Chapter 2.4. General Bacteriology: Antimicrobial Agents and Antimicrobial Resistance

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ANTIMICROBIAL AGENTS

Antimicrobials are the agents that kill or inhibit the growth of microorganisms. They can be classified in various ways:

1. According to microorganisms against which they are used—antibacterial, antifungal, antiparasitic, antiviral agents. Only antibacterial agents are discussed in this chapter
2. According to their ability to kill (ends with suffix cidal) or inhibit (ends with suffix static) the microorganism, e.g. bactericidal and bacteriostatic
3. According to the chemical structure and mechanism of action—the antimicrobial agents can be further divided into many classes, as described in *Table 2.4.1*.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance refers to the development of resistance to an antimicrobial agent by a microorganism. It can be of two types—intrinsic and acquired resistance.

Intrinsic Resistance

It refers to the innate ability of a bacterium to resist a class of antimicrobial agents due to its inherent structural or functional characteristics.

- This imposes negligible threat as it is a defined pattern of resistance and is non-transferable. However, the clinicians must be aware to exclude these antibiotics from therapy
- Some of the important examples include—
  - Gram-negative bacteria are resistant to vancomycin
  - Gram-positive bacteria are resistant to colistin

- Aerobic bacteria are resistant to metronidazole
- *Klebsiella pneumoniae* are resistant to ampicillin and ticarcillin
- *Proteus* species are resistant to ampicillin, first and second-generation cephalosporins, tetracyclines, nitrofurantoin, and polymyxins
- *Pseudomonas aeruginosa* is resistant to ampicillin, ceftriaxone, amoxicillin-clavulanate, ampicillin-sulbactam, ertapenem, tetracyclines, tigecycline, co-trimoxazole, and chloramphenicol
- *Acinetobacter baumannii* is resistant to ampicillin, amoxicillin, amoxicillin-clavulanate, ertapenem, aztreonam, chloramphenicol, and fosfomycin.

Acquired Resistance

This refers to the emergence of resistance in bacteria that are ordinarily susceptible to antimicrobial agents, by acquiring the genes coding for resistance. Most of the antimicrobial resistance shown by bacteria belongs to this category.

Table 2.4.1. Antimicrobial agents—classification and indication.

Class/mechanism		***Drugs***	***Spectrum of activity***
A. Inhibit Cell wall Synthesis			
#-lactam antibiotics: Binds to penicillin-binding protein, thereby blocking peptidoglycan cross-linking			
Penicillins	Penicillin	Penicillin G Procaine penicillin G Benzathine penicillin G	*Streptococcus,* pneumococcus, meningococcus, gonococcus, *Corynebacterium diphtheriae, Clostridium perfringens,* and *Treponema pallidum*
	Penicillinase-resistant-penicillins	Cloxacillin, dicloxacillin, nafcillin, oxacillin, and methicillin	*Same as penicillin plus* Penicillinase producing *Staphylococcus aureus*
	Aminopenicillins (extended-spectrum)	Ampicillin, amoxicillin	*Same as penicillin plus Enterococcus faecalis, Escherichia coli, Salmonella* and *Shigella*
	Ureidopenicillins	Ticarcillin, piperacillin	*Same as aminopenicillins plus Pseudomonas aeruginosa*
Cephalosporin	1st generation	Cefazolin, cephalexin	*Staphylococcus aureus, Escherichia coli,* and *Klebsiella*
	2nd generation	Cefuroxime, cefoxitin	Same as 1st generation *plus* gram-negative activity and anaerobic activity (cefoxitin)

Class/mechanism		***Drugs***	***Spectrum of activity***
	3rd generation	Ceftriaxone, cefotaxime Ceftazidime, cefoperazone	*Escherichia coli* and *Klebsiella* *Pseudomonas* (ceftazidime) Pneumococci, meningococci (ceftriaxone)
	4th generation	Cefepime	Good activity against gram-positive and negative bacteria including *Pseudomonas*
	5th generation	Ceftobiprole, ceftaroline	Same as 4th generation and MRSA
#-lactam + #-*lactamase inhibitors*		Amoxicillin-clavulanate* Cefoperazone-sulbactam Piperacillin-tazobactam* Ceftazidime-avibactam	Same as the spectrum of the respective #-lactam drug plus active against β-lactamase producing bacteria *Have excellent anaerobic coverage
Carbapenems		Imipenem, meropenem, doripenem	Broadest range of activity against most bacteria, which include gram-positive cocci, Enterobacteriaceae, *Pseudomonas, Listeria*, and anaerobes
Monobactam		Aztreonam	Gram-negative rods
Other cell wall inhibitors			
Glycopeptides		Vancomycin, teicoplanin	Active against most gram-positive bacteria including MRSA (drug of choice), and for *Clostridioides difficile*
Fosfomycin		Fosfomycin	Active against *Escherichia coli*, *Klebsiella*, *Enterococcus*, etc.
B. Protein Synthesis Inhibition			
Binds and inhibits 30S ribosomal subunit			
Aminoglycosides		Gentamicin, amikacin, tobramycin	Enterobacterales, *Pseudomonas*, *Acinetobacter* *Enterococcus*: Gentamicin *plus* cell wall active agent given

Class/mechanism		***Drugs***	***Spectrum of activity***
Tetracyclines		Tetracycline, doxycycline, minocycline	Rickettsiae, Chlamydiae, *Mycoplasma, Vibrio cholerae* Minocycline: *Acinetobacter, Burkholderia*
Glycylglycines		Tigecycline	*Acinetobacter, Enterococcus, Staphylococcus*
Binds and inhibits 50S ribosomal subunit			
Chloramphenicol		Chloramphenicol	*Haemophilus influenzae,* anaerobic infection
Macrolides		Erythromycin, azithromycin	*Streptococcus, Haemophilus influenzae, Mycoplasma*
Lincosamides		Clindamycin	*S. aureus*, streptococci, anaerobic infection
Oxazolidinones		Linezolid	Resistant gram-positives like MRSA and VRE infections
Streptogramins		Quinupristin-dalfopristin	MRSA and VRE infections
Mupirocin		Mupirocin	Topical ointment—skin infections, nasal carriers of MRSA
C. Nucleic Acid Synthesis Inhibitors			
DNA synthesis inhibitors			
Fluoroquinolones		Inhibit DNA gyrase and topoisomerase IV, thus inhibiting DNA synthesis	
	1st generation	Norfloxacin, ciprofloxacin, ofloxacin	Enterobacterales
	2nd generation	Levofloxacin, moxifloxacin, sparfloxacin	Others: *Haemophilus, Pseudomonas*
Nitroimidazoles (damage DNA)		Metronidazole, tinidazole	Anaerobic organisms, also active against protozoa: *Entamoeba, Giardia* and *Trichomonas*
RNA synthesis inhibitors			
Rifamycins		Rifampicin	Mycobacteria *(M. tuberculosis, M. leprae*, etc.)
D. Mycolic Acid Synthesis Inhibitors			
Isonicotinic acid hydrazide		Isoniazid (INH)	*M. tuberculosis*
E. Folic Acid Synthesis Inhibitors			

Class/mechanism	***Drugs***	***Spectrum of activity***
Bacteriostatic: Competitively inhibit enzymes involved in two steps of folic acid synthesis		
Antifolates (Sulfonamides and trimethoprim)	• Sulfadiazine • Cotrimoxazole (Trimethoprim + sulfamethoxazole)	*Sulfadiazine:* Used topically in burn wound surface *Cotrimoxazole* is indicated for: UTI pathogens *(E. coli, Klebsiella,* etc.) *Toxoplasma gondii, Pneumocystis jirovecii*
F. Antimicrobial Agents that Act on the Cell Membrane		
Lipopeptides	Daptomycin	Gram-positive bacteria including VRE and MRSA
Polymyxins	Polymyxin B and colistin	Multidrug-resistant gram-negative bacterial infections
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*		

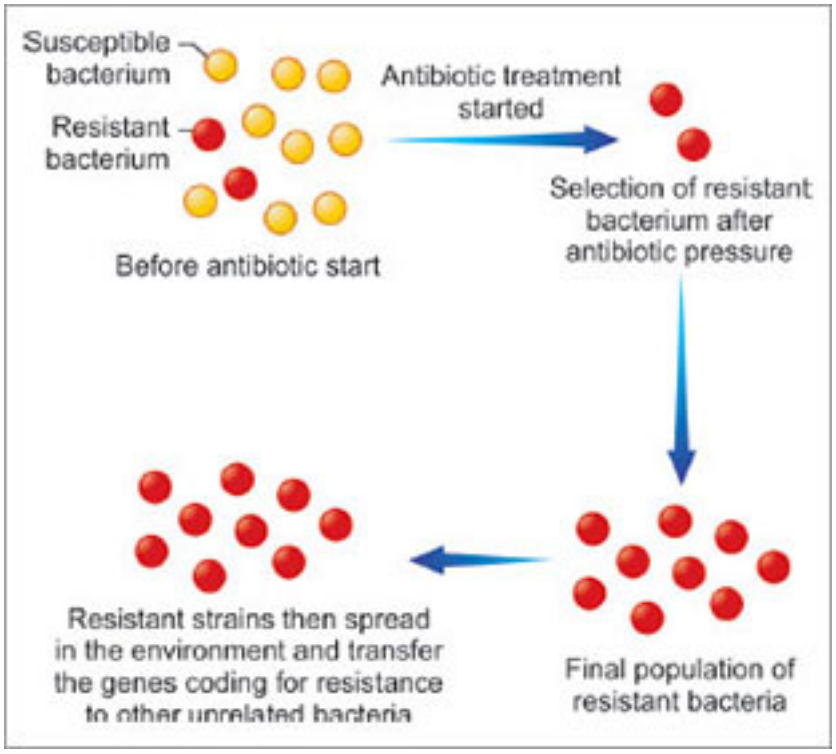
The emergence of resistance is a major problem worldwide in antimicrobial therapy. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher healthcare expenditures, and a greater risk of death.

- Overuse and misuse of antimicrobial agents is the single most important cause of the development of acquired resistance

- The evolution of resistant strains is a natural phenomenon, which can occur among bacteria especially when an antibiotic is an overuse

- The use of a particular antibiotic poses selective pressure in a population of bacteria which in turn promotes resistant bacteria to thrive and the susceptible bacteria to die off **(Fig. 2.4.1)**

Fig. 2.4.1. Mechanism of development of acquired resistance.



- Thus the resistant bacterial populations flourish in areas of high antimicrobial use, where they enjoy a selective advantage over susceptible populations
- The resistant strains then spread in the environment and transfer the genes coding for resistance to other unrelated bacteria.

Other factors favoring the spread of antimicrobial resistance include—

- Poor infection control practices in hospitals, e.g. poor hand hygiene practices can facilitate the transmission of resistant strains
- Inadequate sanitary conditions
- Irrational use of antibiotics by doctors, not following antimicrobial susceptibility report
- Uncontrolled sale of antibiotics over the counters without prescription.

Mutational and Transferable Drug Resistance

In presence of selective antibiotic pressure, bacteria acquire new genes (i.e. acquired resistance) mainly by two broad methods.

Mutational Resistance

Resistance can develop due to mutation of the resident genes.

- It is typically seen in *Mycobacterium tuberculosis*, developing resistance to anti-tubercular drugs
- Mutational drug resistance differs from transferable drug resistance in many ways **(Table 2.4.2)**

- Usually, it is a low-level resistance, developed to one drug at a time; which can be overcome by using a combination of different classes of drugs
- That is why multidrug therapy is used in tuberculosis using 4–5 different classes of drugs, such as isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.

Table 2.4.2. Mutational vs transferable drug resistance.

Mutational drug resistance	***Transferable drug resistance***
Resistance to one drug at a time	Multiple drugs resistance at the same time
Low-degree resistance	High-degree resistance
Resistance can be overcome by a combination of drugs	Cannot be overcome by drug combinations
Virulence of resistance mutants may be lowered	Virulence not decreased
Resistance is not transferable to other organisms	Resistance is transferable to other organisms
Spread to off-springs by vertical spread only	Spread by: Horizontal spread (conjugation, or rarely by transduction/transformation)

Transferrable Drug Resistance

In contrast, transferrable drug resistance is plasmid coded and usually transferred by conjugation or rarely by transduction, or transformation (explained in Chapter 2.3)

- The resistance coded plasmid (called R plasmid) can carry multiple genes, each coding for resistance to one class of antibiotic
- Thus, it results in a high degree of resistance to multiple drugs, which cannot be overcome by using combination of drugs.

Mechanism of Antimicrobial Resistance

Bacteria develop antimicrobial resistance through several mechanisms.

Decreased Permeability across the Cell Wall

Certain bacteria modify their cell membrane porin channels; either in their frequency, size, or selectivity; thereby preventing the antimicrobial agents from entering the cell. This resistance mechanism has been observed in many gram-negative bacteria, such as *Pseudomonas, Enterobacter,* and *Klebsiella* species against drugs, such as imipenem, aminoglycosides, and quinolones.

Efflux Pumps

Certain bacteria possess efflux pumps that mediate expulsion of the drug(s) from the cell, soon after their entry; thereby preventing the intracellular accumulation of drugs. This strategy has been observed in:

- *Escherichia coli* and other Enterobacteriaceae against tetracyclines, chloramphenicol
- *Staphylococcus aureus* and *Streptococcus pneumoniae* against fluoroquinolones.

By Enzymatic Inactivation

Certain bacteria can inactivate the antimicrobial agents by producing various enzymes, such as:

- β-*lactamase* enzyme production: It breaks down the #-lactam rings, thereby inactivating the #-lactam antibiotics. There are various types of #-lactamase enzymes
  - Gram-positive bacteria produce: Penicillinase
  - Gram-negative bacteria produce enzymes such as extended-spectrum #-lactamase (ESBL), AmpC #-lactamase, and carbapenemases.
- **Aminoglycoside modifying enzymes** can be produced by both gram-negative and gram-positive bacteria—they destroy the structure of aminoglycosides.

By Modifying the Target Sites

Modification in the target sites of antimicrobial agents (which are within the bacteria) is a very important mechanism. It is observed in:

- **MRSA (Methicillin-resistant Staphylococcus aureus):** In these strains, the target site of penicillin, i.e. penicillin-binding protein (PBP) gets altered to PBP-2a. The altered PBP, coded by a chromosomally coded gene *mec A*, does not sufficiently bind to #-lactam antibiotics and therefore prevents them from inhibiting the cell wall synthesis
- **Vancomycin resistance in enterococci (VRE):** These strains have a change in the target site of vancomycin (i.e. D-alanine D-alanine side chain of peptidoglycan).

EXPECTED QUESTIONS

1. **I. Write short notes on:**
   1. Mechanism of antibiotic resistance.
   2. Mutational and transferable drug resistance.
2. **II. Multiple Choice Questions (MCQs):**
   1. **MRSA is mediated by:**
      a. Plasmid
      b. *mecA* gene
      c. Transposons
      d. None
   2. **All of the following antimicrobial agents act on the cell membrane,** *except:*
      a. Gramicidin
      b. Daptomycin
      c. Polymyxins
      d. Vancomycin
   3. **All of the following are true regarding transferrable drug resistance, except:**
      a. Multiple drugs resistance at the same time
      b. Virulence not decreased

c. Low-degree resistance

d. Cannot be overcome by drug combinations

Answers

1. b	**2.** d	**3.** c