EDUCATIONAL COMMENTARY – A PRIMER IN ANTIBIOTICS FOR THE LABORATORY PROFESSIONAL

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Learning Objectives

On completion of this exercise, the participant should be able to

• describe the role of the clinical microbiology laboratory in antibiotic prescribing;
• discuss empiric, definitive, and prophylactic antimicrobial therapy;
• explain the clinical approach to prescribing antibiotics;
• compare the different classes of antibiotics, providing examples of each; and
• summarize the mechanism of action for each class of antibiotics.

Introduction

The terms antimicrobial, anti-infective, and antibiotic encompass a wide variety of pharmaceutical agents that include antibacterial, antimycobacterial, antifungal, antiviral, and antiparasitic drugs. An antibiotic is an antibacterial agent that inhibits the growth of or destroys microorganisms. They are commonly used to treat bacterial infections and are one of the types of medications most frequently prescribed by physicians.

An antibiotic may kill a bacterial organism or inhibit its growth. Antibiotics that inhibit the growth of the organism without killing it are termed bacteriostatic. Bacteriostatic antibiotics work with the patient’s immune system to resolve the infection. Bactericidal antibiotics kill the organism without any help from the immune system. Bactericidal antibiotics are necessary in patients with a weakened immune system such as those with a neutropenic syndrome, or in severe infections such as septicemia or meningitis.

Types of Antimicrobial Therapy

The use of antimicrobial chemotherapy falls into one of three general categories: prophylaxis, empiric use, and definitive therapy.

Prophylactic Therapy

Prophylaxis is treatment given to prevent an infection that has not yet developed. Clinicians use prophylactic therapy in situations in which a patient has a high risk of developing an infection. Examples include patients who are taking immunosuppressive therapy, who are having surgery, or are traveling to a
region where a specific microorganism is endemic and there is a high probability of contracting the infection.

Empiric Therapy

Unlike prophylactic therapy, empiric therapy is given to patients who have a proven or suspected infection, but the causative organism(s) has not yet been identified or the antimicrobial susceptibility testing results have not been reported. Because the entire process from specimen collection to organism identification and antimicrobial susceptibility testing can take several days, empiric therapy is often initiated to start treatment of the infection. It is a “best guess” of which antimicrobial agent(s) will be most active against the likely cause of infection. Empiric therapy often includes the use of select broad-spectrum antimicrobial agents, and sometimes a combination of antibiotics, with the intent to cover the possible pathogens commonly associated with the patient’s specific clinical syndrome.1-3

Definitive Therapy

After the clinical microbiology laboratory has identified the etiologic pathogen(s) via culture or other detection tests and antimicrobial susceptibility testing, if applicable, has been performed, the definitive therapy phase of antimicrobial treatment can begin. This form of therapy is also referred to as directed or targeted antimicrobial therapy. Once the antimicrobial susceptibility data are available and reviewed by the clinician, the patient’s antimicrobial therapy is targeted to the specific cause and site of the infection, and there is an attempt to narrow the antibiotic spectrum. This step is a crucial part of antimicrobial therapy, because it can reduce the cost and toxic effects to the patient and prevent the emergence of antimicrobial-resistant organisms.

Considerations for Prescribing Antimicrobial Therapy

Clinicians must consider many factors when prescribing antimicrobial therapy for treatment of infections. Antibiotic considerations include the spectrum of activity, ability to reach the site of infection, cost, safety, form of administration (e.g., intravenous or oral), and adverse effects.1-3

Patient considerations include the specific clinical syndrome,3 age, pregnancy or lactation status, history of allergies or intolerances to antimicrobial agents, renal and hepatic function, and history of recent antimicrobial use.1 Renal and hepatic function must be evaluated because most antibiotics are metabolized by the liver and eliminated from the body by the kidneys.2 Prior to prescribing antibiotics, it is important to consider whether any antimicrobial therapy has been administered in the past 3 months for the same infection. Development of resistance or a change in infecting microorganism are possibilities in unresolved or repeat infections of the same site.
The pharmacokinetic/pharmacodynamic properties of the antibiotic must be considered along with the patient factors. Antibiotic pharmacokinetics refers to the absorption (how antibiotics enter the body), distribution (where they go once inside), and metabolism/excretion (how they are removed). Pharmacokinetics is key to the effectiveness of the antibiotic and treatment of the infection. Pharmacodynamics refers to the relationship between concentration and the antimicrobial effect, or how the antibiotic interacts with the microorganism causing the infection. This is often determined via antimicrobial susceptibility testing in the clinical microbiology laboratory by obtaining a minimum inhibitory concentration (MIC). Whether the antibiotic is bacteriostatic or bactericidal should be considered. Antibiotic pharmacokinetic/pharmacodynamic relationships must be carefully considered in terms of time-dependent vs concentration-dependent killing. Antibiotics that exhibit time-dependent activity, such as β-lactams and vancomycin, need a dosing regimen wherein the patient's serum concentration of antibiotic exceeds the MIC for the duration of the dosing interval. Administration of these antibiotics often involves continuous or prolonged infusions because of their time-dependent activity. Antibiotics that exhibit concentration-dependent killing, such as aminoglycosides, have enhanced bactericidal activity when the serum concentration is increased. In these types of agents, the peak serum concentration is closely associated with clinical efficacy, so they are administered as a single, large, daily dose to achieve the concentration-dependent activity.1,2

Microorganism factors that contribute to antibiotic selection include the identity of the pathogen causing infection, body site infected, susceptibility profile, ability to develop resistance, and length of therapy necessary to resolve the infection.2,7

Role of the Laboratory Professional

The clinical microbiologist plays an important role in antimicrobial prescribing by identifying the microorganism causing the infection and performing antimicrobial susceptibility testing. The susceptibility profile guides the clinician's selection of antibiotic to treat the patient's infection. As a key player in the treatment of infectious disease, it is imperative that the clinical microbiologist have an understanding of the different antibiotics and their classes. Clinical microbiologists should be well versed in the antibiotic mechanism of action, spectrum of activity, appropriate antibiotics for the type of infection, and prescribing considerations of the clinician.

Classes of Antibiotics

Each antibiotic class has a mechanism of action, the process by which the antibiotic kills (or inhibits the growth of) the microorganism. In addition, antibiotics have a spectrum of activity, or the number of types of bacteria affected by the drug. Spectrum of activity is thought of as, “does this drug cover this bug?” Broader-spectrum agents affect the growth of many different types of bacteria, whereas narrow-spectrum...
agents affect the growth of fewer types of bacteria, sometimes one or two genera. Spectrum of activity is a complicated concept and may vary depending on the organism. Some antibiotics are always active against some organisms (e.g., penicillin to treat *Streptococcus pyogenes*), and some antibiotics are never active against some organisms (e.g., vancomycin to treat gram-negative rods). More often, there is a degree of variability in susceptibility across different isolates of organisms, which results in an undefined pattern of susceptibility (e.g., ampicillin and *Escherichia coli*). Clinicians also consider the clinical syndrome, or body site infected, when prescribing antibiotics, because some antimicrobial agents can reach only specific body sites and different antibiotics treat the most probable pathogens from specific clinical syndromes.

**β-Lactams**

β-Lactam antibiotics include a wide variety of broad-spectrum and narrow-spectrum antibacterial agents. Penicillins, cephalosporins, carbapenems, monobactams, and β-lactam/β-lactamase–inhibitor combinations are all within this class. β-Lactam antibiotics’ mechanism of action is the inhibition of transpeptidases in the bacterial cell wall. They act by binding to the penicillin-binding proteins, which are enzymes that mediate peptidoglycan cross-linking. This inhibits the cross-linking of peptidoglycan in the cell wall, inhibiting cell wall synthesis, which leads to autolysis and cell death of the bacteria.2-6

**Penicillins (β-Lactam)**

Within the β-lactam antibiotics is the penicillin group. Penicillins are not created equal and can be divided into subgroups including the natural penicillins, antistaphylococcal penicillins, amino penicillins, antipseudomonal penicillins, and β-lactam/β-lactamase–inhibitor combinations.3,4 The natural penicillins are penicillin G and penicillin V. Resistance to the natural penicillins has developed substantially but they still have good activity toward *Treponema pallidum* and most streptococci. They have moderate activity against enterococci and poor activity against other organisms, including staphylococci, which are almost universally resistant. Most often, the natural penicillins are used to treat syphilis and susceptible bacterial streptococcal infections such as pharyngitis and endocarditis.3,4

The antistaphylococcal penicillins were developed to treat staphylococcal infections in which the organism produces β-lactamases (i.e., penicillinases), rendering the natural penicillins useless. This subgroup includes nafcillin, oxacillin, and methicillin.3,4 Methicillin is no longer used for treatment of patient infections but is a historical name for the multidrug-resistant *Staphylococcus aureus*, methicillin-resistant *S aureus* (MRSA).6 Antistaphylococcal penicillins have good activity toward methicillin-susceptible *S aureus* (MSSA) and streptococci. They have poor activity toward gram-negative rods (GNRs), enterococci, anaerobes, and MRSA. They are often used to treat infections caused by MSSA, such as skin and soft-tissue infections.3,4
Gram-negative coverage within the penicillins includes the use of aminopenicillins and antipseudomonal penicillins. The aminopenicillins include amoxicillin and ampicillin, agents that are inactivated by β-lactamases. The aminopenicillins are rarely active against staphylococci, because they produce penicillinases, and they do not have useful activity against *Pseudomonas aeruginosa*. They do have good activity toward streptococci, enterococci, susceptible enteric GNRs, and *Haemophilus*. Amoxicillin is frequently prescribed for infections of the upper respiratory tract, including streptococcal pharyngitis and otitis media.3,4

Antipseudomonal penicillins include piperacillin and ticarcillin. These agents are active against *P aeruginosa* and other, more drug-resistant, GNRs, but are also inactivated by β-lactamases. They are not used alone for treatment but instead in combination with β-lactamase inhibitors such as tazobactam for treatment of *P aeruginosa* and other resistant GNR infections.3,4

**Cephalosporins (β-Lactam)**

The cephalosporins consist of many different antibiotics and are grouped into “generations” that correlate with their spectrum of activity. To date, there are first- through fourth-generation cephalosporins and a final cephalosporin with anti-MRSA activity.3,4 Most health care facilities use a few select individual cephalosporins, because it is not feasible to stock them all.

Common first-generation cephalosporins include cefazolin and cephalexin. Their spectrum of activity is good for MSSA, streptococcal infections, and susceptible enteric GNRs. They have poor activity toward MRSA, *Pseudomonas*, anaerobes, and enterococci. First-generation cephalosporins are often used for treatment of skin infections, staphylococcal bloodstream infections, and MSSA endocarditis.3,4 It is important to state that first-generation cephalosporins do not cross the blood-brain barrier and should not be used for central nervous system infections.4

Second-generation cephalosporins have better gram-negative activity and somewhat weaker gram-positive activity than first-generation cephalosporins. Examples of second-generation cephalosporins include cefuroxime and cefprozil. They have good activity against susceptible enteric GNRs, *Haemophilus*, and *Neisseria*, owing to their stability to β-lactamases. They have poor activity against enterococci, anaerobes, MRSA, and *Pseudomonas*. Like first-generation cephalosporins, they do not cross the blood-brain barrier efficiently and should not be used to treat central nervous system infections.4 Second-generation cephalosporins are good for treatment of upper respiratory tract infections, community-acquired pneumonia, and surgical prophylaxis.2,4

Another class of antibiotic is the cephemycins. They are grouped with the second-generation cephalosporins because they have similar activity, with the exception of anaerobes. Cephemycins have
activity against many anaerobes in the gastrointestinal tract and are often used for surgical prophylaxis in abdominal surgery.\textsuperscript{2-4} These antibiotics are also used as predictors of specific resistance mechanisms in antimicrobial susceptibility testing.\textsuperscript{6,7}

Third-generation cephalosporins have greater gram-negative activity than the first- and second-generation agents. Common examples include ceftazidime, cefdinir, ceftriaxone, and cefotaxime. They have good activity against streptococci (except ceftazidime), enteric GNRs, and \textit{Pseudomonas} (ceftazidime only). They have poor activity against enterococci, anaerobes, MRSA, and \textit{Pseudomonas} (except ceftazidime). The third-generation cephalosporins are broad-spectrum antibiotics that are used to treat lower respiratory tract infections, meningitis, gonorrhea, skin infections, and pyelonephritis.\textsuperscript{2-4} It is important to note that these antibiotics can induce resistance among GNRs, and overutilization can result in resistance.\textsuperscript{7}

There is only one fourth-generation cephalosporin approved in the United States, cefepime. It is the broadest-spectrum cephalosporin, with activity against gram-negative and gram-positive organisms. It has good activity against MSSA, \textit{Pseudomonas}, enteric GNRs, and streptococci. It has poor activity against enterococci, anaerobes, and MRSA. Cefepime is used primarily for nosocomial infections.\textsuperscript{2-4}

The last cephalosporin to be developed is ceftaroline. It is a β-lactam agent that has anti-MRSA activity, unlike other β-lactam antibiotics. Some authors refer to it as “the fifth-generation cephalosporin,” but it has poor activity toward \textit{P aeruginosa}, \textit{Enterococcus faecalis}, \textit{Acinetobacter}, and anaerobes. It does have good activity toward MSSA, streptococci, enteric GNRs, and MRSA and moderate activity toward \textit{Enterococcus faecalis}.\textsuperscript{2-4} In the United States, ceftaroline is approved for treatment of complicated skin and soft-tissue infections and community-acquired pneumonia.\textsuperscript{4} Ceftaroline’s most important characteristic is its activity against MRSA, which is why the Clinical Laboratory Standards Institute has designated it an anti-MRSA cephalosporin.\textsuperscript{7}

\textbf{β-Lactamase Inhibitor Combinations (β-Lactam)}

β-lactamase inhibitor combinations are β-lactam antibiotics that are combined with a β-lactamase inhibitor. β-lactamase inhibitors include clavulanate (clavulanic acid), sulbactam, tazobactam, and avibactam. These drugs mimic the structure of β-lactam antibiotics but have limited antibacterial activity. They were developed to counteract the resistance mechanism of organisms that produce β-lactamases. The inhibitors bind to the β-lactamase produced by the organism, which prevents the β-lactamase from destroying the antibiotic that is coadministered. They allow the antibiotic to work to resolve the patient’s infection although the bacteria possess a resistance mechanism.\textsuperscript{6}
The penicillin/β-lactamase inhibitor combinations include ampicillin/sulbactam, amoxicillin/clavulanate, and piperacillin/tazobactam. They have good activity against enteric GNRs, MSSA, streptococci, enterococci, anaerobes, and *P aeruginosa* (piperacillin/tazobactam only). They have poor activity against MRSA. The penicillin/β-lactamase inhibitor combinations are used for empiric therapy for nosocomial infections, diabetic ulcers, aspiration pneumonia, and mixed aerobic and anaerobic infections such as abdominal infections. Amoxicillin/clavulanate is used for upper and lower respiratory tract infections when β-lactamase–producing organisms are identified or suspected.\(^2\)\(^-\)\(^4\)

The cephalosporin/β-lactamase inhibitor combinations include ceftazidime/avibactam and ceftolozane/tazobactam. These combinations are recently developed antibiotics that fight infections caused by organisms that produce carbapenemases, which render carbapenem antibiotics ineffective. Avibactam is the newest β-lactamase inhibitor and has a different mechanism of action, which works against many β-lactamases produced by *Klebsiella pneumoniae* and *P aeruginosa*.\(^4\) The cephalosporin/β-lactamase–inhibitor combinations have good activity against *Pseudomonas* and enteric GNRs. They have poor activity to MRSA, MSSA, *Acinetobacter*, and anaerobes. These antimicrobial agents should be reserved for resistant GNR infections. Both can be used for multidrug-resistant *Pseudomonas* infections, intra-abdominal infections, and mixed aerobic/anaerobic infections caused by extended-spectrum β-lactamase–producing organisms. Ceftazidime/avibactam is useful against carbapenem-resistant Enterobacteriaceae infections.\(^2\)\(^-\)\(^4\)

**Carbapenems (β-Lactam)**

Carbapenems are the broadest-spectrum antibacterial drugs that treat both gram-positive and gram-negative infections. Examples include imipenem, meropenem, ertapenem, and doripenem. They are structurally different from the penicillins and cephalosporins, making them less susceptible to resistance mechanisms.\(^8\) Imipenem, meropenem, and doripenem have a similar spectrum of activity, whereas ertapenem has decreased activity for certain organisms, including *Pseudomonas* and *Acinetobacter*. Carbapenems have good activity against enteric GNRs, extended-spectrum β-lactamase–producing GNRs, MSSA, streptococci, anaerobes, *Pseudomonas* (except ertapenem) and *Acinetobacter* (except ertapenem). They have poor activity against MRSA and penicillin-resistant streptococci.\(^2\)\(^-\)\(^4\)

Carbapenems are used to treat mixed aerobic and anaerobic infections, intra-abdominal infections, and infections caused by extended-spectrum β-lactamase–producing organisms. They are not recommended for general empiric therapy because of their exceedingly broad-spectrum activity and the availability of other broad-spectrum agents. Specific situations may warrant the use of carbapenems for empiric therapy; therefore, usage of these drugs is often under scrutiny by Antimicrobial Stewardship Teams.
They can be a good choice for empiric therapy for some types of nosocomial infections, particularly in patients not responding to other antimicrobial therapy.\textsuperscript{2-4}

**Monobactams (β-Lactam)**

Aztreonam is the only monobactam. It has good activity toward most GNRs including *Pseudomonas*. It has poor activity against gram-positive organisms and anaerobes. Aztreonam can be used to treat gram-negative infections, particularly in patients with a history of β-lactam allergy. It does not seem to elicit the same allergic response as other β-lactam antibiotics, except in patients with a specific allergy to eftazidime.\textsuperscript{4}

**Glycopeptides and Lipoglycopeptides**

Glycopeptide antibiotics are cell wall–active antimicrobial agents that bind to the terminal D-ala-D-ala chains on peptidoglycan in the cell wall, which prevents elongation of the peptidoglycan chains. The two glycopeptides available in the United States are vancomycin and telavancin (which was recently approved).\textsuperscript{2,4} Telavancin is a lipoglycopeptide that was modified from vancomycin’s structure to have improved activity against MRSA that is less susceptible to vancomycin.\textsuperscript{2,4} Nephrotoxicity can result with the administration of vancomycin, and the dosage should be adjusted for patients with impaired renal function.\textsuperscript{4}

In general, gram-positive organisms are susceptible to vancomycin, and this drug is invaluable for the treatment of MRSA. There have been a few noted vancomycin-resistant *S. aureus*, but this is rare.\textsuperscript{6} However, a phenomenon known as “MIC creep” has been noted with *S. aureus* and vancomycin. The MICs of *S. aureus* to vancomycin have been rising in many institutions, particularly in patients receiving vancomycin for severe infections. The MIC has not reached a range where the organism is resistant, but stays 2.0 µg/mL or less within the susceptible range.\textsuperscript{7} These data should be monitored closely, because outcomes for serious infections caused by *S. aureus* with an MIC of 2 µg/mL to vancomycin are worse than those with lower MICs.\textsuperscript{6} Enterococci, specifically *E. faecium*, have developed resistance mechanisms to vancomycin, and are termed vancomycin-resistant enterococci (VRE).\textsuperscript{4,6,7}

Glycopeptides have good activity toward MRSA, MSSA, streptococci, and *Clostridioides difficile*. They have moderate activity toward susceptible enterococci and poor activity toward gram-negative organisms. Vancomycin is the drug of choice for MRSA infections and for empiric use when MRSA is suspected. It is important to remember that if MRSA has been ruled out and the infection is caused by MSSA, a β-lactam antibiotic will resolve the patient’s infection faster and with fewer toxic effects, so cefazolin, nafcillin, or oxacillin should be used.\textsuperscript{4} Vancomycin is also used for gram-positive infections in patients with severe β-lactam allergy. Telavancin is approved for skin infections and hospital-acquired pneumonia.\textsuperscript{2-4}
Aminoglycosides

Gentamicin, tobramycin, amikacin, and streptomycin are examples of aminoglycosides. Their mechanism of action is to inhibit protein synthesis by binding to the bacterial ribosome, causing misreading of the genetic code. The use of aminoglycosides has decreased owing to their risk for toxic effects to the kidneys and eyes.

Gentamicin, tobramycin, and amikacin have good activity toward GNRs including *Pseudomonas* and *Acinetobacter*. They have moderate activity toward staphylococci, enterococci, and viridans streptococci when combined with a β-lactam or glycopeptide antibiotic. For treatment of enterococcal infections, gentamicin and streptomycin are the best choices. Aminoglycosides have poor activity toward anaerobes, atypical bacteria, and gram-positive organisms when used as the sole antibiotic. Atypical bacteria include *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

Aminoglycosides are used in combination with other antibiotics for treatment of serious infections, including endocarditis, osteomyelitis, and sepsis. For serious gram-positive infections, an aminoglycoside, most commonly gentamicin, is used in conjunction with a β-lactam or glycopeptide antibiotic. For gram-negative pathogens, a β-lactam agent is combined with an aminoglycoside for treatment of sepsis, ventilator-associated pneumonia, and febrile pneumonia.

Fluoroquinolones

Fluoroquinolones interfere with DNA synthesis in microorganisms by inhibiting DNA topoisomerases. This mechanism of action leads to breaks in the DNA and death of the cell. Fluoroquinolones are broad-spectrum antimicrobial drugs that can be used to treat gram-positive, gram-negative, and atypical organisms. For this reason, they have been overprescribed and there has been an increase in antimicrobial resistance to the fluoroquinolones. Examples of fluoroquinolones include ciprofloxacin, moxifloxacin, levofloxacin, and gemifloxacin. The US Food and Drug Administration has issued a black box warning on the use of fluoroquinolones because they have been associated with tendinitis, tendon rupture, peripheral neuropathy, and adverse effects on the central nervous system.

Ciprofloxacin has good activity toward enteric GNRs and *H. influenzae*. It has poor activity toward enterococci, staphylococci, *Streptococcus pneumoniae*, and anaerobes. Levofloxacin, moxifloxacin, and gemifloxacin have excellent activity toward *S. pneumoniae* and good activity toward enteric GNRs, atypical bacteria, and *H. influenzae*. They have poor activity toward enterococci and anaerobes. Fluoroquinolones have different indications, depending on the antibiotic. These include treatment of community-acquired pneumonia, sinusitis, urinary tract infections, intra-abdominal infections, systemic gram-negative infections, and skin/soft-tissue infections.
Macrolides

Macrolides include clarithromycin, azithromycin, and erythromycin. They work by inhibiting ribosomal synthesis by binding to the 50S subunit of the ribosome, which prevents the elongation of the protein chain. These antibiotics have good activity toward atypical bacteria, *H influenzae*, *Moraxella catarrhalis*, and *Helicobacter pylori*. They have moderate activity toward *S pneumoniae* and *Streptococcus pyogenes* but poor activity to staphylococci, enteric GNRs, enterococci, and anaerobes. The macrolide antibiotics are often used to treat upper and lower respiratory tract infections and chlamydia. Azithromycin is used for traveler’s diarrhea, and clarithromycin is the go-to antibiotic for treatment of *H pylori* ulcer disease in combination with other medications.

*Fidaxomicin*

Fidaxomicin is a new macrolide antibiotic that inhibits ribosomal protein synthesis. It differs from the other macrolides in that it is not absorbed in the gastrointestinal tract and currently has one indication for use. Fidaxomicin is used for the treatment of *C difficile* infections.

*Oxazolidinones*

The two oxazolidinones currently available in the U.S. are linezolid and tedizolid. They have activity toward gram-positive organisms. The oxazolidinones inhibit protein synthesis by binding to the 50S ribosomal subunit, which blocks the formation of the 70S initiation complex and prevents translation. They have good activity toward MRSA, MSSA, streptococci, and enterococci. They have poor activity to all gram-negative organisms and anaerobes. The oxazolidinones are agents used to treat multidrug-resistant organisms including *S pneumoniae* and enterococci (including VRE). Linezolid is a key antibiotic for treatment of MRSA infections. It is prescribed for pneumonia, skin infections, urinary tract infections, and other infections. Tedizolid is currently only indicated for skin infections.

*Tetracyclines*

Tetracyclines also inhibit ribosomal synthesis by binding to the bacteria ribosome, which prevents the docking of transfer RNA carrying new amino acids. Examples include doxycycline, minocycline, tetracycline, and tigecycline.

Tetracycline, doxycycline, and minocycline have good activity toward atypical bacteria, rickettsia, spirochetes, and *Plasmodium* species. They have poor activity against GNRs, anaerobes, and enterococci. Tigecycline has good activity toward atypical bacteria, staphylococci including MRSA, enterococci including VRE, and *S pneumoniae*. It has poor activity against *Pseudomonas, Proteus*, and *Providencia*. Tetracyclines are used to treat uncomplicated respiratory tract infections such as sinusitis, community-acquired pneumonia, and bronchitis. They are also the drug of choice for tick-borne diseases
owing to their good activity toward rickettsia and spirochetes. Malaria prophylaxis and treatment is also an indication for tetracycline.2-4

Cyclic Lipopeptides

Daptomycin is the only cyclic lipopeptide and has a unique mechanism of action. It inserts itself into the cell membrane of gram-positive organisms, which leads to the leakage of cations, cell depolarization, and rapid death.5,6 It has good activity toward MSSA, MRSA, and streptococci. Daptomycin does exhibit moderate activity toward enterococci including VRE, but poor activity toward gram-negative organisms. This agent is used to treat skin infections caused by gram-positive organisms and staphylococcal bacteremia.2-4

Folate Antagonists

The most common folate antagonist is the combination antibiotic trimethoprim/sulfamethoxazole (TMP/SMX). These agents inhibit the steps in the folate synthesis pathway of bacteria, which ultimately leads to the inhibition of DNA synthesis.5,6 TMP/SMX has good activity toward S. aureus including many MRSA strains, H. influenzae, Stenotrophomonas maltophilia, Listeria, Pneumocystis jirovecii, and Toxoplasma gondii. TMP/SMX is an important treatment option for susceptible MRSA infections. It has poor activity against Pseudomonas, enterococci, and anaerobes. TMP/SMX is used for treatment of uncomplicated urinary tract infections, treatment of Listeria meningitis, treatment and prophylaxis for P. jirovecii pneumonias, and treatment of Toxoplasma encephalitis.2-4

Lincosamides

Clindamycin acts by binding to the 50S ribosome to prevent protein synthesis.5,6 It has good activity toward many gram-positive anaerobes, Plasmodium species, and S. pyogenes. It does exhibit moderate activity toward S. aureus including some MRSA, and gram-negative anaerobes. Clindamycin has poor activity toward enterococci, C. difficile, and gram-negative aerobes. This antibiotic is used to treat skin and soft-tissue infections, infections of the oral cavity, and anaerobic intra-abdominal infections. It is also used to treat bacterial vaginosis, and in combination with other drugs to treat malaria.2-4

Nitroimidazoles

Metronidazole and tinidazole are within the class of nitroimidazoles. These antibiotics are used to treat anaerobic bacteria and protozoal organisms that cause infections toward which other major drug classes are not active. Their mechanism of action is to damage DNA and cause cell death by activating part of the nitroimidazole molecule that forms free radicals.6 The nitroimidazoles have good activity toward gram-negative and gram-positive anaerobes, including Bacteroides, Fusobacterium, and
Clostridioides species. They also have excellent activity toward protozoa, including Trichomonas, Entamoeba, and Giardia. They have poor activity toward aerobic organisms and anaerobes that are normal flora in the mouth, including Peptostreptococcus, Actinomyces, and Propionibacterium. The nitroimidazoles are used to treat vaginal trichomoniasis and gastrointestinal infections caused by protozoans. Suspected or definitively identified anaerobic infections are treated with a nitroimidazole, and if a coinfection with an aerobic bacteria is present, an additional antibiotic is added. Metronidazole is an important treatment option for mild to moderate C difficile infections.2-4

Nitrofurantoin and Fosfomycin

Nitrofurantoin and fosfomycin have similar indications for treatment of bladder infections but different modes of action. Fosfomycin inhibits cell-wall synthesis by preventing the production of peptidoglycan.4,6 The mechanism of action of nitrofurantoin is not well understood. These two antibiotics have good activity toward E coli and Staphylococcus saprophyticus. This is why they are good for treatment of uncomplicated cystitis, especially with the emergence of E coli resistance to the fluoroquinolones and TMP/SMX which were previously first-line treatment agents. They have poor activity toward Acinetobacter and moderate activity to Citrobacter, Klebsiella, Proteus, enterococci, Pseudomonas (fosfomycin), and Serratia (fosfomycin).2-4

Streptogramins

The streptogramins are a combination of two agents, quinupristin and dalfopristin. They are two drugs combined in one formulation, which when given together act synergistically to produce bactericidal activity against some gram-positive cocci. The streptogramins’ mechanism of action is to bind to different sites on the 50S subunit of the bacterial ribosome to prevent protein synthesis.5 They have good activity to MRSA, MSSA, streptococci, and E faecium (including VRE), and poor activity to any gram-negative organism and E faecalis. Quinupristin/dalfopristin is mostly used for infections caused by MRSA or E faecium that do not respond to other antimicrobial drugs.2-4

Polymyxins

The polymyxins include colistin and polymyxin B. They bind to the outer membrane of gram-negative bacteria, leading to leakage of cellular contents and cell death.5,6 These antibiotics are an older class and have nephrotoxic and possibly neurotoxic adverse effects, which has decreased their use. They have good activity toward many GNRs, including multidrug-resistant organisms. They have poor activity toward gram-positive organisms, anaerobes, Providencia, Proteus, Burkholderia, and Serratia. The polymyxins are used for treatment of multidrug-resistant gram-negative infections, including pneumonia, bacteremia, sepsis, and complicated urinary tract infections.2-4
Conclusion

Antibiotics are one of the most frequently prescribed types of medications. Selection of antimicrobial therapy involves many important considerations. Clinicians must evaluate factors from the patient, the microorganism causing the infection, and antibiotic characteristics. Appropriate use of antimicrobial agents necessitates identification of the pathogen, pinpointing the site of infection, knowledge of the antibiotic spectrum of activity and uses, understanding the dosing effects of the antibiotic, and tailoring treatment to patient needs. The clinical laboratory microbiologist plays a key role in antibiotic selection by identifying the microorganism causing the infection and performing antimicrobial susceptibility testing. These test results directly inform the antimicrobial therapy decisions of the prescribing clinician. For these reasons, laboratory professionals should have an understanding of the antibiotic classes, their mechanism of action, spectrum of activity, and indications for treatment.

References


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