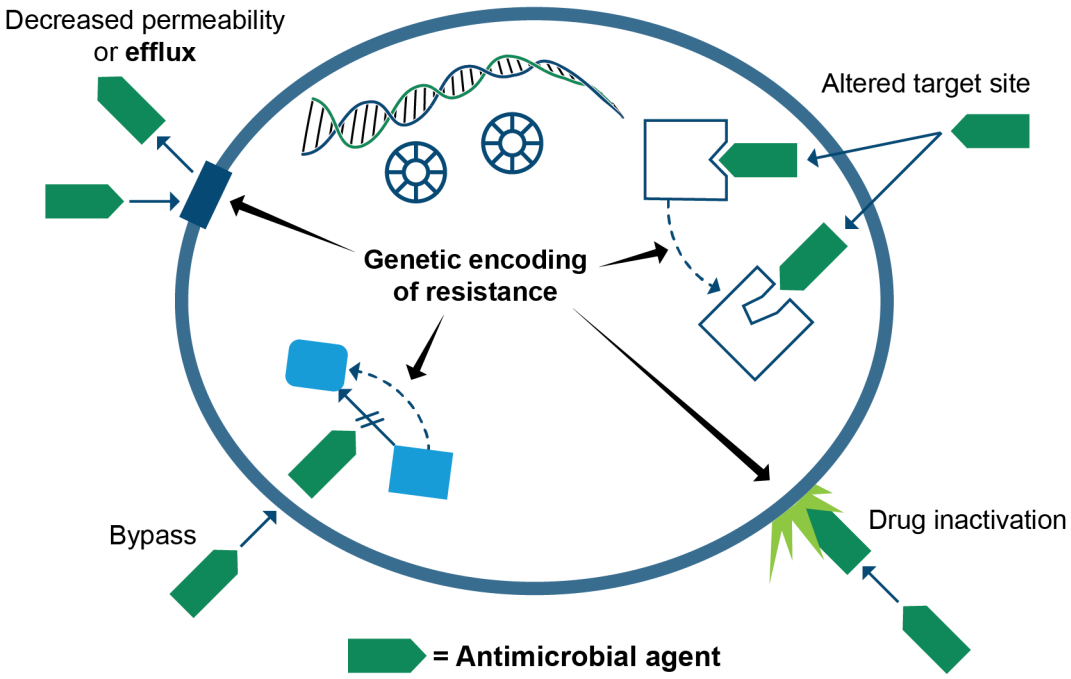
Antimicrobial Misuse and Resistance Patterns

The misuse and overuse of antimicrobials is considered one of the world's most pressing public health problems. According to the CDC, 47 million unnecessary antibiotic prescriptions are written in doctor's offices, emergency rooms, and hospital-based clinics annually in the United States alone. Widespread antimicrobial use is the main selective pressure responsible for increasing resistance in community and healthcare facilities. The end result of widespread use is loss of antibiotic effectiveness.

Major mechanisms of antimicrobial resistance include drug inactivation, alteration in target site, decreased permeability or efflux, and bypass of a metabolic pathway, as shown in Exhibit 7-10.

Exhibit 7-10: Mechanisms of Antimicrobial Resistance



Let's review these major cellular mechanisms of antimicrobial resistance:

- **Drug inactivation.** Drug inactivation occurs when a bacterium produces an enzyme that can destroy or inactivate the antimicrobial. Bacteria may produce β-lactamase enzymes that destroy penicillins and cephalosporins. This is the primary mechanism of resistance for ESBLs (expanded spectrum β-lactamases) that produce β-lactamases and CREs (carbapenem-resistant Enterobacterales) that produce carbapenemases.

- **Altered target site.** Drug receptor or target binding sites may undergo alteration, as observed in methicillin-resistant *S. aureus* (MRSA) when the penicillin-binding protein (PBP) is altered to PBP2a, coded for by the better-known mecA gene.

- **Decreased permeability or efflux.** Changes in drug permeability or an efflux of drug may be observed, as in the case of *P. aeruginosa* that has developed resistance to the carbapenems.

- **Bypass.** Bacteria may develop alternative metabolic pathways to bypass the pathway that was inhibited by the antimicrobial. Resistance to trimethoprim/sulfamethoxazole commonly occurs in this manner.

Resistance develops in microorganisms as a result of either point mutations in existing genes or the acquisition of new genes.

Point mutations are random errors that occur during DNA replication; they occur infrequently at the correct locations of the bacterial genome necessary to cause resistance. When point mutations are responsible for resistance, it usually is because they have a slight structural change in a drug receptor or target site.

The acquisition of genes may occur in a few different ways:

- **Transformation,** which occurs when naked DNA in the environment, possibly from dead bacteria, enters the bacterium.
- **Conjugation,** which occurs when all or part of a plasmid (a DNA molecule not essential to the bacteria under some conditions) is transferred from a donor cell to a recipient cell.
- **Transduction,** which occurs when bacteria DNA is transferred from a donor cell to a recipient cell via a virus capable of infecting bacteria.

No matter the method of gene transfer, it may result in a variety of changes that can make the bacteria more dangerous or harder to treat. For example, genes that determine antimicrobial resistance may transfer from one bacterium to another, creating a strain that is resistant to traditional treatment methods. Other genes may result in typically harmless bacteria becoming pathogenic by transferring genes that result in toxin production by the bacteria.

Now that we know the mechanisms by which antimicrobial resistance develops, let's cover the major ways that antimicrobials are misused, thereby creating the conditions for resistance to develop.

Antimicrobial Misuse

Misuses of antimicrobials include the following:

- Prolonged empiric antimicrobial therapy without clear evidence of infection
- Treating a positive clinical culture in the absence of infection
- Failure to narrow the antimicrobial therapy after a causative pathogen is identified
- Prolonged prophylaxis
- Excessive use of certain antimicrobials (For example, widespread use of fluoroquinolones has led to the fluoroquinolone-resistant strain of *C. difficile.*)

Societal Overuse Harm

From a societal perspective, overuse hinders the ability of physicians to treat certain infections. To illustrate, let's look at a few of the more recent examples of antimicrobial resistance.

ESBLs are found in common Gram-negative bacteria, such as *E. coli* and *K. pneumoniae,* and they confer resistance to all β-lactam drugs except the carbapenems. CREs are Gram-negative pathogens that are resistant to most antimicrobials, including carbapenems that have been useful for multiple-drug-resistant pathogens until now. The media has publicized CRE as a "superbug." From an infection prevention perspective, patients with ESBL or CRE are typically placed in transmission-based precautions in addition to standard precautions.

Another example is vancomycin-resistant *S. aureus* (VRSA), and, unfortunately, resistance has been reported with linezolid and daptomycin use. Antimicrobial stewardship is critical to preventing antimicrobial prescribing habits that provide an environment conducive to such a resistant pathogen.

Patient Misuse Risks

Inappropriate antibiotic use increases the risk for medication side effects, adverse events, antibiotic resistance, medication interactions, anaphylaxis, prolonged hospitalization, additional financial costs, patient duress, and mortality. Examples of patient misuse include:

- Stopping use of an antibiotic once they feel better.
- Using antibiotics left over from a previous illness.
- Pressuring providers into writing prescriptions for them.
- Sharing prescriptions with others.

Antimicrobial Misuse Interventions

The World Health Organization has produced a guide outlining how to intervene to prevent antimicrobial misuse, titled "Antimicrobial Stewardship Interventions: A Practical Guide." In it, they detail a variety of methods, separated into interventions prior to or at the time of prescription and interventions after the prescription. These interventions are listed at a high level below. For more information, see the publication.

- Interventions prior to or at the time of prescription:
  - Clinician education
  - Patient and public education
  - Institution-specific guidelines for the management of common infections
  - Cumulative antibiograms
  - Prior authorization of restricted antimicrobials
  - De-labeling of spurious antibiotic allergies

- Interventions after prescription:
  - Prospective audit and feedback
  - Self-directed antibiotic reassessments by prescribing clinicians (antibiotic timeouts)
  - Antibiotic dose optimization
  - Antibiotic duration