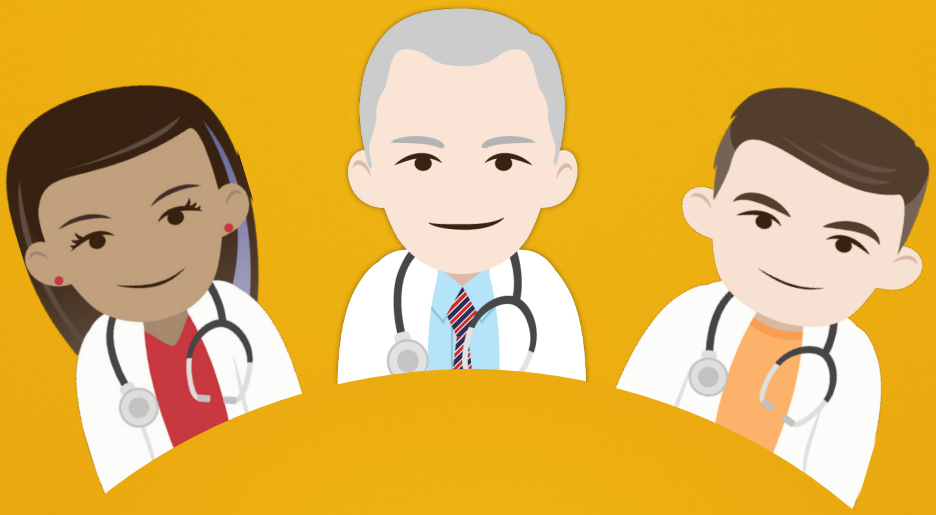
ANTIMICROBIAL STEWARDSHIP ESSENTIALS



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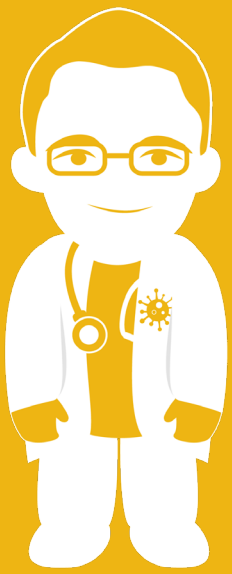
Chapter 1

AN INTRODUCTION TO ANTIMICROBIALS



Grasping the principles of antimicrobial therapy

Antimicrobial stewardship programs aim at minimizing the emergence of antimicrobial resistance through the judicious use of antibiotics. These strategies generally involve using antibiotics only when necessary and selecting the appropriate antibiotics at the right dose, frequency, and duration to optimize outcomes and minimize adverse effects.

Antimicrobial stewardship can reduce morbidity and mortality while also reducing health-care-related costs.

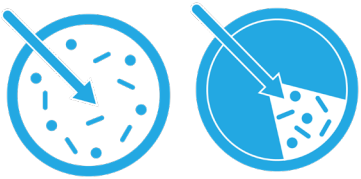
Some principles to keep in mind when treating patients with infectious diseases.

Make the diagnosis

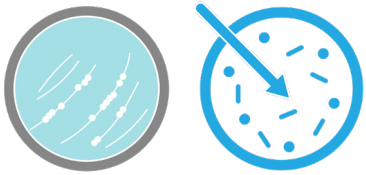
It is crucial to first make a precise diagnosis of the location of the infection and the microbial cause.

Identify opportunities to de-escalate

For many infections, empirical therapy with a broad-spectrum agent should be started immediately. However, once a precise microbial diagnosis has been made by culture, a physician should seek an opportunity to de-escalate or choose an antimicrobial agent, which is just as effective but has a more narrow-spectrum and therefore does not favor colonization by resistant organisms.



Unfortunately, if cultures are negative, a full course of the broad-spectrum compound may be necessary for the survival of the patient and de-escalation is impossible.



Understand drug characteristics

Choosing the correct antimicrobial depends on how the drug is handled (particularly with respect to absorption and excretion). For example, treating a urinary tract infection with an antibiotic that is metabolized by the liver and minimally excreted in urine, may not be a wise choice.

Whether to treat orally or intravenously depends, not only on the patient's condition, but also whether the chosen antibiotic attains achievable levels in blood or tissue when given by mouth. For example, vancomycin is an important antistaphylococcal drug, but must be given IV because oral absorption is negligible.

Consider dose, frequency, and duration

In general, always prescribe the maximum recommended dose for life-threatening infections. There is limited data for the appropriate duration for many infections. Clinical judgment can help for some of these. For example, when a patient treated with an antibiotic for pneumonia is no longer febrile, appetite has returned to baseline, and oxygenation has become satisfactory, the antibiotics can be continued for an additional 72 hours then stopped in most cases.

If an oral form of the antibiotic is available, the intravenous form may be stopped when the patient has reached baseline status, which will lessen

the impact on native flora and hopefully reduce the risk of developing antimicrobial resistance.

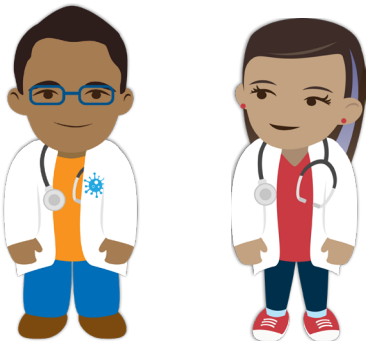
Consider adverse reactions

It is also important to understand the possible adverse effects associated with a drug, and how the development of side effects might affect your specific patient.

For example, choosing an aminoglycoside for an elderly person with hearing impairment and marginal renal function is generally unwise in light of the toxicity of aminoglycosides to the kidney and cranial nerve VIII.

Don't forget to ask for help

This is especially important for complicated patients with serious infections. Infectious disease physicians should be consulted.



If you keep these basic principles in mind, you will be better equipped to provide your patient with the most effective treatments, while minimizing the opportunity for the development of multidrug-resistant organisms.

Interpreting and verifying microscopy

Microscopy is a powerful method for making an on-the-spot diagnosis, and is therefore an important tool for diagnosing infectious diseases.

Gram's stain

Gram positive

Gram negative

- Used to stain bacteria

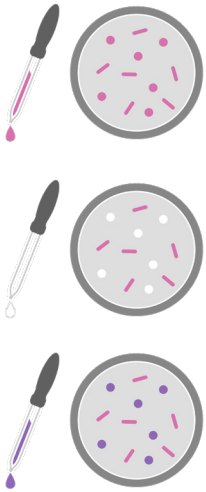
Gram-positive bacteria

- Thick outer layer of peptidoglycan on cell wall
- Appear blue

Gram-negative bacteria

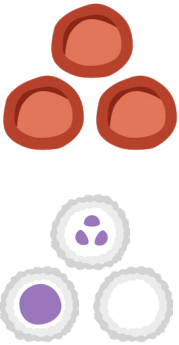
- Thin layer of peptidoglycan beneath an outer membrane
- Appear red

Acid-fast stain



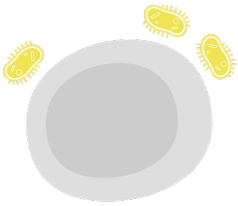
- Used to identify bacteria that take up Gram stain poorly (e.g., *Mycobacterium*, *Nocardia*)
- Acid-fast organisms retain the red dye (carbol-fuchsin) even after treatment with a decolorizing agent (e.g., hydrochloric acid)
- Non-acid-fast organisms are colourless after decolorization and are visualized using a blue counterstain
- Acid-fast organisms appear red
- Non-acid-fast organisms appear blue

Wright's stain



- Stains white and red blood cells
- Used to distinguish between types of white blood cells and view morphology of red blood cells
- Does not distort morphology of human cells because methanol is used as a fixative
- Can be used to look for intracellular parasites in red and white blood cells

Gram and acid-fast based smears are useful when identifying extra-cellular bacteria. When examining for intracellular microorganisms a stain which does not distort the morphology of red or white blood cells, such as Wright's stain, is best.



Gram / acid-fast

Wright's stain

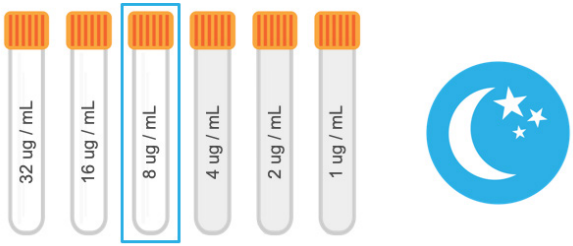
Wet mount

- Sample material placed directly on slide with a coverslip and viewed essentially as it comes out of patient
- Allows larger organisms to become visible (e.g., protozoa, worms, eggs, fungal hyphae, yeast, etc.)

Deciphering susceptibility testing

Minimal inhibitory concentration (MIC)

The minimal concentration of antibiotic in which visible growth of bacteria is inhibited.
In the original tube dilution method, the tubes below contain the test bacterium, broth to help it grow, plus the test antibiotic in decreasing concentrations (ug / mL). The tubes are incubated overnight and observed for growth of the test organism.



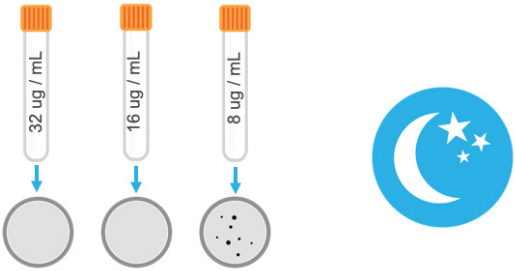
In this example, bacterial growth, indicated by cloudiness, is apparent in the tubes containing 1, 2, and 4 ug / mL drug concentrations. In the tubes with 32, 16, and 8 ug / mL, there is no visible growth. Therefore, the MIC is 8 ug / mL.

Minimal bactericidal concentration (MBC)

The lowest antibiotic concentration which kills all organisms.

In the example above, there is still a possibility that some living organisms may be present in the clear tubes—just not enough to cloud the tube.

To prove that there are no living organisms, broth from the clear tubes is plated on agar plates and incubated overnight again.



The black dots on the 8 ug / mL plate indicate bacterial growth. No growth is present on the other agar plates. Therefore, the MBC is 16 ug / mL.

Rating susceptibility

An organism is considered to be susceptible to an antibiotic when, at the usual doses, antibiotic levels in blood or tissue are **above the MIC**, intermediate when, at usual doses, the antibiotic levels in blood or tissue are **at the MIC** value, and resistant when, at the usual doses, the blood or tissue levels are **below the MIC**. These achievable blood levels vary among antimicrobials and are taken into account in automated systems used by the lab. Such systems allow for more efficient testing and smaller sample volume requirements.

Susceptible > MIC Intermediate = MIC Resistant < MIC

Appreciating multidrug-resistant organisms

Multidrug resistance is a major obstacle in the area of infectious disease.

Any organism has the potential to develop resistance to any antimicrobial drug at any time. However, due to the rampant use of antimicrobials over the past decades, there are a number of **multidrug-resistant (MDR) bacteria** that are now relatively commonplace, especially in the hospital setting. Because these do not respond to the traditional treatments, it is important for clinicians to be aware of situations in which there is a high(er) risk of the presence of MDR organisms.

Staphylococcus aureus

Methicillin resistance in *Staphylococcus aureus* (MRSA) was first recognized in the 1950s. Today, 50–70% of these organisms are resistant to methicillin. Methicillin is no longer used for staphylococcal infections because of a high incidence of interstitial nephritis with the drug. The resistance also applies to similar compounds, which are currently available like nafcillin and oxacillin as well as most beta-lactam antibiotics.

Risk factors for MRSA

- Recent hospitalization or surgery
- Nursing home residence
- Having an indwelling vascular catheter

Hospital-acquired MRSA is susceptible to fewer antibiotics than the community-acquired form.

Enterococcus faecium

Enterococcus spp are normal inhabitants of the gastrointestinal tract and are notorious for colonizing and / or infecting pressure sores. They may gain access to the bloodstream from these infections or from complicated urinary tract infections or following instrumentation of the urinary tract.

They cause about 10% of cases of infective endocarditis and are difficult to treat on native or especially prosthetic valves, producing high relapse rates.

Moreover enterococci, especially *E. faecium*, have increasingly developed resistance to antibiotics over many years of antibiotic use. *E. faecium* that are resistant to vancomycin (VRE) and ampicillin are now commonplace.

Acinetobacter baumannii

Acinetobacter baumannii is actually a complex of gram-negative coccobacillary organisms, which are ubiquitous in soil and water. Human carriage is on skin and in the pharynx.

It is a common nosocomial environmental contaminant found on hospital door handles, mops, keyboards, and mechanical ventilators. Almost 20% of the isolates are multidrug-resistant organisms. Infection with these organisms is often in the form of ventilator-associated pneumonia (VAP). Because of antimicrobial resistance along with serious illness, which prolongs hospital stays, the mortality from VAP due to *A. baumannii* approaches 70%.

Pseudomonas aeruginosa

Pseudomonas aeruginosa has been a notorious hospital pathogen since the mid-20th century and is the single most common cause of ventilator-associated pneumonia (VAP).

The organism has intrinsic resistance properties, such as the ability to produce a thick biofilm on endotracheal tubes, and is capable of acquiring multidrug-resistant genes. Moreover, unlike many enteric organisms, it has an arsenal of toxins, which target immune cells in the lungs.

Enterobacteriaceae

Organisms belonging to the *Enterobacteriaceae* family are residents of the human gastrointestinal tract.

This group is responsible for infections in many organ systems (including the following)

- Wound infections
- Urinary tract infections
- Gastrointestinal tract infections
- Pneumonia (both community-acquired and VAP)

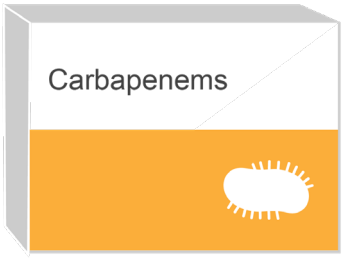
They are capable of acquiring a variety of resistance genes, including genes for beta-lactamases.

New beta-lactamase enzymes have since emerged that have rendered these organisms resistant to many of the extended-spectrum cephalosporins in common use. These have been referred to as ex-

tended-spectrum, beta-lactamases (ESBLs) and the organisms which possessed them were termed **ESBL-producing *Enterobacteriaceae***. These first appeared in *Klebsiella pneumoniae* and *E. coli* and in the non-*Enterobacteriaceae*, *P. aeruginosa*. Today 10–40% of these organisms in certain geographic areas possess these ESBLs.

Risk factors for ESBL-producing Enterobacteriaceae

- Diabetes mellitus
- Prior quinolone use
- Recurrent urinary tract infections
- Prior hospital admissions
- Older age

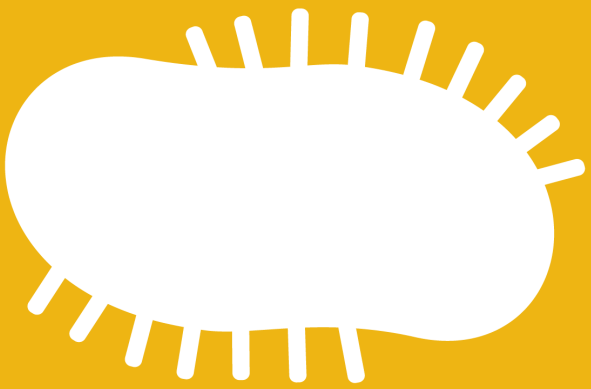


The drugs of choice for infections due to these organisms are the carbapenems.

To avoid development of resistance to carbapenems, it is crucial to curtail inappropriate use of extended-spectrum compounds and to de-escalate to narrow-spectrum agents whenever possible (after culture results and antibiotic susceptibilities are available).

Chapter 2

ANTIBIOTICS

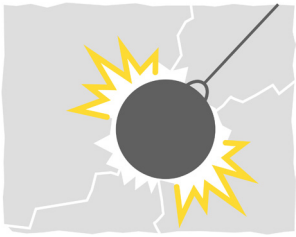


Administering penicillins

Some common examples are penicillin G, benzathine penicillin G, and aminopenicillins (amoxicillin, ampicillin).

Mechanism

Penicillins work by disrupting the bacterial cell wall, causing the bacteria to take on water and burst.



Spectrum

- Most gram-positive bacteria (e.g., *Streptococcus, Actinomyces*)
- Some gram-negative bacteria (e.g., *Neisseria meningitidis*)
- Aminopenicillins have better activity against gram-negative enteric rods (e.g., *E.coli*) than penicillin G
- No activity against *Staphylococcus aureus*

Indications

- Pharyngitis (tonsillitis), cellulitis, prevention of rheumatic fever caused by *Streptococcus pyogenes* (group A strep)
- Pneumonia due to penicillin-susceptible strains of *Streptococcus pneumoniae*
- Pneumococcal and meningococcal meningitis

- Streptococcal endocarditis
- Syphilis at all stages (benzathine penicillin G)
- Puerperal infections due to anaerobic streptococci or *Streptococcus agalactiae* (group B strep)
- Genital clostridial infections
- Infections caused by anaerobic oral bacteria including gram-positive and gram-negative cocci and *Actinomyces*
- Prevention of rheumatic fever recurrence (penicillin V)
- Early- and late-stage Lyme disease (amoxicillin)
- Cystitis (amoxicillin)

Adverse effects

- IgE-mediated anaphylaxis
  - 0.05% incidence
  - 5–10% fatality rate
- Morbilliform rash
  - appears up to 72 hours after treatment
  - rare but not serious
- Diarrhea
  - 20% incidence with amoxicillin; 10% with other penicillins

Considering beta-lactamase inhibitors

Beta-lactam antibiotics

Some classes of antibiotics contain a beta-lactam ring as an important component of their structure. These are known as **beta-lactam antibiotics** (e.g., penicillins, cephalosporins, carbapenems, monobactams).

Beta-lactamase

Some organisms produce enzymes known as **beta-lactamases** (of which there are many different varieties). These enzymes allow the bacteria to hydrolyze the beta-lactam ring of penicillin and other beta-lactam antibiotics, inactivating the drug.

Some bacteria—such as almost all *S. aureus*—naturally express these enzymes, while others can acquire beta-lactamase expression, contributing to the development of multidrug resistance.

Antistaphylococcal penicillins

Early medicinal chemists tried to prevent beta-lactamase from inactivating penicillins by placing a bulky, organic ring that would prevent the enzyme from hydrolyzing the drug. The first successful antistaphylococcal agent employing this strategy was methicillin.

Methicillin is no longer used because of a high incidence of interstitial nephritis; however, there are still some antistaphylococcal penicillins,

such as nafcillin, oxacillin, flucloxacillin, and dicloxacillin, that remain in use today.

Beta-lactamase inhibitors

These drugs block the beta-lactamase enzyme because of the bulky group (steric hindrance). Most have little to no antibacterial activity alone; however, when combined with penicillins, they bind up beta-lactamases allowing the active penicillins to avoid destruction.

Some common examples are amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam.

Spectrum

- Same coverage as penicillins but broadened
- Anaerobic bacteria
- Methicillin-susceptible *Staphylococcus aureus*
- Enteric organisms (e.g., some resistant *E. coli*)
- *Pseudomonas aeruginosa* (piperacillin-tazobactam only)

Indications

- Many hospital-acquired infections
- Mixed infections, (e.g., wound and intraabdominal infections)
- Ventilator-associated pneumonia (piperacillin-tazobactam)

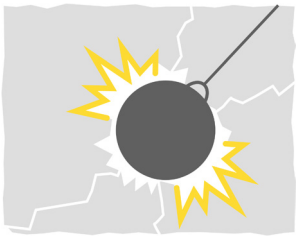
Adverse effects

- Similar to penicillins

Employing cephalosporins

Mechanism

Cephalosporins also contain a beta-lactam ring structure. Like other beta-lactam antibiotics, they interfere with the cell wall, causing the bacterial cell to take on water and burst.



First generation

A common example is cefazolin.

Spectrum

- Gram-positive cocci (e.g., *Streptococcus*)
- Gram-negative rods
- Activity against *Staphylococcus aureus*
- No activity against MRSA, *Enterococcus* or *Pseudomonas*

Indications

- Skin and soft tissue infections
- Bacterial pneumonias
- Urinary tract infections

Second generation

Some common examples are cefoxitin and cefotetan.

Spectrum

- Better anaerobic coverage than later generations
- More narrow-spectrum than later generations (therefore not commonly used nowadays)

Indications

- Not commonly used nowadays

Third and fourth generation

Some common examples are ceftriaxone (has long half-life which allows for once-daily dosing), ceftazidime, and cefepime.

Spectrum—ceftriaxone

- Most gram-positive bacteria (including *Staphylococcus* and *Streptococcus*)
- Most enteric gram-negative rods
- No activity against *Pseudomonas*

Spectrum—ceftazidime

- Gram-negative bacteria (including *Pseudomonas*)
- Limited activity against gram-positive cocci

Spectrum—cefepime

- Gram-positive cocci
- Gram-negative rods (including *Pseudomonas*)

Indications—ceftriaxone

- Bacterial pneumonia
- Skin and soft tissue infections
- Urinary tract infections
- Bacterial meningitis

Indications—ceftazidime and cefepime

- *Pseudomonas* infections (including pneumonias, skin infections, and sepsis)

Fifth generation

A common example is ceftaroline.

Spectrum

- Gram-negative rods
- Streptococci
- MRSA

Indications

- Community-acquired pneumonia
- Skin and soft tissue infections (including those caused by MRSA)

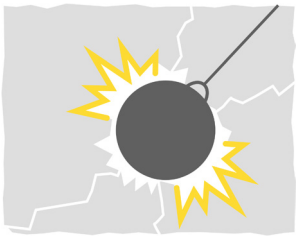
Adverse effects

- Similar to penicillins
- Diarrhea
- Potential for cross-reactivity with other beta-lactam antibiotics
  - incidence of cross-reactivity with penicillins and carbapenems is low
  - should be avoided in patents who are anaphylactic to penicillins
- Ceftriaxone may cause abdominal pain (due to bile sludging)
  - ceftriaxone should not be given to newborns

Using carbapenems and monobactams

Mechanism

Similar to other beta-lactam antibiotics, carbapenems and monobactams also interfere with the bacterial wall structure, eventually leading to osmotic disruption and bursting of the cell.



Carbapenems

Some common examples include imipenem, meropenem, ertapenem, and doripenem.

Spectrum

- Gram-positive bacteria (e.g., *Streptococcus*, *Staphylococcus*)
- Aerobic gram-negative rods (including *Pseudomonas*—not ertapenem)
- Most anaerobes
- No activity against MRSA

Indications

- Hospital-acquired infections (including ventilator-associated pneumonia and urinary tract infections)
- Mixed infections (e.g., wound and intraabdominal infections)

Monobactams

Aztreonam is currently the only available monobactam.

Spectrum

- Susceptible gram-negative bacteria and aerobic organisms (including *Pseudomonas)*

Indications

- *Pseudomonas* infections (including ventilator-associated pneumonia, urinary tract infections, and intraabdominal infections)

Adverse effects

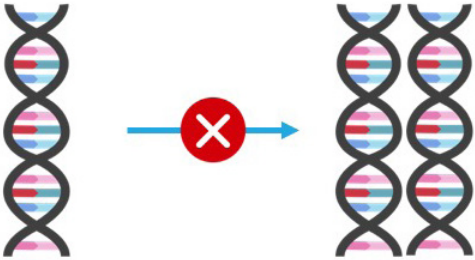
- Similar to other beta-lactam antibiotics (anaphylaxis, morbilliform rash, diarrhea)
- Seizures (carbapenems)
  - more common in patients with renal failure or neurological problems
  - more common with imipenem (1–2%) than with meropenem or doripenem (0.1–0.3%)
- Carbapenems have a low incidence of cross-allergenicity to penicillins and cephalosporins but should be avoided in persons with anaphylaxis to those agents
- Aztreonam can be used in patients with an allergy to penicillins and cephalosporins (with the exception of ceftazidime because of its structural similarity)

Administering fluoroquinolones

Some common examples include ciprofloxacin, levofloxacin, delafloxacin, moxifloxacin, and gemifloxacin.

Mechanism

Fluoroquinolones act by inhibiting the synthesis and replication of DNA in bacterial cells.



Spectrum

- Gram-negative rods
- Gram-positive cocci

Indications

- Complicated and uncomplicated urinary tract infections
- Chronic prostatitis
- Atypical pneumonias (caused by *Legionella, Chlamydophila,* and *Mycoplasma*)
- Acute exacerbations of COPD

Adverse reactions

- High incidence of *C. difficile* colitis
- Confusion and central nervous system toxicity
- Abnormal glucose metabolism (hypoglycemia or hyperglycemia)
- Cardiac disturbances (e.g., prolonged QT interval)
- Tendinopathy

Contraindications

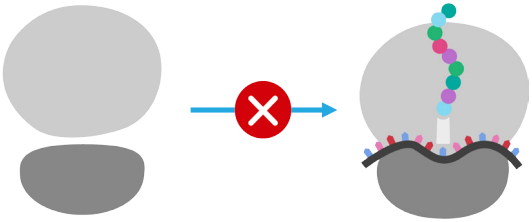
- Fluoroquinolones should not be used in children

Working with aminoglycosides

Some common examples include gentamicin, tobramycin, amikacin, and neomycin.

Mechanism

Aminoglycosides work by binding to the ribosome and interfering with proper bacterial protein production.



Spectrum

- Aerobic gram-negative rods (e.g., *E. coli, Klebsiella, Pseudomonas*)
- Not active against gram-positive cocci unless combined with cell wall agent

Indications

- Multidrug-resistant infections in critically ill patients
- Ventilator-associated pneumonia (VAP)
- Endocarditis (when combined with cell wall agent)
- Zoonotic infections (e.g., tularemia, brucellosis)

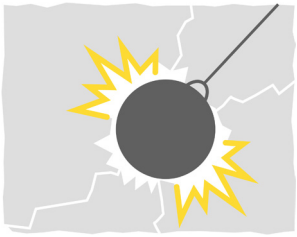
Adverse reactions

- Nephrotoxicity
- Ototoxicity (permanent hearing loss and permanent equilibrium impairment)
- Neuromuscular blockade may make postoperative transition from mechanical ventilation difficult

Administering vancomycin

Mechanism

Vancomycin acts by preventing assembly of the bacterial cell wall, albeit through a different mechanism than beta-lactams.



Lipoglycopeptides, such as dalbavancin and oritavancin, have a similar mechanism of action to vancomycin but they have a much longer half-life which allows for once-weekly dosing.

Spectrum

- Gram-positive organisms (e.g., *Streptococcus, Enterococcus,* MRSA, MRSE*, Clostridium*)

Indications

- MRSA infections of skin and soft tissue
- Gram-positive infections in patients with history of serious allergic reactions to beta-lactam antibiotics
- Infections in prosthetic devices
- Vascular access site infections
- *C. difficile* colitis (administered orally)

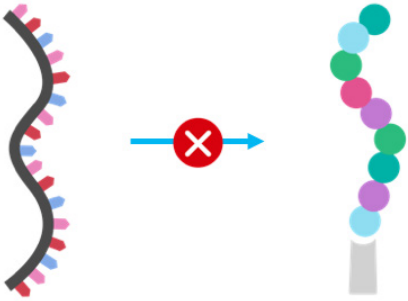
Adverse reactions

- Red man syndrome
- Fever
- Reversible nephrotoxicity
- Immune thrombocytopenia

Utilizing macrolides and clindamycin

Mechanism

These drugs interfere with protein synthesis through a different mechanism than aminoglycosides.



Macrolides and azalides

Some common examples include erythromycin or clarithromycin (macrolides) and azithromycin (azalide).

Spectrum

- Gram-negative bacteria (not enteric rods or *Pseudomonas*)
- Gram-positive bacteria
- *Mycobacterium*
- *Rickettsiae*
- *Treponema*
- *Mycoplasma*
- *Chlamydia* / *Chlamydophila*
- Intracellular bacteria (e.g., *Legionella*)

Indications

- Upper and lower respiratory tract infections
- Chlamydial sexually transmitted infections
- Non-tuberculous mycobacterial infections
- *H. pylori* infections

Adverse effects

- Prolonged QT interval (when combined with antiarrhythmics)
- Transient and reversible tinnitus or deafness (erythromycin)
- Worsens symptoms of myasthenia gravis (azithromycin)

Clindamycin

Spectrum

- Aerobic gram-positive organisms
- MRSA
- Anaerobic bacteria (gram-positive / -negative but not some *clostridia*)
- Protozoa (e.g., *Toxoplasma gondii*)

Indications

- Complicated and mixed intraabdominal infections (in combination with a drug active against aerobic enteric rods)
- Community-acquired MRSA infections
- Brain abscess in AIDS patients (in combination with pyrimethamine)
- *Pneumocystis jiroveci* pneumonia in AIDS patients

Adverse effects

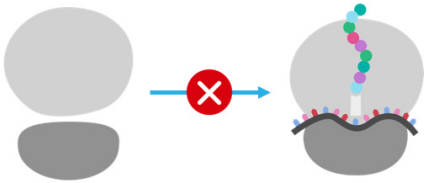
- Diarrhea
- Mild reversible increase in liver enzymes

Targeting multidrug-resistant gram-positive organisms

Linezolid and tedizolid

Mechanism

Linezolid and the newer tedizolid are ribosomal protein inhibitors. They bind to the ribosome and prevent the initiation of protein synthesis.



Spectrum

- Gram-positive organisms (including MRSA and VRE)

Indications

- Infections caused by resistant gram-positive organisms
- Skin and soft tissue infections
- Community-acquired or hospital-acquired pneumonia (with or without bacteremia)

Adverse effects

- Bone marrow suppression / thrombocytopenia
- Peripheral neuropathy
- Optic neuropathy
- Lactic acidosis

Daptomycin

Mechanism

Daptomycin is a large molecule that can accumulate in the cell membranes of susceptible gram-positive organisms, leading the membranes to become porous (leaky) and osmotically unstable, and eventually leading to cell death.

Spectrum

- Multidrug-resistant gram-positive organisms

Indications

- Staphylococcal bacteremia (especially MRSA)
- Right-sided infective endocarditis
- Complicated skin and soft tissue infections
- Should not be used for pneumonia (inactivated by lung surfactant)

Adverse reactions

- Skeletal muscle toxicity
- Immune thrombocytopenia

Treating with colistin

Mechanism

Colistin is an amphipathic antibiotic (both hydrophobic / nonpolar and hydrophilic / polar components). It disrupts the outer membrane of gram-negative organisms, like a detergent making them osmotically unstable and killing them.

Spectrum

- Multidrug-resistant gram-negative rods (e.g., *Pseudomonas, Klebsiella, Acinetobacter, E. coli*)

Indications

- Last resort for treating infections caused by multidrug-resistant gram-negative rods (particularly in critically ill patients or those with decreased immunity)

Adverse reactions

- Nephrotoxicity (30–60% risk)
- Reversible neurotoxicity

Employing nitroimidazoles

Some common examples include metronidazole and tinidazole.

Mechanism

Nitroimidazoles disrupt the electron transport system of anaerobic bacteria, depriving the organism of ATP and resulting in a metabolic product that damages anaerobe DNA, killing the organism.

Spectrum

- Most anaerobic organisms

Indications

- Intraabdominal infections
- Gynecological infections
- *C. difficile* colitis
- Anaerobic protozoal infections

Adverse reactions

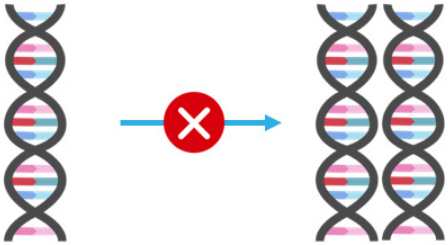
- Seizures
- Peripheral neuropathy (with prolonged use)
- Alcohol should be avoided for 72 hours after taking metronidazole

Administering rifamycins

Some common example include rifampin, rifabutin, and rifaximin.

Mechanism

The rifamycins block the interaction of DNA with RNA polymerase, thus inhibiting nucleic acid replication.



Spectrum

- Aerobic and anaerobic gram-positive cocci and rods

Indications

- Tuberculosis (rifampin)
- Prosthetic valve endocarditis (rifampin)
- Disseminated *Mycobacterium avium* complex infections in patients with advanced AIDS (rifabutin)
- Traveller's diarrhea (rifaximin)
- Hepatic encephalopathy (rifaximin)

Adverse reactions

- Discoloration of body fluids
- Flu-like symptoms
- Hepatotoxicity
- Drug-drug interactions (increase metabolism of some drugs)

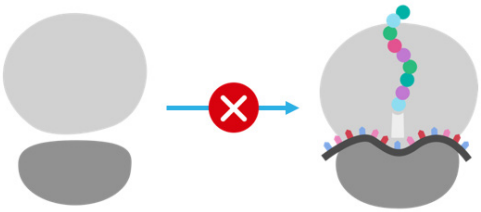
NOTE: Resistance occurs rapidly (often within 48 hours) if not combined with another effective antimicrobial. Thus, these agents are rarely used alone.

Using tetracyclines

Some common examples include doxycycline and tigecycline.

Mechanism

Tetracyclines inhibit bacterial growth by binding to the bacterial ribosome and interfering with protein production.



Spectrum

- Intracellular bacteria
- *Rickettsiae*
- *Mycoplasma*
- *Chlamydia / Chlamydophila*
- Highly resistant gram-negative bacilli (including *Acinetobacter baumannii*—tigecycline)

Indications

- Rickettsial disease (e.g., Rocky Mountain spotted fever [RMSF] and ehrlichiosis)
- Complicated skin and skin structure infections (including MRSA—tigecycline)
- Complicated intraabdominal infections (tigecycline)
- Ventilator-associated pneumonia (tigecycline)

Adverse reactions

- Permanent tooth discoloration in children
- Photosensitivity
- Hepatotoxicity in pregnant women

Contraindications

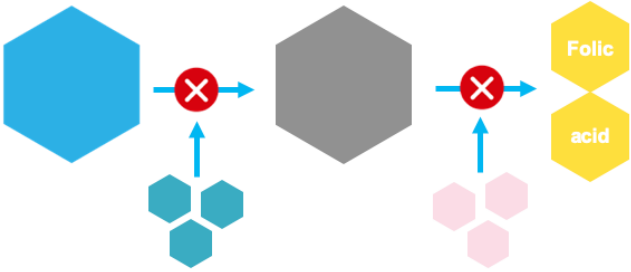
- Children and pregnant women

Combining sulfonamides and trimethoprim

A common example is trimethoprim-sulfamethoxazole.

Mechanism

The sulfonamides—or sulfa drugs—prevent the growth of bacteria by interfering with folic acid synthesis. Trimethoprim blocks a different enzyme involved in folic acid synthesis. Therefore, trimethoprim combined with sulfamethoxazole (trim / sulfa) has an additive or synergistic effect on inhibiting bacterial growth, compared to either drug alone.



Spectrum

- Gram-positive bacteria (including MRSA)
- Gram-negative bacteria
- *Mycobacterium*
- Fungi (e.g., *Pneumocystis*)
- Parasites (e.g., *Toxoplasma gondii*)

Indications

- *Pneumocystis* pneumonia
- Community-acquired MRSA infections
- Urinary tract infections due to susceptible *Enterobacteriaceae*
- Cerebral toxoplasmosis (sulfadiazine alone)
- Infections caused by *P. jirovecii and Nocardia*

Adverse reactions

- Drug-drug interactions
- Hyperkalemia
- Hemolytic anemia (rare, except in patients with glucose-6-phosphate deficiency)
- Stevens-Johnson syndrome (rare)
- Adverse effects seem to be more common in HIV-infected individuals

Chapter 3

ANTIFUNGALS

Treating with echinocandins

Mechanism

The echinocandins are large lipopeptide molecules. The lipid side chain binds to the cell membrane of susceptible fungi, interfering with the function of specific enzymes and eventually causing the fungal cell wall to become osmotically unstable.

Indications

- Severe *Candida* infections
  - disseminated candidiasis
  - candidemia
  - intraabdominal abscesses
  - peritonitis
  - pleural space infections
- *Candida* esophagitis
- Invasive *Aspergillus* infections (when other treatments have failed)
- Not for CNS or urinary tract infections (not concentrated in urine or CSF)

Adverse reactions

- Pruritus at IV infusion site
- Headache
- Fever and chills
- Gastrointestinal upset

Administering azoles

Some common examples include fluconazole, voriconazole, itraconazole, and posaconazole.

Mechanism

All the azoles currently in use interfere with the integrity of the fungal cell membrane by interfering with ergosterol synthesis.

Indications

- Endemic fungal infections (itraconazole)
- *Coccidioides* meningitis (fluconazole)
- Invasive mold infections

Mild / moderate infection

Severe infection

Adverse reactions

- Hepatotoxicity (rare)
- Drug-drug interactions (other drugs may be metabolized more slowly)
- Photosensitivity
- Visual hallucinations (voriconazole)

Employing polyenes

Some common examples include amphotericin B (also the lipid formulations liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion) and nystatin.

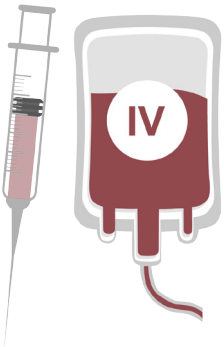
Mechanisms

The polyenes are amphoteric compounds, having a lipophilic side and a hydrophilic side. They bind to ergosterol in the cell membrane of susceptible fungi, creating a pore that leaks vital intracellular potassium and amino acids and is lethal to the fungus.

Amphotericin B

Indications

- Life-threatening manifestations of fungal disease
- Severe histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Cryptococcal meningitis
- Invasive mold infections



Once patients become clinically stable, it may be possible to switch to an alternative oral antifungal.

Adverse reactions

- Fever and chills
- Infusion-related phlebitis (common)
- Nephrotoxicity (almost universal with prolonged use)

Nystatin

Indications

- Superficial *Candida* infections
- Oral
- Vaginal
- Cutaneous

Using terbinafine

Mechanism

Terbinafine is a squalene epoxidase inhibitor and inhibits the conversion of squalene, a sterol precursor, into lanosterol. Thus, it ultimately prevents the formation of the normal fungal membrane sterol, ergosterol.

Indications

- Superficial fungal infections due to dermatophytes and *Candida*
- Infections of the fingernails or toenails
- Tinea corporis (ringworm)
- Tinea pedis (athletes foot)

Adverse effects

- Abnormal sense of taste and smell
- Hepatotoxicity
- Bone marrow suppression
- Depression
- Stevens-Johnson syndrome (very rare)

Contraindications

- Should not be used in patients with underlying liver disease

Considering flucytosine

Mechanism

Fungi that are susceptible to flucytosine (5-fluorocytosine) possess two enzymes, one allows the drug to enter the fungal cell and the other converts the drug to 5-fluorouracil (an anticancer drug), which acts on fungal nucleic acids as a chain terminator, killing the organism.

Indications

- Cryptococcal meningitis (first phase of treatment)
  - initial therapy with amphotericin B plus flucytosine for first two weeks of treatment followed by fluconazole for duration of treatment (this is superior to fluconazole alone)
- Invasive candidiasis
- *Candida* urinary tract infections refractory to other therapies

Adverse reactions

- Bone marrow suppression
- Gastrointestinal tract toxicity (interference with normal rapid turnover of gastrointestinal epithelium)
  - diarrhea (initial sign)
  - intestinal perforation (possible with prolonged use)

Discontinue use of the drug if signs of gastrointestinal tract toxicity occur

Chapter 4

ANTIVIRALS

Administering anti-influenza medications

Neuraminidase inhibitors

Common examples

Zanamivir

Oseltamivir

Peramivir

Mechanism

After infecting and replicating in bronchial epithelial cells, Influenza virus requires an enzyme called neuraminidase in order to allow it to freely leave the cell and infect nearby cells. As their name suggests, neuraminidase inhibitors inhibit this enzyme, effectively trapping the virus within the infected cell, and preventing spread to neighboring cells.

Indications

- **Preventing** influenza among household contacts or nursing home settings during an outbreak
- Not particularly effective for **treating** influenza (especially if given after the infection has been present for more than 48 hours)

Adverse reactions

Osteltamivir

- Nausea
- Epigastric distress
- Emesis
- Erythematous rashes
- Severe eruptions or Stevens-Johnson syndrome (rare)

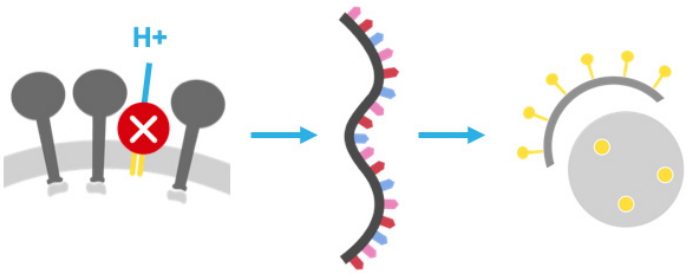
Zanamivir

- Bronchospasm
- Should not be used in persons with serious underlying respiratory disease (e.g., COPD)

Amantadine and rimantadine

Mechanism

The ion channel protein, M2, on influenza A viruses allows acids in respiratory epithelial cells to enter the virus. This triggers the virus to release genetic instructions, uncoat, and replicate. Amantadine and rimantadine sterically interfere with the function of the M2 protein channel, thus preventing viral replication.



Indications

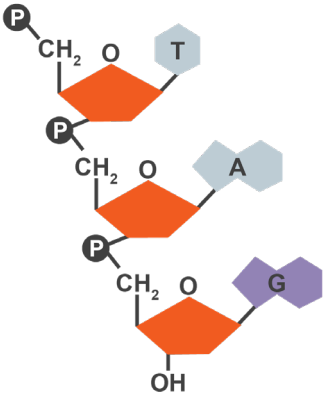
- Once reasonably effective for prophylaxis
- Minimally effective for treatment (due to fairly widespread resistance)
- Not ideal for prevention in nursing home settings
- Generally reserved for seriously ill patients

Adverse reactions

- Central nervous system toxicity
- Nervousness
- Anxiety
- Difficulty concentrating
- Light headedness
- Confusion
- Delirium
- Hallucinations

Considering other antivirals

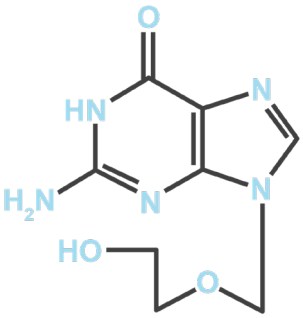
To understand how antiviral medications work, it is necessary to remember that DNA and RNA are made up of a series of nucleotides, which are attached to each other through the sugar / phosphate backbone.



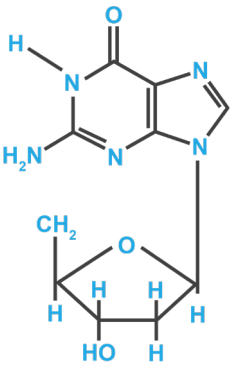
Acyclovir

Mechanism

Acyclovir is a nucleotide analogue—meaning that it has a similar structure to the nucleotide guanine but it does not contain the full pentose sugar. Consequently, when it is incorporated into DNA (or RNA) it causes termination of the chain, blocking replication of the viral DNA / RNA and inhibiting replication of the virus itself.



Acyclovir



Guanine

Spectrum

- Herpes simplex virus (HSV)
- Herpes simplex virus (HSV) II
- Varicella zoster

Indications

- Recurrent genital HSV infections
- Zoster (shingles)
- Herpes zoster
- Severe varicella zoster infections
- Herpes encephalitis

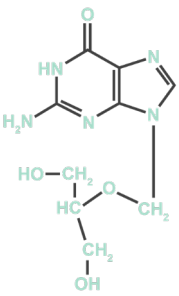
Adverse effects

- Diarrhea
- Vertigo
- Arthralgias
- Myalgias
- Neurotoxicity
  - hallucinations
  - involuntary movements
- Reversible renal dysfunction

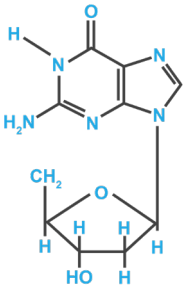
Ganciclovir

Mechanism

Ganciclovir is also a guanosine analogue, which is phosphorylated by viral kinases and like acyclovir is a chain terminator.



Ganciclovir



Guanine

Spectrum

- Herpes simplex virus (HSV)
- Cytomegalovirus (CMV)

Indications

- CMV disease in immunocompromised patients
  - retinitis
  - colitis
- HSV infections that are resistant to acyclovir

Adverse effects

- Neutropenia (common)
- Thrombocytopenia (common)
- Anemia (common)
- Gastrointestinal upset (common)
- Headache
- Psychiatric disturbances
- Seizures (rare)

APPENDIX

Basic characteristics of common pathogenic bacteria

Short name	Full name	Gram stain	Shape	Characteristics
A. hydrophila	*Aeromonas hydrophila*	Negative	Rod	
A. baumannii	*Acinetobacter baumannii*	Negative	Cocco-bacillus	Aerobic
B. cereus	*Bacillus cereus*	Positive	Rod	Anaerobic
B. burgdorferi	*Borrelia burgdorferi*	Neither	Spirochete	Primarily extracellular
C. trachomatis, Chlamydia	*Chlamydia trachomatis*	Negative	Elementary bodies	Intracellular
C. pneumoniae	*Chlamydophila pneumoniae*	Negative	Elementary bodies	Intracellular
C. botulinum	*Clostridium botulinum*	Positive	Rod	Anaerobic, produces botulinum toxin
C. difficile	*Clostridium difficile*	Positive	Rod	Anaerobic
C. perfringens	*Clostridium perfringens*	Positive	Rod	Anaerobic
E. coli	*Escherichia coli*	Negative	Rod	Aerobic
	Enterobacter spp	Negative	Rod	Aerobic
E. faecium	*Enterococcus faecium*	Positive	Coccus	Aerobic

H. influenzae	*Haemophilus influenzae*	Negative	Cocco-bacillus	Aerobic
K. kingae	*Kingella kingae*	Negative	Cocco-bacillus	Aerobic
K. pneumoniae	*Klebsiella pneumoniae*	Negative	Rod	Aerobic
L. pneumophila	*Legionella pneumophila*	Negative	Rod	Aerobic
M. catarrhalis	*Moraxella catarrhalis*	Negative	Coccus	Aerobic
M. tuberculosis	*Mycobacterium tuberculosis*	Positive	Rod	Aerobic, intracellular
N. gonorrhoeae	*Neisseria gonorrhoeae*	Negative	Coccus	Aerobic
N. meningitidis	*Neisseria meningitidis*	Negative	Coccus	Aerobic
P. multocida	*Pasteurella multocida*	Negative	Cocco-bacillus	Aerobic
P. aeruginosa	*Pseudomonas aeruginosa*	Negative	Rod	Aerobic
S. agalactiae	*Streptococcus agalactiae*	Positive	Coccus	Anaerobic, group B strep
S. gallolyticus	*Streptococcus gallolyticus*	Positive	Coccus	Aerobic
S. pneumoniae	*Streptococcus pneumoniae*	Positive	Coccus	Aerobic
S. pyogenes	*Streptococcus pyogenes*	Positive	Coccus	Aerobic, group A strep

S. aureus	*Staphylococcus aureus*	Positive	Coccus	Aerobic
S.saprophyticus	*Staphylococcus saprophyticus*	Positive	Coccus	Aerobic, coagulase-negative
T. pallidum	*Treponema pallidum*	Neither	Spirochete	Aerobic
	Vibrio spp	Negative	Rod (comma-shaped)	Aerobic
Y. enterocolitica	*Yersinia enterocolitica*	Negative	Cocco-bacillus	Aerobic

Multidrug-resistant bacteria

Short name	Full name	Gram stain	Shape	Characteristics
ESBL-producing *Enterobacteria-ceae*	***Extended-spectrum, beta-lactamase-producing*** *Entero-bacteriaceae*	Negative	Rods	Aerobic, includes *E.coli*, *Klebsiella*, *Salmonella*, *Shigella*, and *Yersinia*
MRSA	***Methicillin-resistant*** *Staphylo-coccus aureus*	Positive	Coccus	Aerobic
MRSE	***Methicillin-resistant*** *Staphylo-coccus epidermidis*	Positive	Coccus	Aerobic

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