1 Antibiotics in Otolaryngology: A Practical Approach

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Introduction

This chapter provides an overview of common antibiotics encountered in otolaryngology with a summary of microbial spectrum, clinical indications, and adverse effects. A clinical approach to choosing antibiotics is outlined. Antibiotic stewardship, with an emphasis on appropriate use of antibiotics, is highlighted.

There is a current worldwide focus on antibiotic stewardship. Antibiotic stewardship programs aim to improve patient care and patient safety by ensuring that the correct antibiotic is given only when it is needed, at the correct dose and for the shortest duration for best clinical outcome [1]. Antibiotic stewardship is the responsibility of all antibiotic prescribers. Efforts should be made to understand when and why an antibiotic is needed as well as when it can be stopped.

Multidrug-resistant infections have become more common. The Centers for Disease Control and Prevention (CDC) defines a multidrug-resistant organism (MDRO) as one that is resistant to one or more classes of antibiotics. Antibiotic resistance is an emerging local, national, and international issue. The CDC, the World Health Organization, and the United Nations have all made antibiotic resistance a top priority and are supporting programs to combat the emergence of resistance. Antibiotic research and development continue to lag behind the need for novel agents.

The CDC estimates that each year in the United States, two million people develop infections due to MDROs and that at least 23,000 people die of these infections [2]. The use of antibiotics is the single most important risk factor leading to MDROs [2]. Inappropriate use of antibiotics is estimated to affect 13–39% of hospitalized patients and up to 30% of outpatients [3, 4]. About one-third of prescribed outpatient antibiotics are for otitis media, sinusitis, and pharyngitis, and narrow spectrum antibiotics are recommended as first-line therapy by national guidelines [4]. In the United States from 2010 to 2011, only 52% of prescriptions for these conditions were for first-line, narrow spectrum agents [5]. Improving appropriate antibiotic use will help to decrease antibiotic resistance.

General Considerations

Antibiotic Selection

Selecting an appropriate antibiotic depends on several factors: (1) the suspected infection (e.g., otitis media, pneumonia, abscess); (2) the likely

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organisms and antibiotic susceptibilities; (3) host factors (e.g., immunosuppression, antibiotic allergies); and (4) antibiotic properties (e.g., dose, route of administration, potential toxicities).

Initial antibiotic therapy is usually empiric and broad-spectrum, covering a wide variety of organisms that are likely to cause a specific infection. For example, a patient with sepsis from an unknown source may be started on vancomycin, cefepime, and metronidazole to treat empirically for Gram-positive, Gram-negative, and anaerobic bacteria. Microbiologic specimens should be obtained prior to starting antibiotics whenever possible, to increase the likelihood of isolating a causative pathogen. Antibiotics should be tailored once culture results are available.

Local antibiograms can help guide initial empiric antibiotic choices, especially in critically ill patients. The antibiogram provides susceptibilities of common pathogens at a given institution or at the local or regional level. Risk factors for MDROs also should be considered for each patient. Risk factors for MDROs have been studied in patients admitted to the intensive care unit and those admitted with pneumonia [6, 7]. These MDRO risk factors include receipt of intravenous antibiotics within the preceding 90 days, residence in a nursing home, and an extended hospital stay within the previous 6 months [6, 7].

Gram stain of fluids can provide early clues to the etiology of an infection. Culture and susceptibility testing may take several days. Polymerase chain reaction testing can be useful for rapid identification of some pathogens (e.g., respiratory viruses). Antibiotics should be adjusted (directed therapy) as clinical and microbiologic data become available. Anti-bacterial agents should be stopped if a non-bacterial diagnosis is made.

Antibiotic Susceptibilities and Site of Infections

Antibiotic susceptibility testing is often performed on the bacterial isolates in positive cultures. The microbiology laboratory tests bacteria for susceptibility to a variety of antibiotics likely to be effective. Susceptibility testing guidelines are standardized by the Clinical and Laboratory Standards Institute and are commonly reported as minimum inhibitory concentration (MIC) with an interpretation of susceptible, intermediate, or resistant. The MIC is the lowest concentration of antibiotic needed to inhibit growth of the bacteria. The MIC varies by organism and by antibiotic and is not necessarily directly comparable across antibiotics.

Antibiotics are only effective if they are delivered adequately to the site of infection and this varies by agent and by dose. Antibiotics penetrate and achieve different concentrations in different bodily fluids. For example, patients with *Staphylococcus aureus* meningitis should not be treated with cefazolin because this antibiotic does achieve therapeutic concentrations in cerebrospinal fluid. Similarly, a patient with an undrained neck abscess may not improve on antibiotics alone because of poor penetration of the antibiotics into the abscess.

Antibiotic Dosing

Antibiotic dosing may be based on age, weight, renal function, the location of the infection, the targeted organism, and its susceptibility profile (if known). Some antibiotics should be avoided, if possible, at the extremes of age due to an increased risk of toxicity [8, 9]. Weight-based dosing of antibiotics is recommended in children and sometimes in overweight or underweight adults. Weight-based dosing is also recommended for certain antibiotics, such as vancomycin.

Many antibiotics need to be adjusted for renal function. Dosing should be based on estimated creatinine clearance. Some antibiotics can cause renal dysfunction and need close monitoring of electrolytes, creatinine, and drug levels during use (e.g., vancomycin and the aminoglycosides).

Antibiotics are nearly always given intravenously when a patient presents with a serious illness or is critically ill. As the patient improves, oral antibiotics may be suitable alternatives

depending on the clinical syndrome. Antibiotic bioavailability varies. Some antibiotics, such as fluoroquinolones, linezolid, azithromycin, clindamycin, doxycycline, metronidazole, and trimethoprim-sulfamethoxazole, have very good oral bioavailability while others, such as penicillins and cephalosporins, do not. Of note, oral bioavailability may be altered by food or other medications (e.g., antacids or iron supplements), and the prescribing clinician should be aware of such interactions.

Comorbid Conditions

Comorbidities may change the differential diagnosis of pathogens causing a clinical syndrome. Patients who are immunosuppressed (e.g., patients with HIV, organ or bone marrow transplant, cancer receiving chemotherapy, rheumatologic disease receiving immunosuppressive therapy) are susceptible to infection from a broader spectrum of pathogens than are immunocompetent hosts. For example, patients receiving TNFα (tumor necrosis factor alpha) inhibitors such as infliximab, adalimumab, or etanercept have an increased risk of tuberculosis and fungal infections [10]. Patients with diabetes are susceptible to invasive otitis externa by *Pseudomonas* even if their diabetes is in good control, and patients with diabetes out of control are susceptible to rhinocerebral mucormycosis. Exposures to sick contacts, animals, and travel, both recent and remote, should be considered when evaluating a patient as these factors can also alter the likely organisms causing disease.

Pregnancy and Lactation

Pregnancy and lactation need to be considered when selecting an antibiotic. Safety for both the pregnant mother and fetus or breastfeeding mother and infant must be considered [11]. Antibiotic concentrations in the placental tissue and breast milk vary. Dosing also varies as the pregnancy-related increase in glomerular filtration rate may clear antibiotics faster. Reviewing antibiotic selection and dosing with the patient's obstetrician or the infant's pediatrician is essential. The U.S. Food and Drug Administration (FDA) also has a description of the safety of various antibiotics during pregnancy and lactation.

Adverse Reactions and Allergies

Antibiotic complications are common and include hypersensitivity reactions, drug toxicity, and development of MDRO infections. In the U.S., 16% of emergency room visits for adverse drug events are due to antibiotics and this rate increases to 56% for children 5 years of age or younger and 32% for children ages 6–19 years [12]. Decreasing inappropriate antibiotic use would reduce the risk of adverse reactions requiring emergency room visits.

Antibiotic allergies should be confirmed prior to antibiotic prescribing. Antibiotics cause a variety of reactions including maculopapular rash, hives, Stevens-Johnson Syndrome, drug fever, and anaphylaxis. True allergic reactions should be distinguished from antibiotic-related side effects such as mild gastrointestinal upset, for example. Approximately 10% of the general population reports an allergy to penicillin (15.6% in some series) [13]. However, up to 90% of these individuals are not truly allergic to penicillin and were labeled as such unnecessarily [14]. Beta-lactams are the preferred antibiotics for many infections and substitution with broader-spectrum, non-beta-lactam therapies may result in poorer outcomes, higher rates of MDRO and *Clostridium difficile* infections, and longer lengths of stay [14–16]. A test dose or "graded challenge" procedure may allow many patients who report a penicillin or cephalosporin allergy to safely receive beta-lactam antibiotics. A test dose protocol introduced at a large teaching hospital in Boston resulted in an increase in the use of beta-lactams and a decrease in the use of some alternative antibiotics (vancomycin, fluoroquinolones, aminoglycosides, aztreonam) but without an increase in adverse drug events [17].

Drug toxicities and side effects vary by antibiotic and may be dose related (Table 1.1). Diarrhea may occur during or after an antibiotic course and may be either a side effect of the antibiotic or due to *C. difficile* infection. Antibiotics alter the normal microbiome of the gastrointestinal tract

Table 1.1 Antibiotic toxicities and side effects[a,b]

Antibiotic	Toxicities and side effects
Aminoglycosides	Renal dysfunction, vestibular and auditory toxicity, neuromuscular blockade.
Penicillins, cephalosporins, carbapenems	Allergic reactions, rash, diarrhea, central nervous system toxicity (e.g., seizure risk with high-dose penicillin), neutropenia with high doses or prolonged use
Clindamycin	Nausea, vomiting, diarrhea (not including *Clostridium difficile* infection), rash
Fluoroquinolones	Central nervous system toxicity (especially in the elderly), tendinopathy and tendon rupture (increased risk if >60 years old, using corticosteroids, or solid organ transplant recipient), QT prolongation on electrocardiogram.
Macrolides (azithromycin, clarithromycin, erythromycin)	Nausea, vomiting, diarrhea, abdominal pain, QT prolongation on electrocardiogram
Metronidazole	Metallic taste, adverse reaction (severe vomiting) with alcohol; prolonged use can lead to peripheral neuropathy
Trimethoprim-sulfamethoxazole	Nausea, vomiting, diarrhea, rash, nephrotoxicity, bone marrow suppression, aseptic meningitis, hyperkalemia, rare but severe skin reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis, hemolytic anemia in patients with G6PD deficiency
Tetracyclines (doxycycline, minocycline, tetracycline)	Gastrointestinal upset, sun sensitivity, discolored teeth in children <8 years old, affects growing bones in fetus
Vancomycin	Nephrotoxicity (increased risk with higher serum concentrations), ototoxicity. "Red man syndrome" (infusion reaction with itching, flushing, hypotension) usually can be avoided with slower infusions.

G6PD = glucose-6-phosphate dehydrogenase

[a]This table is not all-inclusive (does not list all antibiotics or all potential toxicities)

[b]Some antibiotics within a given antibiotic class cause fewer side effects than others (e.g., azithromycin has fewer gastrointestinal side effects than erythromycin); see the text for details

allowing overgrowth of *C. difficile*, whose toxin can cause frequent watery diarrhea, fever, leukocytosis, and in severe cases, toxic megacolon, intestinal perforation, and death. Each year in the U.S. approximately 250,000 people develop *C. difficile* infections, resulting in 14,000 deaths [2]. Half of these infections occur in hospitalized or recently hospitalized patients, while approximately half occur in residents of nursing homes or patients recently cared for in doctors' offices or clinics [2]. Many infections are associated with current or recent antibiotic use. Some antibiotic classes carry a higher risk than others. Clindamycin, fluoroquinolones, and cephalosporins carry the highest risk of community-acquired *C. difficile* infection, increasing the risk by 20-fold, six-fold, and four-fold, respectively, over no antibiotics [18]. A recent study from the United Kingdom found that decreasing fluoroquinolone use nationally resulted in a national decline of *C. difficile* infection [19]. Appropriate antibiotic use focusing on narrow spectrum agents for the shortest duration with best therapeutic effect can also help decrease *C. difficile* infection.

Duration of Therapy

Duration of therapy varies by the type of infection, causative pathogen, and antibiotic used. Society guidelines should be reviewed for duration of therapy including those from the Infectious Diseases Society of America (IDSA), available at www.idsociety.org/IDSA_Practice_Guidelines. Shorter antibiotic durations seem to be as effective as longer durations for urinary tract infections, community and hospital-acquired pneumonia, and drained intra-abdominal infections [7, 20–22]. One recent example of failure of shorter course antibiotic therapy, however, was for acute otitis media in children 6–23 months of age: 5 days of therapy resulted in less favorable outcomes than 10 days of therapy [23]. Longer duration of antibiotics is associated with increased adverse effects including toxicities of the drug, development of antibiotic resistance, and increased risk for *C. difficile* infection [2].

De-escalation of Therapy

In hospitalized patients receiving empiric antibiotic therapy, the need for antibiotic therapy should be re-evaluated at the 48–72-h mark. This timeframe allows for microbiologic data to mature and for an assessment of the clinical situation and potential response or nonresponse to antibiotic therapy. Antibiotics should be narrowed, if possible. "Response to therapy" should not be the only reason for antibiotic continuation if another explanation is likely. Additionally, culture data should be interpreted critically including the potential for positive cultures to represent colonization instead of infection. For example, a stable patient with a tracheostomy may grow highly resistant bacteria from tracheostomy cultures. Treatment of these bacteria may not be necessary in a patient who has no signs or symptoms of active infection.

Surgical Antibiotic Prophylaxis

Antibiotic prophylaxis for surgery targets bacteria that may contaminate the wound at the time of surgery. Antibiotic prophylaxis is recommended for nearly all clean-contaminated surgeries and for some clean surgeries. Skin flora, especially *Staphylococcus aureus*, and streptococci, especially Group A *Streptococcus*, are the primary targets of prophylaxis for clean surgeries. For clean-contaminated surgeries, broader-spectrum antibiotics are indicated since these must also cover the flora of the respiratory or gastrointestinal tract. Antibiotics should be started within 1 h prior to surgical incision (or within 2 h for vancomycin and fluoroquinolones) to be most effective [24, 25]. Antibiotics may need to be redosed intraoperatively for longer procedures [24]. Continuation of prophylactic antibiotics beyond skin closure has not been shown to improve outcomes [24], and the CDC recommends stopping prophylactic antibiotics after the incision is closed in the operating room, even in the presence of a drain [26]. Surgical prophylaxis in otolaryngology is discussed further in Chap. 30.

Antibacterial Agents

Beta-Lactam Antibiotics

Beta-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. Beta-lactam antibiotics have a four-member core ring structure (Fig. 1.1) and are bactericidal. They inhibit bacterial cell wall synthesis. Table 1.2 provides a summary of commonly used beta-lactam antibiotics, their general spectrum of activity, and common indications.

Penicillins. Penicillin was first used to treat a patient in Oxford, England, in 1941. It was initially effective against *S. aureus* in addition to streptococci, but resistance in staphylococci quickly developed. Group A *Streptococcus*, however, never developed resistance to penicillin. Methicillin was developed in 1961 as a penicillin derivative with efficacy against *S. aureus*, but this was subsequently replaced by less toxic alternatives, nafcillin and oxacillin. The name "methicillin" remains in "methicillin-susceptible *S. aureus*" (MSSA) and "methicillin-resistant *S. aureus*" (MRSA), and signifies susceptibility or resistance to beta-lactam antibiotics such as oxacillin, nafcillin, ampicillin-sulbactam, cefazolin, cefuroxime, ceftriaxone, and cefepime.

Cephalosporins. The first cephalosporin was isolated in Oxford, England, in 1961 and the first clinically useful cephalosporin, cephalothin, was marketed in 1964. Subsequent development of multiple cephalosporins has led to their classification in "generations" (Table 1.2). Clinically important features that distinguish various cephalosporins include their activity against *S. aureus* (e.g., cefazolin, cefuroxime, cefepime), *S. pneumoniae* (e.g., ceftriaxone), anaerobes (e.g., cefoxitin), and Gram-negative bacilli. All cephalosporins have activity against Gram-negative bacilli, but the number of susceptible pathogens generally increases as the generation of cephalosporin increases. The few cephalosporins (e.g., ceftazidime, cefepime) with activity against *Pseudomonas* are noteworthy. None of the cephalosporins had activity against MRSA until the

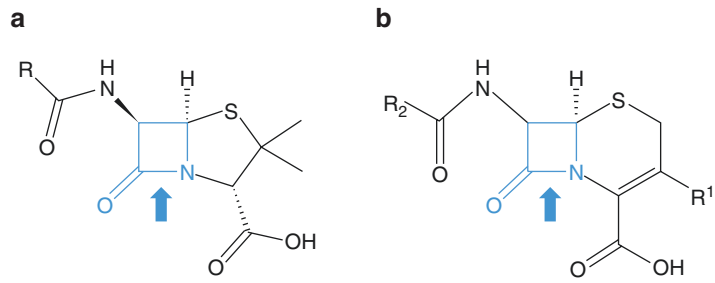

Fig. 1.1 Beta-lactam antibiotics, core structure. (**a**) Penicillins; (**b**) Cephalosporins. The "R" is a variable group. The beta-lactam ring is in blue. The arrow points to the site of action of bacterial beta-lactamase enzymes

advent of the fifth generation cephalosporins, ceftobiprole and ceftaroline.

Carbapenems. Carbapenems provide broad antibacterial therapy treating Gram-positive cocci, Gram-negative bacilli, and anaerobes. They are also active against most bacteria that have an extended-spectrum β-lactamase (ESBL) or an AmpC beta-lactamase (bacterial mechanisms of resistance). They are administered intravenously and include doripenem, ertapenem, imipenem-cilastatin, and meropenem. They are not active against MRSA or *Stenotrophomonas maltophilia*. Ertapenem is not active against *Pseudomonas* or *Acinetobacter*. Carbapenems have good penetration into many tissues, including into the central nervous system, and are valuable agents because of their broad-spectrum of activity. As with all antibiotics, resistance can emerge while on therapy and these agents should only be used when narrower spectrum antibiotics are not an option.

Monobactams. The only FDA-approved monobactam to date is aztreonam, an antibiotic with a similar spectrum of activity as gentamicin and other aminoglycosides, but with significantly less toxicity. Aztreonam is effective against Gram-negative bacteria, including *Pseudomonas*, but has no activity against Gram-positive bacteria or anaerobes. Aztreonam is used primarily for treatment of Gram-negative infections in patients with severe penicillin or cephalosporin allergies, because nearly all patients with beta-lactam allergies can tolerate aztreonam [27, 28]. Aztreonam has a similar side chain as ceftazidime and should be used cautiously in patients with ceftazidime allergy [29]. Aztreonam can be used to treat a variety of infections including bacteremia, urinary tract infections, bone and joint infections, and skin and soft tissue infections. In can be used in combination with a Gram-positive antibiotic in cases requiring broad-spectrum therapy.

Aminoglycosides

Aminoglycosides (e.g., amikacin, gentamicin, tobramycin) are often used in combination with beta-lactam antibiotics to treat some types of bacterial endocarditis and Gram-negative infections. Aminoglycosides have activity against nearly all Gram-negative bacilli, including *Pseudomonas aeruginosa*, and act synergistically with ampicillin to treat serious infections due to susceptible enterococci. Some aminoglycosides (e.g., streptomycin) are used as part of a regimen to treat multidrug-resistant mycobacterial infections. Clinical use of aminoglycosides is largely reserved for the treatment of drug-resistant organisms because renal dysfunction and ototoxicity are significant side effects. Renal function and serum peak and trough aminoglycoside levels should be monitored frequently. Patients should be alerted to the possibility of ototoxicity, and hearing and vestibular function should be monitored unless the aminoglycoside course is expected to be very brief. Ototoxicity can affect hearing and/or vestibular function and usually begins with high-frequency sensorineural hearing loss. This may not be appreciated by the patient but can be detected on hearing tests. Vestibular toxicity may be more prevalent that auditory toxicity. One study of 71 cystic fibrosis patients who had received courses of aminoglycosides for the treatment of *Pseudomonas*

Table 1.2 Select beta-lactam antibiotics and their common uses[a]

Antibiotic[a]	Usual spectrum of activity[a]	Common uses (for susceptible bacterial isolates)[a]
Penicillins		
Penicillin G (IV) Penicillin VK (PO) Benzathine penicillin G (IM) for syphilis	Group A *Streptococcus* Group B *Streptococcus* *Streptococcus anginosus* group viridans streptococci (most) *Streptococcus pneumoniae* (not penicillin-resistant strains) *Arcanobacterium* species Most Gram-positive anaerobes *Actinomyces* species *Treponema pallidum*	Pharyngitis *Actinomyces* infection Oral and periodontal infections Necrotizing fasciitis Syphilis (IV/IM)
Nafcillin (IV) Oxacillin (IV) Dicloxacillin (PO)	Methicillin-sensitive *Staphylococcus aureus* (MSSA)	Cellulitis MSSA bacteremia (IV) MSSA endocarditis (IV)
Ampicillin (IV) Amoxicillin (PO)	*Enterococcus faecalis* *Streptococcus* species (penicillin-susceptible isolates only) *Haemophilus influenzae* (beta-lactamase-negative strains only) *Listeria monocytogenes* *Escherichia coli* *Proteus mirabilis* Most Gram-positive anaerobes (similar to penicillin)	Acute otitis media *Listeria* bacteremia or meningitis (IV) *Haemophilus influenzae* meningitis and epiglottitis (IV) (ampicillin-susceptible strains only) Endocarditis due to susceptible enterococci (IV, in combination with aminoglycoside or ceftriaxone)
Ampicillin-sulbactam (IV) Amoxicillin-clavulanic acid (PO)	*Enterococcus faecalis* *Enterococcus faecium* MSSA *Streptococcus* species *Arcanobacterium* species *Listeria monocytogenes* *Escherichia coli* *Proteus mirabilis* *Haemophilus influenzae* (including beta-lactamase-positive isolates) *Moraxella catarrhalis* Most anaerobes including *Bacteroides fragilis* Sulbactam has activity against *Acinetobacter baumanii*	Bacterial sinusitis Acute otitis media Bite wounds Urinary tract infections Community-acquired pneumonia Community-acquired abdominal infections (e.g., diverticulitis) Skin and skin-structure infections
Piperacillin-tazobactam (IV)	Similar to ampicillin-sulbactam plus *Pseudomonas aeruginosa*	Pseudomonal infections Nosocomial infections including pneumonia Intra-abdominal infections
Cephalosporins		
First generation		
Cefazolin (IV) Cefadroxil (PO) Cephalexin (PO)	MSSA Group A *Streptococcus* Some community-acquired Gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*)	Cellulitis MSSA bacteremia (IV) Peri-operative prophylaxis (IV)
Second generation		
Cefaclor (PO) Cefprozil (PO) Cefuroxime (IV or PO)	MSSA *Streptococcus* species *Escherichia coli* *Klebsiella* species *Proteus mirabilis* *Haemophilus influenzae* *Moraxella catarrhalis*	Acute otitis media Bacterial sinusitis Community-acquired pneumonia

(continued)

Table 1.2 (continued)

Antibiotic[a]	Usual spectrum of activity[a]	Common uses (for susceptible bacterial isolates)[a]
Cefotetan (IV) Cefoxitin (IV)	MSSA *Streptococcoccus* species *Escherichia coli* *Klebsiella* species *Proteus* species Anaerobes including *Bacteroides fragilis*	Peri-operative prophylaxis for gastrointestinal and pelvic surgeries, however use has decreased due to increased resistance of *Bacteroides*
Third generation		
Cefdinir (PO) Cefditoren pivoxil (PO) Cefixime (PO) Cefotaxime (IV) Cefpodoxime proxetil (PO) Ceftriaxone (IV)	MSSA *Streptococcus* species *Escherichia coli* *Klebsiella* species *Proteus* species *Neisseria* species *Haemophilus influenzae* *Moraxella catarrhalis* *Borrelia burgdorferi*	Upper respiratory tract infections, including otitis media, and some lower respiratory tract infections Urinary tract infections IV ceftriaxone is commonly used as part of a regimen to treat community-acquired meningitis, community-acquired pneumonia, some types of complicated Lyme disease infections (e.g., neuroborreliosis), and as part of a regimen to treat gonorrhea.
Ceftazidime (IV)	Gram-negative bacilli including *Pseudomonas aeruginosa* Some activity against Gram-positive bacteria (less active against MSSA than most other cephalosporins)	*Pseudomonas* infections including meningitis Nosocomial infections including pneumonia and bacteremia
Fourth generation		
Cefepime (IV)	MSSA *Streptococcus* species Gram-negative bacilli including *Acinetobacter* species *Citrobacter* species *Enterobacter* species *Proteus* species *Pseudomonas aeruginosa* *Serratia* species	Broad Gram-positive and Gram-negative therapy (empiric) *Pseudomonas* infections Nosocomial infections including pneumonia Bacteremia
Fifth generation		
Ceftaroline (IV)	MSSA MRSA *Group A Streptococcus* *Streptococcus pneumoniae* *Haemophilus influenzae* *Escherichia coli* *Klebsiella* species	Skin and skin structure infections (e.g., complicated cellulitis) Community-acquired pneumonia

IV = intravenous, PO = per os (oral), IM = intramuscular, MSSA = methicillin-susceptible *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*

[a]This table is not all-inclusive, nor is it intended to guide therapy for a particular infection. In addition, the indications for use by the U.S. Food and Drug Administration (FDA) may be more limited, or in some cases broader, than those listed under "Common Uses". Some common uses for antibiotics are "off label," and some pathogens are not among those for which the antibiotic has an FDA-approved use. Some of the pathogens listed may have isolates that are resistant to the corresponding antibiotic. Some of the common uses noted for a given antibiotic may apply only when that antibiotic is used in combination with another antibiotic.

infections found that 79% had vestibular dysfunction while 23% had hearing loss (some had both) [30]. Ototoxicity, which is usually irreversible, may start either during or even weeks after completing a course of aminoglycosides.

Clindamycin

Clindamycin is active against susceptible *S. aureus* and *Streptococcus* species as well as many anaerobic Gram-positive cocci such as *Peptostreptococcus*. It has no activity against Gram-negative bacilli, and increasingly poor activity against anaerobic Gram-negative bacilli such as *Bacteroides fragilis*. Clindamycin is often used to treat MRSA skin and soft tissue infections, although MRSA resistance to clindamycin is significant (20–25%) in some regions of the U.S. [31, 32]. Clindamycin is also used to treat some *S. aureus* (MSSA) and streptococcal infections in penicillin-allergic patients, but increasing clindamycin resistance in these pathogens is also a concern. A recent study of Group A streptococcal pharyngitis in children in Wisconsin reported a clindamycin resistance rate of 15% [33]. Clindamycin has excellent oral bioavailability but patients usually tolerate much higher doses of intravenous than oral clindamycin. Clindamycin is cleared by the liver and should be dose adjusted in liver dysfunction.

Daptomycin

Daptomycin, FDA-approved in 2003, is a lipopeptide. It is available only intravenously and has activity solely against Gram-positive bacteria. It is active against most Gram-positive bacteria, including resistant bacteria such as MRSA and vancomycin-resistant *Enterococcus* (VRE). It is approved for treating complicated skin and soft tissue infections, *S. aureus* bacteremia and for right-sided endocarditis. It should not be used for pneumonia and other pulmonary infections as it is ineffective in the presence of surfactant. Daptomycin dosing is weight-based and the drug is generally well tolerated. Creatinine phosphokinase (CPK) should be followed weekly to monitor for treatment-related myopathy.

Fluoroquinolones

Fluoroquinolones are broad-spectrum agents that have excellent oral bioavailability, with oral and intravenous doses achieving similar serum levels in patients with normal gastrointestinal absorption. Oral medications, such as some antacids and dietary supplements that contain divalent and trivalent cations (magnesium, aluminum, iron, or calcium), may significantly reduce oral quinolone absorption and should be given at least 2 h before the quinolone. Quinolones have excellent penetration into tissues including bone. Ciprofloxacin is primarily active against Gram-negative bacteria including enteric Gram-negative bacilli and *Pseudomonas aeruginosa*. Levofloxacin has additional activity against streptococci, including *S. pneumoniae*, and atypical pathogens such as *Legionella* and *Mycoplasma*, making it useful for treatment of community-acquired pneumonia. Moxifloxacin is similar to levofloxacin but has some activity against anaerobes and much less activity against *Pseudomonas*.

Widespread use of the fluoroquinolones has led to increasing resistance and providers should be thoughtful about their use [34, 35]. Additionally, in 2016 the FDA issued a safety announcement about the serious adverse effects of quinolones including tendinitis, tendon rupture, paresthesias, muscle and joint pain, and central nervous system effects [36]. The FDA stated that systemic fluoroquinolones should not be used in patients with other treatment options for acute bacterial sinusitis, acute bronchitis, and uncomplicated urinary tract infections [36].

Linezolid and Tedizolid (Oxazolidinones)

Linezolid was the first FDA-approved (2003) member of a new class of antibiotics, the oxazolidinones. Tedizolid is a second-generation

oxazolididone (FDA-approved 2014) and is more potent than linezolid against staphylococci and enterococci. Both antibiotics are available intravenously and orally, and are used to treat infections due to Gram-positive bacteria, including resistant Gram-positive bacteria such as MRSA and VRE. They also have activity against some mycobacteria, and may be used (off label use) as part of a combination regimen for mycobacteria. They have good oral bioavailability and tissue penetration. Linezolid can be used to treat bacteremia, pneumonia, and complicated skin and soft tissue infections due to Gram-positive bacteria. Use of linezolid can cause cytopenias, particularly thrombocytopenia, which is less likely to occur with tedizolid [37, 38]. Long-term use of these antibiotics can cause peripheral neuropathy and rarely, optic neuropathy. Tedizolid is currently approved only for treating skin and soft tissue infections.

Macrolides

The macrolides, including erythromycin, clarithromycin, and azithromycin, are used primarily to treat community-acquired pneumonia and are often used to treat pharyngitis in penicillin-allergic patients. Clarithromycin and azithromycin are active against susceptible *S. pneumoniae* (although resistance has been increasing), *Legionella pneumophila*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Approximately 15% of Group A streptococcal pharyngitis isolates are resistant to macrolides [33], and macrolides are ineffective against *Fusobacterium necrophorum*, an important cause of pharyngitis in adolescents and young adults and the primary cause of Lemierre's syndrome. Azithromycin is available both intravenously and orally, is given once daily, and is better tolerated than the other macrolides. Clarithromycin is only available orally. Erythromycin is usually poorly tolerated due to gastrointestinal side effects, and it is often used as a gastrointestinal motility agent in the intensive care unit. Azithromycin and clarithromycin are important components of the treatment regimen for nontuberculous mycobacteria infections. Gastrointestinal upset with nausea, vomiting, abdominal pain, and diarrhea is a common side effect (less so with azithromycin) and QT prolongation can occur while on therapy.

Metronidazole

Metronidazole is active against nearly all Gram-negative anaerobes including *Clostridium*, *Bacteroides*, and *Fusobacterium* species. It has poor activity against many Gram-positive anaerobes (see Chap. 2) and no activity against aerobic bacteria. Oral metronidazole is well absorbed. It is often used in combination with antibiotics active against Gram-positive and Gram-negative aerobic bacteria to provide broad-spectrum coverage. It has been used as initial therapy for *C. difficile* infections for many years, but recent evidence suggests that oral vancomycin is superior [39–41]. Metronidazole can cause a metallic taste and when used for extended courses, peripheral neuropathy.

Tetracyclines

Tetracyclines are active against both Gram-positive and Gram-negative bacteria as well as atypical agents such as *Mycoplasma*, rickettsia, and *Borrelia burgdorferi* (the major cause of Lyme disease in the U.S.). Doxycycline is available intravenously and orally and is more commonly prescribed than tetracycline in the U.S. Tetracyclines can be used for the treatment of atypical pneumonia caused by *Mycoplasma* or *Chlamydia pneumoniae*. These agents are also used to treat skin and soft tissue infections caused by MRSA, although many MRSA isolates are resistant. Sun sensitivity (sunburn) can occur with the use of the tetracyclines and patients should be advised to wear sunscreen. Tigecycline is a tetracycline derivative, available only intravenously, that was FDA-approved in 2005. However, tigecycline received an FDA "black box warning" in 2010 due to increased all-cause mortality observed in patients treated with tigecycline versus comparator drugs. The cause of

the higher mortality rate in the tigecycline-treated patients is unknown. Tigecycline has broad-spectrum activity and is used primarily to treat those MDRO infections that are resistant to other antibiotics. It is not active against *Pseudomonas*. Tigecycline does not achieve high serum concentrations and should not be used for bacteremia.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole is active against *Staphylococcus* species as well as Gram-negative bacteria including *H. influenzae*, *Escherichia coli*, *Proteus mirabilis*, and *Stenotrophomonas*. It has excellent bioavailability. It is a first-line agent for urinary tract infections due to susceptible pathogens and can be used to treat susceptible MRSA skin and soft tissue infections. It is important to understand the local susceptibilities of MRSA to be sure trimethoprim-sulfamethoxazole provides adequate therapy. It is also used as prophylaxis to prevent *Pneumocystis jivorecii* pneumonia in HIV patients with low CD4 counts and in solid organ and hematopoetic stem cell transplant recipients.

Vancomycin and Other Glycopeptides

Vancomycin. Vancomycin, FDA-approved in 1958, has activity only against Gram-positive bacteria. Intravenous vancomycin is primarily used to treat infections due to resistant *Staphylococcus* species, *Streptococcus* species, and *Enterococcus* species, while oral vancomycin is used to treat *C. difficile* infections. Oral vancomycin is not absorbed so cannot be used to treat systemic infections. Intravenous vancomycin is the drug of choice for susceptible MRSA infections including bacteremia and pneumonia. Vancomycin can be used for treating *S. aureus* (MSSA) infections in patients who cannot tolerate beta-lactam therapy, but beta-lactam antibiotics clear MSSA bacteremia more quickly. Dosing is based on renal function and weight. Serum vancomycin trough levels should be monitored to achieve therapeutic drug concentrations and minimize toxicity. Renal toxicity can occur with high doses. "Red man syndrome" is a vancomycin infusion reaction due to histamine release that presents with rash, itching, flushing, and sometimes hypotension. It typically occurs with rapid infusion of the antibiotic and can usually be avoided with slower infusion rates.

Other glycopeptides. Telavancin, dalbavancin, and oritavancin are lipoglycopeptides that were FDA-approved in 2009 (telavancin) and 2014 (dalbavancin, oritavancin). They are in the same antibiotic class as vancomycin and have similar activity, but these newer agents have the advantage of once-daily dosing (televancin) or once-weekly dosing (dalbavancin and oritavancin). The once-weekly regimens are only approved for skin and soft tissue infections. Use of these agents should be with guidance from an infectious disease specialist.

Miscellaneous Antibiotics for Urinary Tract Infections

Fosfomycin and nitrofurantoin. Fosfomycin and nitrofurantoin are oral agents available for the treatment of uncomplicated urinary tract infections. Fosfomycin can be administered as a one-time dose. Nitrofurantoin can only be given to those with relatively normal renal function as it requires adequate excretion into the urine to be effective. These agents, along with trimethoprim-sulfamethoxazole, are excellent treatments for uncomplicated urinary tract infections due to susceptible bacteria [20].

Treatment of Infections Due to Multidrug-Resistant Organisms

For MDRO infections, consultation with an infectious disease specialist is recommended. Several of the antibiotics discussed above, such as linezolid, are approved for the treatment of infections caused by resistant Gram-positive bacteria including MRSA and VRE. For treating

infections due to resistant Gram-negative bacilli, there are several options but treatment should be guided by results of susceptibility testing. Ceftolozane-tazobactam and ceftazidime-avibactam have been recently approved (2014, 2015 respectively) for treatment of urinary tract infections and intra-abdominal infections. Ceftolozane-tazobactam was developed to treat highly resistant *Pseudomonas aeruginosa*. It also has activity against many other MDRO Gram-negative bacilli but not those with carbapenamases. Ceftazidime-avibactam is active against resistant Gram-negative bacilli including some that produce carbapenemases.

Other antibiotics used for highly drug-resistant organisms include tigecycline and polymyxins (e.g., colistin). These are primarily drugs of last resort and should be used with guidance from an infectious disease specialist.

Antifungal Agents

Fungal infections are generally divided into yeast infections and mold infections. Most yeast infections in otolaryngology are due to *Candida* species. Mold infections, such as those due to *Aspergillus* and the agents of mucormycosis, are much more difficult to treat than *Candida* infections. In general, antifungal antibiotics with activity against molds also treat *Candida*, while the reverse is not true. Results of antifungal susceptibility testing for *Candida* species are clinically meaningful (correlate with response to therapy), but the same is not true for molds. For treatment of invasive mold infections, results of clinical trials using various antifungal agents have proven to be most reliable in guiding therapy.

Amphotericin. Amphotericin B treats nearly all molds and *Candida* species but has significant toxicities, including renal. Liposomal amphotericin is at least as effective as amphotericin B and has significantly less renal toxicity, but is much more expensive. Both the agents are only available intravenously.

Azoles. The major azoles available in the U.S. are fluconazole, itraconazole, voriconazole, posaconazole, and most recently isavuconazonium sulfate (metabolized to isavuconazole). Azoles have high bioavailability so oral and intravenous formulations often achieve similar serum levels. Fluconazole achieves excellent tissue penetration and is effective against nearly all strains of *Candida albicans*, although some other *Candida* species may be resistant. Fluconazole is not effective against molds. Itraconazole has some activity against molds but therapeutic serum drug levels are difficult to achieve, and itraconazole is less effective against *Aspergillus* than voriconazole. Voriconazole, available orally and intravenously, is the treatment of choice for invasive *Aspergillus* infections. It also has activity against some other molds (e.g., *Fusarium*) although not against the molds that cause mucormycosis (e.g., *Rhizopus*, *Mucor*). Oral voriconazole has excellent bioavailability. Posaconazole has activity against fungi that cause mucormycosis and is available orally and intravenously. Posaconazole is FDA-approved only for the treatment of refractory oropharyngeal candidiasis and for prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk patients, such as immunocompromised hosts. Posaconazole is frequently used as step-down oral therapy in invasive mold infections such as mucormycosis after an initial course of treatment with amphotericin or liposomal amphotericin. Isavuconazonium sulfate (metabolized to isavuconazole) is available both intravenously and orally and has broad-spectrum antifungal activity, including against both *Aspergillus* and the agents of mucormycosis. See Chap. 15 for discussion of invasive fungal sinusitis. Hepatotoxicity is an important side effect of azoles and liver function tests should be monitored. All azoles, except for isavuconazonium sulfate, can prolong the QTc interval and this should be monitored closely while on therapy. Isavuconazonium sulfate can shorten the QTc interval. Azoles are metabolized through the CYP3A4 pathway of the liver and therefore have many drug-drug-interactions. Healthcare providers should evaluate potential interactions with a

patient's other medications before prescribing azoles.

Echinocandins. Echinocandins, including caspofungin and micofungin, are primarily used to treat serious infections due to *Candida* species that are resistant to fluconazole. Echinocandins are generally well tolerated but are available only intravenously.

Conclusion

The discovery of sulfa drugs in 1932 and the first clinical use of penicillin in 1941 ushered in the modern antibiotic era. The introduction of each new antibiotic, however, has been followed by the development of microbial resistance to that antibiotic. Many bacteria are now resistant to multiple classes of antibiotics. It is important for clinicians to use antibiotics appropriately and prudently, as unnecessary antibiotic use contributes to the selection of increasingly resistant organisms.

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