Drug Resistance

Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.

Some organisms are inherently resistant to an antibiotic. For example, most gram-negative organisms are inherently resistant to vancomycin.
Bacterial resistance mechanisms

• The spontaneous rate of mutation in bacteria is very low; about 1 in 10 million cells per division will be a mutant.

• The clinical difficulty arises when the infecting bacteria are already drug resistant.
• Microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection.

• Some of these strains may even become resistant to more than one antibiotic.
Bacterial Resistance Mechanisms

The **four main mechanisms** of resistance include:

A. Production of an enzyme that inactivates the drug.
B. Mutations in the target macromolecule (Receptors).
C. Induction of mechanisms to reduce accumulation of the drug.
D. Multiple drug resistance involving all these mechanisms.
### Figure 37.8
Some mechanisms of resistance to antibiotics.

<table>
<thead>
<tr>
<th>Drug resistance due to altered targets</th>
<th>Drug resistance due to decreased accumulation</th>
<th>Drug resistance due to enzymatic inactivation</th>
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<tbody>
<tr>
<td>Aminoglycosides</td>
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<tr>
<td>Chloramphenicol</td>
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<td>Clindamycin</td>
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<td>Fluoroquinolones</td>
<td>Fluoroquinolones</td>
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<td>β-Lactams</td>
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<td>Macrolides</td>
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<td>Rifampin</td>
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<td>Sulfonamides</td>
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<td>Tetracycline</td>
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<tr>
<td>Trimethoprim</td>
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<tr>
<td>Vancomycin</td>
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</tbody>
</table>

**Permeability**

- Fluoroquinolones enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalosporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.

**Efflux**

- Tetracycline was effective against gynecologic infection due to Bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.

**Enzymatic Inactivation**

- β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.
COMBINATION OF ANTIMICROBIAL AGENTS
It is therapeutically advisable to treat patients with a

- **Single agent**
- **Most specific** to the infecting organism.

- This strategy reduces the possibility of superinfections
- decreases the emergence of resistant organisms
- minimizes toxicity.
Some situations require combinations of antimicrobial drugs.

For example, the treatment of tuberculosis benefits from drug combinations.
Advantages of drug combinations

- Certain combinations of antibiotics, β-lactams and aminoglycosides, show **synergism**.

- Because such synergism among antimicrobial agents is **rare**, multiple drugs used in combination are only indicated in special situations (when an infection is of **unknown origin** or in the treatment of **enterococcal endocarditis**).
Disadvantages of drug combinations

- A number of antibiotics act only when organisms are multiplying.

- Coadministration of an agent that causes *bacteriostasis* plus a second agent that is *bactericidal* may result in the first drug interfering with the action of the second.
Complications of Antibiotic Therapy

- Hypersensitivity
- Direct toxicity
- Superinfections
Rout of administration

- The **oral route** of administration is appropriate for **mild infections** that can be treated on an **outpatient** basis.

- **Economic pressures** have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases.

- In hospitalized patients requiring intravenous therapy initially, the **switch to oral agents** should occur as soon as possible.
Some antibiotics, such as vancomycin, the aminoglycosides, and amphotericin B are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration.
Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents.
Cell Wall Synthesis Inhibitors

- Some antimicrobial drugs selectively interfere with synthesis of the **bacterial cell wall**—a structure that mammalian cells do not possess.

- The cell wall is composed of a polymer called **peptidoglycan** that consists of glycan units joined to each other by peptide cross-links.
To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms.

They have little or no effect on bacteria that are not growing and dividing.

The most important members of this group of drugs are the β-lactam antibiotics (named after the β-lactam ring that is essential to their activity).
## PENICILLINS
- Amoxicillin AMOXIL
- Ampicillin PRINCIPEN
- Dicloxacillin DYNAPEN
- Nafcillin
- Oxacillin
- Penicillin G PFIZERPEN
- Penicillin V
- Piperacillin
- Ticarcillin

## CEPHALOSPORINS
- Cefaclor CECLOR
- Cefadroxil DURACEF
- Cefazolin KEFZOL
- Cefdinir OMNICEF
- Cefepime MAXIPIME
- Cefixime SUPRAX
- Cefotaxime CLAFORAN
- Cefotetan CEFOTAN
- Cefoxitin MEFIXIN
- Cefprozil CEFZIL
- Ceftaroline TEFLARO
- Ceftazidime FORTAZ
- Ceftibuten CEDAX
- Ceftizoxime CEFIZOX
- Ceftriaxone ROCEPHIN
- Cefuroxime CEFTIN
- Cephalexin KEFLEX

## CARBAPENEMS
- Doripenem DORIBAX
- Ertapenem INVANZ
- Imipenem/cilastatin PRIMAXIN
- Meropenem MERREM

## MONOBACTAMS
- Aztreonam AZACTAM

## β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS
- Clavulanic acid + amoxicillin AUGMENTIN
- Clavulanic acid + ticarcillin TIMENTIN
- Sulbactam + ampicillin UNASYN
- Tazobactam + piperacillin ZOSYN

## OTHER ANTIBIOTICS
- Colistin COLOMYCIN, COLY-MYCIN M
- Daptomycin CUBICIN
- Fosfomycin MONUROL
- Polymyxin B AEROSPORIN
- Telavancin VIBATIV
- Vancomycin VANCOCIN
• Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillins.

• Gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entrance.
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Natural penicillins

- Penicillin G
- Penicillin V
- Obtained from fermentations of the fungus Penicillium chrysogenum.

Semisynthetic penicillins

- Amoxicillin
- Ampicillin
- Attaching different R groups to the 6-aminopenicillanic acid nucleus.

- Penicillin V is more acid stable than penicillin G.
- Similar spectrum
Pencillin inactivation by β-lactamases (penicillinases) that are produced by the resistant bacteria.

Despite widespread use and increase in resistance.

Penicillin remains the drug of choice:

- Gas gangrene (Clostridium perfringens) and
- Syphilis (Treponema pallidum).