) IV Or nafcillin IV Or dicloxacillin oral	Clindamycin (Cleocin) oral or IV 1st gen. ceph.: cephalexin or cefazolin with or without metronidazole 2nd gen. ceph.: cefuroxime, *et al*. with or without metronidazole Vancomycin IV plus metronidazole

DACRYOCYSTITIS: *S. pneumoniae* and *Hemophilus influenzae* predominate in children; *Staph. epidermidis*, *Staph. aureus*, and *Strep. pyogenes* are more likely in adults. Anaerobes are occasional.

Drug choices (as dictated by gram stain):

Primary:	Alternatives:
Levofloxacin, moxifloxacin (adult) oral. ceftriaxone IM/IV (child)	Cefpodoxime (Vantin oral) TMP/SMX (if MRSA)

SKIN INFECTIONS.[4]

IMPETIGO (a superficial epidermal infection).
Microbiology: *Strep. pyogenes, Staph. aureus,* often co-isolated.
Drug choices: Mupirocin (Bactroban) ointment plus oral antistaphylococcals:

Primary: Mupirocin ointment plus either:	Alternatives: Mupirocin ointment plus either:
2nd generation cephalosporin or TMP/SMX (if MRSA)	clindamycin or minocycline/doxycycline

FOLLICULITIS/FURUNCULOSIS/CARBUNCLES.
Microbiology: *Staph aureus* (incl. MRSA), *Pseudomonas aeruginosa* (from hot tubs) See pages 49-50.
Drug choices: Clindamycin, TMP/SMX, 2nd gen. ceph., Linezolid, levofloxacin (if pseudomonas).

ERYSIPELAS (an epidermis and dermis infection). CELLULITIS (a subcutaneous infection):
Microbiology: *Strep. pyogenes*, but occasionally other strep., *Staph. aureus*, *S. pneumoniae,* or *Hemophilus influenzae*. (Treat for MRSA until proven otherwise)

Drug choices:

Primary:	Alternatives:
Vancomycin IV plus ceftriaxone IV	Daptomycin or Linezolid plus ceftriaxone

ACUTE CATARRHAL CONJUNCTIVITIS is caused (usually) by *Hemophilus influenzae*, occasionally *S. pneumoniae*, *Staph. aureus*.

Drug choices (eye drops):

Primary:	Alternatives:
Fluroquinolone eye drops: (cipro-, gati-, levo-, moxi-, floxacin)	Polymyxin/TMP ophth. drops

This type of conjunctivitis may be the initial sign of a childhood purpural fever (dusky reddish-purple cellulitis) caused by *Hemophilus influenzae*. Drug choices: same as erysipelas.

ODONTOGENIC INFECTIONS. These infections of the mandible, maxilla, and soft tissues of the face and spaces of the perimandibular/parapharyngeal areas are polymicrobial. Anaerobes predominate over aerobes. They include species of streptococcus, peptostreptococcus, bacteroides, porphyromonas, prevotella, fusobacterium, actinomyces, veillonella, and anaerobic spirochetes.[4] Beta-lactamase production by fusobacterium and prevotella is common and renders penicillin mono-therapy ineffective.

Drug choices:

Primary:	Alternatives:
Clindamycin (Cleocin) oral or IV (especially if osteomyelitis)	Linezolid or Vancomycin plus metronidazole Piperacillin/tazobactam IV Ampicillin/sulbactam IV

BITES, ANIMAL AND HUMAN:[24] (See: *The Sanford Guide to Antimicrobial Therapy*.[5])

Infection from human bites is polymicrobial (from skin and mouth flora), which includes *Strep. viridans* 100 percent, *Staph. epidermidis* 53 percent, corynebacterium 41 percent, *Staph. aureus* 29 percent, bacteroides 82 percent, peptostreptococcus 26 percent, eikenella 15 percent, etc. Dog bites (only 5 percent become infected) and pig bites exhibit infections similar to human bites. Cat bites (80 percent become infected) produce *Pasteurella multicida* (so do dog bites) and *Staph. aureus*. Rat bites cause spirillum and streptobacillus infections. The microbiology of bat, racoon, and skunk bites is not established. Neither is that of non-human primates except that they can additionally transmit *Herpes virus simiae*.

Initial treatment of all mammalian bites is the same: Treat early with oral agents even if no apparent infection. Later, if infection is evident and serious, switch to IV agents.

Drug choices:

Early: Amoxicillin/clavulanate (Augmentin) oral Late/serious: Ampicillin/sulbactam (Unasyn) IV or piperacillin/tazobactam (Zosyn) IV or clindamycin plus either ciprofloxacin IV/oral, or TMP/SMX (for children)

For bat, rat, racoon, and skunk bites, the second choice may be doxycycline. Anti-rabies immunoglobulin and vaccine is also indicated for bites from bats, racoons, skunks, and unknown dogs (but not rats). Non-human primate bites need the addition of acyclovir. Anti-tetanus treatment also needs the usual consideration for traumatic puncture wounds.

Pit viper snake bites require attention for pseudomonas, enterobacteriaceae, *Staph. epidermis*, and clostridium species. Ceftriaxone or clindamycin plus ciprofloxacin (added to either) are logical choices. Tetanus prophylaxis is indicated. Primary therapy is antivenom.

For brown recluse spider bites, treatment with dapsone (50mg po q 24 hr) may be helpful.

LYME DISEASE is caused by the tick borne spirochete *Borrelia burgdorferi*. Any patient with facial palsy plus a history of recent expanding red round skin lesion with central clearing (erythema migrans) or migratory arthralgias should be suspected of the disease. It is the most common cause of facial palsy in children. (See Chapter 59 in Johnson, *et al.*[4]; also *J. Inf. Dis.* 1999; 180:377)

Drug choices:

		Adults	Children dose	Interval
Primary:	Doxycycline	100 mg bid (14-21 days)		
Alternatives:	Amoxicillin	500 mg qid (14-21 days)	50 mg/kg/day	tid
	Cefuroxime	500 mg bid (14-21 days)	30 mg/kg/day	bid
If neurological sx:	Ceftriaxone (IV)	2 Gm/day (14-21 days)		

CERVICAL LYMPHADENITIS[4] reflects the entire spectrum of infections that can occur in the head and neck (as already discussed) plus several systemic infectious diseases.

ACUTE SUPPURATIVE (or PRE-SUPPURATIVE) LYMPHADENITIS

Strep. pyogenes (group A beta hemolytic), from impetigo, tonsillopharyngitis, etc.
Staph. aureus, from skin infections (impetigo, folliculitis, ext. otitis, etc.)
(*Strep. pyogenes* and *Staph. aureus* account for 50-80 percent of cases.)
Peptococcus species, peptostreptococcus species: odontogenic see above
Fusobacterium species, bacteroides species, etc.: odontogenic see above
Corynebacterium diphtheria (rare) from diphtheria

SUBACUTE/CHRONIC (NON-SUPPURATIVE) LYMPHADENITIS [4]

Viruses: Parainfluenza and respiratory syncytial, after a "cold"
Adenoviruses, after "flu" or conjunctivitis
Enteroviruses, with exanthem
Herpes simplex virus, with gingivostomatitis
Human herpes virus-6, with roseola
Epstein-Barr virus, with mononucleosis
Cytomegalovirus, with mono-like illness
Bartonella (Rochalimaea) *henselae*, cat scratch disease[25], see page 83, Section VII.
Toxoplasma gondii toxoplasmosis (from cat feces or improperly cooked/raw beef).

CHRONIC SUPPURATIVE LYMPHADENITIS

Atypical (non-TB) mycobacterium species: clarithromycin +/- excisional biopsy.[26]
Mycobacterium tuberculosis
Actinomyces species, actinomycosis, "lumpy jaw," see page 82, Section VII.
Etc., many others uncommon in U.S.A.[4]

Drug choices for these infections are outlined in previous paragraphs of this section or in Section VII.

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SECTION III

SELECTION OF DRUGS

Section III.A—Selection of Drugs for Pneumococcal Infections

Streptococcus pneumoniae is an alpha hemolytic gram-positive coccus that colonizes the nasopharynx of many children and some adults, especially in winter months and during viral infections. It accounts for at least one-third of acute otitis media and acute sinusitis cases, which makes it the most prevalent pathogen of the upper respiratory tract. It is also the one most likely to cause persistent infections (that fail response to time and treatment) and to cause serious, invasive complications of those infections, such as mastoiditis, bacteremia, and meningitis (*J. Laryngol Otol*. 1997; 162:1316). Historically, pneumococci have been very sensitive to—and easily treated with—any of the penicillins (amoxicillin being most potent), macrolides (erythromycin), cephalosporins, clindamycin, etc.

Drug choices for penicillin-susceptible *S. pneumoniae*:

Primary:
Penicillin
Amoxicillin
Amoxicillin/clavulanate (Augmentin)
(if *Hemophilus influenzae* or *M. catarrhalis* might be present)

Alternatives:
Erythromycin or clarithromycin (Biaxin) or clindamycin (plus sulfonamide with any above if *Hemophilus influenzae* or *M. catarrhalis* is likely)
Cefpodoxime (Vantin) or equivalents (page 5)
"Respiratory quinolones" (page 16, Section I.I) (Levofloxacin or moxifloxacin)

Unfortunately, strains of *Strep. pneumoniae* that are resistant to penicillin have become increasingly and alarmingly prevalent in recent years, accounting for over 30 percent in many U.S.A. communities and for up to 60 percent in certain child day-care populations.[1,2] The following circumstances suggest that pneumococci with reduced susceptibility ("intermediate-level" resistance, MIC = 0.12-1 mcg/ml) or resistance ("high-level" resistance, MIC ≥ 2 mcg/ml) to penicillin is of concern:

1. Acute otitis media or sinusitis worsening despite conventional antibiotic treatment for 2-5 days,
2. Re-infection since recent antibiotic therapy (within 3 months),
3. Child daycare center attendance or exposure,
4. Age 2 years or younger,
5. Otitis-prone children,
6. High prevalence of resistant pneumococci in community (especially nursing homes, health-care facilities, prisons, etc.).

The resistance mechanism relates to protein binding, and it is not a beta-lactamase phenomenon, which means that addition of a beta-lactamase inhibitor (clavulanate) offers advantage only if other pathogens may be present (e.g., *Hemophilus influenzae* or *Moraxella catarrhalis*) but not vs. *S. pneumoniae*.

Penicillin resistance is a relative (dose-related) phenomenon. Strains with intermediate-level resistance to penicillin may still respond to increased (double the usual) dosages of amoxicillin (90 mg/kg, in divided doses, for children, or 3-4 Gm/day, in divided doses, for adults) or to other classes of antibiotics. But, second-generation cephalosporins, macrolides (erythro-, clarithro-, azithromycin), and sulfonamides are less potent, and resistance to them is worse. Telithromycin (Ketek) retains its activity

vs. penicillin-resistant pneumococci. The "respiratory quinolones" (for adults) would be the primary choice for patients with a penicillin (anaphylaxis, angioedema, urticaria, or wheezing type) allergy.

Drug choices for "intermediate level" penicillin-resistant *S. pneumoniae*:[1,2,3,4]

Primary:	Alternatives:
Amoxicillin (enhanced dose) Amoxicillin (enhanced dose)/clavulanate (Augmentin ES, XR) (If *H. influenzae* or *M. catarrhalis* might be present)	Ceftriaxone (Rocephin) IM, IV Levofloxacin (Levaquin 750 mg) oral or Moxifloxacin (Avelox)

Pneumococcal strains "highly" (or "fully") resistant to penicillin also exhibit "multi-drug" resistance to macrolides, tetracyclines, sulfonamides, clindamycin, chloramphenicol, and all oral cephalosporins. They may be treated with "respiratory quinolones" or vancomycin (or possibly linezolid) with or without rifampin. Vancomycin plus ceftriaxone is recommended for intracranial/orbital extensions. The "respiratory quinolones" are the orally administered agents that are most effective vs. highly (multi-drug) resistant pneumococci. Furthermore, they are extremely potent vs. *Hemophilus influenzae* and *M. catarrhalis* (for cases of unidentified serious respiratory tract infections). See page 16, Section I.I, re: use in children.

Drug choices for "highly resistant," multi-drug resistant *S. pneumoniae* (MDRSP):[1-6]

Primary:	Alternatives:
Levofloxacin (Levaquin) oral or IV Moxifloxacin (Avelox) oral or IV	Vancomycin IV (+/- rifampin), with ceftriaxone IV if eye or CSF extension Meropenem (Merrem) or Imipenem (Primaxin) IV Tigecycline (Tygacil) IV

The widespread use of long-term, daily, low (subtherapeutic) dose antimicrobial prophylaxis (vs. otitis media in children) is thought to be an important contributor to the emergence of antimicrobial resistance. Avoidance of that practice has been recommended.[5,6] Local and regional surveillance has now become important to define the extent of the problem and to treat patients. Sensitivity studies should be performed on pneumococcal isolates.

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Susceptibility of bacteria to antibiotics in-vivo depends not only on resistance, but also on the pharmacokinetics and pharmacodynamics (PK/PD) of the drugs. The accompanying table lists susceptibilities of three common respiratory pathogens to various antibiotics accounting for such factors.

Susceptibility of Isolates at PK/PD Breakpoints
Percentage of Strains Susceptible

Agent	*S. pneumoniae*	*H. influenzae*	*M. catarrhalis*
Amox/clav	92	98	100
Amoxicillin	92	70	7
Cefixime/ceftibuten	66	100	100
Cefpodoxime	75	100	85
Cefdinir	76	100	85
Ceftriaxone	96	100	94
Cefuroxime	73	83	50
Erythro-clarithromycin	72	0	100
Telithromycin	84	?	100
Azithromycin	71	2	100
Clindamycin	90	0	0
Doxycycline	80	25	96
Resp. Quinolones	99	100	100
TMP/SMX	64	78	19

Section III.B—Selection of Drugs for *Hemophilus Influenzae* and *Moraxella Catarrhalis* Infections

Hemophilus influenzae is a gram-negative bacillus, upper-respiratory pathogen that is a major cause of acute otitis media, sinusitis, epi(supra)glottitis, uvulitis, meningitis and facial cellulitis (in children), and conjunctivitis. Type B strains are the cause of invasive disease (meningitis, epiglottitis) which has been sharply curtailed in the U.S.A. since the 1990's when the conjugated vaccine became routine as part of pediatric immunizations.

The non-encapsulated ("non-typed" or types A and C-F) strains do not enter the blood stream but stay in respiratory tissue. During infancy, most normal children are colonized by various strains, in the nasopharynx, adenoids, or tonsils. There they await some viral infection or allergic attack to obstruct sinus ostia or eustachian tubes, when they become pathogens in acute sinusitis or otitis media.

Moraxella catarrhalis is a gram-negative diplococcus that similarly colonizes the nasopharynx in over half of children (but only a few adults). Likewise, after a virus or allergy attack, it becomes pathogenic in acute otitis media and sinusitis.

Some 50 percent of *Hemophilus influenzae* caused sinusitis and otitis media will resolve without antimicrobial therapy, and likewise will over 80 percent of *M. catarrhalis* (a less virulent pathogen). But therapy does reduce suffering and complications. Because *S. pneumoniae* is the most prevalent pathogen in these infections, empiric therapy requires antibiotics that cover all three of these organisms (see page 26 and pages 30-32, Section II).

In major U.S. cities, from 20 to 40 percent of *H. influenzae* strains produce beta-lactamase, which inactivates ampicillin, amoxicillin, and first-generation cephalosporins (e.g., cephalexin). Macrolides (erythro-clarithro-azithromycin) have intrinsically poor activity vs. hemophilus, but they are active vs. *M. catarrhalis*. *Hemophilus influenzae* accounts for about 20 percent of the usual cases of acute otitis media and acute sinusitis. *M. catarrhalis* accounts for almost as many childhood cases of acute otitis media, and 90 percent of those strains are ampicillin-resistant because of beta-lactamase production.

Beta-lactamase-stable agents active vs. *Hemophilus influenzae* and *M. catarrhalis* (and *S. pneumoniae*):

Amoxicillin/clavulanate (Augmentin) Cefpodoxime (Vantin) or cefdinir (Omnicef) Ceftriaxone (Rocephin)	Quinolones (levofloxacin, moxifloxacin)

Section III.C—Selection of Drugs for Staphylococcal Infections

Staphylococcus aureus is a gram-positive coccus, generally aerobic, but fully capable of anaerobic growth in abscesses. It is a natural colonizer of skin and nares. It is a destructive, toxic pathogen in skin and surgical or traumatic wound infections. It is also found as a co-pathogen in tissues compromised by other infections, such as deep-neck abscesses, chronic tonsillitis, chronic sinusitis (especially with intracranial extensions and osteomyelitis), otitis externa, and "membranous croup."

Staphylococcus aureus produces penicillinase (a beta-lactamase), which inactivates penicillin and extended-spectrum penicillins such as ampicillin, amoxicillin, ticarcillin, piperacillin, etc. Beta-lactamase inhibitors, when added to these pencillins, can counteract this type of staph.-resistance; eg.: amoxicillin plus potassium clavulanate (Augmentin), or ampicillin plus sulbactam (Unasyn), or tazobactam added to piperacillin (Zosyn).

The antistaphylococcal penicillins (methicillin group, p2) are inherently resistant to penicillinase. Cephalosporins are also resistant to penicillinase and are commonly used against *Staph. aureus*.

Methicillin-resistant *Staph. aureus* (MRSA) achieves resistance by a different process, one which confers resistance to all penicillins, all cephalosporins and all carbepenems (meropenem, etc.). MRSA strains account for 25%-60% of *Staph. aureus* infections in USA hospitals, and they are increasingly prevalent in community associated infections (especially in IV drug users, prisoners, men who have sex with men, contact-sports athletes, persons recently treated with antibiotics, and children[1]). Skin infections and nasal-carriage are likely sources. MRSA (community-associated) have also been isolated from the external ear canal, from tympanostomy tubes that drain after insertion[2], from acute and chronic rhinosinusitis cultures, and from post-op sinus surgery patients and children.[3]

Hospital associated MRSA appears to differ from community associated MRSA in that the latter are more likely to be treatable with inexpensive oral agents such as TMP/SMX, and—to a lesser extent—clindamycin and tetracyclines (minocycline). Because resistances may be unpredictable, culture/sensitivity studies are important.

Nearly all MRSA strains are susceptible to vancomycin IV, tigecycline (Tygacil) IV, daptomycin (Cubicin) IV, or linezolid (Zyvox) IV and oral (for outpatient use).

Clindamycin is useful for *Staph. aureus* osteomyelitis, since it concentrates in bone, and its anaerobic activity is advantageous for mixed infections. But *Staph. aureus* resistance to clindamycin is increasing and is common in hospital associated MRSA.

Macrolides-Erythromycins are unreliable as anti-staph. agents and many strains are resistant. Also, resistance may appear during a course of therapy. For the same reason, rifampin should not be used as a single agent even though it is highly antistaphylococcal (see page 19, Section I.N). But when it is used in combination with other anti-staph. agents, treatment effectiveness is enhanced. Oral rifampin plus TMP/SMX plus topical mupirocin (Bactroban) ointment treats the staph. carrier state inside the nostrils.

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Drug choices for *Staph. aureus*:

Methicillin susceptible (MSSA)	Methicillin resistant (MRSA)
Dicloxacillin oral or nafcillin IV	Vancomycin IV
Cephalexin oral or cefazolin IV	Daptomycin (Cubicin) IV
Clindamycin oral/IV (most strains)	Linezolid (Zyvox) IV, oral
Amoxicillin/clavulanate oral	Tigecycline (Tygacil) IV
Ampicillin/sulbactam IV	TMP/SMX +/- rifampin, oral
	Minocycline or doxycycline (some strains)

Section III.D—Selection of Drugs for Pseudomonas Infections

Pseudomonas aeruginosa is an aerobic gram-negative bacillus of the enterobacteriaceae family (which includes *E. coli*, klebsiella, serratia, citrobacter, proteus, yersinia). It is a ubiquitous organism existing in any moist environment, in tap water, and in hospitals. Thus, it is a frequent, and toxic/destructive, contaminant of traumatic and surgical wounds. It infects the moist external ear canal, and contaminates the middle ear through a perforated tympanic membrane. It contaminates the nose and sinuses in nasally intubated or immunocompromised or cystic fibrosis patients. It is a cause of perichondritis in the injured or pierced ear, and it is the organism usually responsible for "malignant" or necrotizing otitis externa. Several drug classes are available for treatment of pseudomonas infections:

Antipseudomonas aminoglycosides.(see page 14, Section I.H).

Gentamicin IM, IV
Tobramycin (Nebcin) IM, IV
Amikacin (Amikin) IM, IV

Twenty to 30 percent of pseudomonas have become resistant to gentamicin, but some of those respond to tobramycin or amikacin (the most active). However, once a pseudomonas strain becomes resistant to amikacin, it will be resistant to all aminoglycosides, so it is recommended that gentamicin or tobramycin be considered drugs of choice to initiate therapy and that amikacin be reserved for resistant strains. Alternatively, amikacin may be used initially, but when sensitivity studies reveal the pathogen to be sensitive to gentamicin or tobramycin, the appropriate change is made. **For serious or possibly resistant infections, it is best to combine aminoglycosides with agents in any of the following categories.**

Antipseudomonas penicillins (see page 3, Section I.A.5).

Ticarcillin (Ticar) IV, or Ticarcillin/clavulanate (Timentin) IV
Piperacillin (Pipracil) IV, or piperacillin/tazobactam (Zosyn) IV (the most potent)

Because susceptible strains may become resistant during treatment and because pseudomonas resistance to these agents is now commonplace (e.g., ticarcillin over 50 percent, *JAMA* 2003; 289:885), **these drugs are given in combination with aminoglycosides to achieve a synergistic effect**. Timentin and Zosyn combine antipseudomonas action with activity against mixed infections that include anaerobic and beta-lactamase producing organisms.

Antipseudomonas third/fourth-generation cephalosporins (see page 5, Section I.B).
Ceftazidime (Fortaz, etc.) and cefepime (Maxipime) are the most active of the cephalosporins against pseudomonas; **they should be combined with aminoglycosides to deter resistance.** They penetrate into the CSF (in inflammation), which aminoglycosides do not. Cephalosporins do not produce ototoxicity.

Other beta-lactam agents (see page 8, Section I.C).
Imipenem (Primaxin) IV, meropenem (Merrem) IV, and aztreonam (Azactam) IV are non-ototoxic antipseudomonals, equivalent to antipseudomonal third-generation cephalosporins. However, pseudomonas resistance to imipenem is likely to develop during treatment if it is used as a single agent. Meropenem is the preferred choice, **but combination therapy is still advised for serious infections.** Aztreonam may be given to penicillin allergic (even anaphylaxis-history) patients. Experience is limited in treatment of CNS infections.

Polymyxins are useful against pseudomonas as topical therapy (see Section III.H, page 54), but nephrotoxicity limits their IM/IV use. Some multi-drug resistant strains of pseudomonas are susceptible only to polymyxin B.

Antipseudomonas quinolones (page 15, Section I.I)
Ciprofloxacin (Cipro) and levofloxacin (Levaquin) are the preferred ORAL antibiotics effective against systemic pseudomonas infections. They allow outpatient treatment of necrotizing (malignant) otitis externa (*Laryngoscope* 1990; 100:548). In mixed infections, they should be combined with metronidazole or clindamycin to cover anaerobes (i.e., chronic suppurative otitis media with or without cholesteatoma) (*Arch. of HNS* 1989; 115:1063). In sinusitis with polyps (e.g., in cystic fibrosis), they are also useful. Pseudomonas resistance to ciprofloxacin and levofloxacin may appear during therapy, and it has exceeded 30 percent in many U.S. hospitals; **serious infections require combination therapy (addition of any of the previously named agents).**

Section III.E—Selection of Drugs for Anaerobic Infections

The predominant anaerobic bacteria of head and neck infections are of oral flora origin. They include pigmented prevotella and porphyromonas species (formerly the *Bacteroides melaninogenicus* group), fusobacterium species, bacteroides species (all gram negative), and peptococcus or peptostreptococcus species ("anaerobic staph. or strep."). When natural barriers are breached, these lead to dental infections, gingivitis, stomatitis, sialadenitis, abscesses of the peritonsillar, parapharyngeal, and retropharyngeal spaces; Vincent's and Ludwig's anginas; and wound infections following ear, nose, pharynx, head, and neck surgery. Oral and fecal (with *Bacteroides fragilis* and *E. coli*) contamination are probably sources of anaerobic infection in open head and neck wounds and in cholesteatomas.

When aerobic infection becomes chronic and exhausts the oxygen in the middle ear and sinus air spaces, then anaerobic growth begins to flourish, and mixed-synergistic infection ensues: chronic sinusitis, suppurative oto-mastoiditis, and cholesteatoma. Sometimes the original aerobic bacteria can no longer be recovered from a peritonsillar or deep neck abscess.

Anaerobic infections should be suspected under the following circumstances:

WHEN THE INFECTED WOUND PRODUCES AN ODOR. Not all anaerobes produce odors; but anaerobic streptococci (as in peritonsillar abscess) produce a foul, putrid odor, clostridial myonecrosis

(gas gangrene) produces a sweet odor like a steak freshly placed on a grill, and *C. diphtheriae* (diphtheria) produces an odor like mouse feces or a "wet mouse."

WHEN NO GROWTH IS SEEN ON CULTURE STUDIES EVEN THOUGH INFECTION WAS OBVIOUS. Anaerobic bacteria are easily killed by even brief exposure to air (during sampling, transport, or processing). Furthermore, anaerobes are usually so slow-to-grow that all important therapeutic decisions must be made before cultures are reported. Therefore, the gram stain is the more useful test.

WHEN MIXED MORPHOLOGY IS PRESENT ON GRAM STAIN. Oral infections and deep neck abscesses are typically polymicrobial with three to five strains of aerobic, anaerobic, or micro-aerophilic bacteria. Mixed infections are often synergistic.

WHEN INFECTION APPEARS IN A WOUND THAT WAS SUBJECT TO MUCOSAL CONTAMINATION. Typically one milliliter of saliva contains over 100 million anaerobic microorganisms and 10 million aerobes. The implication is that virtually all surgery into the pharynx, nasopharynx, hypopharynx, and larynx, as well as into infected ears and sinuses, is contaminated. Surgical prophylaxis requires antibiotics active vs. anaerobes.

ANTIMICROBIAL CHOICES:

Penicillin and amoxicillin are active against many oral anaerobes. However, over half of the anaerobes produce beta-lactamase-inducing resistance. So penicillins alone are not recommended for patients with these infections. In contaminated wounds, *E. coli* and *Bacteroides fragilis* are both resistant to penicillins. The augmented penicillins, however, (see page 2, Section I.A.4) are highly active against almost all anaerobes and aerobes in mixed infections.

Of the cephalosporins, cefoxitin and cefotetan are active against *B. fragilis* and other anaerobes, except for clostridia. Imipenem and meropenem are highly active against all anaerobes including *B. fragilis*, and they are useful for treating mixed infections which include pseudomonas.

Clindamycin rapidly eliminates the putrid odor of head and neck infections. It is active against *B. fragilis* and almost all anaerobes plus most of the aerobes (strep. & staph.) in these mixed infections. Metronidazole is active against *B. fragilis* and almost all anaerobes, but it is not active against the aerobes or even micro-aerophilic bacteria which are common (i.e., staphylococci and streptococci). For broad coverage, metronidazole may be combined with antibiotics from any other class.

Recommendations: For orodental, tonsillar, and deep-space head and neck infections, where oral flora is probably the source, metronidazole (Flagyl) oral plus either amoxicillin or a first-generation cephalosporin (Keflex) is the least expensive. For single drug therapy: clindamycin (Cleocin) oral or IV, cefoxitin IV, amoxicillin/clavulanate (Augmentin) oral, ampicillin/sulbactam (Unasyn) IV. For contaminated and hospital-acquired mixed infections: ticarcillin/clavulanate (Timentin), piperacillin/tazobactam (Zosyn), meropenem (Merrem), imipenem (Primaxin), any of which may be combined with metronidazole. A well-established regimen for prophylaxis in major head and neck surgery is clindamycin (Cleocin) plus either gentamicin or ceftazidime (Fortaz) IV.

Section III.F—Selection of Drugs for Therapy in Pregnancy

There is no firm evidence that any antimicrobial is teratogenic in humans, but since deliberate research in fetal humans is lacking, the manufacturers include in product descriptions of antibiotics (as in most drugs) the statement "safety for use in pregnancy has not been established." Drugs of any type are administered with caution during pregnancy; but when their use is essential, antibiotics are given, such as erythromycins, cephalosporins, and penicillins-drugs whose years of usage have created a clinical impression of safety.

FDA risk categories: **CATEGORY A:** no risk (no antibiotics listed).

CATEGORY B: Animal studies: no risk Human studies: not adequate	**CATEGORY C:** Animal studies: toxicity Human studies: not adequate Benefit may outweigh risk	**CATEGORY D:** Human studies: risk Benefits may outweigh risk if no suitable alternative
Antibacterials		
Amoxicillin/clavulanate Ampicillin/sulbactam Azithromycin Aztreonam Cephalosporins (all) Clindamycin Daptomycin Erythromycins (except estolate) Ertapenem Meropenem Metronidazole* Penicillins (all)	Ciprofloxacin Clarithromycin Chloramphenicol Gatifloxacin Imipenem/cilastatin Linezolid Levofloxacin Moxifloxacin Ofloxacin Rifampin Sulfonamides and TMP/SMX Telithromycin Vancomycin	Aminoglycosides (gentamicin, tobramycin, amikacin) Chloramphenicol Near term: avoid Erythromycin estolate Sulfonamides at term: avoid Tetracyclines Tigecycline
Antifungals		
Amphotericin B Nystatin Terbinafine	Caspofungin Fluconazole Flucytosine Itraconazole Ketoconazole Miconazole	Griseofulvin Voriconazole
Antivirals**		
Acyclovir, Famciclovir Valacyclovir Zanamivir	Amantadine Rimantadine Oseltamivir	

*Metronidazole is best avoided in first trimester.
**For antiretroviral (HIV) agents, refer to *Sanford Guide to Antimicrobial Therapy* 2006, page 58.

Tetracycline can cause inhibition of fetal bone growth, congenital limb abnormalities, cataracts, and staining and hypoplasia of the baby teeth when administered during pregnancy. Chloramphenicol and sulfonamides (including trimethoprim-sulfamethoxazole) can cause hemolysis in patients with deficiency of glucose-6-phosphate dehydrogenase, a liver enzyme system that is immature in the fetus and newborn. Therefore, sulfonamides given near term may contribute to development of kernicterus of the newborn, and chloramphenicol used in high doses or in premature infants can produce death with the "gray baby syndrome." The aminoglycosides (such as gentamicin) may cause fetal neural arch and renal abnormalities when given early in pregnancy and nephro/ototoxicity when given late in pregnancy.

The estolate preparation of erythromycin offers a higher risk of hepatitis in pregnant women. Griseofulvin and rifampin are teratogenic in rodents.

Section III.G–Selection of Drugs for Intracranial Infections

DIFFUSION OF ANTIMICROBIALS INTO THE CEREBROSPINAL FLUID		
Excellent with or without inflammation of meninges	Good only with inflammation of meninges	Minimal, nil, or unpredictable
Chloramphenicol Metronidazole Rifampin Sulfonamides Trimethoprim-sulfa	Ampicillin Aztreonam Cefepime Cefotaxime Ceftazidime Ceftriaxone Cefuroxime Ciprofloxacin? Fluconazole, flucytosine Gatifloxacin? Imipenem (seizure risk) Levofloxacin? Meropenem Nafcillin Penicillin G: high doses Piperacillin* Ticarcillin* Timentin	Amikacin Amphotericin B Benzathine penicillin Cefazolin** Cefoxitin Erythro/clarithro/azithromycin Gentamicin Imipenem* Moxifloxacin Polymyxins Tetracyclines Tobramycin Vancomycin: high doses

*Insufficient for pseudomonas.
**Good only if protein is high; therefore, not predictable.

In bacterial meningitis, prompt treatment is essential and antimicrobial drugs should not be withheld until laboratory studies are completed. (Dexamethasone is also indicated.) The organisms most commonly encountered are *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*. Penicillin, ampicillin, and chloramphenicol are inadequate for resistant strains.

Ceftriaxone (Rocephin) IV (or cefotaxime [Claforan] IV) is the most widely used drug for treatment of acute intracranial extension of otitis media or sinusitis. Rifampin may be added for resistant pneumococci; so may be vancomycin, but high doses are required. Meropenem is another option.

Brain abscesses are usually mixed infections that include anaerobes micro-aerophilic strep. and *Staph. aureus*. Metronidazole (Flagyl) IV plus ceftriaxone (Rocephin) IV as combined therapy provides

coverage. So would meropenem (Merrem) IV. For CNS pseudomonas, aztreonam (Azactam) IV or ceftazidime (Fortaz) IV or cefepime (Maxipime) IV are indicated, and combination with piperacillin/tazobactam (Zosyn) IV is advisable. If aminoglycosides are required, they must be administered intrathecally.

Section III.H–Selection of Drugs for External Ear Infections (Ototopicals)

Ototopical agents are formulated to treat disorders such as the following:

1. Acute diffuse otitis externa, usually caused by *Pseudomonas aeruginosa*, often by *Staph. aureus* and sometimes by proteus, klebsiella, *E. coli*, or various others;[1]
2. Otomycosis, a fungal infection usually caused by *Aspergillus* species or by *Candida* (monilia) species; occasionally by dermatophytes.
3. Chronic external otitis/dermatitis; e.g., psoriasis, seborrhea, eczema, contact dermatitis;
4. Ceruminosis;
5. *Herpes zoster* oticus;
6. Bullous myringitis;
7. Chronic suppurative otitis media with tympanic membrane perforation;
8. Chronic suppurative otitis media with cholesteatoma (keratoma);
9. Prophylaxis vs. suppurative otitis after tympanostomy tube insertion.[2]

INDICATIONS:

Nonspecific Measures

Pus and debris in the ear canal are impediments to successful topical therapy. Since the edge of the infection is advancing in the opposite direction of its discharge, it is imperative that the physician cleanse away such material, often repetitively, to facilitate penetration of the ear drops to the site of the infection. Furthermore, topicals are more effective the more frequently they are applied—even hourly in severe infections.

Most pathogenic organisms of the ear canal (e.g., pseudomonas and fungi) grow best in an alkaline environment. Therefore, most otic preparations contain some type of acid, such as boric or acetic acid, to lower the pH. Non-antibiotic remedies usually contain not only the acid but also nonspecific antiseptic agents which are effective against both fungi and bacteria.

Swim Ear, Aqua Ear, and Ear Magic are examples of over-the-counter prophylactics against "swimmer's ear" (acute diffuse external otitis). They are equivalent to the home mixture of white vinegar and rubbing alcohol, in equal proportions, applied by dropper to the ear canals after swimming.

Antibiotics

The otic preparations most widely prescribed for treatment of acute otitis externa contain antibiotics (neomycin, polymyxin, ciprofloxacin, ofloxacin). A corticosteroid for relief of inflammation is also commonly added to hasten symptom relief.

Traditionally, neomycin has been used in combination with polymyxin B for their activities against *Staph. aureus* and *Pseudomonas (et. al.)* respectively. Gentamicin, tobramycin, and ciprofloxacin are also efficacious. *Staph. aureus*, *Pseudomonas*, anaerobes (as in infected cholesteatoma[3]), and other potential pathogens may exhibit some degree of resistance to these agents during systemic therapy. But topical therapy delivers antibiotic concentrations 100 to 1000 times higher than can systemic therapy; and any organisms known to cause acute otitis externa will be unlikely to survive contact with such con-

centrations.[4] This explains why these agents all yield excellent cure-rates—which are comparable one to another—when properly used against acute otitis externa.[4]

Ciprofloxacin otic drops (Cipro) and ophthalmic drops (Ciloxan), and ofloxacin (Floxin) otic drops carry no risk of ototoxicity when they pass through a tympanic perforation into the middle ear.[5]

Draining tympanostomy tubes signify infection. When this occurs in children under the age of 2 years,[6] or in wintertime or coexisting with a "cold," it suggests acute otitis media from the ordinary pathogens; e.g., viruses, hemophilus, or pneumococcus. Ciprofloxacin or ofloxacin drops are indicated, but the infection may not clear with ear drop treatment alone; it requires oral antibiotics for acute otitis media (see page 26, Section II).

When tubes drain shortly after their insertion, it suggests either the pathogens of middle ear effusion or an infected surgical wound (pseudomonas, *Staph. aureus* or *Staph. epidermidis*, contaminants from the external ear canal). Ciprofloxacin or ofloxacin drops are usually effective for treatment. Such infections can also be prevented if the surgeon prepares the ear canal before myringotomy (i.e., alcohol to the ear canal) and then places a drop or two of the ciprofloxacin or ofloxacin ototopicals to the surgical site after tube insertion.[2] If previously uninfected tubes begin to drain in a child over 3 years old,[5] especially after swimming or bathing, pseudomonas or staphylococcal contamination is again suspected, and ciprofloxacin or ofloxacin drops are appropriate.

Antifungals and Antiseptics

Amphotericin B (Fungizone), clotrimazole (Lotrimin), and nystatin (Mycostatin) are available in topical preparations for treatment of candidiasis (moniliasis). Topical Ketoconazole cream is effective against both aspergillus and candida.[7]

Nonspecific antiseptics are commonly utilized for otomycosis therapy: 2 percent acetic acid solution (otic Domeboro, VõSol, Acetasol), 3 percent boric acid in 70 percent alcohol, aqueous merthiolate, and 25 percent M-cresyl acetate (Cresylate)*. (Cresylate and merthiolate are not recommended for application into the middle ear through a tympanic perforation.) Sulzberger's** powder is a boric acid and iodine mixture; it is effective for dusting the ear canal or mastoid cavity after the debris and secretions have been cleansed away. Povidone-iodine or gentian violet (2 percent in 95 percent alcohol) are useful in stubborn cases.

Topical povidone-iodine (Betadine) appears to equal the efficacy of ciprofloxacin otic drops in the treatment of chronic suppurative otitis media with non-intact tympanic membrane. It offers a low-cost option with no demonstrated ototoxicity. Oxymetazoline (Afrin) instilled into the ear canal after tympanostomy-tube insertion helps prevent post-op otorrhea, and it is not ototoxic.[9]

Anti-inflammatory Agents

Steroid-containing ointments and otic preparations are useful in treatment of dermatoses such as psoriasis and seborrheic dermatitis. VõSol HC and Otic Tridesilon contain a minimum of other ingredients that might be sensitizing, and they are helpful for long-term therapy (applied every evening) against itching and scaling. Antidandruff shampoos (selenium sulfide [Selsun] or ketoconazole

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*The Recsei Laboratories, Goleta, California, (805) 964-2912.

**See page 58.

[Nizoral]) are also useful, applied topically to the ears. They are antifungals active vs. Malassezia species.

Patients with these dermatoses are susceptible to bacterial and fungal external ear infections, and they may at times require otic preparations that also have antibiotic or antifungal activity as discussed above. Additionally, corticosteroids are added to antibiotic preparations such as Cortisporin (and its generic equivalents), Cipro HC, and Ciprodex to decrease mucosal and cutaneous edema in bacterial infections; e.g., chronic suppurative otitis media and acute otitis externa.

Anesthetic Agents

Auralgan contains benzocaine to reduce pain associated with otitis media and bullous myringitis. It is also sometimes helpful in relief of the itching of external ear canal dermatitis. Auralgan, however, does not contain any antimicrobial ingredients.

Ceruminolytic Agents

Carbamide peroxide in glycerol (Debrox) is the preferred agent for softening hard ear wax. It may require several days of treatment before the wax is soft enough for flushing. Cerumenex works much more rapidly (15 to 30 minutes), but severe eczematoid allergic reactions occasionally occur. Therefore, it can be used to soften wax while the patient is in the physician's office prior to washing of the ears, but it is not usually advised for at-home use.

DISADVANTAGES:

Topical neomycin causes occasional contact dermatitis which may confound evaluation of the disease and treatment progress.

Ototoxicity from neomycin or gentamicin or tobramycin ear drops is a possibility which has been reported.[10] The same is said concerning the propylene glycol in Cresylate and VōSol.[11] The risk is greater with prolonged use, perhaps since inflammation appears to protect the cochlea from absorption of these ototoxic drugs through the round window membrane. However, for patients with a non-intact tympanic membrane (perforation, absence, or tympanostomy tube-in-place) with probable bacterial infection, the non-ototoxic antipseudomonal agents are recommended: ciprofloxacin (Cipro HC otic, Ciprodex otic, Ciloxan ophthalmic) and ofloxacin (Floxin otic).

Pain is frequently experienced by the patient when drops (such as Cortisporin, Domeboro) reach the middle ear through a tympanic membrane perforation. The acid and alcohol contents of the preparation cause the pain, which may be unavoidable in treatment of otomycosis since the acid is the most important ingredient. However, Lotrimin may be less painful. Ophthamic topicals (Ciloxan, et. al.) contain such small amounts of acid or alcohol that they are unlikely to cause middle ear pain.

REFS:

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4. Rosenfeld, et.al.: Clinical Practice Guidelines: Acute Otitis Externa, *Otolaryng., Head, Neck Surg.* 2006; 134 suppl.; S1-23.
5. Tutkun: *Arch. Otolaryng.* 1995; 121:1414, also Wang: *Arch. Otolaryng.* 2005; 131:983

6. Roland: *Otolaryng., Head, Neck Surg*. 2005 133:585.
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9. (Afrin & tympanostomy tubes) *Arch. Otol., Rhinol Laryngol* 2005; 114:645.
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11. Marsh: *Otolaryng., Head, Neck Surg*. 1989; 100:134.

OTIC DROPS—TYPICAL COSTS

Trade Name		Trade	Generic	Generic Name
Betadine (OTC)	8 oz.	$18.97	$8.29	Povidone-iodine
Ciloxan ophth.	5 ml	$82.75	$67.02	Ciprofloxacin
Cipro HC	10 ml	$138.42	none	Ciprofloxacin
Ciprodex	7.5 ml	$138.42		
Cortisporin Otic	10 ml	$99.83	$46.21	Otocort, *et al.*
Debrox	0.5 oz.	$8.09		
Domeboro Otic	60 ml	$31.00	$22.00	Borofair
Floxin Otic	5 ml	$94.75	none	Ofloxacin
Garamycin ophth.	5 ml		$18.95	Gentamicin
Tobradex ophth.	5 ml	$104.45	none	Tobramycin
Tobrex	5 ml	$80.88	$26.75	Tobramycin
VōSol HC	10 ml	$110.00	$24.00	Acetasol HC

DUSTING POWDER FOR EXTERNAL EAR CANAL (for otomycosis) AND MASTOID CAVITY

Sulzberger Powder: To prepare, rub 1.0 Gm iodine crystals in mortar with about 2 oz. ether and incorporate 98.5 Gm boric acid powder. Triturate until of uniform color and ether is evaporated. Dispense in 6 oz. powder jar.

ANTIFUNGAL CREAMS

Lamisil cream	12 gm	$12.74		Terbinafine
Lotrimin (OTC)	10 ml	$19.00	$12.89	Clotrimazole
Nizoral cream	15 gm	N/A	$28.49	Ketoconazole

OTOTOPICAL AGENTS

Product Name	Acid	Antiseptic	Antibiotic(s)	Antifungal	Anti-inflammatory	Anesthetic	Ceruminolytic or Carrier
Auralgan						benzocaine antipyrine	glycerin
Ciloxan soln. (ophth.)	hydrochloric		ciprofloxacin				
Cipro HC	acetic	alcohol	ciprofloxacin	polysorbate	hydrocortisone		
Ciprodex	acetic and boric	benzalkonium chloride	ciprofloxacin		dexamethasone		
Cortisporin Otic solution	hydrochloric	alcohol	polymyxin B neomycin		hydrocortisone		
Cortisporin Otic susp.		alcohol	polymyxin B	polysorbate 80 neomycin	hydrocortisone		
Cresylate		M-cresyl acetate					propylene glycol
Debrox	citric						carbamide peroxide
Floxin Otic solution	hydrochloric	benzalkonium chloride	ofloxacin				
Lotrimin soln.					clotrimazole		polyethylene glycol
Otic Domeboro	acetic and boric	Al acetate					Na acetate
Tobradex susp. (ophth.)	sulfuric		tobramycin		dexamethasone		
VõSol HC Otic (Acetasol HC)	acetic citric	alcohol			hydrocortisone		propylene glyco
VõSol Otic	acetic	alcohol					propylene glycol

Section III.I—Selection of Drugs for Sexually Transmitted Diseases

Pharyngeal and neurological manifestations of sexually transmitted infections are increasingly prevalent. More than one sexually transmitted infection may coexist in a single patient, especially *N. gonorrhoeae* with *Chlamydia trachomatis*. Since chlamydia is not identifiable in pharyngeal cultures, its coexistence (45 percent) should be assumed in cases of pharyngeal gonorrhea, and combined treatment should be instituted. Gonococcal pharyngitis is clinically nondistinctive unless injury to the palate (petechiae) or lingual frenulum (laceration) is evident; diagnosis requires an alert physician and culture on Thayer-Martin medium. A syphilitic chancre is more obvious (see page 39, Section II). Current recommendations for gonorrhea reflect emergence of "Far East" strains that are resistant to tetracycline and penicillin. NOTE: Sexual partners of men or women with any form of gonorrhea should also be treated for both gonorrhea and chlamydia.

INFECTION	FIRST CHOICE	ALTERNATIVES
PHARYNGEAL GONORRHEA	ceftriaxone 125-250 mg IM (single dose)	ciprofloxacin 500 mg PO (single dose) or levofloxacin 250-500 mg PO (single dose)
PLUS: (combine with treatment for) CHLAMYDIA	**PLUS** Azithromycin 1 Gm PO once	doxycycline 100 mg bid x 7 days
SYPHILIS		
Early (all stages under 1 year)	benzathine penicillin G 2.4 mil. U IM once	doxycycline 100 mg PO bid x 14 d ceftriaxone 1 Gm IM daily 8-10 d
Late (over 1 year)	benzathine penicillin G 2.4 mil. U IM/wk x 3	doxycycline 100 mg PO bid x 30 d or tetracycline 500 mg PO qid x 30 d
Neurosyphilis	penicillin G 3 to 4 mil. U IV q 4 h x 14 d or ampicillin 4 Gm IV q 6 h x 10-14 d	penicillin G procaine 2.4 mil. U IM daily plus probenecid PO 500 mg qid, both x 10-14 d
Otosyphilis	above regimen plus additional penicillin G procaine 2.4 mil. U IM weekly x 3 (*Laryngoscope* 1989: 99:365)	

(Modified from *Med. Letter* 2001; 43:1111 and *The Sanford Guide to Antimicrobial Therapy*)

Section III.J—Selection of Drugs for HIV-Infected (AIDS) Patients

Physicians in every discipline are faced with patients suffering from HIV-related problems. Responsibility for their overall care transcends the specialty of otolaryngology, but the current pandemic requires a practicing knowledge of exposure risk precautions generally and of secondary infections these patients suffer in the head and neck specifically.[1,2]

Impairment of immunity can be monitored using the peripheral CD4 lymphocyte count. Patients with counts above 500 have essentially normal immune function. On the other hand, levels below 200 represent severe immune dysfunction, and these patients are at the highest risk for opportunistic and invasive infections. As impaired immune function worsens, susceptibility occurs to various oropharyngeal infections such as mucosal candidiasis of the mouth, larynx, and esophagus (severe dysphagia) (treatable with topical nystatin or clotrimazole or systemic fluconazole—see page 21, Section I.Q), aphthous stomatitis (treatable with topical antimicrobial/corticosteroid combinations—see page 38, Section II), and major (over 1 cm) aphthae (treatable with intralesional injections of corticosteroids: triamcinolone or thalidomide).[3,4] "Hairy" leukoplakia of the tongue (probably caused by Epstein Barr virus) is usually an asymptomatic condition seen in advanced stage HIV disease.

Otitis externa (pseudomonas) is common. The usual topical therapy (page 29, Section II, and page 54, Section III.H) may need supplementation with oral ciprofloxacin. Patients with poor therapeutic response or inflammatory polyps of the canal should be cultured for atypical organisms (AFB, fungus). Early in the epidemic when aerosolized pentamidine was used for *Pneumocystis carinii* pneumonia prophylaxis, pneumocystis was commonly associated with polyps of the middle ear and external canal; however, this condition is rarely seen today.

Otitis media with effusion and recurring acute otitis media are prevalent, due to adenoidal hyperplasia (in adults), nasopharyngeal neoplasm, recurring viral rhinosinusitis, or to IgE allergic respiratory disease (stimulated or enhanced by HIV infection). The usual bacteria are encountered (and so treated, pages 26-28, Section II), but *Staph. aureus* and pseudomonas should also be considered in severe immunodeficiency. If standard therapy for otitis media (amoxicillin/clavulanate or levofloxacin) fails, culture/sensitivity tympanocentesis is indicated.

Neurosensory hearing loss occurs in up to 50 percent of HIV-infected patients (from neurologic demyelinization or neoplasia, or opportunistic infection). Facial nerve palsy occurs in over 7 percent of HIV patients from infection or activation of *Herpes simplex* or *Herpes zoster* or cytomegalovirus disease. Acyclovir is appropriate (see page 23, Section I.R). *Herpes zoster* (shingles) is also quite common in this population and is often associated with significant post-herpetic neualgia.

Skin infections of the face and nose are generally caused by *Staph. aureus*. Compared to non-HIV infected individuals, the nasal carriage rate for *Staph. aureus* (including MRSA) is much higher in this population. Antistaphylococcal therapy (see page 49, Section III.C) must often be prolonged, and addition of rifampin is recommended for recalcitrant cases. Cultures are important to detect methicillin resistance.

Most importantly, nearly 70 percent of AIDS patients will develop acute or chronic sinusitis at some time in the course of their disease. Acute sinusitis may be caused by ordinary pathogens and may be treated in the customary manner (augmented amoxicillin or 2nd/3rd generation cephalosporins or "respiratory" quinolones, etc.—see page 30, Section II). However, unusual or opportunistic organisms are also quite likely, especially in chronic sinusitis (see page 32, Section II) and particularly when the CD4 count dips below 200. Therefore, culture/sensitivity studies are essential, and treatment will likely require coverage against *Staph. aureus* and *epidermidis*, *Pseudomonas aeruginosa*, *Strep. pneumoniae* and *viridans*, and various anaerobic and otherwise peculiar organisms.[5] A logical starting regimen would be the combination of clindamycin plus levofloxacin. This combination can be associated with significant risk of GI toxicity, so these patients should be appropriately counseled and monitored.

Alternatively, an augmented penicillin (Augmentin or Unasyn) plus either ciprofloxacin or an aminoglycoside (gentamicin or others) could be recommended. MRSA needs specific therapy: TMP/SMX or others (see p. 49). Cautious surgical drainage procedures may be required.

Be aware that some of the commonly used antimicrobials may interact adversely with antivirals that the patient may be taking, particularly the macrolides (erythromycin, *et al*.) quinolones (ciprofloxacin, *et al*.), antifungals, rifampin, metronidazole, TMP, etc. See page 23, Section I.R.

Fungi (aspergillus, *et al*.) or viruses (cytomegalovirus) could also require treatment. See pages 21-25, Sections I.Q and I.R.

REFS:

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2. *ENT Jol*. 1995; 74:328-367.
3. Friedman: *Laryngoscope* 1994; 104:566.
4. *Med. Letter* 1998; 40:104. Also *NEJM* 1997; 336:1487.
5. Tami: *ENT Jol*. 1995; 74:360.

For additional reading, see *The Sanford Guide to HIV/AIDS* and *JAMA* 2004; 292:251-268.

Section III.K—-Selection of Drugs for Antibiotic-Associated Diarrhea and Pseudomembranous Enterocolitis

When broad-spectrum antibiotics alter the microbial flora of the intestine, loose stools and diarrhea may appear. In most instances, this is a nuisance; it might be avoided or minimized if a lactobacillus preparation (e.g., Lactinex, Bacid, or yogurt) is administered in between antibiotic doses (*Ann. Med*. 1990; 22:57). Diarrhea requires prompt discontinuance of the antibiotic, which usually solves the problem.

Pseudomembranous (entero) colitis is more serious and can be fatal. It is due (most importantly) to *Clostridium difficile*, an enteric organism that is endemic in many communities and hospitals but is generally innocuous while its growth is suppressed by other enteric inhabitants. It is a toxigenic spore-forming gram-positive bacillus. Its toxins cause watery diarrhea, cramping abdominal pain, fever, leukocytosis, (sometimes) mucus and blood in the stools, fluid/electrolyte loss, shock, and even death (*JAMA* 1993; 269:71-75).

Clindamycin is commonly named as the inducer of antibiotic-associated pseudomembranous colitis, but other antibiotics have also been incriminated, such as cephalosporins (especially cefuroxime or cefpodoxime) and amino-penicillins; rarely, chloramphenicol, erythromycins, fluoroquinolones, tetracyclines, or trimethoprim/sulfa. Either oral or parenteral therapy can induce this colitis. Patients with chronic, debilitating disease are at higher risk.

Most patients develop watery diarrhea between the 4th and 9th days of therapy, and it ceases 4-14 days after antibiotic discontinuance. It will be more protracted if the diarrhea appears 2-10 weeks after the antibiotic course was completed, or if antibiotics were continued in spite of diarrhea.

Drug choices:

Primary:	Alternative: (severe cases)
Metronidazole (Flagyl) oral tabs 250 mg qid to 500 mg tid for 10-14 d	Vancomycin oral 125-500 mg q 6 h for 10-14 d or Bacitracin oral 25,000 U qid 10-14 d

Oral metronidazole is considerably less expensive than vancomycin and is equally effective for mildly or moderately ill patients and should be the primary therapy. When oral therapy cannot be used, IV metronidazole is indicated. (IV Vancomycin doesn't reach colonic mucosa or contents.) Relapses after successful treatment (20 percent of cases) are due to carriage of drug-resistant spores, and repeat courses of metronidazole or vancomycin with addition of rifampin will be necessary for as long as 4 weeks. Lactobacillus preparations are helpful as is the yeast *Saccharomyces boulardii*.

Section III.L–Selection of Drugs in Penicillin Allergy

The frequency of adverse reactions to penicillin in the general population ranges from 1 to 10 percent. But a true "penicillin allergy" is confirmed by skin tests in less than 10 percent of patients who claim to be allergic.[1] Maculopapular (measles-like) rashes that develop during antibiotic therapy are often of other drug or nondrug origin, especially rashes that are common during viral infections (see below).

A methodical history may reveal the true character of the "allergy" and its adverse potentiality.

Penicillin reactions have been classified as follows:

Type	Onset Time after Exposure	Mediator(s)	Clinical Signs	Skin Testing Useful
Immediate (Accelerated) Type I	‹ 1 hour	IgE antibodies	Anaphylaxis and/or hypotension, laryngeal edema, wheezing, angioedema, urticaria	Yes
Late Type II Type III Type IV	› 72 hours	IgG Complement IgG and IgM	 Increased clearance of RBC's and platelets by lymphoreticular system Serum sickness Contact dermatitis	No No No No
Other (Idiopathic)	Usually › 72 hours		Maculopapular Morbilliform Measles-like rashes 1-4 % of all patients taking penicillin	No

RASHES (measles-like) of the maculopapular or morbilliform type (but NOT URTICARIAL) are the most common reactions, occurring in 1-4 percent of all patients receiving penicillins. These rashes are

usually minor nuisances, and they often do not recur on subsequent use of penicillin. They may be of other drug or nondrug origin, especially when penicillins are given to patients suffering from viral infections that commonly produce rashes (e.g., Coxsackie virus, Echovirus, mumps, Epstein-Barr virus of mononucleosis, cytomegalovirus, hepatitis B, HIV).

In particular, ampicillin or amoxicillin therapy during a mononucleosis or cytomegalovirus infection results in such rashes in 50-100 percent of such patients. A history of such rashes (nonurticarial type) does not absolutely preclude future use of penicillins. The rash may not reappear with subsequent use of penicillin; it does not have predictive importance regarding anaphylaxis, and many patients with a remote history of a rash-type penicillin "allergy" have subsequently taken other penicillins (e.g., amoxicillin, Augmentin) without a problem. They may be considered NOT allergic to any of the penicillins or cephalosporins.

ANAPHYLAXIS (in contrast to the above) is a rare and serious reaction with a mortality rate of 1/50,000-1/100,000 of treatment courses. Most life-threatening reactions occur within 1 hour of administration. Parenteral therapy is most dangerous, and a patient using B-adrenergic antagonists is at increased risk. Most anaphylactic reactions occur unpredictably, without prior rash history. Skin tests are useful if a history exists suggestive of an immediate-type reaction, but they are positive in fewer than half of cases. History of a penicillin reaction that includes wheezing, bronchospasm, angioedema, laryngeal edema, hypotension, or urticarial rash should preclude future use of any of the penicillin classes, 1st generation cephalosporins, and the carbepenems.

ALTERNATIVE THERAPY: ERYTHROMYCIN, CLARITHROMYCIN, TELITHROMYCIN, CLINDAMYCIN, LINEZOLID, RIFAMPIN, VANCOMYCIN, and the "RESPIRATORY QUINOLONES" (page 15, Section I.I) are all completely unrelated to penicillin and are safe alternatives for treatment of gram-positive coccal infections (staph., strep., pneumococcus, etc.). SULFONAMIDES and the QUINOLONES are safe and effective alternatives for treatment of hemophilus infections. AMINOGLYCOSIDES (gentamicin, *et al.*), AZTREONAM, CIPROFLOXACIN, and LEVOFLOXACIN are safe for treatment of pseudomonas.

2nd and 3rd generation CEPHALOSPORINS (i.e. cefuroxime, cefpodoxime, cefdinir, ceftriaxone) are considered to be safe as penicillin alternatives for patients with history of no more than measles-like (nonurticarial) rash reactions to penicillins.[2] Cross reactivity between the penicillins and 1st generation cephalosporins (cephalothin, cephalexin, cefadroxil plus cephaloridine and cefamandole) is rare (0.5%). Nevertheless, a history of a Type I immediate reaction to penicillin (anaphylaxis as above) suggests 1st generation cephalosporin avoidance since a recurrence could be catastrophic.

TESTS FOR ALLERGY. The penicillin skin test is of little importance in patients with no history of a Type I reaction. And it is unnecessary for "allergic" patients when equally efficacious alternative antibiotics are available. Furthermore, a negative skin test does not exclude the possibility of a life-threatening anaphylactic reaction; it suggests only a lessened probability.

DESENSITIZATION. When alternative agents are unsatisfactory (a rare circumstance) and when the risk of the infection outweighs the risk of penicillin use, desensitization may be considered. This is potentially dangerous and should be attempted only in a hospital under circumstances where personnel, drugs, and equipment for respiratory and circulatory support are at the bedside. A method is described in *The Sanford Guide to Antimicrobial Therapy*, 2006, p 58.

REF:
1. *JAMA* 2001; 285:2498, also *CID* 2002; 35:26.
2. Pichiehero: *Otolaryngol, Head, Neck Surg*. 2007; 136:337-339.

Section III.M–Selection of Drugs in Toxic Shock Syndrome

TOXIC SHOCK SYNDROME (24-48 hours post-op/injury)
Sepsis, fever, nausea/vomiting, hypotension, macular rash, multi-organ involvement, later skin desquamation.

Microbiology: *Staph. aureus* toxigenic strains (30 percent of elective nasal surgery patients carry *Staph. aureus* in nares, 40 percent of those carry toxigenic strains).[1] Other aerobes/anaerobes may be present as mixed infection.
Treatment: Remove packs/splints/implants and cleanse nasal cavities and wounds.
IV fluids, etc., supportive.

Drug choices:[2] Intravenous immunoglobulin plus:

Primary:	Alternatives: Clindamycin*
Vancomycin or Linezolid*	Cefazolin +/- metronidazole
+/- metronidazole	

* Linezolid and clindamycin each inhibit bacterial toxin production.

Prevention: Logic suggests that anti-staphylococcal prophylaxis in surgery (pre-op cefazolin [Kefzol, Ancef] IV or clindamycin [Cleocin] IV) might prevent toxic shock syndrome. But statistical proof is lacking. Logic also suggests the cleansing of nasal vestibules with antiseptic preparation and impregnating with antibiotics any nasal packing that is used.[3] Polymyxin (as in Neosporin or Cortisporin ointments) binds toxin.[1]

Unusual "strep" toxic shock syndrome (from *Strep. pyogenes*, group A beta hemolytic) is associated with necrotizing fasciitis and marked pain at infected site. Origin: pharynx. See page 41, Section II. Clindamycin plus either penicillin or ceftriaxone is recommended.[2]

REFS:

1. Anon, in Johnson and Yu (ed.): *Infectious Diseases and Antimicrobial Therapy of the Ears, Nose, and Throat*. Philadelphia, W.B. Saunders Co., 1997, page 601.
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SECTION IV

ANTIMICROBIAL PROPHYLAXIS[1]

An estimated 5 to 10 percent of hospitalized patients acquire a nosocomial ("hospital") infection, which adds a substantial cost and an average of 4 extra days to the hospital stay. Antibiotics are effective in reducing the incidence of such infections, even in "clean" operative cases, when the drugs are properly selected and administered (although in clean otologic and nasal surgery, infections are so infrequent that data may not justify prophylaxis). Patients should be selected for prophylaxis if the medical condition or the surgical procedure is associated with a considerable risk of infection or if a postoperative infection would pose a serious hazard to the patient's recovery and wellbeing.[2]

CIRCUMSTANCES IN WHICH PROPHYLAXIS MAY OR MAY NOT BE RECOMMENDED:

1. Streptococcal pharyngitis contacts: culture and/or treat: amoxicillin, clindamycin, etc.
2. Otitis media prophylaxis is recommended for high risk children such as Eskimos and Native Americans and those with cleft palates. Additionally, it may be appropriate for children who suffer over four episodes of acute otitis media per year but clear their middle ears of fluid between episodes.[3] However, widespread, prolonged use (for months) in low doses probably is a causal factor in emergence of resistant bacteria.[3] Frequent recurring acute otitis media: Use amoxicillin (see page 26, Section II) in a single daily dose (1/4 to 1/2 of full therapeutic daily doses) throughout the infection season. Preferably the "pulse method" utilizes full therapeutic doses at the earliest onset of "cold" symptoms, given until they clear.
3. Lengthy elective surgery in clean operative fields: see following.
4. Intranasal packing for epistaxis or surgery: Use infection-resistant or antibiotic-impregnated packing and give IV antistaph. agent (i.e., cefazolin, ampicillin/sulbactam, or clindamycin) pre op.[4]

CIRCUMSTANCES IN WHICH PROPHYLAXIS IS USUALLY RECOMMENDED:

1. *Hemophilus influenzae* type B infections (epiglottitis, cellulitis, meningitis). In households with unvaccinated children under age 4 years, all contacts (except pregnant women) should receive rifampin for prophylaxis (see page 19, Section I.N) against carrier state, as should index case after completion of treatment for primary infection (see page 48, Section III.B).[5]
2. Surgery in patients with risk of bacterial endocarditis. (See following.)
3. Surgery for traumatized or contaminated wounds.
4. Surgical incisions into contaminated areas or across mucosal edges (e.g., mouth, pharynx, tonsils/adenoids,[6] infected nose/sinuses, skull base[7]).
5. Surgery on patients with compromised host defenses: irradiated tissues; steroid therapy; cancer chemotherapy; impaired vascularity; debility.
6. Surgery for prosthetic device implantation.
7. Cerebrospinal fluid exposure, otorrhea or rhinorrhea.
   a. If surgical or traumatic in the presence of active infection: treat contamination with vancomycin plus ceftazidime + metronidazole[7] (see Section III.G, page 54).
   b. If traumatic "clean": careful observation and no antibiotics, but treat at earliest signs/symptoms of acute otitis media or sinusitis with IM ceftriaxone (Rocephin) or oral medications, as in Section III.G.

THE AMERICAN HEART ASSOCIATION RECOMMENDS ENDOCARDITIS PROPHYLAXIS.[8]

1. For patients with
   a. Prosthetic or homograft heart valves
   b. Previous history of endocarditis
   c. Congenital or acquired heart defects such as
      - •Congenital malformations
      - •Damaged valves: rheumatic, surgical, mitral valve prolapse with regurgitation
      - •Hypertrophic cardiomyopathy
2. For such patients undergoing invasive procedures (that would cause bleeding) involving oral or respiratory mucosa, such as:
   a. Dental procedures
   b. Oral/pharyngeal procedures
   c. Tonsillectomy and/or adenoidectomy
   d. Nasal/sinus surgery
   e. Rigid bronchoscopy or esophagoscopy

Microbiology: *Strep. viridans* (alpha hemolytic strep.)

Drug selection:

Primary:	Alternatives (penicillin-allergic patients):
Oral amoxicillin 1 hr pre-op Adult: 2 Gm, child: 50 mg/kg*	Oral clindamycin (Cleocin) 1 h pre-op Adult: 600 mg, child: 20 mg/kg* OR Oral cephalexin** (Keflex) or Cefadroxil** 1 hr pre-op (Duricef) Adult: 2 Gm, child: 50 mg/kg*
OR	
IV ampicillin 30 min pre-op Adult: 2 Gm, child: 50 mg/kg*	IV clindamycin (Cleocin) 30 min pre-op Adult: 600 mg, child: 20 mg/kg* OR IV cefazolin** (Kefzol, *et al.*) 30 min pre-op Adult: 1 Gm, child: 25 mg/kg*

*Pediatric dose not to exceed adult dose.
**Cephalosporins should not be used in patients with immediate-type hypersensitivity reactions to penicillin: urticaria, angioedema, anaphylaxis, wheezing.

Earlier recommendations included follow-up doses 6-8 hours later, but this is no longer deemed necessary if blood contamination has ceased. Also, earlier recommendations included gentamicin, vancomycin, and erythromycin as options. These are not listed in current recommendations even though they may be effective. If a macrolide is selected, clarithromycin (adult: 500 mg PO, child 15 mg/kg PO) is preferred over erythromycin because of more predictable pharmacokinetics.

INFECTION PROPHYLAXIS IN SURGERY: PRINCIPLES.

Timing, Pre-op: Antimicrobials must be present at therapeutic levels at the site and at the time of contamination (incision). If given orally: 1 hour pre-op. If given intravenously IV: "on-call" to the operating room or shortly BEFORE anesthetic induction. Therapeutic levels should be maintained for the duration of the procedure. Therefore, extended procedures (over 4 hours) may require a second dose since contamination re-occurs at skin-closure.

Post-op: Antibiotics initiated post-operatively have little effect on wound infections. After 24 hours, continued antibiotic therapy is not protective. Some clinicians continue therapy until wound drainage or incision-line leakage has stopped or packing is removed from wounds, nose, or sinuses. But the efficacy of this has not been established.

Sterile technique: Antimicrobial therapy is not a substitute for proper sterile surgical technique. However, an acknowledged break in technique or an unexpected contamination of a sterile anatomical site (e.g., cerebrospinal fluid) warrants prompt antibiotic therapy.

Antibiotic therapy in contaminated wounds is technically "therapeutic" rather than "prophylactic." But since surgical manipulation disturbs forming barriers, prophylaxis principles still apply.

INFECTION PROPHYLAXIS IN SURGERY.

For CLEAN SKIN-ONLY INCISIONS IN HEALTHY PATIENTS, risk is low, sterile technique is sufficient, and antimicrobial prophylaxis is generally unnecessary.[1]

Microbiology: *Staph. aureus* (including meth-resistant strains: MRSA*), *Staph. epidermidis*
Drug choices (if circumstances deem necessity):

Primary:	Alternative:
IV: cefazolin (Ancef, Kefzol) 1 Gm before anesthesia induction OR Oral: cephalexin (Keflex) 500 mg 1 h pre-op	IV: clindamycin (Cleocin) 600-900 mg (slow drip) before anesthesia OR Oral: clindamycin (Cleocin) 150-300 mg 1 h pre-op

* If MRSA suspected or prevalent: TMP/SMX oral, Vancomycin or Tygecycline IV (p. 49).

For ORAL/PHARYNGEAL SURGERY (TONSILLECTOMY *et al.*), risk is high for mixed aerobic plus anaerobic infection with oral flora plus pathogens. Pharyngeal surgery, by its very nature, is contaminated. Thus, antibiotics are therapeutic rather than prophylactic.

Microbiology: streptococcus sp., peptostreptococcus sp.
bacteroides sp., fusobacterium sp.
prevotella sp., porphyromonas sp.
spirochetes, coliforms (if poor hygiene)

Drug choices ("prophylaxis" is recommended):[1,9]

Primary:	Alternatives:
IV: ampicillin/sulbactam (Unasyn) 3 Gm before anesthesia induction OR Oral amoxicillin/clavulanate (Augmentin) suspension—1 h pre-op	IV clindamycin (Cleocin) 600-900 mg slow drip pre-anesthesia induction OR Cefazolin plus metronidazole pre-anesthesia

Topical antibiotic administration pre-op also exerts a protective effect; e.g., oral rinse/mouthwash and gargle of amoxicillin/clavulanate or clindamycin or bacitracin or chlorhexidine oral rinse. Hydrogen peroxide may also be useful. Amoxicillin suspension post-op speeds recovery.[6]

For MAJOR HEAD AND NECK SURGICAL PROCEDURES that involve both skin and oral/pharyngeal incisions, risk is high for mixed infections of *Staph. aureus* (including MRSA), aerobes and anaerobes, and possibly pseudomonas (or other enterobacteriaceae) from hospitalization, compromised tissues (irradiated, ischemic), or debility, diabetes, etc.

Drug choices (prophylaxis is recommended):[2]

Primary:	Alternatives (pre-anesthesia):
IV clindamycin (Cleocin) 900 mg slow drip pre-anesthesia	IV Vancomycin plus metronidazole OR cefazolin plus metronidazole

PLUS ANY OF THE FOLLOWING:
Gentamicin 80-100 mg IV pre-anesthesia or IM 30 min pre-op
Tobramycin 80-100 mg IV pre-anesthesia or IM 30 min pre-op
Ceftazidime (Fortaz) 1-2 Gm IV pre-anesthesia
Aztreonam (Azactam) 1-2 Gm IV pre-anesthesia

Pre-operative topicals (as above) are also protective as are wound irrigations with piperacillin/tazobactam (Zosyn): 3 Gm in 1 L saline.[1]

FOR CLEAN NASAL SURGERY (rhinoplasty, turbinate/septoplasty), infections are so rare that protective effect of prophylaxis has defied statistical substantiation[1,10] and some authorities have recommended against routine prophylaxis. But some clinicians fear that toxic-shock syndrome[4] is a risk without prophylaxis (although unproven) and that the devastating effect of some infection (even though rare) might argue in favor of prophylaxis.

Microbiology: *Staph. aureus* (see toxic-shock syndrome, page 65, Section III.M), including MRSA.[11] Drug choices: cleanse vibrissae and nasal vestibules with antiseptic surgical preparation and impregnate nasal packing with antimicrobial ointments. Antibiotics, if deemed necessary, are same as for skin (page 68).

For CONTAMINATED NASAL SURGERY (such as acute or chronic sinusitis) or maxillofacial surgery/injury with oral exposure, antimicrobials are therapeutic rather than prophylactic, and they are recommended.

Microbiology: *Staph. aureus* and mixed aerobes/anaerobes
pseudomonas, in sinusitis with polyps
Drug choices: clindamycin or vancomycin-plus-metronidazole as for oral/pharyngeal surgery (page 68-9). If pseudomonas is suspected, add gentamicin or ceftazidime as for major head and neck surgery above. For intracranial contamination, see below.

For CLEAN OTOLOGIC SURGERY (stapes, tympanoplasty in "dry" ears), infections are so rare that any protective effect of antibiotics defies documentation.

Microbiology:	middle ear:	sterile
	external ear canal:	staph. (various species incl. MRSA[11]), streptococci, enterococci corynebacterium, pseudomonas, etc.

The normal external ear canal is not necessarily sterile,[1] but Johnson[1] asserts that antiseptic preparation and sterile techniques are sufficient and that prophylaxis is unnecessary. Some clinicians argue that the risks of labyrinthitis (even though rare) from round or oval window violation is such a serious hazard that it outweighs the risks or costs of antimicrobials.

Drug choices: pre-op antibiotics that have already sterilized the operative field do not necessarily have to penetrate into the cerebral spinal fluid (and labyrinth) for protection. Therefore, IV gentamicin plus either clindamycin or cefazolin or vancomycin (if MRSA is prevalent) should suffice.

Cochlear implantation increases the risk of subsequent bacterial meningitis in children. It is usually of pneumococcal (rarely hemophilus) origin, probably ascending the eustachian tube associated with acute otitis media. It is likely due to deficient formation of the fibrous-seal at the cochleostomy site. Prevention would include antipneumococcal and *Hemophilus influenzae* vaccinations (*NEJM* 2003; 349:435; also *AAO-HNS Bulletin*, September 2003, p.45).

For MYRINGOTOMY WITH TYMPANOSTOMY TUBE INSERTION.[11,12]

Microbiology: ear canal skin as above
middle ear: pneumococcus, hemophilus, *M. catarrhalis*
Drug choices: antiseptics to ear canal (surgical-prep.) alcohol, etc.
Treat otitis media with systemic therapy as on pages 26-29, Section II.
Topical therapy (see page 54, Section III.H):

Primary:	Alternative:
Ofloxacin (Floxin otic) drops	Ciprofloxacin (Ciloxan, Ciprodex, Cipro HC) Oxymetazoline (Afrin)

For CONTAMINATED OTOLOGIC AND/OR OTONEUROLOGIC SURGERY, pre-operative antibiotics are therapeutic and are recommended. Drug choices are culture/sensitivity directed. Protection of adjacent sterile anatomical sites (especially cerebrospinal fluid) is essential.

Microbiology of acute mastoiditis: *Strep. pyogenes* (group A, beta hemolytic)
S. pneumoniae, *Hemophilus influenzae*
Staph. aureus, and coagulase-negative staph.

Drug choices:

Primary:	Alternatives:
IV (slow) vancomycin 5 Gm plus ceftriaxone (Rocephin) 1-2 Gm	Meropenem IV or levofloxacin or Ampicillin/Sulbactam plus rifampin

Microbiology of chronic tympanomastoiditis/cholesteatoma:
pseudomonas, staphylococcus, proteus sp.,
peptostreptococcus, bacteroides, *et al*. anaerobes

Drug choices: Even though preoperative antibiotics are commonly employed, no regimen of drugs has been verified as efficacious prophylaxis against intracranial extension of infection. These suggestions are, therefore, theoretical, based on activity vs. offending organisms and penetration into the cerebral spinal fluid.

Primary:	Alternatives:
Vancomycin IV 1 Gm plus IV ceftazidime (Fortaz) 1-2 Gm +/- metronidazole	Meropenem IV plus Vancomycin Levofloxacin +/- metronidazole

EXPOSURE OF THE INTRACRANIAL SPACE, penetration of the dura, and contamination of the cerebrospinal fluid can have devastating consequences. Immediate administration of IV agents (such as those named above) is advisable. The choice of agent depends on the probable contaminating bacteria. Two neurosurgical studies have demonstrated efficacy of irrigation of the surgical site with bacitracin–50,000 units in 200 ml of normal saline. For penetrating intracranial wounds (including gunshot), vancomycin plus either meropenem or cefazolin/cefapime would cover staph., strep., pseudomonas, etc.

REFS:

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SECTION V

OTOTOXICITY, PREVENTION AND MONITORING[1]

A number of drugs can produce hearing loss and balance disturbances:

OTOTOXIC DRUGS

Aminoglycoside Antibiotics	*Other Antimicrobials*	*Other Drugs*
Streptomycin	Vancomycin	Quinine
Neomycin	Erythromycin (IV)	Quinidine
Kanamycin	Minocycline	Salicylates (aspirin)
Gentamicin	Amphotericin B	Cisplatin
Tobramycin		Loop Diuretics
Amikacin		furosemide (Lasix)
		Radiocontrast (?)
		Cyclosporine

Vancomycin is a parenteral agent for severe gram-positive coccal infections. It is potentially ototoxic and nephrotoxic if therapy is combined with aminoglycosides.

Minocycline-induced vertigo is not uncommon; it is mild and transient. Rare instances of transient hearing loss have been noted with erythromycin intravenous (not oral) doses exceeding 4 Gm/day.

All aminoglycoside antibiotics are ototoxic and nephrotoxic. Streptomycin is considered more toxic to the vestibular system than to the cochlea, but the converse is so for neomycin and kanamycin. Gentamicin and tobramycin toxicity is reported to be similar to that of streptomycin (more vestibulotoxic[2]). Theoretically, amikacin should be similar to kanamycin (more cochlear toxic). In practice, however, toxicity of all these agents appears to affect *both* vestibular *and* cochlear structures.[1]

Gentamicin (Garamycin), tobramycin (Nebcin), and amikacin (Amikin) are the "antipseudomonas aminoglycosides." In practice, the risk of ototoxicity is dependent more on the care taken in administration than whichever of these three agents is selected.

A single dose of gentamicin (e.g., for surgical prophylaxis) poses practically no risk for ototoxicity. For patients requiring prolonged anti-*pseudomonas* therapy, other effective non-ototoxic agents are available (ceftazadime, piperacillin/tazobactam, levofloxacin, etc., p. 50).

There are no indications for the use of kanamycin that outweigh its disadvantages of cochlear toxicity, nephrotoxicity, and ineffectiveness against pseudomonas organisms. Neomycin is the most cochlear toxic of all drugs, so it is recommended for topical usage only. Neomycin is a common ingredient in ear drops (Cortisporin, *et al*.) Ototoxicity from neomycin in ototopicals in the middle ear is a possibility. (p. 57) Parenteral therapy with neomycin is no longer a common practice. Even topical therapy has resulted in hearing loss when large areas were treated, which allowed for high systemic absorption. Examples include extensive burn therapy, peritoneal wound irrigations, and oral or rectal use as a bowel preparation, especially in patients with ulcerative colitis.

Aminoglycosides are excreted almost entirely by the kidneys. Therefore, impaired renal function prolongs the excretion time and results in high tissue concentrations that enhance the risk of ototoxicity. Serum creatinine levels should be monitored before and during therapy.

SUGGESTED SCHEDULES FOR MONITORING RENAL FUNCTION OF PATIENTS TREATED WITH AMINOGLYCOSIDES

1. Patients with normal serum creatinine and
   a. Treatment course of 14 days or less: determine serum creatinine at least twice a week.
   b. Treatment course of more than 14 days: determine serum creatinine at least three times a week.
2. Patients with elevated but stable serum creatinine: determine serum creatinine at least every other day.
3. Patients with rising or falling serum creatinine: determine serum creatinine at least once a day.

In patients with impaired renal function, the maintenance dose of an aminoglycoside is approximately half of the normal dose, and it is given at intervals (in hours) approximately four times the numerical value of the serum creatinine (in mg/100 ml). Serum levels of aminoglycosides should also be monitored to detect elevated or increasing levels which may increase the risks of ototoxicity and nephrotoxicity.

SUGGESTED SCHEDULES FOR DETERMINATION OF AMINOGLYCOSIDE SERUM LEVELS

1. Normal renal function
   a. Peak level within first 1 to 2 days of therapy, or after 3rd dose
   b. Trough level within 1 week
   c. Subsequently, peak and trough levels approximately once a week
2. Impaired but stable renal function
   a. Peak level within first 1 to 2 days of therapy, or after 3rd dose
   b. Trough level and another peak level within 1 week
   c. Subsequently, peak and trough levels approximately twice a week
3. Impaired, unstable renal function
   a. Peak and trough levels after 1st dose
   b. Determination of serum levels as often as daily thereafter for as long as renal function remains unstable.
4. Following any adjustments of dosage, peak and trough levels should be determined within 1 to 2 days.

Peak serum levels are drawn 60 minutes after completion of an intravenous infusion or after an intramuscular injection. Trough levels are drawn 30 minutes before the next dose.

DOSAGE OF AMINOGLYCOSIDES IN ADULTS WITH NORMAL AND IMPAIRED RENAL FUNCTION (from Lerner and Matz[1] and Sanford Guide[4])

	NITIAL DOSE[a,c] "LOAD"	DESIRABLE SERUM LEVEL (µg/ml)			MAINTENANCE DOSE[a,d]	
Aminoglycoside	All Adults	Peak[a]	Trough[b] Renal	Normal Function[e]	Impaired Renal Function	After Each Hemodialysis
Gentamicin IV Tobramycin IV TID DOSING	2 (to 3[c]) mg/kg	4-10	1-2	1.7 mg/kg q 8 hr	0.8-1.0 mg/kg at intervals (hr) approximately 4 times the serum creatinine[e] (mg/100 ml)	50% of the initial dose
ONCE DAILY[f] DOSING	5.1 (to 7[a]) mg/kg	16-24	‹ 1	5.1 mg/kg q 24 hr		
Amikacin IV TID DOSING	7.5 mg/kg	15-30	5-10	7.5 mg/kg	2.5-3.0 mg/kg at intervals (hr) approximately 4 times the serum creatinine[e] (mg/100 ml)	50% of the initial dose
ONCE DAILY[f] DOSING	15 mg/kg	56-64	‹ 1			

[a] Some infections may require higher dosage and serum levels.

[b] Patients with impaired renal function may have higher trough levels.

[c] An initial loading dose higher than the maintenance dose is given to patients with impaired renal function or for whom rapid onset of maximum therapy is essential (e.g., septic shock). Most patients with normal renal function receive the lower maintenance dose for the initiation of therapy.

[d] For obese patients, the appropriate dosage may be less than that indicated on a body weight basis.

[e] For example, if the serum creatinine is 3.0 mg/100 ml, the maintenance dose would be given every 12 hours.

[f] Once daily dosing of high doses of aminoglycosides appears to induce less oto-nephrotoxicity than multiple dosing and may be as effective for therapy.[3]

Factors which increase the risk of ototoxicity include the following:

1. Impaired renal function
2. Prolonged treatment course (over 10 days)
3. Concomitant use of loop diuretics such as ethacrynic acid or furosemide (Lasix)
4. Concomitant use of other nephrotoxic or ototoxic drugs (vancomycin *et al*., page 73, Section V)
5. Advanced age
6. Previous aminoglycoside therapy
7. Sensorineural hearing loss

It is impractical to perform audiological or vestibular function tests on all patients who receive aminoglycosides. The numbers are too large, and many patients are too ill to respond to the tests.* However, such tests are especially important in patients at high risk (as above) and in those for whom loss of inner ear function would create a major handicap (e.g., a musician, a ballet dancer). Audio-vestibular testing should be performed prior to therapy or within the first 3 days. Audiograms performed within 72 hours of the onset of therapy are still considered baseline, since ototoxicity does not occur before then. During therapy, testing should be done weekly. Patients should be questioned daily about symptoms such as decreased hearing, tinnitus, fullness, dysacousis, dizziness, problems of ocular fixation, and nausea.

Patients whose serum levels exceed the recommended levels or those who develop nephrotoxicity or symptoms of ototoxicity should be tested, and the drug dosages should be adjusted. Although ototoxicity may be irreversible and may progress after cessation of therapy, in some patients discontinuation of the drug results in some increment of improvement.

NOTE: Tables and text for this section were adapted from S. A. Lerner and G. J. Matz[1] and are used by permission of the *American Journal of Otolaryngology* and *Otolaryngology, Head and Neck Surgery*.

REFS:

1. Lerner, Matz: *Am. J. Otolaryng*. 1980; 1:169. *Otolaryng., Head, Neck Surg*. 1979; 87:222.
2. Fee: *Laryngoscope* 1980; 90:Suppl No. 24.
3. Nordstrom: *J. Antimic. Chemoth*. 1990; 25:159-173.
4. Gilbert, *et al*.: *The Sanford Guide to Antimicrobial Therapy*, 2006, p 134.

* The "Head-shake test" is a simple screening test for vestibular dysfunction: the patient is required to sit-up and shake his/her head briskly from side to side in a 10º–20º arc. Individuals with vestibular dysfunction experience blurring of vision or dizziness or nausea during head-shake. Such a response would suggest that aminoglycoside therapy be discontinued and formal vestibular function be evaluated. (*Arch. Otolaryngol, Head, Neck Surg*. 2005; 131:48.)

SECTION VI

ADVERSE INTERACTIONS DRUGS TAKEN IN COMBINATION[1,2]

Antibiotics	Interacting Drugs
Ampicillin and amoxicillin	Allopurinol: increases frequency of rashes
Macrolides: Erythromycin, dirithromycin (Dynabac), clarithromycin (Biaxin), azithromycin (Zithromax)	
Erythromycin Dirithromycin Clarithromycin	Pimozide (Orap): increases Q-T interval: arrhythmias Cyclosporine: increases its levels: toxicity Carbamazepine (Tegretol): increases its levels: nystagmus, ataxia, nausea, vomiting. Should be avoided. "Statin" drugs (Lipitor, *et al.*): increases its levels, rhabdomyolysis Ergot alkaloids: increases levels of ergot alkaloids Phenytoin (Dilantin): increases level of phenytoin Triazolam (Halcion): increases level of triazolam Valproic acid (Depakene): increases level of valproic acid Warfarin: increases prothrombin time, bleeding
Azithromycin	Pimozide, cyclosporine, digoxin, digitoxin: increases effects of dig.
Erythromycin Clarithromycin	Antiretroviral (HIV) agents (page 24) Cimetidine (Tagamet): increases level of cimetidine Digoxin, digitoxin: increases effects of dig. Rifampin: decreases level of erythromycin and clarithromycin Tacrolimus: increases its levels Theophylline: increases theo. level; nausea, vomiting, seizures, apnea Sildenafil (Viagra): increases blood levels of Viagra
Erythromycin	Midazolam (Versed): increases sedative effect Clindamycin: mutual antagonism Corticosteroids: increases their effects Clozapine: increases its CNS effects
Clindamycin	Erythromycin: mutual antagonism Muscle relaxants (atracurium, baclofen, diazepam): prolongs paralysis
Fluoroquinolones: cip: ciprofloxacin (Cipro); oflox: ofloxacin (Floxin); gati: gatifloxacin (Tequin); levo: levofloxacin (Levaquin); moxi: moxifloxacin (Avelox); gemi: gemifloxacin (Factive)	
All fluoroquinolones	Didanosine (Videx): decreases quinolone absorption (except gemi) Al^{+++}, Ca^{++}, Fe^{++}, Mg^{++}, Zn^{++} (antacids, vitamins/mineral supplements): decrease fluroquinolone bioavailability Insulin and oral hypoglycemics: alterations blood sugar (except gemi) Sucralfate (Carafate): decreases absorption of f'quinolones (except moxi)
Cip, oflox, levo	NSAIDS (ibuprofen, etc.): increases risk CNS stimulation/seizures Warfarin: increases prothrombin time

Cip, oflox	Cimetidine (Tagamet): increases its level Cyclosporine: increases its level
Cip, gemi, oflox	Probenecid: decreases clearance of ciprofloxacin and ofloxacin
Cip	Caffeine: increases level of caffeine Phenytoin (Dilantin): alters level of phenytoin Theophylline (Theo-Dur, etc.): increases level of theophylline
Gemi	Foscarnet levels increase, seizure risk Methadone levels increase
Moxi, levo, gati	Antarrhythmics: increase Q-T: arrhythmias (Levo: precaution; Moxi: warning - avoid)
<u>Aminoglycosides</u> Gentamicin Tobramycin Amikacin	Amphotericin B, cisplatin, cyclosporine, furosemide (Lasix), vancomycin, radiocontrast, NSAIDS: increased oto or nephrotoxicity Neuromuscular blockers and non-polarizing relaxants: apnea
Metronidazole (Flagyl)	Disulfiram (Antabuse): acute toxic psychosis Dilantin and phenobarbital decrease metronidazole levels Alcohol: Antabuse-like reaction: tachycardia, flushing, diarrhea Oral anticoagulants: increases anticoagulant effect
Cefotetan	Oral anticoagulants: increases bleeding
Tetracyclines Doxycycline	Atovaquone levels decrease Digoxin: increases level of digoxin, toxicity (up to 10%) several months Antacids, sucralfate (Carafate): decrease absorption of tetra Methoxyflurane: renal toxicity Warfarin: bleeding (doxy) Barbiturates, phenytoin and carbamazepine decrease doxy levels
Sulfonamides and TMP/SMX	Amantadine: increases level of amantadine Digoxin: increases level of digoxin Diuretics: $\uparrow K^+$ $\downarrow Na^+$ Cyclosporine: decreases level, increases creatinine Methotrexate: increases marrow suppression Oral contraceptives: decreases effect Phenobarbital, decreases sulfa Rifampin: increases level of rifampin Warfarin *et al*. anticoagulants: bleeding Phenytoin (Dilantin): increases level of phenytoin Loperamide (Imodium): increases level of loperamide
Vancomycin	Aminoglycosides: oto-nephrotoxicity

Rifampin	Avoid combined use with antiretroviral (HIV) agents: delavirdine, nevirapine, and all protease inhibitors (see page 24). Decreases their effectiveness. Rifampin decreases serum levels and effectiveness of: beta-blockers (metoprolol, propranolol), ACE inhibitors (lisinopril, *et al*.), azole-antifungals, clarithromycin, corticosteroids, cyclosporine, dapsone, diazepam, digoxin, disopyramide, doxycycline, fluvastatin, haloperidol, methadone, oral anticoagulants, oral contraceptives, progestins, phenytoin, quinidines, sulfonylureas (oral hypoglycemics), tacrolimus, theophylline, tocainide, triazolam, tricyclics. Rifampin converts INH to toxic hydrazine. TMP/SMX increases rifampin levels.
Antivirals Amantadine Rimantadine	Alcohol: increases CNS effects Anticholinergics and anti-Parkinson agents: increases side effects (dry mouth, ataxia, blurred vision, slurred speech, psychosis) Digitoxin: increases level digitoxin Trimethoprim: increased levels both
Other antivirals	See HIV - many interactions. See pages 24-25.
Antifungals: (as below)	
Amphotericin B	Antineoplastic drugs: increases nephrotoxicity Digitalis: increases toxicity Other nephrotoxic drugs (aminoglycosides, etc.): increases toxicity
Azole agents: flu: fluconazole (Diflucan); itr: itraconazole (Sporanox); ket: ketoconazole (Nizoral); vor: voriconazole (Vfend)	
Flu, itr, ket, vor	Calcium channel blockers levels increase Cyclosporine: increases levels and risk nephrotoxic Phenytoin (Dilantin): increases levels and decreases flu, itr, ket levels Midazolam (Versed) triazolam (Halcion): increases levels midazolam and triazolam Proton pump inhibitors (Prevacid *et al*.) (except flu) Oral anticoagulants: increases levels of anticoagulants Rifampin: increases levels rifampin and decreases levels flu, itr, ket, vor. (Vor contraindicated)
Flu, itr	Oral hypoglycemics: increases levels of hypoglycemics Amitriptyline: increases levels of amitriptyline
Flu, ket	Tacrolimus (Prograf): increases levels and toxicity of tacrolimus Theophylline: increases levels of theophylline

Itr, ket	Didanosine (Videx): decreases absorption antifungals H_2 blockers (Tagamet *et al*.), antacids, sucralfate (Carafate): decreases antifungal absorption Isoniazid decreases antifungals Sildenafil (Viagra) increases blood levels sildenafil Protease inhibitors increased
Flu	Zidovudine: increases levels of zidovudine
Itr, vor	Carbamazepine (Tegretol): decreases itra, vor (vor contraindicated) Lovastatin (Mevacor), simvastatin (Zocor): rhabdomyolysis
Vor	Pimozide increases, sirolimus (vor contraindicated)
Caspofungin	Cyclosporine hepatoxicity; carbamazepine, dexamethasone, efavirenz, nevirapine, rifamycin: all decrease levels of caspofungin.

REFS:

1. Modified from Gilbert, *et al*.: *The Sanford Guide to Antimicrobial Therapy*, 2006, p 146 ff.
2. *The Med. Letter*, 1999; 41:61-2.

SECTION VII
DRUGS OF CHOICE ACCORDING TO INFECTING ORGANISM[1,2]

ORGANISM	FIRST CHOICE	ALTERNATIVES
Gram-Positive Cocci		
**Staphylococcus aureus* (see Section III.C, page 49)	Nafcillin; dicloxacillin, etc. or 1st/2nd gen. ceph: cephalexin, cefazolin, *et al*., p. 6	amox/clav[a] or ampi/sulbac clindamycin or vancomycin erta-, imi-, meropenem[h] quinolones[g]
Methicillin resistant (MRSA)	vancomycin +/- rifampin linezolid (Zyvox)	TMP/SMX[b] plus rifampin daptomycin (Cubicin) fusidic acid
Staphylococcus epidermidis (coag. neg.)	vancomycin with or without rifampin	daptomycin (Cubicin) rifampin plus quinolone [g] rifampin plus TMP/SMX[b]
Streptococcus pyogenes Gr. A Strep. Groups B, C, G, F	penicillin or amoxicillin or all cephalosporins (+ genta[e] if serious Group B)	amox/clav[a] or ampi/sulbac clindamycin or vancomycin erythro- or clarithromycin[c] telithromycin
*Streptococcus Group D (Enterococcus)	ampi/sulbac or penicillin G with gentamicin[e] (for serious)	vancomycin with gentamicin[e] linezolid, amox/clav
**Streptococcus pneumoniae* (pneumococcus)	see Section III.A, page 46	
Streptococcus anaerobic (peptostreptococcus)	clindamycin or penicillin + metronidazole	amox/clav[a] or ampi/sulbac vancomycin, meropenem
**Strep. viridans*	PenG or Ampi or ceftriaxone or vancomycin: all plus genta[e]	meropenem levo- or moxifloxacin
Gram-Negative Cocci		
Moraxella catarrhalis	amoxicillin/clavulanate see Section III.B, page 48	3rd gen. cephalosporin quinolone,[g] azithro-, erythro-, clarithromycin
**Neisseria gonorrhoeae* (see Section III.I, page 60)	ceftriaxone or cefpodoxime	any fluoroquinolone[g]

* Because drug resistance may be a problem, sensitivity studies are indicated.
[a] Amox/clav: amoxicillin/potassium clavulanate (Augmentin). Ampi/sulbac: ampicillin/sulbactam (Unasyn).
[b] TMP/SMX: trimethoprim-sulfamethoxazole (Septra). Some strains resistant.
[c] Erythro-clarithro-azithro: erythromycin or clarithromycin (Biaxin) or azithromycin (Zithromax).
[d] Ticar/clav: ticarcillin/potassium clavulanate. Pipr/taz: piperacillin/tazobactam (Zosyn).
[e] Gentamicin or tobramycin or amikacin.
[f] When history of anaphylaxis from penicillins.
[g] fluoroquinolones: ciprofloxacin (Cipro), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox), gemifloxacin (Factive).
[h] Carbepenems: ertapenem, imipenem, meropenem.

ORGANISM	FIRST CHOICE	ALTERNATIVES
Neisseria meningitidis	penicillin G or ceftriaxone	cefotaxime, cefuroxime TMP/SMX[b] (some resistant) chloramphenicol (some resistant)
Gram-Positive Bacilli		
**Actinomyces israeli*	penicillin or ampicillin	doxycycline, ceftriaxone clindamycin, erythromycin
Bacillus anthracis	ciprofloxacin or doxycycline For systemic infections, add rifampin and/or clindamycin and/or imi- or meropenem	penicillin or amoxicillin levofloxacin
Clostridium difficile	metronidazole or vancomycin	bacitracin
Clostridium perfringens	penicillin plus clindamycin or doxycycline	ceftriaxone, erythromycin cefoxitin, carbepenems[h] piperacillin/tazobactam
Clostridium tetani	metronidazole and/or penicillin	doxycycline imi- or meropenem
Corynebacterium diphtheriae	erythromycin or clindamycin plus antitoxin	rifampin or penicillin plus antitoxin
Listeria monocytogenes	ampicillin with or without gentamicin[e]	TMP/SMX[b] pen. G (high dose), erythromycin
*Nocardia	TMP/SMX[b] (high dose)	minocycline amikacin plus ceftriaxone
Enteric Gram-Negative Bacilli		
*Bacteroides, intestinal and oropharyngeal anaerobes, see Section III.E, page 51	clindamycin or metronidazole	amox/clav[a] or ampi/sulbac cefoxitin, piperacillin/tazobactam imi- , erta- or meropenem[h]
*Enterobacter	erta-, imi-, or meropenem[h] OR piperacillin plus genta[e] or fluoroquinolones[g]	gentamicin, etc.[e] ticar/clav or pipr/taz[d] 3rd/4th gen. cephalosporins
**Proteus mirabilis*	ampicillin or TMP/SMX amox/clav or ampi/sulbac[a]	cephs., quinolones,[g] penems[h] gentamicin[e], pipr/taz[d]

*Because drug resistance may be a problem, sensitivity studies are indicated.
[a]Amox/clav: amoxicillin/potassium clavulanate (Augmentin). Ampi/sulbac: ampicillin/sulbactam (Unasyn).
[b]TMP/SMX: trimethoprim-sulfamethoxazole (Septra). Some strains resistant.
[c]Erythro-clarithro-azithro: erythromycin or clarithromycin (Biaxin) or azithromycin (Zithromax).
[d]Ticar/clav: ticarcillin/potassium clavulanate. Pipr/taz: piperacillin/tazobactam (Zosyn).
[e]Gentamicin or tobramycin or amikacin.
[f]When history of anaphylaxis from penicillins.
[g]fluoroquinolones: ciprofloxacin (Cipro), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox), gemifloxacin (Factive).
[h]Carbepenems: ertapenem, imipenem, meropenem.

ORGANISM	FIRST CHOICE	ALTERNATIVES
**E. coli* **Klebsiella pneumoniae* Other *Proteus *Providencia *Serratia	3rd gen. cephalosporin: cefotaxime or ceftizoxime or ceftriaxone or ceftazidime or cefepime or quinolones[g]	ampicillin with gentamicin, etc. aztreonam, imi-, meropenem ticar/clav, pipr/taz,[d] ampi/sulbac[a] (not serratia)
Other Gram-Negative Bacilli		
Acinetobacter	imipenem or meropenem OR amikacin with ciprofloxacin	amikacin plus ceftazidime amox/clav or ampi-sulbac[a]
Bartonella (formerly Rochalimaea) (cat scratch)	azithromycin or clarithromycin or doxycycline	ciprofloxacin, TMP/SMX,[b] rifampin (combined with others if severe)
Bordetella pertussis (Whooping cough)	erythromycin or clarithromycin or telithromycin	TMP/SMX[b] quinolones[g] (probably)
*Brucella	doxycycline with either: gentamicin[e] or rifampin	quinolone[g] plus rifampin plus gentamicin TMP/SMX[b] plus gentamicin
Chlamydophila pneum.	erythro-clarithro-azithro[c] or doxycycline	telithromycin cipro- or levo- or moxifloxacin[g]
Eikenella corrodens	ampicillin or Pen. G or amox/clav[a] or ampi/sulbac	TMP/SMX, quinolone[g], doxycycline, cefotaxime, imi[h]
F. tularensis	gentamicin[e]	doxycycline, TMP/SMX rifampin
**Hemophilus influenzae* Meningitis/epiglottitis	ceftriaxone or cefotaxime	quinolone,[g] meropenem ampicillin/sulbactam, (pen allergy) chloramphenicol
**Hemophilus influenzae* Otitis, sinusitis, etc. See Section III.B, page 48	Amox/clav[a] or ampi/sulbac	cefpodoxime, ceftriaxone levo-gati-moxifloxacin[g] ceftibuten, doxycycline
Legionella pneumophila	erythromycin (with or without rifampin) or azithromycin levo-gati-moxifloxacin[g]	clarithromycin or telithromycin TMP/SMX[b], doxycycline
M. catarrhalis	Amox/clav[a] or azithro-clarithro-erythro[c]	3rd/4th gen. cephalosporins levofloxacin[g], moxifloxacin

*Because drug resistance may be a problem, sensitivity studies are indicated.
[a]Amox/clav: amoxicillin/potassium clavulanate (Augmentin). Ampi/sulbac: ampicillin/sulbactam (Unasyn).
[b]TMP/SMX: trimethoprim-sulfamethoxazole (Septra). Some strains resistant.
[c]Erythro-clarithro-azithro: erythromycin or clarithromycin (Biaxin) or azithromycin (Zithromax).
[d]Ticar/clav: ticarcillin/potassium clavulanate. Pipr/taz: piperacillin/tazobactam (Zosyn).
[e]Gentamicin or tobramycin or amikacin.
[f]When history of anaphylaxis from penicillins.
[g]fluoroquinolones: ciprofloxacin (Cipro), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox), gemifloxacin (Factive).
[h]Carbepenems: ertapenem, imipenem, meropenem.

ORGANISM	FIRST CHOICE	ALTERNATIVES
[*]*Pseudomonas aeruginosa* (see Section III.D, page 50) (Serious infections require combination therapy to deter resistance.)	Piperacillin/tazobactam plus plus genta-tobra-amikacin[e] orally: ciprofloxacin or levofloxacin	ceftazidime, cefepime, aztreonam, ticarcillin imipenem, meropenem IV cipro-levofloxacin (any of above need combination therapy)
Miscellaneous Organisms		
Mycoplasma pneumoniae	erythro-clarithro-azithro[c] or telithromycin	doxycycline levo-gati-moxifloxacin[g]
Rickettsia	doxycycline	chloramphenicol quinolones[g]
Spirochetes *Borrelia burgdorferi* (Lyme) See page 44, Section II. *Treponema pallidum* (syphilis) (see Section III.I, page 60) *T. pertenue* (yaws)	 ceftriaxone or cefuroxime or doxycycline or amoxicillin penicillin penicillin	 cefotaxime, pen. G (high dose) clarithromycin doxycycline ceftriaxone tetracycline
Fungi: Systemic (see page 21, Section I.Q, for topicals, etc., information)		
Aspergillus species	voriconazole	itraconazole, ampho. B, caspofungin
Blastomyces dermatitidis	itraconazole or amphotericin B	fluconazole
Candida species, systemic	fluconazole or amphotericin B	voriconazole, caspofungin
Candida, mucocutaneous	topical: nystatin or miconaz or clotrimazole (p. 22) oral: fluconazole, itraconazole, ketoconazole	
Chromomycosis	itraconazole	
Coccidioides immitis	itraconazole	fluconazole amphotericin B
Cryptococcus neoformans	amphotericin B	fluconazole, itraconazole
Histoplasma capsulatum	amphotericin B (meningitis)	itraconazole (pulmonary)

[*]Because drug resistance may be a problem, sensitivity studies are indicated.
[a]Amox/clav: amoxicillin/potassium clavulanate (Augmentin). Ampi/sulbac: ampicillin/sulbactam (Unasyn).
[b]TMP/SMX: trimethoprim-sulfamethoxazole (Septra). Some strains resistant.
[c]Erythro-clarithro-azithro: erythromycin or clarithromycin (Biaxin) or azithromycin (Zithromax).
[d]Ticar/clav: ticarcillin/potassium clavulanate. Pipr/taz: piperacillin/tazobactam (Zosyn).
[e]Gentamicin or tobramycin or amikacin.
[f]When history of anaphylaxis from penicillins.
[g]fluoroquinolones: ciprofloxacin (Cipro), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox), gemifloxacin (Factive).
[h]Carbepenems: ertapenem, imipenem, meropenem.

ORGANISM	FIRST CHOICE	ALTERNATIVES
Malassezia	Ketoconazole	selenium sulfide
Mucor species	amphotericin B	posaconazole
Paracoccidioides brasiliensis	itraconazole or ketoconazole	amphotericin B sulfonamide
Pseudallescheria boydii	itraconazole	miconazole, voriconazole
Sporothix schenckii	cutaneous: potassium iodide systemic: itraconazole	fluconazole amphotericin B (meningitis)

REFS:

1. *Medical Letter* 2001; 43:69-78.
2. Gilbert, *et al*.: *The Sanford Guide to Antimicrobial Therapy*.

SECTION VIII

DOSAGES AND COSTS (TO PATIENT)

Section VIII.A–Typical Adult Dosages and Costs[a] for 10-Day[b] Course Oral Antibiotics

Generic Name	Brand Name	Dose	#	Rx[c]	Generic $	Brand $
Penicillins						
K Penicillin V		250 mg	40	1 qid, 1 hr ac	$ 11	
		500 mg	40	1 qid, 1 hr ac	17	
Dicloxacillin		250 mg	40	1 qid, 1 hr ac	22	
		500 mg	40	1 qid, 1 hr ac	33	
Amoxicillin	Amoxil	500 mg	30	1 tid c meals	18	24
Amoxicillin with clavulanate	Augmentin	875 mg	20	1 bid c meals	80	187
	Augmentin XR	1000 mg	40	2 bid c meals		159
Cephalosporins						
Cephalexin	Keflex	500 mg	40	1 qid, 1 hr ac	29	221
Cefadroxil	Duricef	500 mg	20	1 bid c meals	70	
Cefuroxime	Ceftin	250 mg	20	1 bid c meals	56	197
		500 mg	20	1 bid c meals	83	338
Cefprozil	Cefzil	500 mg	20	1 bid c meals	175	219
Cefpodoxime	Vantin	200 mg	20	1 bid c meals	145	169
Cefdinir	Omnicef	300 mg	20	2 daily c meals	108	129
Cefditoren	Spectracef	200 mg	20	1 bid c meals		81
Ceftibuten	Cedax	400 mg	10	1 daily, 1 hr ac		137
Macrolides						
Erythromycin base	ERYC	250	40	1 qid, 1 hr ac	15	30
	PCE	500	30	1 tid c meals		110
Erythro. ethylsucc.	EES-400	400	40	1 qid c meals	16	
Erythro. stearate		250	40	1 qid c meals	13	10
		500	40	1 qid c meals	21	17
Clarithromycin	Biaxin	250	20	1 bid c meals	104	145
		500	20	1 bid c meals	93	143
	Biaxin XL	500	20	2 daily c meals	103	134
Azithromycin	Zithromax	250	6[d]	1 daily, 1 hr ac		
	Z-PAK	as directed		(2 first day)	52	73
Telithromycin	Ketek	400 mg	10[d]	2 daily c meals		67

Generic Name	Brand Name	Dose	#	Rx[c]	Generic $	Brand $
Quinolones						
Ciprofloxacin	Cipro	500 mg	20	1 bid c meals[*]	$ 41	157
	Cipro	750 mg	20	1 bid c meals[*]		164
Ofloxacin	Floxin	400 mg	20	1 bid c meals[*]	122	171
Levofloxacin	Levaquin	500 mg	10[b]	1 daily c meals[*]		136
	Levaquin	750 mg	10[b]	1 daily c meals[*]		273
Leva Pak	Levaquin	750 mg	5	1 daily c meals		156
Moxifloxacin	Avelox	400 mg	10[b]	1 daily c meals[*]		135
Tetracyclines						
Doxycycline		100 mg	11	2 1st day, then 1 daily c meals	11	81
Minocycline		100 mg	11	2 1st day, then 1 daily c meals	20	132
Tetracycline		250 mg	40	1 qid, 1 hr ac	11	
		500 mg	40	1 qid, 1 hr ac	11	
Sulfonamides						
Trimethoprim/sulfa DS (double strength)	Septra DS or Bactrim DS	160/800	20	1 bid c meals	13	55
Others						
Clindamycin	Cleocin	150	40	1 qid c meals	48	165
		300	40	1 qid c meals	110	311
Linezolid	Zyvox	600 mg	20	1 bid c meals		1582
Metronidazole	Flagyl	500 mg	40	2 bid no alcohol	40	247
Rifampin	Rifadin	300 mg	20[d]	1 bid, 1 hr ac	36	77
Vancomycin		250 mg	40+	1 or 2 qid c meals		687
Antivirals						
Amantadine	Symmetrel	100 mg	10[d]	1 bid c meals	17	22
Rimantadine	Flumadine	100 mg	10[d]	1 bid c meals	24	38
Oseltamivir	Tamiflu	75 mg	10[d]	1 bid c meals		104
Zanamivir	Relenza	10 mg	1 pkg[d]	2 inhalations bid		87

[*]Quinolones: Take several hours before or after antacids, vitamins with minerals (zinc) or iron supplements, or sucralfate (Carafate). See page 17, Section I.I, for specific timing.

Section VIII.B–Pediatric Suspensions for 10-day Treatment for 40-lb. Child

		Generic $	Brand $
Penicillin V 250 mg/tsp, 1 tsp qid, 1/2 hr ac	200 ml	11	
Amoxicillin (Amoxil) 400 mg/tsp, 1 tsp bid c meals	100 ml	13	17
Amoxicillin and clavulanate			
(Augmentin ES 600) 1.5 tsp bid c meals	200 ml	107	143
(Augmentin '400') 400 mg/tsp, 1 tsp bid c meals	100 ml	95	118
Erythromycin plus sulfisoxazole (Pediazole) 1 tsp qid c meals	200 ml	23	45
Azithromycin (Zithromax) 200 mg/tsp, 1 tsp day 1, then 1/2 tsp daily, 1 hr ac	15 ml[d]	36	53
Clarithromycin (Biaxin) 125 mg/tsp, 1 tsp bid c meals	100 ml	46	64
Trimethoprim with sulfamethoxazole (Septra or Bactrim) 2 tsp bid c meals	200 ml	11	41
Loracarbef (Lorabid) 200 mg/tsp, 1 tsp bid 1 hr ac	100 ml		103
Cefaclor (Ceclor) 250 mg/tsp, 1 tsp tid, 1 hr ac	150 ml	57	73
Cefuroxime (Ceftin) 125 mg/tsp, 2 tsp bid c meals	200 ml		90
Cefprozil (Cefzil) 250 mg/tsp, 1 tsp bid c meals	100 ml	46	57
Cefpodoxime (Vantin) 100 mg/tsp, 1 tsp bid c meals	100 ml	115	144
Cefixime (Suprax) 100 mg/tsp, 1.5 tsp/day c meals	100 ml		131
Cefdinir (Omnicef) 125 mg/tsp, 2 tsp/day c meals	100 ml	95	118
Ceftibuten (Cedax) 180 mg/tsp, 1 tsp/day	120 ml		139
Compare to: Ceftriaxone 1 Gm (50 mg/kg), one injection IM every other day, for 3 doses: $66/dose plus $30 to administer			288

See page 58, Section III.H, for Otic Drops.

REFS:

[a] July 2007 in a Washington, D.C., CVS pharmacy. Costs are listed for comparison purposes and may not correspond to other communities.

[b] Diseases treated with the more potent of these agents may not require 10-day courses.

[c] "1 daily" means one dose taken every 24 hours.
"1 bid" (twice daily) means one dose taken every 12 hours.
"1 tid" (thrice daily) means one dose taken every 8 hours.
"1 qid" (four times daily) means one dose taken every 6 hours (or close to that).
"c meals" (with meals) means that the drug, generally, may be taken without regard to meals, or that (for some drugs) food enhances absorption or that (for most) food decreases the side effects (nausea).
"1 hr ac" means that the drug should be taken one hour before or two hours after a meal. Food in the stomach stimulates acid, which impairs absorption of many of these drugs (many penicillins, cephalosporins, erythromycins). Cations such as calcium (in milk products or antacids), aluminum and magnesium (in antacids), and iron and zinc (in vitamins and supplements) impair absorption of tetracycline and the quinolones.

[d] Courses shorter than 10 days are indicated.

Section VIII.C–Dosages and Patient Cost of Frequently Used Parenteral Antibiotics (Sibley Memorial Hospital, Washington, D.C., 2007)

Drug (Brand) Name	Unit Cost ($) Drug plus solution[1]	Typical Dose[2]	Daily Cost[3]
Penicillin G, 10 MU[4]	9.29 +33	10 MU q6hr	$141.28
Ampicillin, 1 Gm	4.06 +33	1 Gm q6hr	136.06
Nafcillin, 1 Gm	6.44 +33	1 Gm q6hr	138.44
Piperacillin (Pipracil) 3 Gm	9.36 +33	3 Gm q6hr	141.36
Ticar/Clav (Timentin) 3 Gm	13.30 +33	3 Gm q6hr	145.30
Ampi/Sulbac (Unasyn) 3 Gm	3.75 +33	3 Gm q6hr	135.75
Pipr/Taz (Zosyn) 3 Gm/375 mg	13.97 +33	3 Gm q6hr	145.97
Cefazolin (Ancef, Kefzol)1 Gm	1.00 +33	1 Gm q8hr	100.00
Cefuroxime (Zinacef) 750 mg	5.64 +33	750 mg q8hr	104.64
Cefotetan (Cefotan) 1 Gm	11.70 +33	1 Gm q12hr	77.70
Cefoxitin (Mefoxin) 1 Gm	4.95 +33	1 Gm q6hr	136.95
Cefotaxime (Claforan) 1 Gm	2.51 +33	1 Gm q8hr[2]	101.51
Ceftazidime (Fortaz) 1 Gm	4.68 +33	1 Gm q12hr[2]	70.68
Cefepime (Maxipime) 2 Gm	31.13 +33	2 Gm q12 hr	97.13
Ceftriaxone (Rocephin) 1 Gm	3.77 +33	1 Gm q24hr[2]	36.77
2 Gm	7.62 +33	2 Gm q24hr	40.62
Aztreonam (Azactam) 1 Gm	24.38 +33	1 Gm q8hr	123.38
Imipenem/Cilas.(Primaxin) 500 mg	25.69 +33	500 mg q6hr	157.69
Meropenem (Merrem) 1 Gm	30.90 +33	1 Gm q8hr	129.90
Ertapenem (Invanz) 1 Gm	48.18 +33	1 Gm q6-8hr	180.00-147.00
Gentamicin, 80 mg	0.53 +33	80 mg q8hr	99.53[3]
Tobramycin (Nebcin) 80 mg	1.07 +33	80 mg q8hr	100.07[3]
Amikacin (Amikin) 500 mg	4.71 +33	500 mg q12hr	70.71[3]
Erythromycin, 1 Gm	11.58 +33	1 Gm q6hr	143.58
Clindamycin (Cleocin) 900 mg	10.11 +33	900 mg q8hr	109.11
Metronidazole (Flagyl) 500 mg	1.27 +33	500 mg q6hr	133.27
Vancomycin 1 Gm	5.93 +33	1 Gm q12hr	71.93[3]
Linezolid (Zyvox) 600 mg	71.78 +33	600 mg q 12hr	209.56
Daptomycin (Cubicin)	71.28 +33	250 mg q 24hr	104.28
Tigecycline	46.84 +33	100 mgx1 then 50 mg q12hr	159.68
Ciprofloxacin (Cipro) 400 mg	5.92 +33	400 mg q12hr	71.92
Levofloxacin (Levaquin) 750 mg	48.47 +33	750 mg q24hr	81.47
Moxifloxacin (Avelox) 400 mg	11.83 +33	400 mg q 24hr	44.83

[1] Intravenous administration incurs additional charge of $33 per dose for drugs that require pharmacy preparation in a solution bag (not applied to intramuscular administration).

[2] Typical or average doses listed may not be appropriate for certain specific infections or patients (e.g., for serious infections, doses of the penicillins or cephalosporins may be doubled or more).

[3] Laboratory costs for monitoring (serum levels or renal function) are not included.

Section VIII.D—Pediatric Dosages of Commonly Used Oral Agents

Dosages are usually calculated on a weight basis except that such a method tends to overdose older children. In general, a child who has reached 80-100 pounds is given adult dosages. One teaspoon equals 5 ml (5 cc), one kg equals 2.2 lbs.

AMOXICILLIN (Amoxil) in various preparations. Usual dose: 45 mg/kg/day in divided doses, every 12 hours with meals.

Example: 400 mg/tsp suspension (or 400 mg chewable tablet) Supplied as:

9 kg (20 lbs.)	½ tsp q 12 h	50 ml bottle: 10 days
14 kg (30 lbs.)	¾ tsp q 12 h	75 ml bottle: 10 days
18 kg (40 lbs.)	1 tsp q 12 h	100 ml bottle: 10 days
23 kg (50 lbs.)	1 ¼ tsp q 12 h	50 + 75 ml bottles: 10 days
27 kg (60 lbs.)	1 ½ tsp q 12 h	50 + 100 ml bottles: 10 days
80 lbs. and over	adult doses	

Enhanced dose: 90 mg/kg/day in divided doses every 12 hours is recommended for ear and sinus infections due to pneumococcal strains that could exhibit reduced susceptibility to penicillin (see page 27, Section II, and page 46, Section III.A). In such instances, all doses suggested above should be doubled.

AMOXICILLIN/CLAVULANATE (Augmentin: many preparations, dosage based on the amoxicillin component). USUAL dose for pharyngeal and skin infections: 45 mg/kg/day (amoxicillin component) in divided doses every 12 hours with meals.

Example: Augmentin 200 (200 mg amox. per 5 ml suspension or per chewable tablet)

9 kg (20 lbs.)	1 tsp q 12 h	75 ml bottle: 10 days

Example: Augmentin 400 (400 mg amox. per 5 ml suspension or per chewable tablet)

14 kg (30 lbs.)	¾ tsp q 12 h	75 ml bottle: 10 days
18 kg (40 lbs.)	1 tsp q 12 h	100 ml bottle: 10 days
23 kg (50 lbs.)	1 ¼ tsp q 12 h	50 + 75 ml bottles: 10 days
27 kg (60 lbs)	1 ½ tsp q 12 h	50 + 100 ml bottles: 10 days
80 lbs. and over	adult doses	

ENHANCED amoxicillin dose for ear and sinus infections due to pneumococcal strains that could exhibit reduced susceptibility to penicillin (see page 27, Section II, and page 46, Section III.A): 90 mg/kg/day in divided doses every 12 hours with meals.

Example: Augmentin ES-600 (600 mg amox./42.9 mg clav. per 5 ml susp)

8 kg (18 lbs.)	3 ml (½ tsp) q 12 h	75 ml bottle: 10+ days
12 kg (26 lbs.)	4.4 ml (1 tsp) q 12 h	75 ml bottle: 8.5 days
16 kg (36 lbs.)	6.2 ml (1 ¼ tsp) q 12 h	125 ml bottle: 10 days
20 kg (44 lbs.)	7.5 ml (1 ½ tsp) q 12 h	125 ml bottle: 8.3 days
24 kg (52 lbs.)	8.9 ml (1 ¾ tsp) q 12 h	200 ml bottle: 11+ days
28 kg (62 lbs.)	10.6 ml (2 ¼ tsp) q 12 h	200 ml bottle: 9.4 days
32 kg (70 lbs.)	12 ml (2 ½ tsp) q 12 h	200 ml bottle 8.3 days

AMPICILLIN Usual dose: 50-100 mg/kg/day in divided doses q 6 hr, ½ hour before or 2 hours after meals.

Example:	250 mg/tsp preparation @ 50 mg/kg/day		Supplied as:
	10 kg (22 lbs.)	½ tsp q 6 h	100 ml bottle: 10 days
	15 kg (33 lbs.)	¾ tsp q 6 h	150 ml bottle: 10 days
	20 kg (44 lbs.)	1 tsp q 6 h	200 ml bottle: 10 days
	20 kg and over	adult doses	

Example:	100 mg/ml pediatric drops, 20 ml (for under 6month old infant)	
	up to 5 kg (11 lbs.)	62.5 mg (½ dropperful) q 6 h
	5-7.5 kg (11-16.5 lbs)	94 mg (¾ dropperful) q 6 h
	7.610 kg (16.622 lbs.)	125 mg (1 dropperful) q 6 h

AZITHROMYCIN (Zithromax) Usual dose: 10 mg/kg day 1; 5 mg/kg daily, days 2-5, ½ hr ac

Example:	100 mg/tsp preparation, supplied as 300 mg (15ml) bottle	
	10 kg (22 lbs.)	1 tsp day 1, ½ tsp daily days 2-5

Example:	200 mg/tsp preparation		Supplied as:
	20 kg (44 lbs.)	1 tsp day 1, ½ tsp daily days 2-5	600 mg (15 ml) bottle
	30 kg (66 lbs.)	1.5 tsp day 1, ¾ tsp daily days 2-5	900 mg (22.5 ml) bottle

CEFDINIR (Omnicef) Usual dose: 14 mg/kg once daily without regard to food.

Example:	125 mg/5 ml (1 tsp)		Supplied as:
	9 kg (20 lbs.)	1 tsp daily	60 ml: 12 days
	18 kg (40 lbs.)	2 tsp daily	100 ml: 10 days
		27 kg (60 lbs.)	1 Tbs. daily

CEFIXIME (Suprax) Usual dose: 8 mg/kg/day, once daily with meals.

Example:	100 mg/tsp preparation @ 8 mg/kg/day		Supplied as:
	12.5 kg (27.5 lbs.)	1 tsp once daily	50 ml: 10 days
	19 kg (42 lbs.)	1.5 tsp once daily	50 ml: 7 days
	25 kg (55 lbs.)	2 tsp once daily	100 ml: 10 days
	35 kg (77 lbs.)	3 tsp once daily	
	55 kg and over (110 lbs.)	4 tsp or one 400 mg tab daily (adult dose)	

CEFPODOXIME (Vantin) Usual dose: 5 mg/kg q 12 hr with food (to enhance absorption)

Example:	50 mg/tsp preparation @ 10 mg/kg/day		Supplied as:	
	10 kg (22 lbs.)	1 tsp bid	100 ml:	10 days
	15 kg (33 lbs.)	1.5 tsp bid	100 ml:	7 days

Example:	100 mg/tsp preparation @ 10 mg/kg/day			
	15 kg (33 lbs.)	¾ tsp bid	75 ml:	10 days

20 kg (44 lbs.)	1 tsp bid	100 ml:	10 days
30 kg (66 lbs.)	1.5 tsp bid	100 ml:	7 days
40 kg (88 lbs.)	2 tsp bid (adult dose)	100 ml:	5 days

CEFTIBUTEN (Cedax) Usual dose: 9 mg/kg once daily, 2 hrs ac or 1 hr pc.

Example:	180 mg/tsp preparation @ 9 mg/kg/daily	Supplied as:
10 kg (22 lbs.)	1/2 tsp daily	60 ml: 12 days
15 kg (33 lbs.)	3/4 tsp daily	
20 kg (44 lbs.)	1 tsp daily	120 ml: 12 days
30 kg (66 lbs.)	1 1/2 tsp daily	
40 kg (88 lbs.)	2 tsp daily	

CEFUROXIME (Ceftin) Usual dose: 30 mg/kg/day in divided doses bid with meals.

Example:	125 mg/tsp preparation @ 30 mg/kg/day	Supplied as:
9.1 kg (20 lbs.)	1 tsp bid	100 ml bottle: 10 days
13.6 kg (30 lbs.)	1.5 tsp bid	100 ml + 50 ml bottles: 10 days
18.2 kg (40 lbs.)	2 tsp bid	200 ml bottle: 10 days
27.3 kg (60 lbs.)	1 tablespoon bid	

CEPHALEXIN (Keflex) Usual dose: 2550 mg/kg/day, divided into 4 doses. May be doubled for severe infections. May be given without regard to meals.

Example:	125 mg/tsp preparation @ 25 mg/kg/day	Supplied as:
10 kg (22 lbs.)	1/2 tsp qid	100 ml bottle: 10 days
15 kg (33 lbs.)	3/4 tsp qid	

Example:	250 mg/tsp preparation @ 25 mg/kg/day	
20 kg (44 lbs.)	1/2 tsp qid	100 ml bottle: 10 days
40 kg (88 lbs.)	1 tsp qid	200 ml bottle: 10 days
40 kg and over	adult doses	

CLARITHROMYCIN (Biaxin) Usual dose: 15 mg/kg divided into 2 doses/day, with meals to enhance absorption.

Example:	125 mg/tsp	Supplied as:
9 kg (20 lbs.)		1/2 tsp q 12 h
17 kg (37 lbs.)	1 tsp q 12 h	100 ml bottle: 10 days

Example:	250 mg/tsp	
25 kg (55 lbs.)	3/4 tsp q 12 h	
33 kg (73 lbs.)	1 tsp q 12 h	100 ml bottle: 10 days

ERYTHROMYCIN (EES, E-Mycin, etc.) Usual dose: 30-50 mg/kg/day in doses every 6 hours; may be doubled for severe infections. Ethylsuccinate (EES) preparation may be given without regard to meals.

Example:	200 mg/tsp preparation	Supplied as:
10-15 lbs.	1/4 tsp q 6 h	60 ml bottle: 12 days

16-25 lbs.	1/2 tsp q 6 h	100 ml bottle: 10 days
26-50 lbs.	1 tsp q 6 h	200 ml bottle: 10 days
51-100 lbs.	1.5 tsp q 6 h	200 ml bottle: 7 days
100 lbs. and over	adult doses	

ERYTHROMYCI-SULFISOXAZOLE (Pediazole) Usual dose: 50 mg erythromycin and 150 mg sulfisoxazole per kg/day, with meals.

Example: Fixed dose preparation 200 mg erythromycin ethylsuccinate and 600 mg sulfisoxazole/tsp

		Supplied as:
8 kg (18 lbs.)	1/2 tsp q 6 h	100 ml bottle: 10 days
16 kg (35 lbs.)	1 tsp q 6 h	200 ml bottle: 10 days
24 kg (53 lbs.)	1.5 tsp q 6 h	200 ml bottle: 7 days
45 kg/over (100 lbs.)	2 tsp q 6 h or adult doses	

PENICILLIN V Usual dose: 25-50 mg/kg/day in 3-6 divided doses; may be increased according to severity of infection. Prefer 1/2 hour before or 2 hours after meals.

Example: 250 mg/tsp preparation @ 50 mg/kg/day

		Supplied as:
10 kg (22 lbs.)	1/2 tsp q 6 h	100 ml bottle: 10 days
15 kg (33 lbs.)	3/4 tsp q 6 h	150 ml bottle: 10 days
20 kg (44 lbs.)	1 tsp q 6 h	200 ml bottle: 10 days
20 kg and over	adult doses	

TRIMETHOPRIM-SULFAMETHOXAZOLE [TMP-SMX] (Septra) Usual dose: 6-12 mg TMP and 30-60 mg SMX/kg/day in divided doses every 12 hours.

Example: Fixed dose preparation @ 8 mg TMP and 40 mg SMX/kg/day (1 tsp for every 20 lbs. twice daily)

9 kg (20 lbs.)	1 tsp q 12 h	Dispensed in amounts requested
18 kg (40 lbs.)	2 tsp q 12 h	Dispensed in amounts requested
27 kg (60 lbs.)	3 tsp q 12 h	Dispensed in amounts requested
36 kg (80 lbs.)	4 tsp q 12 h	Dispensed in amounts requested
36 kg and over	adult doses	Dispensed in amounts requested

Section VIII.E–Pediatric (Over One Month Age) Dosages of Selected Parenteral Drugs

Generic (Trade) Names	Daily Dose	Usual Interval Dose
Penicillin G (1 mg=1600 U) IV	25,000-300,000 U/kg/day	12,500 U/kg q 6 h
Ampicillin IV	200 mg/kg/day	50 mg/kg q 6 h
Ampi/Sulbactam (Unasyn) IV	100-300 mg/kg/day	25-75 mg/kg q 6 h
Nafcillin IV	100-200 mg/kg/day	37 mg/kg q 6 h
Piperacillin/tazobactam IV	100-300 mg/kg/day	75 mg/kg q 4-6 h slowly*
Ticarcillin (Ticar) IV	100-300 mg/kg/day	75 mg/kg q 4-6 h slowly*
Ticarcillin/clavulanate (Timentin) IV	100-300 mg/kg/day	75 mg/kg q 4-6 h slowly*
Cefazolin (Ancef, Kefzol) IV	50-100 mg/kg/day	20 mg/kg q 8 h
Cefuroxime (Zinacef IV)	150-240 mg/kg/day	50 mg/kg q 8 h 80 mg/kg q 8 h (meningitis)
Cefotaxime (Claforan) IV	200-300 mg/kg/day	50 mg/kg q 6 h 75 mg/kg q 6 h (meningitis)
Ceftazidime (Fortaz) IV	150 mg/kg/day	50 mg/kg q 8 h
Ceftriaxone (Rocephin) IM 24 h(once/d IM for otitis media) IV	100 mg/kg/day	50-75 mg/kg/day 24 h (once/d IV for meningitis)
Erythromycin IV	20-50 mg/kg/day	10 mg/kg q 6 h slowly*
Clindamycin (Cleocin) IV	25-40 mg/kg/day	7.5 mg/kg q 6 h
Chloramphenicol IV only	50-100 mg/kg/day	12.5-25 mg/kg q 6 h
Amikacin (Amikin) IV, IM	30 mg/kg/day	10 mg/kg q 8 h
Gentamicin or tobramycin IV, IM	7.5 mg/kg/day	2.5 mg/kg q 8 h
Vancomycin IV	40-60 mg/kg/day	10-15 mg/kg q 6 h slowly*
Linezolid	25-40 mg/kg/day	10 mg/kg q 8 h
Metronidazole (Flagyl) IV	30 mg/kg/day	7.5 mg/kg q 6 h

*Slowly: 2 hr per dose or by continuous drip.

REF: Modified from Gilbert, *et al*.: *The Sanford Guide to Antimicrobial Therapy* 2006, page 133.

SECTION IX

INDEX ACCORDING TO DRUG NAME

(Numbers in bold indicate dosage information.)

SECTION X

INDEX OF BACTERIA

Additional resource material:

The Medical Letter Handbook of Antimicrobial Therapy (current edition)
Published by The Medical Letter, Inc.
56 Harrison Street
New Rochelle, New York 10801

Johnson, J.T., Yu, V.L. (ed.): *Infectious Diseases and Antimicrobial Therapy of the Ears, Nose, and Throat*. Philadelphia, W.B. Saunders Co., 1997.

Gilbert, *et al.: The Sanford Guide to Antimicrobial Therapy (current annual edition)*
Published by Antimicrobial Therapy, Inc.
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Sperryville, VA 22740-0276
Tel (540) 987-9480
Fax (540) 987-9486
www.sanfordguide.com

Brook, I. (ed.): Upper Respiratory, Head, and Neck Infections, *Current Infectious Disease Reports* 2000; 2:97-167.

Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis, *Otolaryng., Head, Neck Surg*. January 2004; 130:Suppl S1-S50.

Clinical Practice Guidelines: Otitis Media with Effusion, *Otolaryng., Head, Neck Surg*. May 2004; 130: Suppl S95-S118.

American Academy of Pediatrics, Subcommittee on Management of Acute Otitis Media: Diagnosis and Management of Acute Otitis Media, *Pediatrics* 2004; 113:1451-1465.

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