2 Antibiotic-Resistant Pathogens in Ear, Nose, and Throat Infections

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Introduction

The management of ear, nose, and throat (ENT) infections requires an accurate clinical and bacteriological diagnosis, followed by an initial empiric antimicrobial therapy that may be adjusted once the identification of the causative organism(s) is available. The increasing antimicrobial resistance of many respiratory tract bacterial pathogens has made the treatment of these infections more challenging [1, 2].

The microflora of the upper airways, including the oral cavity, nasopharynx, and oropharynx, is complex and contains many types of aerobic, facultative, and obligate anaerobic bacteria [3]. The ratio of anaerobic to aerobic bacteria in saliva is approximately 10:1. The total count of anaerobes in the saliva and elsewhere in the oral cavity reaches 10^7–10^8 bacteria/ml.

Table 2.1 lists the major pathogens that cause various ENT infections. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the predominant aerobic pathogens recovered in acute respiratory tract infections. Their resistance to antimicrobials has significantly increased in the past 30 years. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and endogenous oropharyngeal anaerobes are commonly recovered in chronic head and neck infections, some of which can be life-threatening [4]. Because anaerobes are difficult to isolate, they are often overlooked. Furthermore, their exact role is difficult to ascertain from many past reports because of the inconsistent methodologies used for their isolation and identification in many of these studies [5, 6]. Isolation and identification of anaerobes require appropriate methods of collection, transportation, and cultivation of specimens. Treatment of anaerobic infections is complicated by their polymicrobial nature and the growing antimicrobial resistance and slow growth of these bacteria [5, 6].

Antibiotic Resistance Mechanisms

Antibiotics are naturally produced by many bacteria and fungi, and antibiotic-producing microbes are resistant to the antibiotics they produce. Antibiotic resistance therefore preceded the advent of antibiotics by many millennia. Antibiotic resistance genes have been found within bacteria contained in samples of 30,000-year-old permafrost. Selective pressure by human use of antibiotics over the past 80 years has led to rapid expansion in antibiotic resistance in clinically important pathogens. Multidrug-resistant organisms,

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Table 2.1 Some of the aerobic and anaerobic bacteria isolated in upper respiratory tract and head and neck infections

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Otitis media: acute	*Streptococcus pneumoniae*	*Peptostreptococcus* spp.
	Haemophilus influenzae[a]	
	Moraxella catarrhalis[a]	
Otitis media: chronic, and Mastoiditis	*Staphylococcus aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.
	Escherichia coli[a]	*Bacteroides* spp.[a]
	Klebsiella pneumoniae[a]	*Fusobacterium* spp.[a]
	Pseudomonas aeruginosa[a]	*Peptostreptococcus* spp.
Peritonsillar and retropharyngeal abscess	*Streptococcus pyogenes*	*Fusobacterium* spp.[a]
	S. aureus[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	S. pneumoniae	
Recurrent tonsillitis	*S. pyogenes*	*Fusobacterium* spp.[a]
	H. influenzae[a]	
	S. aureus[a]	
Suppurative thyroiditis	*S. pyogenes*	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	S. aureus[a]	
Sinusitis: acute	*H. influenzae*[a]	*Peptostreptococcus* spp.
	S. pneumoniae	
	M. catarrhalis[a]	
Sinusitis: chronic	*S. aureus*[a]	*Fusobacterium* spp.[a]
	S. pneumoniae	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	H. influenzae	
Cervical lymphadenitis	*S. aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Mycobacterium spp.	*Peptostreptococcus* spp.
Postoperative infection disrupting oral mucosa	*Staphylococcus* spp.[a]	*Fusobacterium* spp.[a]
	Streptococcus spp.[a]	*Bacteroides* spp.[a]
	Enterobacteriaceae[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Pseudomonas[a]	*Peptostreptococcus* spp.
Deep neck space	*Streptococcus* spp.[a]	*Bacteroides* spp.[a]
	Staphylococcus spp.[a]	*Fusobacterium* spp.[a]
		Peptostreptococcus spp.
Odontogenic complications	*Streptococcus* spp.[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Staphylococcus spp.[a]	*Peptostreptococcus* spp.
Oropharyngeal: Vincent's angina	*Streptococcus* spp.[a]	*Fusobacterium necrophorum*[a]
Necrotizing ulcerative gingivitis	*Staphylococcus* spp.[a]	*Spirochetes*, *Prevotella Intermedia*, *Fusobacterium* spp[a]

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

defined as those organisms with resistance to one or more classes of antibiotics, are now prevalent.

Bacteria can be genetically resistant to an antibiotic or acquire resistance through mutation or acquisition of foreign DNA (e.g., uptake of naked DNA left by dying bacteria, or acquisition of a plasmid carrying resistance genes). Plasmids, small circular strands of DNA that replicate independently of chromosomes, are commonly found in bacteria. Plasmids can be transferred from one bacterium to another in several ways, including during bacterial conjugation and via a bacterial

virus (bacteriophage). Resistance genes may be continuously expressed ("constitutive"), or expressed only when needed ("inducible"). Resistance usually costs the bacterium energy so inducible resistance is more common.

Bacteria have several mechanisms of resistance (Table 2.2). These include permeability barriers, inactivating enyzmes, target site alteration, overproduction of the target, and efflux mechanisms. An example of a permeability barrier is that of Gram-negative bacilli to penicillin. Gram-negative bacilli have a lipopolysaccharide outer membrane that envelops the cell wall. This outer membrane is absent in Gram-positive bacteria. The outer membrane is hydrophobic, and hydrophilic antibiotics such as nafcillin do not penetrate. Hydrophilic antibiotics may penetrate the outer membrane through their porins (permeability channels), but loss of favorable porins will lead to resistance. This may occur during imipenem treatment of *Pseudomonas*, for example. Another common mechanism is alteration of the target site of the antibiotic. Penicillin acts by attaching to penicillin binding protein (PBP), a bacterial enzyme that is used in cell wall synthesis. *Staphylococcus aureus* can acquire a gene (*mecA*) which encodes for an altered PBP (PBP2a) that does not bind penicillin. Acquisition of the *mecA* gene by *S. aureus* results in MRSA (methicillin-resistant *S. aureus*), a bacterial species resistant to all beta-lactams except fifth generation cephalosporins.

Table 2.2 Some common mechanisms of bacterial resistance and examples of antibiotics affected

Mechanism	Example
Permeability barrier to antibiotic	Outer membrane of Gram-negative bacteria serves as a barrier to nafcillin
Enzymatic inactivation of antibiotic	Beta-lactamases (e.g., *Staphylococcus aureus* inactivation of penicillin by a beta-lactamase)
Alteration of target site for the antibiotic	(1) Alteration of the bacterial enzyme, penicillin binding protein, in MRSA so that penicillin cannot bind (2) Alteration of the ribosomal target site by methylation so erythromycin or clindamycin cannot bind
Overproduction of the target	Overproduction of the target bacterial enzyme (dihydropteroate synthase) involved in folate production
Efflux pumps to pump antibiotic out of cell	Efflux of tetracycline by some Gram-negative bacilli, resulting in low intracellular concentrations

MRSA methicillin-resistant *Staphylococcus aureus*

Beta-Lactamase Production

A major resistance mechanism is inactivation of the antibiotic by a bacterial enzyme. Beta-lactamases are the most important examples of such enzymes, and these include penicillinases, cephalosporinases, carbapenemases. Some are produced by the bacterial chromosome and some by a plasmid within the bacterium. Beta-lactam antibiotics have a four-member beta-lactam ring, and beta-lactamases hydrolyze this ring, rendering the antibiotic ineffective (Fig. 2.1).

Beta-lactamase production is an important mechanism of antimicrobial resistance of both aerobic bacteria (e.g., *Staphylococcus aureus*, *H. influenzae*, and *M. catarrhalis*), and anaerobic Gram-negative bacilli (e.g., pigmented *Prevotella* and *Porphyromonas*). Beta-lactamase-producing bacteria can play an important role in respiratory infections [7]. They can cause the infection as well as have an indirect effect through their ability to produce the beta-lactamase [8]. These bacteria may not only survive penicillin therapy but can also, as was demonstrated in vitro [9], in vivo [10, 11], and in clinical [12] studies, protect other penicillin-susceptible bacteria from penicillin by releasing the free enzyme into their environment [8].

Aerobic Bacteria

Haemophilus influenzae

About 40% of *H. influenzae* resist beta-lactam antimicrobials through production of beta-lactamases. Increased prevalence of nontypeable *H. influenzae* strains that resist ampicillin and/or other beta-lactams was noted in the

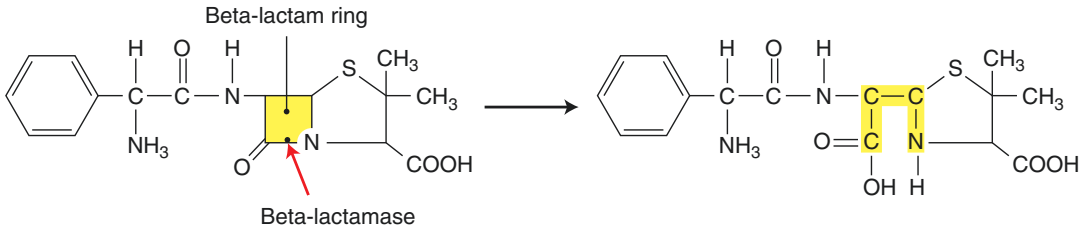

Fig. 2.1 Inactivation of ampicillin by beta-lactamase. The red arrow points to the chemical bond that is hydrolyzed by beta-lactamase

past decade [13]. Ampicillin resistance is usually due to plasmid-mediated production of beta-lactamase so it can be overcome by beta-lactam, beta-lactamase inhibitor combination antibiotics (e.g., amoxicillin-clavulinate). However, *H. influenzae* resistance to beta-lactams has expanded to include production of an altered penicillin binding protein (PBP3) [14]. This type of resistance cannot be overcome by a beta-lactamase inhibitor, so amoxicillin-clavulinate and similar antibiotics will be ineffective. The frequency of non-beta-lactamase resistance in *H. influenzae* has increased. In a retrospective study that evaluated 465 *H. influenzae* isolates from the blood or cerebrospinal fluid from patients in Sweden between 1997 and 2010, a significant increase in beta-lactam–resistant isolates was observed over the course of the study period. Ninety-one isolates (20%) were resistant to one or more beta-lactam antibiotics (including penicillin, ampicillin, a cephalosporin, or a carbapenem), and nearly half of the resistant bacteria were beta-lactamase-negative [15].

Beta-lactamase–negative, ampicillin-resistant *H. influenzae* strains are being recovered in greater frequency worldwide. The prevalence of such strains has increased in Japan (by 34%) [16], Spain (by 56%) [17], and in other parts of Europe and Canada [18]. Prevalence in the U.S. has remained low (3%) [19]. Possible explanations for this discrepancy include inadequate vaccination against *H. influenzae* type b in some regions, increased use of cephalosporins, and underdosing of ampicillin [16, 17]. These types of ampicillin-resistant, beta-lactamase-negative *H. influenzae* strains are still susceptible to ceftriaxone [20], which may be a good choice for treatment of clinical infections due to these organisms.

Moraxella catarrhalis

Over 90% of *M. catarrhalis* produce a beta-lactamase and are therefore resistant to ampicillin. Nearly all strains express beta-lactamase from a chromosomal locus. Three types of beta-lactamases, BRO-1, BRO-2, and BRO-3, that are inducible and intracellular were identified and characterized [21]. *Moraxella catarrhalis* acquired beta-lactamase in the 1970s and the 1980s, and its antimicrobial susceptibility has remained relatively stable. However, recent macrolide and tetracycline-resistant strains were recovered from the Asia Pacific region and China [22].

The oral antibiotics that are active against *M. catarrhalis* as well as *H. influenzae* are amoxicillin-clavulanate, fluoroquinolones, extended-spectrum cephalosporins, newer macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), and tetracyclines. Parenteral antimicrobials effective against these organisms include second and third-generation cephalosporins, aminoglycocides, ticarcillin, and piperacillin. The *M. catarrhalis* strains are resistant to penicillin, ampicillin, and clindamycin [23].

Streptococcus pneumoniae

Resistance of pneumococci to many antimicrobials has increased in the past two decades [23]. Pneumococcal resistance has increased to beta-lactams (penicillins, cephalosporins, and carbapenems), macrolides (erythromycin, azithromycin, clarithromycin), lincosamides (clindamycin), tetracyclines, folate inhibitors (TMP-SMX), and fluoroquinolones (ciprofloxacin, levofloxacin, gemifloxacin, and moxifloxacin). Most

strains of penicillin-resistant *S. pneumoniae* are also resistant to other antimicrobials. Resistance to antimicrobials is determined genetically. The resistance to beta-lactam antimicrobials is through changes in penicillin binding proteins, to chloramphenicol through inactivating enzymes, and to fluoroquinolones through decreased drug permeability [24]. Macrolide resistance is due to efflux pump, and binding blockage. The latter mechanism also blocks clindamycin. There is no resistance to vancomycin or linezolid. Although vancomycin resistance is not known in *S. pneumoniae*, the phenomenon of vancomycin tolerance has been observed in a few strains [25]. Risk factors for the acquisition of antibiotic-resistant pneumococcal strains include recent antibiotic use; previous time spent in daycare (for children), in an institutional setting, or a shelter for the homeless (for adults); and recent respiratory infections [26–28].

The affinity of beta-lactams for one or more of the penicillin binding proteins is lowered in pneumococcal strains that have reduced susceptibility to penicillins [29]. Decreased susceptibility of pneumococci to beta-lactams can frequently be overcome with higher doses of penicillins, cephalosporins, and carbapenems. Whether in-vitro resistance to macrolides [30] or the fluoroquinolones [31] can be overcome by increased doses is controversial. Resistance to folate inhibitors or tetracyclines cannot be overcome by increasing the antibiotic dose [32]. Non-susceptible isolates are divided into intermediate and resistant strains. The penicillin breakpoints for non-meningitis pneumococcal infections are: susceptible minimum inhibitory concentration (MIC) ≤2 mcg/mL, intermediate (MIC = 4 mcg/mL), and resistant (MIC ≥8 mcg/mL) [33]. For meningitis, the penicillin breakpoints are much lower and there is no intermediate category: susceptible MIC ≤ 0.06 mcg/mL, resistant MIC ≥ 0.12 mcg/mL.

There has been a recent decrease in penicillin-resistant pneumococcal strains. This is probably due to both the change in definition of resistance and the widespread use of pneumococcal conjugate vaccine, which has greatly reduced the prevalence of resistant strains in the population. Among isolates obtained in the U.S. from normally sterile sites such as blood culture, pleural fluid, and cerebrospinal fluid (CSF), 95.5% were found to be susceptible, 2.5% intermediate, and 2.2% resistant [34].

Staphylococcus aureus

Staphylococcus aureus can resist beta-lactam antimicrobials through the production of beta-lactamase. It can also resist methicillin which is defined as an oxacillin MIC ≥ 4 mcg/mL Isolates resistant to oxacillin or methicillin also resist all beta-lactam agents, including cephalosporins (with the exception of the fifth-generation cephalosporins, ceftobiprole and ceftaroline).

The prevalence of infection and colonization with MRSA is increasing [35] in all infections including head and neck. A 16.3% increase in the rate of pediatric *S. aureus* head and neck infections occurred between 2001 and 2006 in a study of 21,009 patients [36]. The highest rate of MRSA infections was in otological (34%), followed by sinonasal (28.3%), and oropharynx/neck (14.2%) infections. The association between previous antimicrobial use and increased isolation of MRSA was noticed in various infections [37, 38], including sinusitis [39, 40]. Brook et al. [39] and Gerencer [40] found that most patients with chronic sinusitis due to MRSA, who were previously treated with antimicrobials, had been treated with either a fluoroquinolone or macrolides.

Methicillin resistance is mediated by the mecA gene that encodes for low-affinity penicillin binding protein, PBP2a. This gene is located on a mobile genetic element called staphylococcal cassette chromosome (SCCmec). Most MRSA strains isolated during the 1960s originated most likely from a single clone; by 2002, five major MRSA clones emerged throughout the globe [41].

Oral Antibiotics Active Against MRSA. Oral antibiotics that can be used for the treatment of MRSA infections include clindamycin, TMX-SMT, tetracyclines (such as doxycycline or minocycline), and linezolid. Because resistance to these agents is rising, their use should be supported by susceptibility testing whenever

possible and by clinical response. Clindamycin inhibits bacterial production of toxins, including Panton-Valentine leukocidin and other virulence factors, and has excellent tissue, bone, and abscess penetration [42]. The agent should not be administered empirically when local MRSA resistance rates to clindamycin are >15% [43]. Clindamycin-susceptible isolates that are resistant to erythromycin may become resistant to clindamycin in its presence [44]. Inducible clindamycin resistance can be detected with D testing in the microbiology laboratory [45]. Trimethoprim-sulfamethoxazole and tetracyclines are not advisable for empiric management of infections that may be due to group A streptococci. Resistance of MRSA to fluoroquinolones may emerge during therapy [46]. Oxazolidinones (linezolid or tedizolid) are effective for the treatment of MRSA-related head and neck infections [47]. Their use is limited by cost and toxicity.

Parenteral Agents Active Against MRSA. Parental agents for treating MRSA infections include vancomycin, daptomycin, linezolid, ceftaroline, telavancin, dalbavancin, oritavancin, tedizolid, tigecycline, teicoplanin, and quinupristin-dalfopristin. Some of these are limited by toxicity concerns, as discussed in Chap. 1. The greatest cumulative clinical experience for the treatment of MRSA infections is with the glycopeptide vancomycin. It is still an important agent for treating these infections despite the overall decrease in the in-vitro susceptibility. Its tissue penetration is variable and increases with inflammation. Daptomycin, a cyclic lipopeptide, is inhibited by pulmonary surfactant and should not be used for the treatment of MRSA pneumonia [48]. Previous exposure to vancomycin can increase resistance to daptomycin [49]. Linezolid, a synthetic oxazolidinone, has excellent tissue distribution, and inhibits toxin production [50]. Linezolid resistance has emerged among MRSA isolates, mostly in healthcare associated strains. The mechanism of resistance is via the bacterial cfr gene located in a potentially mobile genetic element [51]. Linezolid use is limited because of safety concerns, including thrombocytopenia, anemia, lactic acidosis, peripheral neuropathy, serotonin toxicity, and ocular toxicity (rare cases of optic neuropathy with treatment beyond 2 weeks).

Ceftaroline, a fifth-generation cephalosporin, is active against Gram-positive organisms (including MRSA, vancomycin-intermediate *S. aureus*) as well as Gram-negative pathogens (including *Enterobacteriaceae* but not *Pseudomonas* species or extended-spectrum beta-lactamase producers) [52]. Telavancin, a semisynthetic lipoglycopeptide, has a half-life of 7–9 h, allowing once-daily dosing. Oritavancin, a semisynthetic glycopeptide, has a half-life of 100 h. Dalbavancin, a semisynthetic lipoglycopeptide, has a half-life of 6–12 days, permitting once-weekly dosing. Teicoplanin, a glycopeptide, can be administered once daily. Quinupristin-dalfopristin, a streptogramin, use is limited by adverse effects (e.g., hyperbilirubinemia, myalgias, arthralgias, and nausea). Tigecycline, a glycylcycline, is active in-vitro against many Gram-positive cocci (including MRSA, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*), aerobic and facultative Gram-negative bacilli (except *Pseudomonas* and *Proteus* spp.), anaerobes, and atypical bacteria. However, the U.S. Food and Drug Administration (FDA) issued "boxed warnings" in 2011 and 2013 because of increased risk of death in patients treated with tigecycline compared with other antibiotics.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is commonly found in chronic otitis media and external otitis [53, 54]. *Pseudomonas* possesses intrinsic resistance to several antimicrobials and can attain resistance during therapy. Some strains are highly drug-resistant, resisting three or more classes of antibiotics [55]. Only a small number of antimicrobials possess reliable efficacy against *P. aeruginosa*. These include some penicillins (ticarcillin-clavulanate, piperacillin-tazobactam), cephalosporins (ceftazidime, cefepime, cefoperazone), monobactams (aztreonam), fluoroquinolones (ciprofloxacin, levofloxacin), carbapemens (imipenem, meropenem, doripenem), aminoglycosides (gentamicin, tobramycin, amikacin), and

polymixins (colistin, polymyxin B). All of these antimicrobials are administered parentally except for the fluoroquinolones that can be given also orally [56]. Monobactams require higher dosing. Aminoglycosides are generally not used as single agents because of inadequate clinical efficacy. Polymixins are administered only in the setting of resistance to other antimicrobials because of their toxicity. A combination of anti-*Pseudomonas* antimicrobials can be administered for serious infections due to *P. aeruginosa* [57].

Anaerobic Bacteria

Anaerobic bacteria predominate in the oropharyngeal mucous membranes, and are therefore a common cause of bacterial infections of endogenous origin of upper respiratory tract and head and neck [5, 6]. These infections include chronic otitis media, mastoiditis and sinusitis, pharyngotonsillitis, peritonsillar, retropharyngeal and parapharyngeal abscesses, suppurative thyroiditis, cervical lymphadenitis, parotitis, siliadenitis, and deep neck infections including Lemierre's Syndrome. The recovery from these infections depends on prompt and proper medical and when indicated also surgical management. Because anaerobes generally are isolated mixed with aerobic bacteria, the antimicrobial(s) used should cover these organisms.

The most effective antimicrobials against anaerobic organisms are: metronidazole, the carbapenems (imipenem, meropenem, dorapenem, ertapenem), chloramphenicol, the combinations of a penicillin and a beta-lactamase inhibitor (e.g., amoxicillin plus clavulinate, ampicillin plus sulbactam, ticarcillin plus clavulanate, piperacillin plus tazobactam), tigecycline, cefoxitin and clindamycin. Table 2.3 lists the susceptibility of various anaerobes to antimicrobial agents.

Beta-Lactams and Anaerobes

Penicillins. Penicillin is used when the infecting strains are susceptible. Most *Clostridium* strains and *Peptostreptococcus* spp. are susceptible to penicillin. *Bacillus fragilis* group anaerobes are resistant to penicillin. Other strains that may show penicillin resistance are growing numbers of anaerobic Gram-negative bacilli commonly found in head and neck infections (e.g., pigmented *Prevotella* and *Porphyromonas* spp.,

Table 2.3 Susceptibility of common anaerobes to various antibiotics (includes intermediate resistant strains) [58, 74, 80, 108]

Anaerobe	Ampicillin-sulbactam (%)	Amoxicililin-clavulinate (%)	Piperacillin-tazobactam (%)	Clindamycin (%)	Moxifloxacin (%)	Imipenem (%)
Anaerobic Gram-positive cocci[a]	100	94–100	97–100	73–95	64–97	100
Clostridium species	100	95–100	100	75–84	47–93	85
Fusobacterium species		89–100	100	69–82	75–90	96
Prevotella species	100	81–100	≥99	67–87	58–89	94–100
Bacteroides fragilis[b]	89–97	63–96	95–100	58–90	59–90	93–99.7
Bacteroides thetaiotaomicron[b]	85–95	63–88	88–100	40–60	25–87	93–100
Bacteroides fragilis group[b]		80–90	92–100	48–68	43–86	≥99

Susceptibility breakpoints (MIC μg/ml), *S* = susceptible, *R* = resistant: ampicillin-sulbactam ($S \leq 8/4$, $R \geq 32/16$); amoxicillin-clavulinate ($S \leq 4/2$, $R \geq 16/8$); piperacillin-tazobactam ($S \leq 32/4$, $R \geq 128/4$); clindamycin ($S \leq 2$, $R \geq 8$); moxifloxacin ($S \leq 2$, $R \geq 8$), imipenem ($S \leq 4$, $R \geq 16$)

Metronidazole is not listed but >99% of anaerobic Gram-negative bacilli are susceptible

[a]Includes *Peptostreptococcus* species and others

[b]These comprise the majority of *Bacteroides* isolates found in infections above the neck [108]

Prevotella oralis, *Prevotella bivia*), *Bacteroides disiens*, strains of clostridia, *Fusobacterium* spp. (*Fusobacterium varium* and *Fusobacterium mortiferum*), and microaerophilic streptococci. Some of these strains show MIC of 8–32 units/mL of penicillin G. In these instances, administration of very high dosages of penicillin G (for non-beta-lactamase producers) may be effective [58]. Ampicillin and amoxicillin have activity equal to penicillin G, but nafcillin or oxacillin are either not active or have unpredictable activity [59]. Penicillin and ampicillin/amoxicillin are of limited utility because of the production of beta-lactamases by many oral anaerobes [59–61], but beta-lactam/beta-lactamase inhibitor combinations are effective. Carboxy-penicillins (carbenicillin, ticarcillin) and ureidopencillins (piperacillin, azlocillin, mezlocillin) generally are administered in large quantities to achieve high serum concentrations [62].

Cephalosporins. Cephalosporins have limited utility because many anaerobes produce cephalosporinases [63]. The activity of cephalosporins against the beta-lactamase-producing anaerobic Gram-negative bacilli varies. The antimicrobial spectrum of the first-generation cephalosporins against anaerobes is similar to penicillin G, although on a weight basis, they are less active. Most strains of the *B. fragilis* group and many *Prevotella*, *Porphyromonas*, and *Fusobacterium* spp. are resistant to these agents [64]. Cephalosporinases have little or no hydrolytic activity for the second-generation cefoxitin (a cephamycin), making it the most effective cephalosporin against the *B. fragilis* group. However, susceptibility to cefoxitin may vary by geographic location and is generally directly related to its clinical use. Cefoxitin is relatively inactive against most species of *Clostridium*, including *Clostridium difficile*, with the exception of *Clostridium perfringens* [64–66]. With the exception of moxalactam (not available in the U.S.), the third-generation cephalosporins are not as active against *B. fragilis* group.

Carbapenems. The carbapenems (imipenem, meropenem, ertapenem, doripenem) have excellent activity against anaerobes [67]. Imipenem is effective against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms including *B. fragilis* group [68, 69] It is also effective against most *Enterobacteriaceae* and about 5–15% of *Pseudomonas* spp. are resistant [70]. To overcome the problem of renal metabolism of imipenem, it is combined at a 1:1 ratio with an inhibitor of the renal dipeptidase, cilastatin. Imipenem is an effective single agent for the therapy of mixed aerobic-anaerobic infections. Meropenem possesses antibacterial activity similar to imipenem. However, it is less active against staphylococci and enterococci, and provides better coverage of aerobic and facultative Gram-negative bacteria [71, 72]. Ertapenem also has a broad antibacterial spectrum [73] but it is not active against *Pseudomonas*, *Enterococcus* spp., and *Acinetobacter* spp. Doripenem has a similar antimicrobial spectrum to meropenem and imipenem [69]. Resistant *P. aeruginosa* mutants appear to be harder to select in vitro with doripenem than with other carbapenems. Doripenem is not FDA-approved to treat pneumonia. Recent reports have noted the emergence of some carbapenem resistance among anaerobes [74] ranging from 1.1% to 2.5% in a multicenter U.S. survey. Higher resistance was noted in a small number of isolates from Taiwan [75].

Resistance of Anaerobes to Beta-Lactam Antibiotics. Anaerobes exhibit three major resistance mechanisms to beta-lactam antibiotics: inactivating enzymes, mainly beta-lactamases, which include penicilliniases and cephalosporinases; low affinity penicillin binding proteins (PBPs); and decreased permeability through alterations in the porin channel [76]. The production of beta-lactamases is the commonest mechanism, especially among the *B. fragilis* group and *Prevotella* spp. [77]. The cephalosporinases are most often of the 2e class type and can be inhibited by three beta-lactamase inhibitors, clavulanic acid, sulbactam, and tazobactam. Each individual cephalosporin may have either a class or specific inhibitor enzyme capable of inactivating it. Carbapenemases are active against the carbapenems as well as all beta-lactam antibiotics.

Carbapenem resistance was found in <1% of U.S. isolates, and up to 3% of *Bacteroides* strains harbor one of the genes that is expressed at a very low level.

With some exceptions among some *Clostridium* spp., strains of *Clostridium*, *Porphyromonas*, and *Fusobacterium* can express resistance through one or more beta-lactamases. Beta-lactamase-producing *Fusobacterium* and *Clostridium* spp. express enzymes that are usually inhibited by clavulanic acid [78]. Resistance to beta-lactam antibiotics through changes in the outer membrane porin channels, decreased PBP affinity, and efflux pumps [79] have not been well studied. *Bacteroides fragilis* group species are generally resistant to penicillins (average 90%), and less often to piperacillin (25%) cefoxitin (25%), cefotetan (30–85%), and third-generation cephalosporins (14–57%) [80, 81].

Beta-lactam/beta-lactamase inhibitor antibiotics and carbapenems have maintained their excellent antibacterial activity against anaerobes, including against members of the *B. fragilis* group [80]. However, species-to-species variation in susceptibility occurs [40]. *Bacteroides fragilis* group resistance rates for piperacillin-tazobactam are generally <1% [82], although one member of the group (*Parabacteroides distasonis*) has relatively high (20%) resistance. The carbapenems are very effective against all the members of the *B. fragilis* group, and resistance is <0.1% [79, 82, 83]. Some members of the *B. fragilis* group have lower MICs for imipenem and meropenem than for ertapenem [80]. Half of *Prevotella* spp. may produce beta-lactamases, causing penicillin resistance, and a multicenter survey [68] also detected penicillin resistance in *Fusobacterium* spp. (9%), *Porphyromonas* spp. (21%), and *Peptostreptococcus* spp. (6%). No resistance was found to cefoxitin, cefotetan, beta-lactam/beta-lactamase combinations, and carbapenems in that survey, with the exception of *Peptostreptococcus* spp. (4%) and *Porphyromonas* spp. (5%). Beta-lactamases were identified in several *Prevotella* and *Porphyromonas* spp. recovered from pediatric intra-abdominal infections [62].

Chloramphenicol and Anaerobes

Chloramphenicol, a bacteriostatic agent, is active against most anaerobic bacteria but is rarely used in the U.S. [6] due to potentially significant toxicity. The risk of fatal aplastic anemia with chloramphenicol is approximately one per 25,000–40,000 patients treated. This complication is unrelated to the reversible, dosage-dependent leukopenia. Other side effects include the production of the potentially fatal "gray baby syndrome" when given to neonates, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and optic neuritis in those who take the agent for a prolonged time. Chloramphenicol has a unique property of lipid solubility that permits penetration across lipid barriers. Levels in the cerebrospinal fluid (CSF), with or without meningitis, usually are one-third to three-fourths the serum concentrations. Levels in brain tissue can be substantially higher than serum levels [83].

Macrolides (Erythromycin, Azithromycin, Clarithromycin) and Anaerobes

The macrolides have moderate to good in vitro activity against anaerobic bacteria other than *B. fragilis* group and fusobacteria [58, 64]. They are active against microaerophilic streptococci, Gram-positive non-spore-forming anaerobic bacilli, and certain clostridia. They are less effective against *Peptostreptococcus* spp. [84]. Macrolides have relatively good activity against *C. perfringens* and poor or inconsistent activity against anaerobic Gram-negative bacilli. Clarithromycin is the most active of the macrolides against Gram-positive oral cavity anaerobes, including *Actinomyces* spp., *Propionibacterium* spp., *Lactobacillus* spp., and *Bifidobacterium dentium*. Azithromycin is slightly less active than erythromycin against these species [84]. Azithromycin is the most active macrolide against *Aggragatibacter actinomycetemcomitans*, including those isolates

resistant to erythromycin. Clarithromycin possess similar activity to erythromycin against most anaerobic Gram-negative bacilli [85]. Emergence of erythromycin-resistant organisms during therapy has been documented [86, 87].

Clindamycin and Anaerobes

Clindamycin has a broad activity against anaerobes, is well absorbed from the gastrointestinal tract [88–90], and rapidly penetrates into most body tissues and fluids [52] although not the central nervous system (CNS). Clindamycin should not be administered in CNS infections. The side effect of most concern is *C. difficile* associated colitis [91]. Because *B. fragilis* resistance to clindamycin is increasing worldwide (over 33%) it is no longer recommended as empiric therapy for intra-abdominal infections [65, 74, 80, 92]. Resistance to clindamycin has also increased for other anaerobes. Up to 10% resistance was noted for *Prevotella*, *Fusobacterium*, *Porphyromonas*, and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (especially *C. difficile*) [68]. Clindamycin has lost some of its activity against anaerobic Gram-positive cocci (i.e., *Finegoldia magna*-30% resistant), and *Prevotella* spp. (*P. bivia*, 70% resistant, *P. oralis* and *Prevotella melaninogenica* both 40% resistant), although its activity against *Fusobacterium* and *Porphyromonas* spp. remains good. Among the other resistant anaerobes are various species of clostridia especially *C. difficile*. About 20% of *Clostridium ramosum* are resistant to clindamycin, as are a smaller number of *C. perfringens*.

Metronidazole and Anaerobes

Metronidazole and tinidazole are nitroimidazoles with similar in vitro activity against anaerobic bacteria. Metronidazole has excellent in vitro efficacy against most obligate anaerobic bacteria, such as *B. fragilis* group, other species of *Bacteroides*, fusobacteria (including *F. necrophorum*, the etiology of Lemierre's Syndrome), other anaerobic Gram-negative bacilli, and clostridia [93]. These agents have excellent penetration into the CNS. Resistance to metronidazole among *B. fragilis* group is uncommon [65, 94]. Resistance of anaerobic Gram-positive cocci is rare and resistance of nonsporulating bacilli is common. Most microaerophilic streptococci, *P. acnes*, and *Actinomyces* spp. are resistant [94]. Aerobic and facultative anaerobes are usually highly resistant. Because of its lack of activity against aerobic bacteria, an antimicrobial effective against these organisms (e.g., a cephalosporin, a fluoroquinolone) needs to be added when treating a polymicrobial infection. Adverse reactions to metronidazole include gastrointestinal side effects, central nervous system toxicity, and peripheral neuropathy. Possible mutagenic activity found in mice given large doses of metronidazole [95] was not confirmed by experiments in rats and hamsters [96], and no evidence of mutagenicity was ever found in humans [97].

Tetracyclines and Anaerobes

The tetracycline analogues, doxycycline and minocycline, are more active than the parent compound [58]. However, because of the significant resistance to these drugs, they are useful only when susceptibility tests show efficacy or in less severe infections in which a therapeutic trial is feasible. The use of tetracyclines is not recommended before 8 years of age because of the adverse effect on teeth; tetracyclines are also contraindicated in pregnancy. Tigecycline is a direct analog of minocycline with broad-spectrum activity including anaerobes and some drug-resistant pathogens [98, 99]. Resistance of members of the *B. fragilis* group varies from 3.3% to 7.2% [100]. As noted above, tigecycline carries an FDA boxed warning about increased mortality rates compared with other treatments for various infections.

Fluoroquinolones and Anaerobes

Of the systemic quinolones available in the U.S. (ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, gemifloxacin), moxifloxacin is the most effective against anaerobes [101]. Quinolones

with the greatest in vitro activity against anaerobes include clinafloxacin and sitafloxacin [102], but these are not available in the U.S. Quinolones' use is restricted in growing children because of possible adverse effects on the cartilage. In addition, in July 2016, the FDA issued a boxed warning on the use of quinolones for less serious infections, such as acute bacterial sinusitis, due to concern for serious and potentially irreversible side effects on "tendons, muscles, joints, nerves, and the central nervous system" [103]. Increasing resistance to quinolones in *B. fragilis* group as well as anaerobic Gram-positive cocci has been reported. *Bacteroides* spp. resistance to fluoroquinolone has been attributed to either an alteration in efflux of the antibiotic or a mutation in gyrase A gene (gyrA) [104]; high-level resistance can be caused by both the mechanisms.

Other Agents Active Against Anaerobes

Bacitracin is active in vitro against pigmented *Prevotella* and *Porphyromonas* spp. but is inactive against *B. fragilis* and *Fusobacterium nucleatum* [58]. Vancomycin and daptomycin are effective against all Gram-positive anaerobes, but are not active against anaerobic Gram-negative bacilli [105]. Quinupristin/dalfopristin exhibits antibacterial activity against *C. perfringens*, *Lactobacillus* spp., and *Peptostreptococcus* spp. [106]. Linezolid is effective against *Fusobacterium* spp. (including *Fusobacterium nucleatum*) and *Porphyromonas*, *Prevotella*, and *Peptostreptococcus* spp. [84, 85]. However, there is little clinical experience in the treatment of anaerobic infections using these agents.

Treating Infections in Otolaryngology

Infections in otolaryngology are often polymicrobial, so antimicrobials effective against both the aerobic and anaerobic components of the infection should be administrated. When such therapy is not given, the infection may persist, and serious complications may occur [5, 6, 107]. 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 levels in the infected site, cause minimal toxicity, and possess maximum stability and longevity.

When selecting antimicrobials for the therapy of mixed infections, their aerobic and anaerobic antibacterial spectrum and their availability in oral or parenteral form should be considered (Table 2.1). Selection of antimicrobial agents is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens. For this reason, many patients are treated empirically based on suspected, rather than established pathogens. Fortunately, the types of anaerobes involved in many infections and their antimicrobial susceptibility patterns tend to be predictable [6, 7]. However, some anaerobes have become resistant to antimicrobials, and many can develop resistance while a patient is receiving treatment [91]. Resistance among some anaerobes has increased significantly over the past three decades. The potential for growing resistance of anaerobes to antimicrobials is especially noted with penicillins, cephalosporins, clindamycin, and fluoroquinolones.

Aside from susceptibility patterns, other factors influencing the choice of antimicrobial therapy include the pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity [2, 3]. Although identification of the infecting organisms and their antimicrobial susceptibility may be needed for the selection of optimal therapy, the clinical setting and Gram stain preparation of the specimen may suggest the types of bacteria present in the infection as well as the nature of the infectious process.

Conclusion

Many microbes naturally produce antibiotics and are resistant to the antibiotics they produce. Antibiotic resistant microbes have been present in the environment for millennia. However, the

discovery of antibiotics in the twentieth century has led to increasing antibiotic resistance in clinically important microbes. Antibiotics must be chosen carefully and used wisely to prevent further selection and widespread dissemination of multidrug-resistant pathogens.

References

1. Niederman MS. Principles of appropriate antibiotic use. Int J Antimicrob Agents. 2005;26:S170–5.
2. 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.
3. Hentges DJ. The anaerobic microflora of the human body. Clin Infect Dis. 1993;16:S175–80.
4. Gibbons RJ. Aspects of the pathogenicity and ecology of the indigenous oral flora of man. In: Ballow A, Dehaan RM, Dowell VR, Guze LB, editors. Anaerobic bacteria: role in disease. Springfield, IL: Charles C. Thomas Publisher; 1974. p. 267–85.
5. Brook I. Anaerobic infections diagnosis and management. New York, NY: Informa Healthcare USA, Inc; 2007.
6. Finegold SM. Anaerobic bacteria in human disease. New York, NY: Academic Press; 1977.
7. Brook I. β-Lactamase-producing bacteria in upper respiratory tract infections. Curr Infect Dis Rep. 2010;12:110–7.
8. Brook I. The role of beta-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. Rev Infect Dis. 1984;6:601–7.
9. Brook I, Yocum P. *In vitro* protection of group A beta-hemolytic streptococci from penicillin and cephalothin by Bacteroides fragilis. Chemotherapy. 1983;29:18–23.
10. Hackman AS, Wilkins TD. In vivo protection of Fusobacterium necrophorum from penicillin by Bacteroides fragilis. Antimicrob Agents Chemother. 1975;7:698–703.
11. Brook I, Pazzaglia G, Coolbaugh JC, Walker RI. In vivo protection of penicillin susceptible Bacteroides melaninogenicus from penicillin by facultative bacteria which produce beta-lactamase. Can J Microbiol. 1984;30:98–104.
12. Brook I. Beta-lactamase-producing bacteria recovered after clinical failures with various penicillin therapy. Arch Otolaryngol. 1984;110:228–31.
13. Van Eldere J, Slack MP, Ladhani S, Cripps AW. Non-typeable Haemophilus influenzae, an under-recognised pathogen. Lancet Infect Dis. 2014;14:1281–92.
14. San Millan A, Santos-Lopez A, Ortega-Huedo R, Bernabe-Balas C, Kennedy SP, Gonzalez-Zorn B. Small-plasmid-mediated antibiotic resistance is enhanced by increases in plasmid copy number and bacterial fitness. Antimicrob Agents Chemother. 2015;59:3335–41.
15. Resman F, Ristovski M, Forsgren A, et al. Increase of β-lactam-resistant invasive Haemophilus influenzae in Sweden, 1997 to 2010. Antimicrob Agents Chemother. 2012;56:4408–15.
16. Hasegawa K, Kobayashi R, Takada E, et al. High prevalence of type b beta-lactamase-non-producing ampicillin-resistant Haemophilus influenzae in meningitis: the situation in Japan where Hib vaccine has not been introduced. J Antimicrob Chemother. 2006;57:1077.
17. García-Cobos S, Campos J, Lázaro E, et al. Ampicillin-resistant non-beta-lactamase-producing Haemophilus influenzae in Spain: recent emergence of clonal isolates with increased resistance to cefotaxime and cefixime. Antimicrob Agents Chemother. 2007;51:2564–73.
18. Ladhani S, Slack MP, Heath PT, et al. Invasive Haemophilus influenzae Disease, Europe, 1996-2006. Emerg Infect Dis. 2010;16:455–63.
19. Nakamura S, Yanagihara K, Seki M, et al. Clinical characteristics of pneumonia caused by beta-lactamase negative ampicillin resistant Haemophilus influenzae (BLNAR). Scand J Infect Dis. 2007;39:521–4.
20. Ohno A, Ishii Y, Kobayashi I, Yamaguchi K. Antibacterial activity and PK/PD of ceftriaxone against penicillin-resistant Streptococcus pneumoniae and beta-lactamase-negative ampicillin-resistant Haemophilus influenzae isolates from patients with community-acquired pneumonia. J Infect Chemother. 2007;13:296–301.
21. Khan MA, Northwood JB, Levy F, Verhaegh SJ, Farrell DJ, Van Belkum A, Hays JP. bro {beta}-lactamase and antibiotic resistances in a global cross-sectional study of Moraxella catarrhalis from children and adults. J Antimicrob Chemother. 2010;65:91–7.
22. Liu Y, Xu H, Xu Z, Kudinha T, Fan X, Xiao M, Kong F, Sun H, Xu Y. High-level macrolide-resistant moraxella catarrhalis and development of an allele-specific PCR assay for detection of 23S rRNA gene A2330T mutation: a three-year study at a chinese tertiary hospital. Microb Drug Resist. 2015;21:507–11.
23. Sahm DF, Brown NP, Thornsberry C, Jones ME. Antimicrobial susceptibility profiles among common respiratory tract pathogens: a GLOBAL perspective. Postgrad Med. 2008;120(3 Suppl 1):16–24.
24. Andam CP, Hanage WP. Mechanisms of genome evolution of Streptococcus. Infect Genet Evol. 2015;33:334–42.
25. Sujatha S, Praharaj I. Glycopeptide resistance in gram-positive cocci: a review. Interdiscip Perspect Infect Dis. 2012;2012:781679.
26. Moreno F, Crisp C, Jorgensen JH, Patterson JE. The clinical and molecular epidemiology of bacteremias at a university hospital caused by pneumococci not susceptible to penicillin. J Infect Dis. 1995;172:427–32.

27. Ruhe JJ, Myers L, Mushatt D, Hasbun R. High-level penicillin-nonsusceptible Streptococcus pneumoniae bacteremia: identification of a low-risk subgroup. Clin Infect Dis. 2004;38:508–14.
28. Vanderkooi OG, Low DE, Green K, et al. Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis. 2005;40:1288–97.
29. Hakenbeck R, Brückner R, Denapaite D, Maurer P. Molecular mechanisms of β-lactam resistance in Streptococcus pneumoniae. Future Microbiol. 2012;7:395–410.
30. Hotomi M, Billal DS, Shimada J, Suzumoto M, Yamauchi K, Fujihara K, Yamanaka N. Increase of macrolide-resistant Streptococcus pneumoniae-expressing mefE or ermB gene in the nasopharynx among children with otitis media. Laryngoscope. 2005;115:317–20.
31. Jorgensen JH, Weigel LM, Swenson JM, Whitney CG, Ferraro MJ, Tenover FC. Activities of clinafloxacin, gatifloxacin, gemifloxacin, and trovafloxacin against recent clinical isolates of levofloxacin-resistant Streptococcus pneumoniae. Antimicrob Agents Chemother. 2000;44:2962–8.
32. Jacobs MR, Good CE, Windau AR, Bajaksouzian S, Biek D, Critchley IA, Sader HS, Jones RN. Activity of ceftaroline against recent emerging serotypes of Streptococcus pneumoniae in the United States. Antimicrob Agents Chemother. 2010;54:2716–9.
33. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus Streptococcus pneumoniae: coping with antimicrobial susceptibility in an era of resistance. Clin Infect Dis. 2009;48:1596–600.
34. Centers for Disease Control and Prevention. Streptococcus pneumoniae. Active bacterial core surveillance report, emerging infections program Network 2013. Available at: https://www.cdc.gov/abcs/reports-findings/survreports/spneu13.pdf
35. Brook I. Role of methicillin-resistant Staphylococcus aureus in head and neck infections. J Laryngol Otol. 2009;123:1301–7.
36. Naseri I, Jerris RC, Sobol SE. Nationwide trends in pediatric staphylococcus aureus head and neck infections. Arch Otolaryngol Head Neck Surg. 2009;135:14–6.
37. Fong SM, Watson M. Lemierre syndrome due to non-multiresistant methicillin- aureus. J Paediatr Child Health. 2002;38:305–7.
38. Boga C, Ozdogu H, Diri B, Oguzkurt L, Asma S, Yeral M. Lemierre syndrome variant: Staphylococcus aureus associated with thrombosis of both the right internal jugular vein and the splenic vein after the exploration of a river cave. J Thromb Thrombolysis. 2007;23:151–4.
39. Brook I, Foote PA, Hausfeld JN. Increase in the frequency of recovery of methicillin-resistant Staphylococcus aureus in acute and chronic maxillary sinusitis. J Med Microbiol. 2008;57:1015–7.
40. Gerencer RZ. Successful outpatient treatment of sinusitis exacerbations caused by community-acquired methicillin-resistant Staphylococcus aureus. Otolaryngol Head Neck Surg. 2005;132:828–33.
41. Enright MC, Robinson DA, Randle G, et al. The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). Proc Natl Acad Sci U S A. 2002;99:7687–92.
42. Panzer JD, Brown DC, Epstein WL, Lipson RL, Mahaffey HW, Atkinson WH. Clindamycin levels in various body tissues and fluids. J Clin Pharmacol New Drugs. 1972;12:259–62.
43. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N Engl J Med. 2007;357:380–90.
44. Siberry GK, Tekle T, Carroll K, Dick J. Failure of clindamycin treatment of methicillin-resistant Staphylococcus aureus expressing inducible clindamycin resistance *in vitro*. Clin Infect Dis. 2003;37:1257–60.
45. Fiebelkorn KR, Crawford SA, McElmeel ML, Jorgensen JH. Practical disk diffusion method for detection of inducible clindamycin resistance in Staphylococcus aureus and coagulase-negative staphylococci. J Clin Microbiol. 2003;41:4740–4.
46. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA, Methicillin-resistant S. aureus infections among patients in the emergency department. EMERGEncy ID Net Study Group. N Engl J Med. 2006;355:666–74.
47. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus infections. Clin Infect Dis. 2002;34:1481–90.
48. Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: *in vitro* modeling and clinical impact. J Infect Dis. 2005;191:2149–52.
49. Sakoulas G, Alder J, Thauvin-Eliopoulos C, Moellering RC Jr, Eliopoulos GM. Induction of daptomycin heterogeneous susceptibility in Staphylococcus aureus by exposure to vancomycin. Antimicrob Agents Chemother. 2006;50:1581–5.
50. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallace RJ, Bryant AE. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant Staphylococcus aureus. J Infect Dis. 2007;195:202–11.
51. Mendes RE, Deshpande LM, Castanheira M, DiPersio J, Saubolle MA, Jones RN. First report of cfr-mediated resistance to linezolid in human staphylococcal clinical isolates recovered in the United States. Antimicrob Agents Chemother. 2008;52:2244–6.
52. Garrison MW, Kawamura NM, Wen MM. Ceftaroline fosamil: a new cephalosporin active against resistant Gram-positive organisms including MRSA. Expert Rev Anti Infect Ther. 2012;10:1087–103.
53. Cunningham M, Guardiani E, Kim HJ, Brook I. Otitis media. Future Microbiol. 2012;7:733–53.

54. Brook I, Frazier EH, Thompson DH. Aerobic and anaerobic microbiology of external otitis. Clin Infect Dis. 1992;15:955–8.
55. Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015;35:949–62.
56. Rossolini GM, Mantengoli E. Treatment and control of severe infections caused by multiresistant Pseudomonas aeruginosa. Clin Microbiol Infect. 2005;11(Suppl 4):17–32.
57. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis. 2004;4:519–27.
58. Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. Clin Microbiol Rev. 2013;26:526–46.
59. Busch DF, Kureshi LA, Sutter VL, et al. Susceptibility of respiratory tract anaerobes to orally administered penicillins and cephalosporins. Antimicrob Agents Chemother. 1976;10:713–20.
60. Acuna C, Rabasseda X. Amoxicillin-sulbactam: a clinical and therapeutic review. Drugs Today (Barc). 2001;37:193–210.
61. Finegold SM. *In vitro* efficacy of beta-lactam/beta-lactamase inhibitor combinations against bacteria involved in mixed infections. Int J Antimicrob Agents. 1999;12(Suppl 1):S9–14.
62. Goldstein EJC, Citron DM. Resistance trends in antimicrobial susceptibility of anaerobic bacteria, Part I and Part II. Clin Microbiol Newslett. 2011;33:1–14.
63. Strehl E, Kees F. Pharmacological properties of parenteral cephalosporins: rationale for ambulatory use. Drugs. 2000;59(Suppl 3):9–18.
64. Boyanova L, Kolarov R, Mitov I. Recent evolution of antibiotic resistance in the anaerobes as compared to previous decades. Anaerobe. 2015;31:4–10.
65. Hecht DW. Prevalence of antibiotic resistance in anaerobic bacteria: worrisome developments. Clin Infect Dis. 2004;39:92–7.
66. Goldstein EJC, Citron DM, Cole RE, et al. Cefoxitin in the treatment of aerobic/anaerobic infections: prospective correlation of *in vitro* susceptibility methods with clinical outcome. Hosp Pract Symp Suppl. 1990;25(Suppl 4):38–45.
67. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. Mayo Clin Proc. 1999;74:420–34.
68. Aldridge K, Aldridge KE, Ashcraft D, et al. Multicenter survey of the changing *in vitro* antimicrobial susceptibilities of clinical isolates of Bacteroides fragilis group, Prevotella, Fusobacterium, Porphyromonas, and Peptostreptococcus species. Antimicrob Agents Chemother. 2001;45:1238–43.
69. Paterson DL, Depestel DD. Doripenem. Clin Infect Dis. 2009;49:291–8.
70. Nicolau DP, Carmeli Y, Crank CW, et al. Carbapenem stewardship: does ertapenem affect Pseudomonas susceptibility to other carbapenems? A review of the evidence. Int J Antimicrob Agents. 2012;39:11–5.
71. Jorgensen JH, Maher LA, Howell AW. Activity of meropenem against antibiotic-resistant or infrequently encountered gram-negative bacilli. Antimicrob Agents Chemother. 1991;35:2410–4.
72. Kattan JN, Villegas MV, Quinn JP. New developments in carbapenems. Clin Microbiol Infect. 2008;14:1102–11.
73. Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. Drugs. 2005;65:2151–78.
74. Snydman DR, Jacobus NV, McDermott LA, et al. Update on resistance *of Bacteroides fragilis* group and related species with special attention to carbapenems 2006-2009. Anaerobe. 2011;17:147–51.
75. Liu CY, Huang YT, Liao CH, et al. Increasing trends in antimicrobial resistance among clinically important anaerobes and *Bacteroides fragilis* isolates causing nosocomial infections: emerging resistance to carbapenems. Antimicrob Agents Chemother. 2008;52:3161–8.
76. Wexler HM. Susceptibility testing of anaerobic bacteria: myth, magic, or method? Clin Microbiol Rev. 1991;4:470–84.
77. Bush K. Beta-Lactamases of increasing clinical importance. Curr Pharm Des. 1999;5:839–45.
78. Appelbaum PC, Spangler SK, Pankuch GA, et al. Characterization of a beta-lactamase from Clostridium clostridioforme. J Antimicrob Chemother. 1994;33:33–40.
79. Pumbwe L, Chang A, Smith RL, et al. Clinical significance of overexpression of multiple RND-family efflux pumps in Bacteroides fragilis isolates. J Antimicrob Chemother. 2006;58:543–8.
80. Snydman DR, Jacobus NV, McDermott LA, et al. Lessons learned from the anaerobe survey: historical perspective and review of the most recent data (2005-2007). Clin Infect Dis. 2010;50(Suppl 1):S26–33.
81. Snydman DR, Jacobus NV, McDermott LA, et al. Multicenter study of *in vitro* susceptibility of the Bacteroides fragilis group, 1995 to 1996, with comparison of resistance trends from 1990 to 1996. Antimicrob Agents Chemother. 1999;43:2417–22.
82. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* Group: report and analysis of trends for 1997-2000. Clin Infect Dis. 2002;35:S126–34.
83. Balbi HJ. Chloramphenicol: a review. Pediatr Rev. 2004;25:284–8.
84. Goldstein EJC, Citron DM, Merriam CV. Linezolid activity compared to those of selected macrolides and other agents against aerobic and anaerobic pathogens isolated from soft tissue bite infections in humans. Antimicrob Agents Chemother. 1999;43:1469–74.
85. Williams JD, Maskell JP, Shain H, et al. Comparative in-vitro activity of azithromycin, macrolides (erythromycin, clarithromycin and spiramycin) and streptogramin RP 59500 against oral organisms. J Antimicrob Chemother. 1992;30:27–37.

86. Goldstein EJC, Lewis RP, Sutter VL, et al. Treatment of pleuropulmonary and soft-tissue Infections with erythromycin. JAMA. 1979;242:435–8.
87. Sanai Y, Persson GR, Starr JR, et al. Presence and antibiotic resistance of Porphyromonas gingivalis, Prevotella intermedia, and Prevotella nigrescens in children. J Clin Periodontol. 2002;29:929–34.
88. Feigin RD, Pickering LK, Anderson D, et al. Clindamycin treatment of osteomyelitis and septic arthritis in children. Pediatrics. 1975;55:213–23.
89. Klainer AS. Clindamycin. Med Clin North Am. 1987;71:1169–75.
90. Paap CM, Nahata MC. Clinical pharmacokinetics of antibacterial drugs in neonates. Clin Pharmacokinet. 1990;19:280–318.
91. Gorbach SL. Antibiotics and Clostridium difficile. N Engl J Med. 1999;341:1690–1.
92. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intraabdominal infections in adults and children: guidelines by the Surgical Infection Society and The Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133–64.
93. Brook I. Spectrum and treatment of anaerobic infections. J Infect Chemother. 2016;22:1–13.
94. Chow AW, Patten V, Guze LB. Susceptibility of anaerobic bacteria to metronidazole: relative resistance of non-spore forming gram-positive bacilli. J Infect Dis. 1975;131:182–5.
95. Rustia M, Shubik P. Experimental induction of hematomas, mammary tumors and other tumors with metronidazole in noninbred Sas: WRC (WT) BR rats. J Natl Cancer Inst. 1979;63:863–8.
96. Cohen SM, Ertürk E, Von Esch AM, et al. Carcinogenicity of 5-nitrofurans, 5-nitroimidazoles, 4-nitrobenzenes, and related compounds. J Natl Cancer Inst. 1973;51:403–17.
97. Beard CM, Noller KL, O'Fallon WM, et al. Lack of evidence for cancer due to use of metronidazole. N Engl J Med. 1979;301:519–22.
98. Townsend ML, Pound MW, Drew RH. Tigecycline: a new glycylcycline antimicrobial. Int J Clin Pract. 2006;60:1662–7.
99. Goldstein EJC, Citron DM, et al. Comparative *in vitro* susceptibilities of 396 unusual anaerobic strains to tigecycline and eight other antimicrobial agents. Antimicrob Agents Chemother. 2006;50:3507–13.
100. Jacobus NV, McDermott LA, Ruthazer R, et al. In vitro activities of tigecycline against the Bacteroides fragilis group. Antimicrob Agents Chemother. 2004;48:1034–6.
101. Edmiston CE, Krepel CJ, Seabrook GR, et al. *In vitro* activities of moxifloxacin against 900 aerobic and anaerobic surgical isolates from patients with intraabdominal and diabetic foot infections. Antimicrob Agents Chemother. 2004;48:1012–6.
102. Stein GE, Goldstein EJ. Fluoroquinolones and anaerobes. Clin Infect Dis. 2006;42:1598–607.
103. United States Food and Drug Administration. FDA News Release: FDA updates warnings for fluoroquinolone use. July 26, 2016. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm513183.htm.
104. Oh H, Hedberg M, Edlund C. Efflux-mediated fluoroquinolone resistance in the Bacteroides fragilis group. Anaerobe. 2002;8:277–82.
105. Tyrrell KL, Citron DM, Warren YA, et al. In-vitro activity of TD-1792, a multivalent glycopeptide-cephalosporin antibiotic, against 377 strains of anaerobic bacteria and 34 strains of Corynebacterium species. Antimicrob Agents Chemother. 2012;56:2194–7.
106. Finch RG. Antibacterial activity of quinupristin/dalfopristin. Rationale for clinical use. Drugs. 1996;51:31–7.
107. Brook I, Gober E. Emergence of beta-lactamase-producing aerobic and anaerobic bacteria in the oropharynx of children following penicillin chemotherapy. Clin Pediatr. 1984;23:338–42.
108. Wexler HM. *Bacteroides*: the good, the bad, and the nitty-gritty. Clin Microbiol Rev. 2007;20(4):593–621.