ELSEVIER
SAUNDERS

Infect Dis Clin N Am 21 (2007) 355–391

INFECTIOUS
DISEASE CLINICS
OF NORTH AMERICA

Microbiology and Principles of Antimicrobial Therapy for Head and Neck Infections

Itzhak Brook, MD, MSc

Department of Pediatrics and Medicine, Georgetown University School of Medicine, 4431 Albemarle St. NW, Washington, DC 20016, USA

The predominant aerobic and anaerobic bacteria in head and neck infections and their resistance to antimicrobial agents

The predominant aerobic and anaerobic bacteria isolated in common head and neck infections are summarized in Table 1. The major aerobic pathogens recovered in acute upper respiratory tract infections (URTI) are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. Antimicrobial resistance among these micro-organisms has increased significantly in the past 2 decades. Anaerobic bacteria also are common in chronic head and neck infections that are serious and life threatening. The source of anaerobes in these infections is often the oropharynx. Because of their fastidiousness, these organisms are difficult to culture and often are overlooked. Their exact role in health and disease often is difficult to ascertain from the medical literature because of the inconsistent methodologies used for their isolation and identification [1]. Treatment of anaerobic infection is complicated by the slow growth of these organisms, their polymicrobial nature, and increasing antimicrobial resistance.

An important mechanism of antibiotic resistance of both aerobic bacteria (*Staphylococcus aureus, H influenzae*, and *M catarrhalis*) and anaerobic gram-native bacilli (AGNB) is the production of the enzyme β-lactamase. β-Lactamase–producing bacteria (BLPB) can be involved directly in the infection and protect themselves and other penicillin-susceptible organisms in the vicinity from β-lactam antibiotics. This protection can occur when the enzyme is secreted into the infected tissue or abscess fluid in sufficient

E-mail address: ib6@georgetown.edu

0891-5520/07/$ - see front matter
doi:10.1016/j.idc.2007.03.014 *id.theclinics.com*

Table 1
Aerobic and anaerobic bacteria isolated in selected head and neck infections

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Otitis media, acute	*S pneumoniae* *H influenzae*[a] *M catarrhalis*[a]	*Peptostreptococcus* spp
Otitis media and mastoiditis, chronic	*S aureus*[a] *E coli*[a] *K pneumoniae*[a] *P aeruginosa*[a]	Pigmented *Prevotella* and *Porphyromonas* spp *Bacteroides* spp[a] *Fusobacterium* spp[a] *Peptostreptococcus* spp
Peritonsillar and peripharyngeal abscess	*S pyogenes* *S aureus*[a] *S pneumoniae*	*Fusobacterium* spp[a] Pigmented *Prevotella* and *Porphyromonas* spp[a]
Suppurative thyroiditis	*S pyogenes* *S aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp[a]
Sinusitis, acute	*H influenzae*[a] *S pneumoniae* *M catarrhalis*[a]	*Peptostreptococcus* spp
Sinusitis, chronic	*S aureus*[a] *S pneumoniae* *H influenzae*	*Fusobacterium* spp[a] Pigmented *Prevotella* and *Porphyromonas* spp[a]
Cervical lymphadenitis	*S aureus*[a] *Mycobacterium* spp	Pigmeted *Prevotella* and *Porphyromonas* spp[a] *Peptostreptococcus* spp
Postoperative infection disrupting oral mucosa	*Staphylococcus* spp[a] Enterobacgeriaceae[a]	*Fusobacterium* spp[a] *Bacteroides* spp[a] Pigmented *Prevotella* and *Porphyromonas* spp[a] *Peptostreptococcus* spp
Odontogenic and deep neck infections	*Streptococcus* spp *Staphylococcus* spp[a]	Pigmented *Prevotella* and *Porphyromonas* spp[a] *Bacteroides* spp[a] *Fusobacterium* spp[a] *Peptostreptococcus* spp
Necrotizing ulcerative gingivitis, or Vincent's angina	*Streptococcus* spp *Staphylococcus* spp[a]	*Fusobacterium necrophorum*[a] Spirochetes, *P intermedia*

[a] Organisms that have the potential of producing β-lactamase.

quantities to degrade the β-lactam ring of penicillin or cephalosporin before it can kill the susceptible bacteria [2].

Streptococcus pneumoniae

There are 90 antigenically distinct capsular serotypes in 42 distinct serogroups of *S pneumoniae*. Seven serotypes, 14, 6B, 19F, 18C, 23F, 4, and 9V (in order of decreasing prevalence), accounted for 78% of clinical isolates obtained from children in the United States [3]. These seven serotypes constitute the heptavalent conjugated pneumococcal vaccine currently in use

in the United States. Antimicrobial resistance is present mainly in serotypes 6A, 6B, 9, 14, 19F, and 23F, whereas serotypes 1, 3, 4, 5, 7, 11, 15, and 18 are rarely resistant [4].

Resistance to β-lactams occurs following stepwise alterations in penicillin-binding proteins (PBPs) leading to decreased binding affinities for β-lactam antibiotics. Different degrees of resistance to penicillin and other β-lactams emerge because changes can occur in multiple PBPs to change their affinity for β-lactams. There are six known PBPs in *S pneumoniae* (1a, 1b, 2b, 2x, 2z, and 3), and alterations in 1a, 2b, and 2x are most often associated with resistance to penicillin [5]. Isolates with penicillin minimal inhibitory concentrations (MICs) of 0.06 μg/mL or less are defined as penicillin-susceptible, whereas penicillin-intermediate strains have MICs of 0.12 to 1.0 μg/mL, and penicillin-resistant isolates have MICs of 2 μg/mL or higher. The latter two groups are also referred to as "penicillin-nonsusceptible." Multidrug-resistant *S pneumoniae* are defined as organisms resistant to three or more classes of antibiotics.

The increasing prevalence of penicillin-nonsusceptible *S pneumoniae* (MICs of $\geq$ 0.12 μg/mL) in the United States has been a major concern. The Alexander Project is a worldwide surveillance study that collects respiratory tract isolates from community-based physicians and uses pharmacokinetic/pharmacodynamic (PK/PD) susceptibility breakpoints to evaluate the in vitro activity of various antimicrobial agents [6]. Data from the United States portion of the Alexander Project from 1998 to 2000 showed that 12% of isolates were penicillin-intermediate, and 25% were penicillin-resistant. Approximately 26% of *S pneumoniae* isolates were resistant to penicillin and two other classes of agents, and about 16% were resistant to any four classes of agents [7]. The prevalence of penicillin nonsusceptibility peaked in 2001 and since has decreased to 32.7% in 2004 [8]. Resistance to other antimicrobial classes also has decreased. This trend may be the result of several factors, including widespread use of heptavalent protein-polysaccharide pneumococcal conjugate vaccine in children since 2000 as well as less antimicrobial use overall.

Increased use of macrolides, particularly azithromycin, is responsible for the recent increase in macrolide-resistant *S pneumoniae*. Resistance to macrolides is mediated primarily by two genes: *erm*, which encodes for a ribosomal methylase, and *mef*, which encodes for the efflux mechanism [9,10]. The efflux mechanism conveys a relatively moderate degree of resistance, compared with the high-level resistance associated with altered ribosomal methylation. The efflux mechanism is more common in the United States but is relatively rare in most other parts of the world. Ribosomal methylase also confers cross-resistance to clindamycin.

Resistance to fluoroquinolones results from mutations in two target binding sites of these agents, DNA gyrase and topoisomerase IV. Mutations in either the *parC* gene encoding for topoisomerase IV or in the *gyrA* gene encoding for the Gyr A subunit of DNA gyrase result in low-level quinolone

resistance. Mutations in both genes result in high-level quinolone resistance. Even though cross-resistance usually occurs among the fluoroquinolones, the newest agents often remain active against some strains that have become resistant to the older ones. The respiratory fluoroquinolones (ie, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin) remain active against *S pneumoniae*, with less than 3% of all isolates showing resistance [6]. A fluoroquinolone efflux mechanism (*pmrA*) also has been described for *S pneumoniae* [11].

Resistance to trimethoprim (TMP) and sulfonamides results from mutations in the target binding sites of these agents, dihydropteroate synthase and dihydrofolate reductase. The prevalence rates of resistance to trimethoprim/sulfamethoxazole (TMP/SMX), macrolides, doxycycline, and clindamycin were 37%, 29%, 21%, and 10%, respectively [6]. Resistance to these antimicrobial agents generally is higher among penicillin-nonsusceptible isolates [6].

Haemophilus influenzae

The nontypeable strains, which have not been affected by the use of *H influenzae* type b vaccines, are typically the major cause of URTI. The main mechanism of resistance to β-lactams is through the production of β-lactamases [12]. Alterations in PBPs also have been reported in 5% to 10% of *H influenzae* isolates, and these strains are referred to as ''β–lactamase-negative ampicillin-resistant'' (BLNAR). Resistance among BLNAR *H influenzae* strains is attributable to alterations in PBPs 3a and 3b [13]. The prevalence of β-lactamase–producing *H influenzae* ranges from 30% to 40% [6,14]. All *H influenzae* isolates with the exception of BLNAR strains are susceptible to high-dose amoxicillin-clavulanate [6]. BLNAR strains are rarer in the United States than in other countries [6].

β-Lactamase inhibitors (ie, clavulanic acid, sulbactam, tazobactam) block the effects of β-lactamase–mediated resistance. Third-generation cephalosporins (eg, ceftriaxone and cefixime) are stable in the presence of β-lactamases. Combinations of β-lactams and β-lactamase inhibitors (eg, amoxicillin-clavulanic acid) are generally effective in the treatment of many infections caused by BLPB, including *H influenzae, M catarrhalis*, and AGNB.

H influenzae has an effective efflux pump that is chromosomally mediated by *acrAB* genes and is responsible for removing macrolides and azalides from the bacteria. As a result, these agents have intrinsically poor activity against *H influenzae* [15]. Based on PK/PD susceptibility breakpoints, less than 3% of *H influenzae* isolates were susceptible to erythromycin, clarithromycin, and azithromycin [6]. Approximately 22% of recent *H influenzae* isolates from the United States were resistant to TMP/SMX.

Moraxella catarrhalis

The main mechanism of β-lactam resistance by *M catarrhalis* is β-lactamase production. Because these enzymes are different from those produced

by *H influenzae*, some agents (eg, cefpodoxime proxetil, cefuroxime axetil) are less active against *M catarrhalis* than against *H influenzae*. The Alexander Project found that 92% of *M catarrhalis* isolates produced β-lactamases [6]. *M catarrhalis* also is intrinsically resistant to trimethoprim [6,12].

Anaerobic bacteria

The predominant oropharyngeal anaerobes include gram-negative bacilli (*Bacteroides*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Bilophila*, and *Sutterella* spp), gram-positive cocci (primarily *Peptostreptococcus* spp), gram-positive spore-forming bacilli (*Clostridium* spp) and non–spore-forming bacilli (*Actinomyces, Propionibacterium, Eubacterium, Lactobacillus,* and *Bifidobacterium* spp), and gram-negative cocci (mainly *Veillonella* spp) [1]. All with the exception of *Clostridium* spp can be recovered from head and neck infections (Table 2). Most of the infections caused by anaerobes are polymicrobial involving both aerobic and anaerobic organisms [1]. Pigmented *Prevotella* (*P melaninogenica* and *P intermedia*), *Porphyromonas asaccharolytica,* nonpigmented *Prevotella,* and *Fusobacterium nucleatum* are the predominant gram-negative anaerobic species from chronic head and neck infections. Anaerobic streptococci (*Peptostreptococcus* spp) are prevalent in all types of URTI and their complications [1]. Although they frequently are recovered in mixed culture with other aerobic or anaerobic organisms, in many instances they are the only pathogens isolated, particularly in blood cultures. Microaerophilic streptococci also are of importance in chronic sinusitis and brain abscesses.

A steadily increasing prevalence rate of penicillin resistance in oral AGNBs has been noted in the last 2 decades. These include pigmented *Prevotella* and *Porphyromonas* spp, *Fusobacterium* spp, and *P oralis*. The main mechanism of resistance is through the production of β-lactamase. Accurate prevalence rates of antibiotic resistance among oral anaerobes are difficult to obtain because these organisms rarely are identified in routine cultures. Studies that evaluated the prevalence of β-lactamase–producing AGNB in URTI have identified them in more than 50% of patients who have chronic otitis media, sinusitis, tonsillitis, and head and neck abscesses [16].

Principles of antimicrobial therapy

Initial selection of antimicrobial choices

Adequate management of mixed aerobic and anaerobic infections necessitates the administration of agents effective against both types of organisms. A number of factors should be considered when choosing appropriate antimicrobial agents. They should be effective against all target organism(s), induce little or no resistance, achieve sufficient concentration in the infected site, have a good safety record, cause minimal toxicity, and have maximum stability.

Table 2
Anaerobic bacteria most frequently encountered in head and neck infections

Organism	Infectious site
Gram-positive cocci	
Peptostreptococcus spp	Respiratory tract, deep neck, and soft tissue infections
Microaerophilic streptococci[a]	Sinusitis, brain abscesses
Non–spore-forming gram-positive bacilli	
Actinomyces spp	Intracranial abscesses, chronic mastoiditis, head and neck infections
P acnes	Infections associated with foreign body
Bifidobacterium spp	Chronic otitis media, cervical lymphadenitis
Spore-forming ram-positive bacilli	
Clostridium spp	
C perfringens	Soft tissue infection
C difficile	Colitis, antibiotic-associated diarrheal disease
C ramosum	Soft tissue infections
Gram-negative bacilli	
B fragilis group	Chronic otitis and sinusitis (rare)
Pigmented *Prevotella* and *Porphyromonas*	Orofacial and deep neck infections, periodontitis
P oralis	Orofacial infections
P oris-buccae	Orofacial infections
Fusobacterium spp	
F nucleatum	Orofacial, deep neck, and respiratory tract infections, brain abscesses, bacteremia
F necrophorum	Bacteremia

[a] Non-obligate anaerobes.

The selection of antimicrobial agents should be guided by their predicted antibacterial spectrum and bioavailability in oral or parenteral forms. Some antimicrobial agents have a narrow spectrum of activity. For example, metronidazole is effective only against most anaerobes and therefore cannot be administered as a single agent for the therapy of mixed infections. Others (eg, the carbapenems) possess a wide spectrum of activity including Enterobacteriaceae. The selection of antimicrobial agents is simplified considerably when reliable culture results are available, but culture results may not always be available because of the difficulty in obtaining appropriate specimens. Many patients therefore are treated empirically on the basis of suspected rather than known pathogen(s). Fortunately, the types of pathogens involved in most mixed or anaerobic infections and their antimicrobial susceptibility patterns tend to be predictable. Some anaerobes, however, have become resistant to selected antimicrobial agents or may become so while a patient is receiving therapy [17]. Controversies exist regarding the need to provide coverage against all resistant isolates. Some studies of the treatment of acute maxillary sinusitis have suggested that narrow-spectrum

antimicrobial agents are as effective as antibiotic regimens with a broader spectrum of activity [18]. Other studies, however, have demonstrated the superiority of wider spectrum agents in attaining both clinical and bacteriologic success [19].

The choice of antimicrobial therapy also is influenced by factors other than susceptibility patterns. These include the PK/PD characteristics of the various drugs, their toxicity, effect on the normal flora, and bactericidal activity. The clinical setting and Gram-stain preparation of the specimen may suggest what types of anaerobes are present and the nature of the infectious process.

Duration of therapy

The duration of treatment must be individualized, depending on the clinical response. The duration of therapy for anaerobic infections, which often are chronic, is usually longer than that for infections caused by facultative bacteria. Oral therapy often is substituted for parenteral therapy after an initial period. The number of antimicrobial agents available for oral therapy of anaerobic infections is limited, however; among these agents are amoxicillin-clavulanate, clindamycin, and metronidazole.

Causes of failure of antimicrobial therapy

Antimicrobial therapy may fail for various reasons, including the development of resistance, insufficient tissue concentration of antibiotics, incompatible drug interactions, and the formation of an abscess. The abscess environment is detrimental to many antimicrobial agents. For example, the abscess capsule can interfere with the penetration of antimicrobial agents, and the low pH and high content of binding proteins or inactivating enzymes (ie, β-lactamase) within the abscess may impair their activity [20]. The low pH and the anaerobic environment are especially unfavorable for aminoglycosides and fluoroquinolones [21]. An anaerobic environment with an acidic pH and high osmolarity also can develop at an infection site in the absence of an abscess.

Pharmacokinetic and pharmacodynamic considerations

The ability to predict therapeutic efficacy of antimicrobial agents is based on their PK and PD properties. The PK properties of agents relate to their absorption, distribution, metabolism, and excretion. The PD properties of antibiotics involve the relationship between their tissue concentration and bacterial killing. PD integrates both microbiologic and PK data into clinically relevant relationships and can define the MIC limits at which the PK of a specific antimicrobial agent would not lead to treatment success, can determine the impact of antimicrobial resistance, and can provide the basis for developing dosing strategies that optimize clinical outcomes.

The in vivo bacterial killing of an antimicrobial agent is a function of the duration of its concentration over time relative to its MIC against a specific pathogen. This function is expressed as the area under the curve (AUC). Prediction of therapeutic success in animal models and human studies generally correlates with one of three PK parameters: (1) the time of bacterial exposure to concentrations of the antibiotic above its MIC against the pathogen (T > MIC); (2) the ratio of peak serum concentration of the agent to the MIC of the agent against the pathogen (peak:MIC ratio), and (3) the ratio of the AUC to the MIC of the agent against the pathogen (AUC:MIC ratio) (Fig. 1) [22].

Time-dependent killing of antimicrobial agents

β-Lactam antibiotics exhibit time-dependent killing, and the best predictor of clinical outcome is the duration of T > MIC for the bacteria. Relevant data from in vitro PK simulations, animal models, and human clinical studies suggest that the T > MIC required to achieve bacterial eradication should generally be higher than 40% to 50% of the dosing interval for time-dependent antibiotics [23,24]. Variations in that relation exist, however, because the optimal T > MIC for carbapenems (15%–25%) is lower than that for penicillins (30%–40%) and cephalosporins (40%–50%).

The macrolides (eg, erythromycin and clarithromycin) and azalides (eg, azithromycin) also possess time-dependent killing capabilities. Because of their prolonged postantibiotic effect against gram-positive cocci and *H*

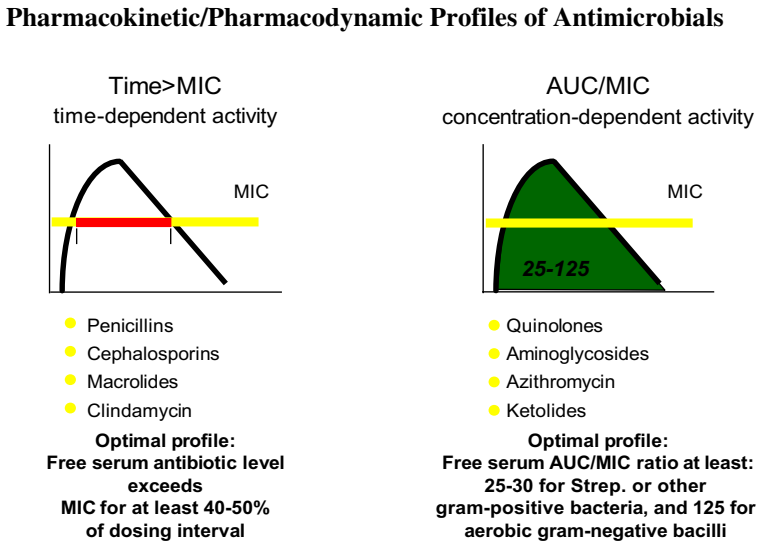

Fig. 1. Pharmacokinetic and pharmacodynamic profiles of antimicrobial agents. AUC, area under the curve; MIC, minimal inhibitory concentration; Strep, streptococcus.

influenzae, however, the parameter that best correlates with efficacy is their AUC:MIC ratio rather than T > MIC. The AUC:MIC ratio leading to maximal efficacy with these agents in animal models is approximately 25 [25]. Azithromycin has the propensity to select for macrolide-resistant bacteria [26]. This propensity may be related to its long serum half-life and prolonged duration of subinhibitory concentrations [27].

Concentration-dependent killing and prolonged persistent effects of antimicrobial agents

The fluoroquinolones, aminoglycosides, and ketolides possess a concentration-dependent mechanism of bacterial killing: they are most effective when their concentrations are significantly above the MIC (see Fig. 1) [24,28]. The AUC:MIC ratio and the peak:MIC ratio are the major parameters that correlate with efficacy. Maximizing the drug concentration at the site of infection is the goal of the dosing regimen. The eradication of organisms by fluoroquinolones is optimal at drug concentrations 10- to 12-fold higher than the MIC for the pathogen; at these concentrations bacterial killing is rapid, and the period of time of drug exposure is minimal [29]. Even though peak:MIC ratios of higher than 10:1 to 12:1 correlate best with optimal bactericidal activity, the AUC:MIC ratio is a better parameter for predicting the efficacy of fluoroquinolones for moderately susceptible bacteria, such as *S pneumoniae*. Based on animal models of sepsis, in vitro pharmacodynamic experiments, and clinical outcome studies, an AUC:MIC ratio of 125 or higher was associated with the highest bacterial eradication rates in the treatment of infections caused by gram-negative enteric pathogens [30]. For gram-positive bacteria such as *S pneumoniae,* the optimal AUC:MIC ratio for therapeutic efficacy is approximately 25 to 30 [31].

Antimicrobial activity according to pharmacokinetic/pharmacodynamic breakpoints

Although the PK/PD breakpoints are the same for all pathogens, the Clinical and Laboratory Standards Institute (CLSI) breakpoints for the same antimicrobial are individualized according to specific pathogens [32]. Whereas the PK/PD breakpoints for *S pneumoniae* are generally similar to the CLSI susceptibility breakpoints, there are significant differences between the PK/PD and CLSI susceptibility breakpoints for several antimicrobial agents against *H influenzae* [6,33]. Because PK/PD breakpoints are based on parameters that resulted in successful outcomes in clinical trials, they are more likely to predict clinical efficacy.

The oral respiratory fluoroquinolones and parenteral ceftriaxone possess the highest in vitro activity against major pathogens in URTIs. Their relative activities against URTI pathogens according to PK/PD breakpoints are

S pneumoniae:
Gatifloxacin/levofloxacin/moxifloxacin (> 99%)
Ceftriaxone/high-dose amoxicillin (± clavulanate) (95%–97%); amoxicillin (± clavulanate)/clindamycin (90%–92%)
Cefpodoxime proxetil/cefuroxime axetil/cefdinir/erythromycin/clarithromycin/azithromycin/telithromycin/cefprozil/TMP/SMX/cefixime (63%–75%)

Loracarbef/cefaclor (< 20%) [6]

H influenzae:
Gatifloxacin/moxifloxacin/ceftriaxone/cefixime/cefpodoxime proxetil/high-dose amoxicillin/clavulanate/amoxicillin/clavulanate (95%–100%)
Cefuroxime axetil/cefdinir/TMP/SMX/amoxicillin (70%–85%)
Cefprozil/cefaclor/loracarbef/doxycycline/erythromycin/clarithromycin/azithromycin/telithromycin (< 25%) [6]

M catarrhalis:
Gatifloxacin/levofloxacin/moxifloxacin/cefixime/high-dose amoxicillin/clavulanate/telithromycin/erythromycin/clarithromycin/azithromycin (100%)
Doxycycline/ceftriaxone/cefpodoxime proxetil/cefdinir (78%–96%)
Cefuroxime axetil (50%)
Cefprozil/amoxicillin/TMP/SMX/cefaclor/loracarbef (< 20%) [6]

Antimicrobial classes useful in head and neck infections

The antimicrobial agents commonly used to treat head and neck infections include the β-lactam antibiotics, macrolides/azalides, lincosamides, metronidazole, fluoroquinolones, tetracyclines, sulfonamides/trimethoprim, rifamycin, and aminoglycosides. Glycopeptides, quinupristin/dalfopristin, linezolid and daptomycin are useful for resistant gram-positive infections, particularly methicillin-resistant *S aureus* (MRSA), penicillin-resistant *S pneumoniae, Streptococcus pyogenes,* and other nosocomial pathogens. The salient features of these antibiotics relevant to the treatment of head and neck infections are summarized here, and their serum half-life, route of administration, and common dosage regimens are shown in Table 3. The FDA recently has reversed its approval of telithromycin (a ketolide) for the treatment of acute bacterial sinusitis and of acute exacerbation of chronic bronchitis, primarily because of serious hepatic toxicities.

β-*Lactam antibiotics*

β-Lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. Their main mechanism of action is interference of bacterial cell wall biosynthesis. Resistance to β-lactam antibiotics can

Table 3
Selected antibiotic classes useful for the treatment of head and neck infections

Class	Antibiotic	Half-life	Usual adult dose and route of administration	Dosing interval
Natural penicillins	Penicillin G (crystalline)	0.5 h	2 MU IV	q 4 h
	Penicillin G (procaine)	24 h	600,000 U IM	q 12 h
	Penicillin G (benzathine)	10–15 d	1.2 MU IM	weekly
	Penicillin V	0.5–1 h	250–500 mg PO	q 6 h
Aminopenicillins	Ampicillin	1 h	2.0 g IV	q 4 h
	Amoxicillin	1 h	500 mg PO	q 6 h
Amoxicillin	Clavulanate	1.4 h	250/62–500/ 124–875/ 125–2000/125 PO	q 12 h q 6 h
Penicillinase-resistant penicillins	Cloxacillin, oxacillin, or nafcillin	0.5 h	500 mg PO or 2 g IV	q 6 h q 4 h
	Dicloxacillin	0.5–0.9 h	500 mg PO	q 6 h
	Methicillin	0.5 h	2 g IV	q 4 h
Carboxypenicillins	Carbenicillin (indanyl)	1 h	382 mg PO	q 6 h
	Ticarcillin-clavulanate	1–1.5 h	3.1 g IV	q 4 h
Ureidopenicillins	Piperacillin-tazobactam	1 h	3.375 g IV	q 4 h
First-generation cephalosporins	Cefadroxil	1.4 h	500 mg PO	q 6 h
	Cefazolin	1.8 h	1 g IV	q 4 h
	Cephalexin	0.9 h	500 mg PO	q 6 h
	Cephalothin	0.5–0.9 h	1 g IV	q 6 h
	Cephradine	0.7–2 h	500 mg PO or 1 g IV	q 6 h q 4–6 h
Second-generation cephalosporins	Cefaclor	0.75 h	500 mg PO	q 8 h
	Cefamandole	0.5–2.1 h	1 g IV	q 4–8 h
	Cefmetazole	1.2 h	2 g IV	q 6–12 h
	Cefonicid	4–5 h	1 g IV	q 24 h
	Cefotetan	3–4 h	1.5 g IV	q 12 h
	Cefoxitin	0.7 h	1 g IV	q 6 h
	Cefprozil	1.3 h	500 mg PO	q 12 h
	Cefuroxime	1.3–1.7 h	1 g IV	q 8 h
	Cefuroxime-axetil	1.2 h	250 mg PO	q 12 h
Third-generation cephalosporins	Cefdinir-pivoxil	1.7 h	300 mg PO	q 12 h
	Cefixime	3–4 h	200 mg PO	q 12 h
	Cefoperazone	1.9–2.5 h	2 g IV	q 12 h
	Cefotaxime	1.1 h	1.5 g IV	q 8 h
	Cefpodoxime-proxetil	2.4 h	200 mg PO	q 12 h

(*continued on next page*)

Table 3 (*continued*)

Class	Antibiotic	Half-life	Usual adult dose and route of administration	Dosing interval
	Ceftazidime	1.5 h	2 g IV	q 8 h
	Ceftibuten	2.4 h	400 mg PO	q 24 h
	Ceftizoxime	1.4–1.8 h	2 g IV	q 6 h
	Ceftriaxone	6–9 h	1 g IV	q 12 h
Fourth-generation cephalosporin	Cefepime	2 h	2 g IV	q 12 h
Carbapenems	Imipenem-cilastatin	1 h	1 g IV	q 6 h
	Meropenem	1 h	1 g IV	q 8 h
	Ertapenem	4.5 h	1 g IV	q 24 h
Monobactams	Azthreonam	2 h	1-2 g IV	q 6 h
Macrolides	Erythromycin	1.2–1.6 h	250 mg-1 g IV or 500 mg PO	q 6 h
	Clarithromycin	4 h	500 mg PO	q 12 h
	Azithromycin	68 h	250 mg PO	q 24 h
Lincosamide	Clindamycin	2–2.5 h	150–300 mg PO or 600 mg IV	q 8 h
Nitroimidazole	Metronidazole	6–14 h	500 mg PO or 500 mg IV	q 6 h
Fluoroquinolones	Ciprofloxacin	4 h	500–750 mg PO or 400 mg IV	q 12 h
	Levofloxacin	7 h	500–750 mg PO or IV	q 24 h
	Moxifloxacin	12 h	400 mg PO or IV	q 24 h
	Gatifloxacin	7 h	400 mg PO or IV	q 24 h
	Gemifloxacin	7 h	320 mg PO	q 24 h
Tetracyclines	Tetracycline	8 h	250–500 mg PO	q 6 h
	Doxycycline	14–25 h	100 mg PO or IV	q 12 h
	Minocycline	11–26 h	100 mg PO or IV	q 12 h
Sulfonamides and Trimethoprim	Sulfadiazine	8–17 h	1 g PO or 30-50 mg/kg	q 6 h
	Sulfisoxazole	3–7 h	1–2 g PO	q 6 h
	Trimethoprim-sulfamethoxazole	8–15 h (trimethoprim) 7–12 h (sulfamethoxazole)	1–2 DS tablets	q 12 h
Rifamycin	Rifampin	2–5 h	600 mg PO or IV	q 24 h

(*continued on next page*)

Table 3 (*continued*)

Class	Antibiotic	Half-life	Usual adult dose and route of administration	Dosing interval
Aminoglycosides	Gentamicin	2 h	1.5–2 mg/kg IV	q 8 h or 5 mg/kg q 24 h
	Netilmicin	2.5 h	1.5–2.0 mg/kg IV	q 8 h
	Tobramycin	2.5 h	1.5–2.0 mg/kg IV	q 8 h
	Amikacin	2 h	7.5 mg/kg IV	q 12 h
	Streptomycin	2.5 h	15 mg/kg IM or IV	q 12 h
Glycopeptides	Vancomycin	4–6 h	250 mg PO or 15 mg/kg IV	q 12 h
	Teicoplanin	45 h	6–12 mg/kg IV	q 24 h
Miscellaneous	Quinupristin-dalfopristin	1.5 h	7.5 mg/kg IV	q 8 h
	Linezolid	5–7 h	600 mg PO or IV	q 12 h
	Daptomycin	8–9 h	4 mg/kg IV	q 24 h

Abbreviations: BID, twice daily; d, day; h, hour; IM, intramuscularly; IV, intravenously; MU, million units; OD, once daily; PO, by mouth; q, every; QID, four times daily.

be caused by (1) reduced antimicrobial permeability through the bacterial cell wall pores; (2) inactivation by β-lactamases excreted to the extracellular fluid (gram-positive bacteria) or present in the periplasmic space (gram-negative bacteria); or (3) reduced affinity of PBPs for the antibiotic.

Penicillins

Penicillins include the natural penicillins (penicillin G and V), penicillinase-resistant penicillins (methicillin, oxacillin, cloxacillin, nafcillin, dicloxacillin), aminopenicillins (ampicillin, amoxicillin, bacampicillin), carboxypenicillins (carbenicillin, ticarcillin), and ureidopenicillins (piperacillin). They are classified according to antibacterial activity but with considerable overlap among the groups. The combination of a penicillin plus a β-lactamase inhibitor (eg, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate, piperacillin/tazobactam) further enhances the antimicrobial spectrum against β-lactamase–producing bacteria, such as *H influenzae, M catarrhalis, Staphylococcus* spp, *Neisseria gonorrhoeae, Escherichia coli*, *Klebsiella pneumoniae, Proteus* spp, *Bacteroides fragilis* group, *Fusobacterium* spp, *Prevotella* spp, and *Porphyromonas* spp.

Major adverse effects include IgE-mediated immediate hypersensitivity reactions resulting in urticaria, angioneurotic edema, bronchospasm and hypotension, serum sickness, Stevens-Johnson syndrome, vasculitis, interstitial nephritis (frequent with methicillin), and hemolytic anemia. High-dose

administration may cause encephalopathy, myoclonus, convulsions, and decreased platelet aggregation resulting in hemorrhagic diathesis (especially with carboxypenicillins).

1. Penicillin G. Procaine and benzathine penicillin are injectable repository forms of aqueous penicillin G. Benzathine penicillin produces prolonged serum levels for 1 or 2 weeks, and procaine penicillin produces serum levels for 12 hours. Penicillin G is active against group A β-hemolytic streptococci (GABHS), alpha-hemolytic streptococcus, meningococci, and *S pneumoniae*. Penicillin-resistant strains of *S pneumoniae* have increased steadily in recent years, but high-dose penicillins are still effective in most oropharyngeal and respiratory infections.
2. Penicillin V is administered orally and resists gastric acidity. Higher serum levels are achieved than with penicillin G. It is less active than penicillin G against gram-negative bacteria, *N gonorrhoeae*, and *H influenzae*. In most other cases it can be used as an oral substitute for penicillin G.
3. Ampicillin usually is administered parenterally and is not penicillinase resistant. It is active against non–β-lactamase–producing *H influenzae*, *Neisseria meningitidis*, pneumococci, and selected gram-negative organisms such as *Salmonella* spp, *Shigella* spp, *Escherichia coli,* and *Proteus mirabilis*.
4. Amoxicillin is better absorbed than ampicillin when administered orally, even with food. Its antibacterial spectrum is similar to that of ampicillin. Intermediate resistance to penicillin by *S pneumoniae* can be overcome by using higher doses of amoxicillin with or without clavulanate. The standard dose of amoxicillin for adults is 1.5 to 1.75 g/d, and the average pediatric dose is 40 to 45 mg/kg/d. When high-dose amoxicillin is prescribed, the dosing is increased to 3.5 to 4.0 g/d or 90 to 100 mg/kg /d. Because of improved PK/PD parameters, high-dose amoxicillin (± clavulanate) has significantly fewer bacteriologic failures against non–β-lactamase–producing ampicillin-resistant *H influenzae*.
5. Methicillin is a semisynthetic compound that is available only in parenteral form and is the least protein-bound among the penicillinase-resistant penicillins. It diffuses well into the brain and joints but is rarely used because of the potential for interstitial nephritis.
6. Oxacillin, cloxacillin, dicloxacillin, and nafcillin are available both orally and parenterally. Only slight differences in absorption and protein binding are observed, and they are considered equivalent clinically. A major concern has been the emergence of resistance among *S aureus* isolates in both hospital- and community-acquired strains.
7. The carboxypenicillins carbenicillin and ticaricillin are active against *Pseudomonas*, *Enterobacter*, and indole-positive *Proteus* spp. Ticarcillin is more active than carbenicillin against *Pseudomonas* spp but is less effective against gram-positive bacteria, especially *Enterococcus* spp.
8. Piperacillin, a ureidopenicillin, is active against *Enterococcus* spp, *Enterobacter*, *Pseudomonas, Serratia, B fragilis*, and *Acinetobacter* spp.

β-Lactamase–producing strains of *S aureus, N gonorrhoeae, H influenzae*, and Enterobacteriaceae are resistant to piperacillin but are susceptible to the piperacillin-tazobactam combination.

Cephalosporins

More than 20 cephalosporin antibiotics are in use today. These agents are classified based on chemical modifications that enhance their antibacterial spectrum. Similar to the penicillins, they inhibit bacterial cell wall biosyntheses. The main mechanism of resistance is the production of β-lactamases that hydrolyze the β-lactam ring. The different cephalosporins vary greatly in susceptibility to β-lactamases. Whereas the first-generation cephalosporins are the most resistant to hydrolysis by β-lactamases produced by *S aureus*, the second-, third-, and fourth-generation cephalosporins are more resistant to β-lactamases produced by aerobic gram-negative rods. Major adverse effects are similar to those of penicillin, and the incidence of primary allergic reactions is 1% to 3%. Cephalosporins should not be administered to patients who have an immediate hypersensitivy reaction to penicillin (urticaria, anaphylaxis, bronchospasm, and hypotension). Cross-hypersensitivity with the penicillins is about 10%. Granulocytopenia and thrombocytopenia are rare. Ethanol intolerance (disulfiram-like reaction) has been described with cefazolin, cefamandole, cefoperazone, and cefotetan.

Drug interactions are also similar to those of the penicillins. The agents that have a N-methyl-thiotetrazole side chain (cefamandole, cefotetan, cefmetazole, and cefoperazone) are associated with an increased incidence of bleeding when taken concomitantly with oral anticoagulants, heparin, platelet aggregation inhibitors, and thrombolytic agents.

1. First generation: Cephalothin, cefazolin, cephapirin, cephalexin, cephradine, and cefadroxil are active against most gram-positive aerobic cocci (except MRSA, *S epidermidis*, and *Enterococcus* spp). They are not active against aerobic and anaerobic gram-negative bacilli.
2. Second generation: Cefamandole, cefaclor, cefuroxime, cefonicid, cefprozil, cefoxitin, cefotetan, and cefmetazole are slightly less active than the first-generation cephalosporins against gram-positive aerobic cocci . Cefoxitin, cefotetan, and cefmetazole have significant activity against anaerobes, including the *B fragilis* group. As a group, the second-generation cephalosporins are more active against gram-negative aerobic organisms, including Enterobacteriaceae, *Enterobacter* spp, indole-positive *Proteus* spp, and *H influenzae*. Cefaclor and loracarbef have poor overall efficacy against respiratory tract pathogens. Cefprozil and cefuroxime axetil have comparable activity against *S pneumoniae* [34]. Cefuroxime axetil is active against *H influenzae* but has lower efficacy than cefpodoxime proxetil [35]. Cefprozil is markedly less active against *H influenzae* [34].

3. Third generation: Cefotaxime, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefixime, and cefpodoxime-proxetil all possess expanded activity against aerobic gram-negative bacilli but are not very active against anaerobic gram-negative bacilli. They also are less active than the first-generation cephalosporins against gram-positive cocci. Cefdinir and cefpodoxime proxetil are active against both *S pneumoniae* and *H influenzae*. Cefixime is active against *H influenzae* but has limited gram-positive coverage including penicillin-resistant *S pneumoniae* and staphylococci. Cefoperazone and ceftazidime are active against *Pseudomonas aeruginosa*.
4. Fourth generation: Cefepime is effective against *P aeruginosa* as well as gram-positive aerobic cocci.

Carbapenems

The carbapenems, which include imipenem, meropenem, and ertapenem, are the most active penicillins against most aerobic and anaerobic bacteria implicated in head and neck infections. Because their PK/PD profiles exhibit time-dependent killing, their antibacterial effectiveness can be maximized further by increasing the dosing frequency or by prolonged administration of high doses [36,37].

1. Imipenem-cilastatin, a parenteral agent, has a broad spectrum of activity against gram-positive cocci (excluding MRSA and *Enterococcus faecium*), gram-negative bacilli (including *P aeruginosa* but not *Stenotrophomonas maltophilia*), and anaerobic organisms (including β-lactamase–producing gram-negative bacilli). When combined with cilastatin, it is prevented from hydrolysis by renal dehydropeptidase, resulting in an enhanced half-life. Seizures can occur in patients receiving high doses, particularly in those who have renal insufficiency or central nervous system disorders.
2. Meropenem, a parenteral agent, is relatively stable to renal dehydropeptidase and does not require an inhibitor of this enzyme. It has activity similar to that of imipenem but is slightly less active against gram-positive cocci and is more active against gram-negative aerobes (Enterobacteriaceae, *H influenzae*, *Neisseria* spp, and *P aeruginosa*).
3. Ertapenem is a new 1-β-methyl carbapenem and is stable to renal dehydropeptidase. It has a broad antibacterial spectrum for penicillin-susceptible *S pneumoniae*, *S pyogenes*, MRSA, *H influenzae*, *M catarrhalis*, *E coli*, *Citrobacter* spp, Klebsiella spp, *Serratia* spp, *Proteus* spp, *Clostridium perfringens*, *Fusobacterium* spp, *Peptostreptococcus* spp, and anaerobic gram-negative bacilli. In comparison to other available carbapenems, ertapenem has a long half-life of 4.5 hours and is given in a single daily dose, making it suitable for outpatient intravenous antibiotic therapy. It is less effective than the other carbapenems against *P aeruginosa*, *Enterococcus* spp, and *Acinetobacter* spp.

Monobactams

Monobactams (eg, aztreonam) have a monocyclic β-lactam ring and are active only against aerobic gram-negative rods. They can be administered to patients allergic to other β-lactam antibiotics because they have different antigenic characteristics.

Macrolides

Macrolides include erythromycin, clarithromycin, and azithromycin. Their mechanism of action is by inhibition of RNA-dependent protein synthesis by reversibly binding to the 50S ribosome, thus preventing chain elongation. Resistance is mediated by decreased permeability through the bacterial cell wall, by alteration of the 50S and the 23S ribosomal RNA receptor site, or by inactivation by enzymatic hydrolysis. Erythromycin-resistant gram-positive bacteria also are resistant to the other macrolides. Telithromycin, the related ketolide, is no longer approved by the Food and Drug Administration for the treatment of acute sinusitis or acute exacerbation of chronic bronchitis, primarily because of serious hepatic toxicities.

These agents have broad activity against gram-positive and some gram-negative bacteria, as well as treponemes, mycoplasmas, chlamydia, and Rickettsia. All are active against *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis,* and *Chlamydophila pneumoniae*. Azithromycin is less active than erythromycin against staphylococci and streptococci but is more active against *H influenzae*. Clarithromycin has good activity against *H influenzae*. The increasing prevalence of macrolide resistance among *S pneumoniae* (about 35% in the United States) and *S pyogenes* (about 12%) is disconcerting because it has been associated with a significant likelihood of clinical failure [38]. Macrolide resistance among these organisms has been correlated with increased clinical usage of macrolides, especially azithromycin [39].

Erythromycin is well absorbed when given orally and also is available for intravenous administration. The base is destroyed by gastric acid, and oral formulations therefore have acid-resistant coatings. Erythromycin is distributed through total body water but does not penetrate well into the cerebrospinal fluid. Clarithromycin and azithromycin have better gastrointestinal absorption. Azithromycin has a very long half-life, resulting in high and prolonged intracellular concentrations. The major adverse effects are gastrointestinal (mostly cramps, nausea, vomiting, and diarrhea with erythromycin), transient hearing loss, allergic reactions (rash, fever, eosinophilia), and cholestatic hepatitis (with estolate). All macrolides prolong the cardiac QT interval. Coadministration with terfenadine (Seldane) or astemizole (Hismanal) is contraindicated because of potential cardiac toxicity. All macrolides except azithromycin increase the serum levels of many drugs such as theophylline, phenytoin, cyclosporine, digoxin, carbamazepine, warfarin, and corticosteroids.

Clindamycin

Clindamycin, a lincosamide antibiotic, binds to the 50S ribosome and inhibits protein synthesis by interfering with chain elongation. It is active against gram-positive cocci such as staphylococci, *S pneumoniae* (including penicillin-resistant strains), *S pyogenes*, and viridans streptococci as well as most anaerobes, including *Peptostreptococcus* spp, *B fragilis, Prevotella*, *Porphyromonas,* and *Fusobacterium* spp. It also reduces toxin production by *S aureus* and *Clostridium* spp and capsule formation by *S pyogenes* and *S pneumoniae,* and it enhances phagocytosis of susceptible organisms. Development of resistance is increasingly recognized in *B fragilis*. The mechanism of resistance is similar to that of macrolides.

Clindamycin is well absorbed following oral dosing, but gastrointestinal absorption is reduced by the co-administration of kaolin. There is good tissue and bone penetration following oral and parenteral administration, but not in the cerebrospinal fluid. Clindamycin possesses a concentration-dependent mechanism of antimicrobial activity [40].

Major adverse effects include erythema multiforme, anaphylaxis, *Clostridium difficile*–associated diarrhea, and pseudomembranous colitis. Hepatotoxicity, thrombocytopenia, and reversible neutropenia are encountered occasionally.

Metronidazole

Metronidazole is highly active against all anaerobic bacteria with the exception of nonsporulating gram-positive bacilli and some *Capnocytophaga* spp. It has no activity against aerobic and facultative bacteria. Its mechanism of action is by the production of intracellular free radicals that are toxic to bacterial cells by interaction with DNA and other macromolecules. Resistance of anaerobic gram-negative bacilli is rarely encountered. Occasional strains of anaerobic gram-positive cocci and nonsporulating bacilli are highly resistant. Microaerophilic streptococci, *Propionibacterium acnes*, and *Actinomyces* spp are almost uniformly resistant. Metronidazole penetrates well into all tissues and body fluids including the cerebrospinal fluid. Oral and intravenous doses achieve equivalent blood levels.

Major adverse effects include seizures, encephalopathy, disulfiram-like reaction with alcohol (flushing, nausea, tachycardia, vomiting, hypotension, headache), cerebellar dysfunction, ataxia, and peripheral neuropathy.

Fluoroquinolones

The fluoroquinolones are well absorbed from the gastrointestinal tract and are available in oral and intravenous forms. The main mechanism of action is inhibition of DNA topoisomerase (gyrase) in bacterial but not mammalian cells. Resistance may arise during therapy and is caused by mutations in the gene encoding for DNA gyrase or mutations that change

the outer porins and efflux pumps. Ciprofloxacin, a second-generation fluoroquinolone, has excellent activity against gram-negative bacteria including *P aeruginosa*. Its AUC:MIC ratio against *S pneumoniae* is only 10 to 20, but it is very active against both *H influenzae* and *M catarrhalis* [24,41]. Levofloxacin has improved activity against *S pneumoniae*. The newer fluoroquinolones (moxifloxacin, gatifloxacin, and gemifloxacin) have excellent activity against *S pneumoniae* (including penicillin-resistant strains), *H influenzae, M catarrhalis*, and respiratory anaerobes [42]. All quinolones show good activity for Rickettsia, Mycoplasma and Legionellae. Their high bioavailability, excellent PK/PD properties, broad spectrum of activity, and generally good overall tolerability have resulted in the extensive clinical use of these agents. Because of toxicities, however, a number of the fluoroquinolones, including temafloxacin, sparfloxacin, grepafloxacin, and trovafloxacin, have been withdrawn from clinical use after initial approval. Another concern is the emergence of cross-resistance among *S pneumoniae* as the result of increased usage of this class of antibiotics.

Major adverse effects include central nervous system manifestations (headache, dizziness, insomnia, agitation, restlessness, abnormal vision, bad dreams, hallucinations, depression, psychotic reactions, grand mal convulsions), anaphylaxis, vasculitis, serum sickness–like reactions, photosensitivity reactions, Achilles tendon rupture and other tendinopathies, increased QT intervals (gatifloxacin, moxifloxacin), rash (gemifloxacin), and hypo- or hyperglycemia (gatifloxacin, levofloxacin). The gastrointestinal absorption of all quinolones is reduced by antacids, dairy products, vitamins, and citric acid.

Tetracyclines

Tetracycline HCP is a short-acting agent (dose interval, 4–8 hours), whereas doxycycline and minocycline are long-acting (dose interval, 12–24 hours). They are well absorbed after oral administration. These agents prevent intracellular protein syntheses at the level of binding of transfer RNA–amino acid complexes to the ribosomes. The main mechanism of resistance is the prevention of penetration of tetracycline into the bacterial cell. All tetracyclines have similar antimicrobial activity. They are active against many gram-positive and gram-negative bacteria. They are also active for *Brucella* spp, *Vibrio cholerae*, *Vibrio vulnificus*, *Mycobacterium marinum*, Chlamydiae, Rickettsia, Mycoplasmas, and *Borrelia burgdorferi*. Many organisms, especially hospital-acquired bacteria, have become resistant, however. Tetracycline, once the drug of choice for anaerobic infections, is presently of limited usefulness because many anaerobic bacteria have developed resistance to tetracycline. The newer tetracycline analogues, doxycycline and minocycline, are more active against anaerobic bacteria than the parent compound. Susceptibility tests should be performed to ensure their efficacy when they are used in severe infections, however. Doxycycline is active

against penicillin-susceptible *S pneumoniae*, but resistance to doxycycline by this organism is increasing [6].

Major adverse effects include teeth discoloration and hypoplasia of the enamel in children younger than 8 years, vertigo (minocycline), aggravation of pre-existing renal failure, hepatotoxicity (especially in pregnancy), increase in intracranial pressure, photosensitivity, and superinfection caused by *Candida* spp (thrush, vaginitis). The use of tetracyclines is not recommended before 8 years of age and in pregnancy because of the adverse effect on teeth.

Sulfonamides and trimethoprim

Short-acting sulfonamides include sulfisoxazole, SMX, sulfadiazine, and sulfamethizole. Sulfadoxine is a long-acting agent. Sulfonamides are well absorbed when given orally. They are metabolized by acetylation and glucuronidation in the liver, and their metabolic products are excreted in the urine. The sulfonamides competitively inhibit the incorporation of *p*-aminobenzoic acid into tetrahydropteroic acid that is required for folic acid synthesis. They are active against a broad spectrum of gram-negative and gram-positive bacteria, as well as actinomyces, Chlamydia, Plasmodia, and Toxoplasma. They are inactive against anaerobic bacteria. Resistance is caused by either chromosomal mutations or plasmid exchange and is common, limiting their clinical usefulness.

TMP, which is a dihydrofolate reductase inhibitor, is synergistic with sulfonamides by the sequential inhibition of folic acid synthesis. TMP is active against many gram-positive cocci and most gram-negative rods. It is not active against *P aeruginosa* and *Bacteroides* spp. The combination of TMP/SMX is effective against *S aureus, S pneumoniae, S pyogenes, P mirabilis, Shigella* spp, *E coli, Salmonella* spp, *Pseudomonas cepacia, Pseudomonas pseudomallei, Yersinia enterocolitica,* and *N gonorrhoeae*. It also is effective against *Pneumocystis carinii*. Resistance to TMP generally is caused by plasmid-mediated mutations in dihydrofolate reductase. A high rate of resistance to these drugs is now present in *S pneumoniae* and *H influenzae* (25%–30%) [6]. *M catarrhalis* is intrinsically resistant to TMP. TMP is very well absorbed after oral administration and distributes in most body fluids especially in the prostrate fluid. It is excreted unchanged in the urine.

Major adverse effects of the sulfonamides include hepatic necrosis, serum sickness–like syndrome, acute hemolytic anemia, agranulocytosis, and Stevens-Johnson syndrome. Major adverse effects of TMP include leukopenia, thrombocytopenia, granulocytopenia, and pseudomembranous colitis.

Rifamycin (Rifampin)

Rifampin binds to the β-subunit of RNA polymerase, thus blocking RNA transcription and initiation of chain formation, resulting in a bactericidal effect. Rifamycin is active against a wide range of organisms, including

S aureus, *S epidermidis, N meningitidis, N gonorrhoeae, H influenzae, Legionella* spp, *C difficile*, and *Mycobacteriu*m spp [43]. Resistance develops rapidly, however, because of mutations of the β-subunit of the DNA-dependent RNA polymerase. Rifamycin is available for oral and intravenous administration. Its long half-life allows once-a-day administration. It penetrates well into all tissues and body fluids, including bone. It is used frequently in combination with penicillinase-resistant penicillins, fluoroquinolones, and TMP/SMX for endovascular and orthopedic infections, chronic prostatitis, and infections associated with prosthetic devices.

Because rifampin is an inducer of several cytochrome p450 isoenzymes, it has a high potential for drug interactions. It inhibits the liver uptake of several compounds and shortens the half-life of numerous agents, resulting in decreased levels of ketoconazole, itraconazole, oral contraceptives, methadone, nevirapine, β-adrenergic blockers, delavirdine, digoxin, and disopyramide, among others.

Aminoglycosides

Despite concerns of nephrotoxicity and auditory as well as vestibular dysfunction, aminoglycosides have remained important in clinical practice, particularly for the treatment of antibiotic-resistant gram-negative infections. These agents include gentamicin, netilmicin, tobramycin, and amikacin. Their mechanism of action is inhibition of protein syntheses. Resistance develops through the induction of aminoglycoside-inactivating enzymes or through alterations in intracellular transport, resulting in failure to penetrate the bacterial cells. Gentamicin is active against aerobic gram-negative bacilli and *S aureus* and exhibits excellent synergistic potential with penicillins against aerobic gram-positive bacteria. Netilmicin is similar to gentamicin and tobramycin but has less ototoxicity. Tobramycin is active against many gentamicin-resistant *Pseudomonas* and *Acinetobacter* spp, but not against Enterobacteriaceae resistant to gentamicin. Amikacin is active against many species that are resistant to gentamicin, netilmicin, and tobramycin and is particularly useful for infections caused by resistant *Pseudomonas*, *Serratia*, and *Providencia* spp. Streptomycin is used primarily in combination with isoniazid and rifampin for the treatment of tuberculosis. It has synergistic activity with penicillin against *Enterococcus* spp and is useful for infective endocarditis caused by this organism.

Aminoglycosides are not absorbed orally but are well distributed after intramuscular or intravenous injection. They are poorly protein bound and do not penetrate the central nervous system. They are excreted primarily by glomerular filtration. Peak and trough serum concentrations should be monitored routinely in patients receiving prolonged therapy. Elevated peak concentration correlate with toxicity, and elevated trough concentrations indicate drug accumulation. Once-a-day dosing reduces the nephrotoxic effects of aminoglycosides and is the preferred regimen.

Glycopeptides

Vancomycin and teicoplanin are active against *S aureus* and *S epidermidis* (including strains resistant to methicillin), *S pyogenes, S pneumoniae,* and other *Streptococcus* spp, Enterococci, *Corynebacterium JK*, and *C difficile*. They inhibit the assembly and synthesis of the second stage of cell wall peptidoglycan polymers of susceptible bacteria. Resistance is acquired by mutation and/or alterations in cell wall biosynthesis resulting in a thickened cell wall caused by accumulation of excess amounts of peptidoglycan, thus preventing intracellular penetration to reach their target sites. They are used primarily to treat systemic infections caused by *E faecium*, penicillin-resistant *S pyogenes* or *S pneumoniae,* and methicillin-susceptible or –resistant *S aureus* or *S epidermidis*. The glycopeptides are not absorbed when administered orally but are effective against *C difficile*–associated colitis. Intravenous administration is required for systemic infections. Peak serum levels of 20 to 30 μg/mLand trough levels of 5 to 10 μg/mL are desirable. Teicoplanin has a longer half-life than vancomycin, allowing once-daily dosing, but requires an initial loading dose.

Major adverse effects include rash, ''red man syndrome'' (caused by rapid intravenous administration and release of histamines), leukopenia, and tinnitus and hearing loss (serum concentration $>$ 40 μg/mL).

Quinupristin/dalfopristin

The combination quinupristin/dalfopristin is used primarily for serious or life-threatening infections associated with vancomycin-resistant *E faecium* bacteremia or complicated skin and soft tissue infections caused by penicillin-resistant *S pyogenes* and methicillin-susceptible or -resistant *S aureus*. In this drug combination, dalfopristin inhibits the early phase, and quinupristin inhibits the late stage of bacterial protein synthesis. Resistance occurs through efflux, target modification, and enzymatic inactivation. It is available for intravenous administration and has a wide tissue distribution. It is metabolized in the liver and is eliminated either by hepatic (75%) or renal (25%) routes.

The major adverse effects are severe and incapacitating muscular inflammation and pain, allergic reactions, phlebitis, pancreatitis, and pseudomembranous colitis.

Linezolid

Linezolid, an oxazolidinone antibiotic, acts by inhibiting the initiation of bacterial protein syntheses. It possesses a wide spectrum of activity against aerobic gram-positive organisms including methicillin-resistant staphylococci, penicillin-resistant pneumococci, and vancomycin-resistant *Enterococcus faecalis* and *E faecium*. Anaerobes such as *Clostridium* spp, *Peptostreptococcus* spp, and *Prevotella* spp also are susceptible. Linezolid is bacteriostatic against most susceptible organisms but displays bactericidal

activity against some strains of pneumococci, *B fragilis*, and *C perfringens*. Resistance by clinical isolates of *E faecium* has been reported.

Major adverse effects include thrombocytopenia and leucopenia that emerge after 2 to 3 weeks of therapy.

Daptomycin

Daptomycin, a cyclic lipopeptide antibiotic, is used primarily for the treatment of complicated skin and soft tissue infections caused by susceptible aerobic gram-positive bacteria including methicillin-susceptible and -resistant *S aureus*, vancomycin-resistant enterococci, and penicillin-resistant *S pyogenes* or *S pneumoniae*. Daptomycin binds to components of the cell membrane of susceptible bacteria, causing rapid depolarization and inhibition of intracellular DNA, RNA, and protein synthesis. It is bactericidal in a concentration-dependent manner. It is highly protein bound (92%) and is excreted unchanged in the urine (78%) and the feces (6%).

Major adverse effects include severe myopathy with markedly elevated serum creatinine phosphokinase (10-fold higher than baseline), peripheral neuropathy, anaphylaxis, thrombocytopenia, and respiratory failure.

Antimicrobial management of selected head and neck infections

Although the management of various head and neck infections is discussed in detail in other articles in this issue, the microbiology and antimicrobial therapy of selected head and neck infections are briefly reviewed here and are summarized in Table 4.

Dental infections

Gingivitis

The development of gingivitis is associated with a significant increase in gram-negative anaerobes (*F nucleatum*, *P intermedia*, and *Bacteroides* spp), spirochetes, and motile rods. Necrotizing ulcerative gingivitis, also known as "acute narcotizing ulcerative gingivitis," "trench mouth," or "Vincent's angina," is caused by a synergistic infection between unusually large spirochetes and fusobacteria [44,45]. The unique organisms associated with this infection are fairly constant and include oral treponemes, *Selenomonas* spp, *P intermedia*, and *Fusobacterium* spp. This condition responds dramatically to systemic metronidazole [46]. Other regimens, including penicillin G, clindamycin, and amoxicillin-clavulanate, are also effective [47].

Periodontitis

Periodontal disease develops in the presence of two events in the oral cavity: a quantitative increase in bacterial counts of anaerobic gram-negative

Table 4
Initial empiric antibiotic treatment for selected head and neck infections

Infection	Common pathogens	Recommended regimens
Dental		
Acute necrosing ulcerative gingivitis	Treponemes, *Selenomonas* spp, *P intermedia*, *Fusobacterium* spp	Metronidazole ± penicillin IV
Periodontal abscess	*A actinomycetemcomitans* and *P gingivalis*	Metronidazole PO; amoxicillin-clavulanate PO
Otologic		
Otitis media, acute	*S pneumoniae*, *H influenzae*, *M catarrhalis*	Amoxicillin (high dose) PO
Otitis media, chronic	*P aeruginosa* and *S aureus*; AGNB and *Peptostreptococcus* spp	Amoxicillin-clavulanate PO; ciprofloxacin + clindamycin PO; imipenem or piperacillin-tazobactam IV
Mastoiditis, acute and chronic	*S pneumoniae, S pyogenes*, *S aureus, H influenzae,* *P* aeruginosa, *Enterobacteriaceae,* AGNB and *Peptostreptococcus* spp	Amoxicillin-clavulanate PO; ticarcillin-clavulanate IV; imipenem or piperacillin-tazobactam IV
Rhinologic		
Sinusitis, acute	*S pneumoniae, H influenzae, M catarrhalis, S pyogenes* and *S aureus*	Amoxicillin-clavulanate PO; levofloxacin, moxalactam, gatifloxacin or gemifloxacin PO
Sinusitis, chronic	*S aureus, S pneumoniae, H influenzae,* AGNB, *Peptostreptococcus* spp	Amoxicillin-clavulanate PO; ticarcillin-clavulanate IV; gemifloxacin PO; moxalactam, or gatifloxacin IV or PO
Oropharyngeal		
Pharyngotonsillitis	Groups A, B, C and G streptococci, *N gonorrhoeae, N meningitidis, C diphtheriae, A hemolyticum*	Penicillin PO; amoxicillin PO; clindamycin or macrolides PO
Peritonsillar, retropharyngeal, and odontogenic deep neck infections	*Prevotella, Porphyromonas, Fusobacterium*, *Peptostreptococcus* spp, GABHS, *S aureus, H influenzae*.	Ticarcillin-clavulanate IV; piperacillin-tazobactam IV; imipenem or meropenem IV
Parotitis & Sialoadenitis	*S aureus,* AGNB, *Peptostreptococcus* spp *Streptococcus* spp (including *S pneumoniae*), gram-negative bacilli (including *E coli*)	Nafcillin or cloxacillin plus clindamycin IV; cefazolin IV; amoxicillin-clavulanate PO; ticarcillin-clavulanate IV

(*continued on next page*)

Table 4 (*continued*)

Infection	Common pathogens	Recommended regimens
Suppurative thyroiditis	*S aureus,* GABHS, *S pneumoniae,* AGNB, *Peptostreptococcus* spp, *Actinomyces* spp	Dicloxacillin or moxicillin-clavulanate PO; macrolides or clindamycin IV or PO; ticarcillin-clavulanate IV
Cervical lymphadenitis	Viral causes most common if bilateral, but bacterial causes associated with an oropharyngeal infection (*S aureus* and GABHS, oral anaerobes, *Mycobacterium* spp) should be suspected if unilateral	Dicloxacillin or amoxicillin-clavulanate PO; macrolides or clindamycin IV or PO
Infected thyroglossal duct or branchial cleft cysts	*S aureus, S pyogenes,* other *Streptococcus* spp, oral anaerobes	Cefoxitin or clindamycin IV; ticarcillin-clavulanate IV
Wound infection complicating head & neck surgery	*S aureus*, enteric gram-negative rods, AGNB, *Peptostreptococcus* spp	Cefoxitin or clindamycin IV; ampicillin-sulbactam PO; clindamycin or metronidazole plus a fluoroquinolone PO or IV

Abbreviations: AGNB, anaerobic gram-negative bacilli, including pigmented *Prevotella* and *Porphyromonas* spp, *Bacteroides* spp, and *Fusobacterium* spp; GABHS, group A β-hemolytic streptococci; IV, intravenous; PO, by mouth.

bacteria and a change in the balance of bacterial types from harmless to disease-causing bacteria. Among the bacteria most often implicated in periodontal disease and bone loss are *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. Other bacteria associated with periodontal disease are *Bacteroides forsythus*, *Treponema denticola, Treponema sokranskii*, and *P intermedia* [48]. Aggressive periodontitis is now recognized as a contagious infection that can be passed between family members. *A actinomycetemcomitans* and *P gingivalis* are believed to have a major role in this infection. Therapy should include the combination of antimicrobial agents and drainage of the infected root and resection of inflamed periodontal tissues [49]. Although penicillin has been effective, its use has been associated with the increasing recovery of BLPB [50]. Other agents that are resistant to β-lactamase may be superior in such a setting, but controlled clinical trials are not available. Systemic therapy with tetracyclines has been effective in the past, but the rapid emergence of tetracycline-resistant aerobic and anaerobic bacteria limits their usefulness. Furthermore, tetracyclines are contraindicated in children younger than 8 years of age because of tooth staining. Metronidazole has been shown to be superior or comparable to penicillin in the treatment of periodontal infection [51].

Otitis and mastoiditis

Acute otitis media

S pneumoniae, *H influenzae*, and *M catarrhalis* are the principal etiologic agents in bacterial acute otitis media (AOM), accounting for about 80% of the bacterial isolates [52]. Of special concern is the increased rate of penicillin-resistant strains of *S pneumoniae* [53] and amoxicillin-resistant *H influenzae* isolated from infected ears [53]. The incidence of such strains reached 50% in some geographic areas. Whereas the rate of *S pneumoniae* has decreased following the introduction of the pneumococcal conjugate vaccine in 2000, the frequency of isolation of nontypeable *H influenzae* has increased [54]. Viruses were recovered in the middle ear fluid in 14.3% of children [55]. Anaerobes are infrequently studied in AOM but were recovered from 5% to 15% of acutely infected ears [56] and from 42% of culture-positive aspirates of serous otitis media [57,58]. *Peptostreptococcus* spp and *Propionibacterium acnes* were the predominant isolates, and AGNB were also recovered.

Antimicrobial therapy should be directed at eradication of the primary pathogen(s) and prevention of recurrences and other complications. Although spontaneous resolution is common and may occur in 75% of patients, it is impossible to predict which patient will require antimicrobial agents to hasten improvement. The new guidelines for the treatment of AOM from the American Academies of Pediatrics and Family Practice offer an option of initial observation rather than antibacterial treatment in children between the ages of 6 months and 12 years who have an uncertain diagnosis and nonsevere illness [59]. If empiric antibacterial treatment is contemplated, increasing the dose of amoxicillin to 90 mg/kg/d to overcome β-lactamase–producing *S pneumoniae* and *H influenzae* is recommended, although controlled trials demonstrating superiority of this approach are lacking. The combination of amoxicillin plus clavulanic acid is effective against penicillinase-producing *H influenzae* and *M catarrhalis*. The newer second- or third-generation cephalosporins (cefuroxime, cefdinir, and cefpodoxime) also have been effective. The growing resistance of *S pneumoniae* to macrolides (about 35%) and the poor pharmacokinetics of azithromycin for *H influenzae* render the initial selection of macrolides less attractive. Anaerobes recovered in AOM are susceptible to aminopenicillins and other antibiotics commonly used to treat AOM. TMP/SMX, however, is active against only 50% of *Peptostreptococcus* spp, the major anaerobe isolated in AOM.

Chronic otitis media

Bacterial isolates from chronic suppurative otitis media usually are polymicrobial, with recovery of mixed aerobes and anaerobes ranging between two and six isolates per specimen. Many of these organisms produce β-lactamase that may have contributed to the high failure rate of β-lactam antibiotics. The most common aerobic isolates are *P aeruginosa* and

S aureus. Anaerobes are isolated from approximately 50% of patients, predominantly AGNB and *Peptostreptococcus* spp [1,60].

Antimicrobial treatment includes clindamycin, cefoxitin, a combination of metronidazole plus either clindamycin or a macrolide, or a penicillin (ie, amoxicillin, ticarcillin) plus a β-lactamase inhibitor (ie, clavulanic acid, sulbactam) [61]. In instances in which *P aeruginosa* is considered a true pathogen, parenteral therapy with a fluoroquinolone (ciprofloxacin), an anti-pseudomonal β-lactam (piperacillin-tazobactam, imipenem-cilastatin), or an aminoglycoside should be added. Parenteral therapy with a carbapenem or a ureidopenicillin provides adequate coverage for all potential pathogens, including anaerobic as well as aerobic bacteria.

Acute and chronic mastoiditis

S pneumoniae, S pyogenes, *S aureus,* and *H influenzae* are the most common aerobes recovered in acute mastoiditis [62]. *P aeruginosa,* Enterobacteriaceae*, S aureus,* AGNB, and *Peptostreptococcus* spp are the predominant isolates in chronic mastoiditis. *S pneumoniae* and *H influenzae* are rarely recovered [63]. Treatment should be guided by culture and susceptibility testing. Parenteral agents with the combination of a penicillin plus a β-lactamase inhibitor (ie, ticarcillin-clavulanate) are appropriate. Treatment should be continued for 7 to 10 days.

Sinusitis

Acute sinusitis

Bacteria commonly recovered from pediatric and adult patients who have community-acquired acute purulent sinusitis include *S pneumoniae, H influenzae, M catarrhalis*, *S pyogenes*, and *S aureus* [64–66]. *S aureus* is a common pathogen in sphenoid sinusitis [67]. The infection is polymicrobial in about one third of the cases. Enteric bacteria are recovered less commonly. Approximately 8% of isolates recovered from acute maxillary sinusitis have an odontogenic origin, mostly as an extension of the infection from the roots of the premolar or molar teeth [68]. *P aeruginosa* and other gram-negative rods are common in sinusitis of nosocomial origin (especially in patients who have nasal tubes or catheters), the immunocompromised, and patients who have cystic fibrosis or HIV infection [69]. Anaerobic also bacteria can be recovered in these patients, however.

The choice of antimicrobial therapy is similar to that for AOM. The recommendations of the Sinus and Allergy Partnership guidelines for the optimal treatment of acute bacterial sinusitis are based on predicted microbiologic data and PK/PD parameters of antimicrobial agents with expected clinical efficacy rates [61]. For adults, the best antibacterial efficacy rates are predicted for amoxicillin-clavulanate and the respiratory fluoroquinolones ($>$ 90% efficacy). They are followed by high-dose amoxicillin, cefpodoxime proxetil, cefuroxime axetil, and TMP/SMX (80%–90% efficacy),

clindamycin, doxycycline, cefprozil, and macrolides (70%–80% efficacy), and cefaclor or loracarbef (50%–60% efficacy). These predictions have not been subjected to randomized clinical trials for direct comparison. Fluoroquinolones are not advocated in children. Macrolides or TMP-SMX is recommended in patients who have hypersensitivity to β—lactams.

In patients who do not show significant improvement within 48 hours or who show signs of deterioration, antral puncture for surgical drainage is recommended, and aspirate cultures and susceptibility testing should be performed to guide further antimicrobial therapy [70,71].

Chronic sinusitis

Although the etiology of chronic sinusitis is uncertain, bacteria are frequently isolated in the sinus cavity of these patients [67]. The clinical significance of some of the low-virulence organisms, such as *S epidermidis*, is questionable because they regularly colonize the nasal cavity [72–76]. When adequate anaerobic culture techniques were employed, however, strict anaerobes were recovered from more than half of the patients [67]. Chronic sinusitis caused by anaerobes is a particular concern because many of the complications (eg, mucocele formation, osteomyelitis, intracranial abscess) are associated with recovery of these organisms [1].

Antimicrobial therapy for chronic sinusitis should be directed against both aerobic and anaerobic bacteria, including BLPB. Choices include clindamycin, metronidazole plus a penicillin or a macrolide, or a penicillin–β-lactamase inhibitor combination (eg, amoxicillin-clavulanate or ticarcillin-clavulanate). The newer fluoroquinolones that provide antianaerobic coverage (eg, moxifloxacin, gatifloxacin, gemifloxacin) are suitable alternatives and are available in both oral and parenteral forms. Treatment for chronic sinusitis should be extended to at least 21 days. Fungal sinusitis can be treated with surgical débridement and antifungal agents.

Pharyngotonsillitis

The pathogens implicated in acute pharyngotonsillitis include groups A, B, C, and G streptococci, *N gonorrhoeae, N meningitidis, Corynebacterium diphtheriae,* and *Arcanobacterium hemolyticum*. Indirect evidence supports the involvement of obligate anaerobes (*Fusobacterium* spp, pigmented *Prevotella* and *Porphyromonas* spp, and *Peptostreptococcus* spp) in both acute and chronic tonsillitis [77]. For example, obligate anaerobes frequently are recovered from tonsillar, peritonsillar, or retropharyngeal abscesses, in many cases without any aerobic bacteria [78]. Obligate anaerobes are isolated from 25% of suppurative cervical lymph nodes associated with dental or tonsillar infections [79], and encapsulated pigmented *Prevotella* and *Porphyromonas* spp are found frequently within acutely inflamed tonsils [1], often directly from the core of recurrently inflamed tonsils that fail to yield GABHS [80,81]. Furthermore, an immune response against *P intermedia*

can be detected in patients who have non-GABHS tonsillitis [82] and against *P intermedia* and *F nucleatum* in patients who recovered from peritonsillar cellulitis or abscesses [83].

The growing inability of penicillin to eradicate GABHS from the oropharynx leading to clinical and bacteriologic failure is an important clinical dilemma. Recent studies have shown that treatment with oral penicillin failed to eradicate GABHS in 35% of patients who had acute-onset pharyngitis treated with oral penicillin V and in 37% of those who received intramuscular penicillin [84]. Various theories have been proposed to explain this failure of penicillin therapy (Box 1) [20,85,86]. The success rate in the treatment of acute GABHS tonsillitis was found to be consistently higher with cephalosporins than with penicillin. The greater efficacy of cephalosporins may result from their activity against aerobic BLPB such as *S aureus, Haemophilus* spp, and *M catarrhalis*. Another possibility is that the normal resident oropharyngeal flora, which may compete with GABHS, is less susceptible to cephalosporins than to penicillin [85]. Nevertheless, penicillin still is recommended as the antibiotic of choice in recent treatment guidelines because of its proven efficacy, safety, narrow spectrum, and low cost [87]. More importantly, penicillin is effective in preventing the nonsuppurative sequelae of acute rheumatic fever, an important goal for antimicrobial therapy of GABHS pharyngotonsillitis. This advantage has not been established for other available therapeutic regimens. The macrolides are an alternative choice. Compliance with the newer macrolides (clarithromycin and azithromycin) is better than with erythromycin, because of improved gastrointestinal tolerance. The

Box 1. Possible causes for antibiotic failure or relapse in therapy of GABHS tonsillitis

Bacterial interactions
- The presence of BLPB that ''protect'' GABHS from penicillins
- Co-aggregation between GABHS and *M catarrhalis*
- Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition for nutrients)

Internalization of GABHS (survives within epithelial cells, escaping eradication by penicillins)
Resistance (ie, erythromycin) or tolerance (ie, penicillin) to the antibiotic used
Inappropriate dose, duration of therapy, or choice of antibiotic
Poor compliance
Reacquisition of GABHS from a contact or an object (ie, toothbrush or dental braces)
Carrier state, not disease

increased use of macrolides for the treatment of various respiratory tract infections has resulted in a significant increase in resistance by GABHS to these agents, however [88–92]. When *C diphtheriae* is suspected, erythromycin is the drug of choice, with penicillin or rifampin as alternatives.

Peritonsillar, retropharyngeal, and odontogenic deep neck infections

Deep neck infections commonly originate from an odontogenic or oropharyngeal infection and generally are polymicrobial, involving both aerobic and anaerobic bacteria from the primary source. Predominant anaerobic organisms include *Prevotella, Porphyromonas, Fusobacterium*, and *Peptostreptococcus* spp; aerobic organisms include GABHS, *S aureus,* and *H influenzae*. More than two thirds of deep neck abscesses contain BLPB [78,93]. Retropharyngeal cellulitis and abscess in young children is more likely to involve aerobic isolates alone, such as *S pyogenes* and *S aureus* [94]. *Fusobacterium necrophorum* is especially common in deep neck infections associated with septic thrombophlebitis of the internal jugular vein resulting in bacteremia and metastatic abscesses (Lemierre disease) [95]. Accurate localization of the primary source of infection as well as the anatomic route of spread by appropriate imaging techniques is critical to a successful outcome. Surgical drainage of loculated pus and protection of the airway are essential. Because these infections are life threatening, initial empiric antimicrobial therapy should include broad coverage for BLPB including *S aureus*, *S pyogenes,* AGNB, and *Peptostreptococcus* spp. A penicillin–β-lactamase inhibitor combination (ticarcillin-clavulanate or piperacillin-tazobactam) or a carbapenem (imipenem or meropenem) is appropriate in view of the severity of these infections. If MRSA is suspected, the addition of vancomycin or linezolid is warranted.

Parotitis and sialadenitis

The parotid gland is the salivary gland most commonly affected by inflammation. The pathogens most commonly associated with acute bacterial parotitis and sialadenitis are *S aureus* and anaerobic bacteria. The predominant anaerobes include AGNB and *Peptostreptococcus* spp. Isolation of *Streptococcus* spp (including *S pneumoniae*) and gram-negative bacilli (including *E coli*) also has been reported [96,97]. Gram-negative organisms often are seen in hospitalized patients. Organisms less frequently found are Arachnia, *H influenzae, K pneumoniae, Salmonella* spp, *P aeruginosa, Treponema pallidum,* cat-scratch bacillus, and *Eikenella corrodens*. *M tuberculosis* and atypical mycobacteria are rare causes of parotitis. Broad-spectrum antimicrobial therapy is indicated to cover all possible aerobic and anaerobic pathogens, including *S aureus,* GABHS, and anaerobic bacteria. A penicillinase-resistant penicillin or a first-generation cephalosporin generally is adequate. Clindamycin plus a fluoroquinolone is an alternative. Vancomycin

for MRSA and ceftazidime for broader coverage of gram-negative organisms may be required in seriously ill patients.

Suppurative thyroiditis

S aureus, GABHS, *S epidermidis,* and *S pneumoniae* are the predominant aerobic isolates in suppurative thyroiditis. The most common anaerobic bacteria are AGNB, *Peptostreptococcus* spp, and *Actinomyces* spp [98,99]. Agents that are rarely recovered include *Klebsiella* spp, *H influenzae, Streptococcus viridans, Salmonella* spp, Enterobacteriaceae, *M tuberculosis*, atypical mycobacteria, *Aspergillus* spp, *Coccidioides immitis*, *Candida* spp, *Treponema pallidum*, and *Echinococcus* spp. Viruses associated with subacute thyroiditis include measles, mumps, influenza, enterovirus, Epstein-Barr virus, adenovirus, echovirus, and St. Louis encephalitis virus. Treatment with broad-spectrum antibiotics is indicated at least until culture results are available. Empiric therapy should cover *S aureus* and GABHS. A penicillinase-resistant penicillin (ie, dicloxacillin) or a penicillin–β-lactamase inhibitor combination (ie, amoxicillin-clavulanate) is suitable for oral therapy. Patients allergic to penicillin can be treated with a macrolide or clindamycin. Antibiotic treatment should be administered for at least 14 days.

Cervical lymphadenitis

The cervical lymphatic system is a first line of defense against various infections of the head and neck, including the upper respiratory tract, oropharynx, and soft tissues of the face and scalp. Viruses, including Epstein-Barr virus, cytomegalovirus, herpes simplex virus, adenovirus, enterovirus, roseola, rubella, and HIV, are the most common cause of bilateral cervical lymphadenitis in children [100]. Other pathogens include *M pneumoniae* and *C diphtheriae*. The most common bacterial organisms causing acute unilateral infection associated with facial trauma or impetigo are *S aureus* and GABHS [79,100,101]. Anaerobic bacteria are associated with a dental or periodontal source of infection; the predominate isolates include AGNB and *Peptostreptococcus* spp [79,101]. Other causes include *Bartonella henselae, H influenzae, Francisella tularensis, Pasteurella multocida, Yersinia pestis, Y enterocolitica, Listeria monocytogenes, A actinomycetemcomitans, Burkholderia gladioli, Spirillum minor, Nocardia brasiliensis, Mycobacterium tuberculosis,* and non-TB *mycobacterium* [102]. Cervical adenitis in the newborn often is associated with group B streptococci. The most common fungi involved in cervical lymphadenitis are *Histoplasma capsulatum, C immitis,* and *Paracoccidioides* spp.

Most patients who have cervical lymphadenitis do not require specific antibiotic therapy because these infections are commonly associated with a viral pharyngitis or stomatitis. Empiric antimicrobial therapy should provide adequate coverage for *S aureus* and GABHS with a penicillinase-resistant penicillin such as cloxacillin and dicloxacillin, or a penicillin–β-lactamase

inhibitor combination (ie, amoxicillin-clavulanate). Patients allergic to penicillin can be treated with a macrolide or clindamycin. Treatment should be administered for at least 14 days. When mycobacterial or cat-scratch disease is suspected, incision and drainage should be avoided because chronically draining cutaneous fistulae may develop. Therapy with rifampin, TMP/SMX, or gentamicin, directed at *B henselae*, should be considered in cat-scratch disease. Total surgical removal is the most effective therapy for nontuberculous mycobacterial infection. Empiric antituberculous therapy with rifampin and isoniazid usually is initiated until the organisms are identified positively as atypical mycobacteria.

Infected thyroglossal duct and branchial cleft cysts

The organisms causing infections of the thyroglossal duct and brachial cleft cysts usually originate from the skin or the oropharynx and include *S aureus, S pyogenes,* other *Streptococcus* spp, and oral anaerobes [103,104]. Surgical drainage of an abscess is the therapy of choice, but administration of antimicrobial agents is required also. Because aerobic and anaerobic BLPB are isolated from the majority of these infections, antimicrobial therapy effective against these organisms is recommended. Effective agents include cefoxitin or clindamycin, a penicillin–β-lactamase inhibitor combination (eg, ticarcillin-clavulanate), or a carbapenem (ie, imipenem or meropenem) for seriously ill patients. A penicillinase-resistant penicillin (ie, nafcillin) or first-generation cephalosporin generally is adequate when the infection is caused by staphylococci. If MRSA is suspected, the addition of vancomycin or linezolid may be warranted.

Wound infection complicating head and neck surgery

Wound infections result from disruption of the oral mucosa at the surgical site and exposure to oropharyngeal flora. They generally are polymicrobial; the most frequently recovered isolates include *S aureus*, enteric gram-negative rods, AGNB, and *Peptostreptococcus* spp [105]. Cefoxitin, ampicillin-sulbactam, or a combination of clindamycin or metronidazole with a fluoroquinolone is suitable for initial empiric therapy [106]. Antimicrobial prophylaxis with cefoxitin or clindamycin is effective in preventing postsurgical wound infections of the head and neck and should be administered for only 24 hours.

References

[1] Finegold SM. Anaerobic infections in humans: an overview. Anaerobe 1995;1:3–9.
[2] Brook I. The role of beta-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. Rev Infect Dis 1984;6:601–7.
[3] Butler JC. Epidemiology of pneumococcal serotypes and conjugate vaccine formulations. Microb Drug Resist 1997;3:125–9.

[4] Joloba ML, Windau A, Bajaksouzian S, et al. Pneumococcal conjugate vaccine serotypes of *Streptococcus pneumoniae* isolates and the antimicrobial susceptibility of such isolates in children with otitis media. Clin Infect Dis 2001;33:1489–94.
[5] Nagai K, Davies TA, Ednie LM, et al. Activities of a new fluoroketolide, HMR 3787, and its (des)-fluor derivative RU 64399 compared to those of telithromycin, erythromycin A, azithromycin, clarithromycin, and clindamycin against macrolide-susceptible or -resistant *Streptococcus pneumoniae* and S. *pyogenes*. Antimicrob Agents Chemother 2001;45:3242–5.
[6] Jacobs MR, Felmingham D, Appelbaum PC, et al. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother 2003;52:229–46.
[7] Mera RM, Miller LA, Daniels JJ, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States over a 10-year period: Alexander Project. Diagn Microbiol Infect Dis 2005;51:195–200.
[8] Fedler KA, Biedenbach DJ, Jones RN. Assessment of pathogen frequency and resistance patterns among pediatric patient isolates: report from the 2004 SENTRY Antimicrobial Surveillance Program on 3 continents. Diagn Microbiol Infect Dis 2000;56:427–36.
[9] Fasola E, Bajaksouzian S, Appelbaum P, et al. Variation in erythromycin and clindamycin susceptibilities of *Streptococcus pneumoniae* in four test methods. Antimicrob Agents Chemother 1997;41:129–34.
[10] Tait-Kamradt A, Davies T, Cronan M, et al. Mutations in 23S rRNA and ribosomal protein L4 account for resistance in pneumococcal strains selected in vitro by macrolide passage. Antimicrob Agents Chemother 2000;44:2118–25.
[11] Gill MJ, Brenwald NP, Wise R. Identification of an efflux pump gene, pmrA, associated with fluoroquinolone resistance in *Streptococcus pneumoniae*. Antimicrob Agents Chemother 1999;43:187–9.
[12] Felmingham D, Washington J. Trends in the antimicrobial susceptibility of bacterial respiratory tract pathogens—findings of the Alexander Project 1992–1996. J Chemother 1999;11: 5–21.
[13] Ubukata K, Shibasaki Y, Yamamoto K, et al. Association of amino acid substitutions in penicillin-binding protein 3 with beta-lactam resistance in beta-lactamase-negative ampicillin-resistant *Haemophilus influenzae*. Antimicrob Agents Chemother 2001;45:1693–9.
[14] Jacobs MR, Bajaksouzian S, Zilles A, et al. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. Surveillance study. Antimicrob Agents Chemother 1999;43:1901–8.
[15] Peric M, Bozdogan B, Jacobs MR, et al. Effects of an efflux mechanism and ribosomal mutations on macrolide susceptibility of *Haemophilus influenzae* clinical isolates. Antimicrob Agents Chemother 2003;47:1017–22.
[16] Brook I. Antibiotic resistance of oral anaerobic bacteria and their effect on the management of upper respiratory tract and head and neck infections. Semin Respir Infect 2002;17: 195–203.
[17] Hecht DW. Antibiotic resistance, clinical significance, and the role of susceptibility testing. Anaerobe 2006;12:115–21.
[18] Lindbaek M. Acute sinusitis: guide to selection of antibacterial therapy. Drugs 2004;64: 805–19.
[19] Brook I, Foote PA, Hausfeld JN. Eradication of pathogens from the nasopharynx after therapy of acute maxillary sinusitis with low- or high-dose amoxicillin/clavulanic acid. Int J Antimicrob Agents 2005;26:416–9.
[20] Brook I. The role of beta-lactamase producing bacteria and bacterial interference in streptococcal tonsillitis. Int J Antimicrob Agents 2001;17:439–42.
[21] Verklin RM, Mandell GL. Alteration of antibiotics by anaerobiosis. J Lab Clin Med 1977; 89:65–72.
[22] Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996;15:255–9.

[23] Vogelman B, Gudmundsson S, Leggett J, et al. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 1988;158: 831–47.
[24] Craig W. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.
[25] Maglio D, Nicolau DP. The integration of pharmacokinetics and pathogen susceptibility data in the design of rational dosing regimens. Methods Find Exp Clin Pharmacol 2004; 26:781–8.
[26] Leach A, Shelby-James T, Mayo M, et al. A prospective study of the impact of community-based arithromycin treatment of trachoma on carriage and resistance of *Streptococcus pneumoniae*. Clin Infect Dis 1997;24:356–62.
[27] Doern GV. Macrolide and ketolide resistance with *Streptococcus pneumoniae*. Med Clin North Am 2006;90:1109–24.
[28] Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155:93–9.
[29] Lister PD, Sanders CC. Pharmacodynamics of moxifloxacin, levofloxacin, and sparfloxacin against *Streptococcus pneumoniae*. J Antimicrob Chemother 2001;47:811–8.
[30] Forrest A, Nix D, Ballow C. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073–81.
[31] Lacy MK, Lu W, Xu X, et al. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin *against Streptococcus pneumoniae* in an in vitro model of infection. Antimicrob Agents Chemother 1999;43:672–7.
[32] Stass H, Dalhoff A. The integrated use of pharmacokinetic and pharmacodynamic models for the definition of breakpoints. Infection 2005;33(Suppl 2):29–35.
[33] Jacobs MR, Bajaksouzian S, Windau A, et al. Effects of various test media on the activities of 21 antimicrobial agents against *Haemophilus influenzae*. J Clin Microbiol 2002;40: 2369–76.
[34] Doern GV. Activity of oral β-lactam antimicrobial agents versus respiratory tract isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the era of antibiotic resistance. Otolaryngol Head Neck Surg 2002;127:S17–23.
[35] Steele RW, Thomas MP, Begue RE. Compliance issues related to the selection of antibiotic suspensions for children. Pediatr Infect Dis J 2001;20:1–5.
[36] Mattoes HM, Kuti JL, Drusano GL, et al. Optimizing antimicrobial pharmacodynamics: dosage strategies for meropenem. Clin Ther 2004;26:1187–98.
[37] Kuti JL, Nightingale CH, Nicolau DP. Optimizing pharmacodynamic target attainment using the MYSTIC antibiogram: data collected in North America in 2002. Antimicrob Agents Chemother 2004;48:2464–70.
[38] Dagan R, Leibovitz E, Fliss DM, et al. Bacteriologic efficacies of oral azithromycin and oral cefaclor in treatment of acute otitis media in infants and young children. Antimicrob Agents Chemother 2000;44:43–50.
[39] Doern GV. Antimicrobial use and emergence of antimicrobial resistance with *Streptococcus pneumoniae* in the United States. Clin Infect Dis 2001;33(Suppl 3):S187–92.
[40] Christianson J, Andes DR, Craig WA. Pharmacodynamic characteristics of clindamycin against *Streptococcus pneumoniae* in a murine thigh-infection model [abstract A-1100]. Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago (IL), December 16–19, 2001.
[41] Craig WA. Does the dose matter? Clin Infect Dis 2001;33(Suppl 3):S233–7.
[42] Ambrose P, Owens R. New antibiotics in pulmonary critical care medicine; focus on advanced generation quinolones and cephalosporins. Semin Respir Crit Care Med 2002;21: 19–32.
[43] Doern GV, Heilmann KP, Huynh HK, et al. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including

a comparison of resistance rates since 1994–1995. Antimicrob Agents Chemother 2001;45: 1721–9.
[44] Loesche WJ, Syed SA, Laughon BE, et al. The bacteriology of acute necrotizing ulcerative gingivitis. J Periodontol 1982;53:223–30.
[45] Socransky SS, Haffajee AD. Evidence of bacterial etiology: a historical perspective. Periodontol 2000, 1994;5:7–25.
[46] Shinn DL. Vincent's disease and its treatment. In: Finegold SM, editor. Metronidazole. Bridgewater (NJ): Excerpta Medica; 1977. p. 307–8.
[47] Brook I, Douma M. Antimicrobial therapy guide for the dentist. Newton (PA): Handbooks in Healthcare Co.; 2004.
[48] Darby I, Curtis M. Microbiology of periodontal disease in children and young adults. Periodontol 2000, 2001;26:33–53.
[49] Loesche WJ. Rationale for the use of antimicrobial agents in periodontal disease. Int J Technol Assess Health Care 1990;6:403–17.
[50] Heimdahl A, Von-Konow L, Nord CE. Isolation of beta-lactamase producing *Bacteroides* strains associated with clinical failures with penicillin treatment of human orofacial infections. Arch Oral Biol 1980;25:689–92.
[51] Loesche WJ, Giordano JR. Treatment paradigms in periodontal disease. Compend Contin Educ Dent 1997;18:221–32.
[52] Pichichero ME, Pichichero CL. Persistent otitis media: causative pathogen. Pediatr Infect Dis J 1995;14:178–83.
[53] Leibovitz E, Raiz S, Piglansky L, et al. Resistance pattern of middle ear fluid isolates in acute otitis media recently treated with antibiotics. Pediatr Infect Dis J 1998;17:463–9.
[54] Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. Pediatr Infect Dis J 2004;23:824–8.
[55] Heikkinen T, Thint M, Chonmaitree T. Prevalence of various respiratory viruses in the middle ear during acute otitis media. N Engl J Med 1999;340:260–4.
[56] Brook I, Anthony BV, Finegold SM. Aerobic and anaerobic bacteriology of acute otitis media in children. J Pediatr 1978;92:13–5.
[57] Brook I, Yocum P, Shah K, et al. The aerobic and anaerobic bacteriology of serous otitis media. Am J Otolaryngol 1983;4:389–92.
[58] Brook I, Frazier EH. Microbial dynamics of persistent purulent otitis media in children. J Pediatr 1996;128:237–40.
[59] American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics 2004;113:1451–65.
[60] Brook I. Prevalence of beta-lactamase-producing bacteria in chronic suppurative otitis media. Am J Dis Child 1985;139:280–4.
[61] Clinical practice guidelines: management of sinusitis. Pediatrics 2001;108:798–807.
[62] Niv A, Nash M, Peiser J, et al. Outpatient management of acute mastoiditis with periosteitis in children. International Journal of Pediatric Otorhinolaryngology 1998;46:9–13.
[63] Brook I. Aerobic and anaerobic bacteriology of chronic mastoiditis in children. Am J Dis Child 1981;135:478–9.
[64] Gwaltney JM Jr, Scheld WM, Sande MA, et al. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90: 457–62.
[65] Wald ER, Milmore GJ, Bowen AD, et al. Acute maxillary sinusitis in children. N Engl J Med 1981;304:749–54.
[66] Brook I, Foote PA, Hausfeld JN. Frequency of recovery of pathogens causing acute maxillary sinusitis in adults before and after introduction of vaccination of children with the 7-valent pneumococcal vaccine. J Med Microbiol 2006;55:943–6.
[67] Nord CE. The role of anaerobic bacteria in recurrent episodes of sinusitis and tonsillitis. Clin Infect Dis 1995;20:1512–24.

[68] Brook I. Microbiology of acute and chronic maxillary sinusitis associated with an odontogenic origin. Laryngoscope 2005;115:823–5.
[69] Decker CF. Sinusitis in the immunocompromised host. Curr Infect Dis Rep 1999;1:27–32.
[70] Brook I. Management of chronic suppurative otitis media: superiority of therapy effective against anaerobic bacteria. Pediatr Infect Dis J 1994;13:188–93.
[71] Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head and Neck Surg 2004;130(Suppl 1):1S–45S.
[72] Gordts F, Halewyck S, Pierard D, et al. Microbiology of the middle meatus: a comparison between normal adults and children. J Laryngol Otol 2000;14:184–8.
[73] Brook I. Bacteriology of acute and chronic ethmoid sinusitis. J Clin Microbiol 2005;43: 3479–80.
[74] Brook I. Bacteriology of acute and chronic frontal sinusitis. Arch Otolaryngol Head Neck Surg 2002;128:583–5.
[75] Brook I, Foote PA, Frazier EH. Microbiology of acute exacerbation of chronic sinusitis. Ann Otol Rhinol Laryngol 2005;114:573–6.
[76] Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxillary sinusitis. J Med Microbiol 1996;45:372–5.
[77] Brook I. The role of anaerobic bacteria in tonsillitis. Int J Pediatr Otorhinolaryngol 2005; 69:9–19.
[78] Brook I. Aerobic and anaerobic microbiology of peritonsillar abscess in children. Acta Paediatr Scand 1981;70:831–5.
[79] Brook I. Aerobic and anaerobic bacteriology of cervical adenitis in children. Clin Pediatr 1980;19:693–6.
[80] Brook I, Yocum P. Comparison of the microbiology of group A streptococcal and non-group A streptococcal tonsillitis. Ann Otol Rhinol Laryngol 1988;97:243–6.
[81] Brook I, Gober AE. Treatment of non-streptococcal tonsillitis with metronidazole. Int J Pediatr Otorhinolaryngol 2005;69:65–8.
[82] Brook I, Foote PA Jr, Slots J, et al. Immune response to *Prevotella intermedia* in patients with recurrent non-streptococcal tonsillitis. Ann Otol Rhinol Laryngol 1993;102:113–6.
[83] Brook I, Foote PA, Slots J. Immune response to *Fusobacterium nucleatum* and *Prevotella intermedia* in patients with peritonsillar cellulitis and abscess. Clin Infect Dis 1995;20:S220–1.
[84] Kaplan EL, Johnson DR. Unexplained reduced microbiological efficacy of intramuscular benzathine penicillin G and of oral penicillin V in eradication of group A streptococci from children with acute pharyngitis. Pediatrics 2001;108:1180–6.
[85] Brook I. The role of bacterial interference in otitis, sinusitis and tonsillitis. Otolaryngol Head Neck Surg 2005;133:139–46.
[86] Brook I, Gober AE. Increased recovery of *Moraxella catarrhalis* and *Haemophilus influenzae* in association with group A beta-haemolytic streptococci in healthy children and those with pharyngo-tonsillitis. J Med Microbiol 2006;55:989–92.
[87] Bisno AL, Gerber MA, Gwaltney JM Jr, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Disease Scoeity of America. Clin Infect Dis 2002;35:113–25.
[88] Colakoglu S, Alacam R, Hascelik G. Prevalence and mechanisms of macrolide resistance in Streptococcus pyogenes in Ankara, Turkey. Scand J Infect Dis 2006;38:456–9.
[89] Richter SS, Heilmann KP, Beekmann SE, et al. Macrolide-resistant *Streptococcus pyogenes* in the United States, 2002-2003. Clin Infect Dis 2005;41:599–608.
[90] Casey JR, Pichichero ME. Meta-analysis of cephalosporins versus penicillin for treatment of group A strepharyngo-tonsillitisococcal tonsillopharyngitis in adults. Clin Infect Dis 2004;38:1526–34.
[91] Brook I. Antibacterial therapy for acute group a streptococcal pharyngotonsillitis: short-course versus traditional 10-day oral regimens. Paediatr Drugs 2002;4:747–54.
[92] Khayr W, Taepke J. Management of peritonsillar abscess: needle aspiration versus incision and drainage versus tonsillectomy. Am J Ther 2005;12:344–50.

[93] Brook I. Microbiology of abscesses of the head and neck in children. Ann Otol Rhinol Laryngol 1987;96:429–33.
[94] Asmar BI. Bacteriology of retropharyngeal abscess in children. Pediatr Infect Dis J 1990;9: 595–6.
[95] Hughes CE, Spear RK, Shinabarger CE, et al. Septic pulmonary emboli complicating mastoiditis: Lemierre's syndrome. Clin Infect Dis 1994;18:633–5.
[96] Brook I. Aerobic and anaerobic microbiology of suppurative sialadenitis. J Med Microbiol 2002;51:526–9.
[97] Brook I. Acute bacterial suppurative parotitis: microbiology and management. J Craniofac Surg 2003;14:37–40.
[98] Shah SS, Baum SB. Infectious thyroiditis: diagnosis and management. Curr Infect Dis Rep 2000;2:147–53.
[99] Jeng LB, Lin JD, Chen MF. Acute suppurative thyroiditis: a ten year review in a Taiwanese hospital. Scand J Infect Dis 1994;26:297–300.
[100] Peters TR, Edwards KM. Cervical lymphadenopathy and adenitis. Pediatr Rev 2000;21: 399–405.
[101] Brook I, Frazier EH. Microbiology of cervical lymphadenitis in adults. Acta Otolaryngol 1998;118:443–6.
[102] Hazra R, Robson CD, Perez-Atayde AR, et al. Lymphadenitis due to nontuberculous mycobacteria in children: presentation and response to therapy. Clin Infect Dis 1999;28:123–9.
[103] Brook I. Microbiology of infected epidermal cysts. Arch Dermatol 1989;125:1658–61.
[104] Lemierre A. On certain septicemias due to anaerobic organisms. Lancet 1936;2:701–3.
[105] Brook I, Hirokawa R. Post surgical wound infection after head and neck cancer surgery. Ann Otol Rhinol Laryngol 1989;98:322–5.
[106] Fraioli R, Johnson JT. Prevention and treatment of postsurgical head and neck infections. Curr Infect Dis Rep 2004;6:172–80.