Module: Infection & Immunity
Semester: 5
Session:2
Lecture Duration: 1h.

Lecture Title: Antimicrobials & resistance

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This Lectur was loaded in blackboard and you can find the material in:
Jawetz, Meinik & Adelberg's MEDICAL MICROBIOLOGY, 27 th Edition

For more detailed instructions, any question, or you have a case you need help in, please post to the group of session

Learning Objectives (LOs)

1- A classification of antimicrobials

2- Mechanisms of action

3- Types and mechanisms of antibiotic resistance

4-Genetics of resistance

5-Susceptibility testing

6- Brief information on key antibacterial

7- An introduction to antifungal, antiviral & antiprotozoal agents

Ideal features of antimicrobial agents LO-1

1. Selective toxicity is based on the ability of an antimicrobial agent to attack microorganism but not humans.
2. Few or no side effects
3. Able to achieve high concentrations at the site of infection.
4. A long half-life that reduces the need to frequently repeat doses.

Agents used in bacterial infections

LO-1

Antibacterial drugs are organized into seven groups

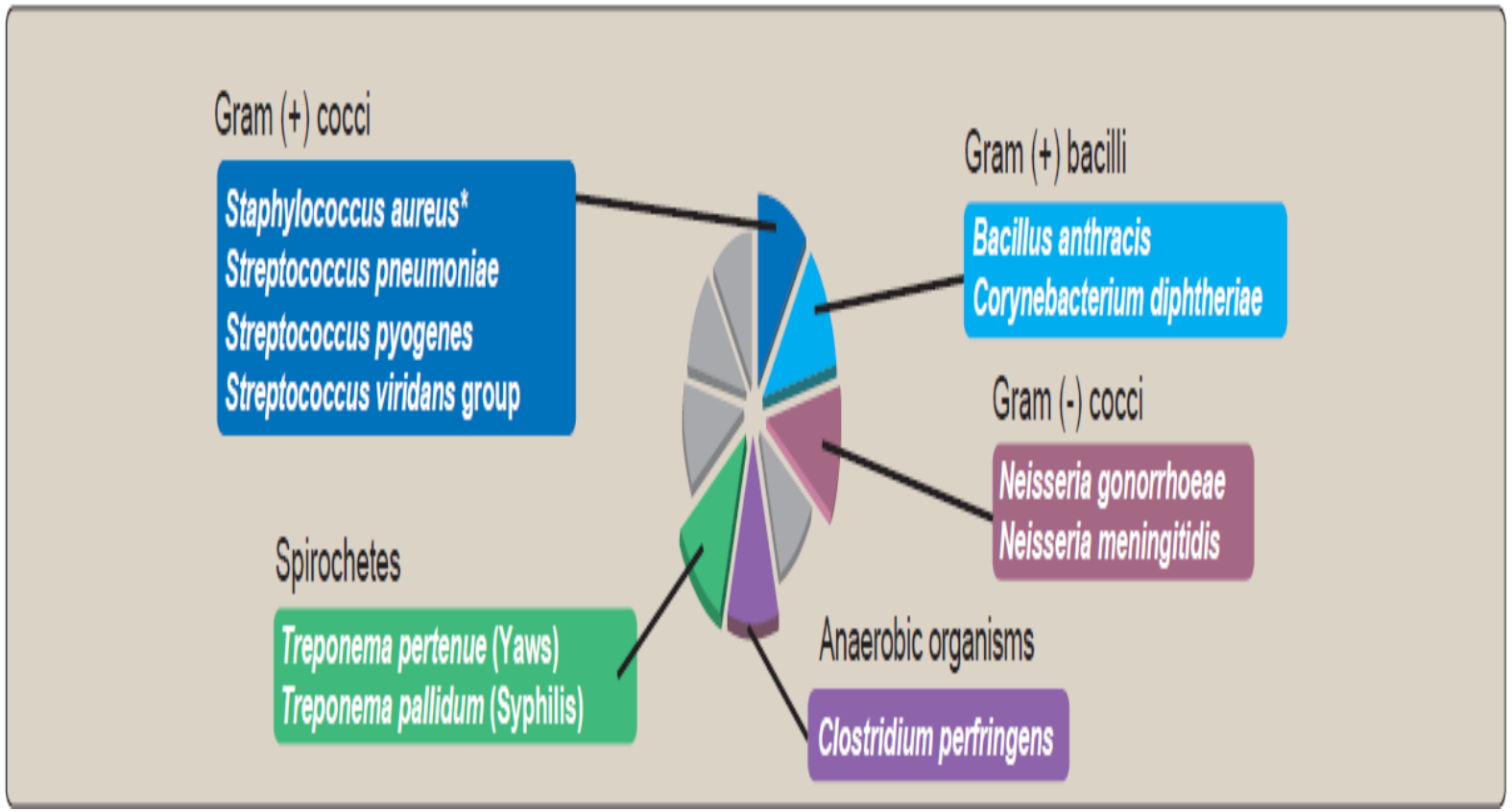
1. **Penicillin**
2. **Cephalosporins**
3. **Tetracyclines**
4. **Aminoglycosides**
5. **Macrolides**
6. **Fluoroquinolones**
7. **Other**

1- Penicillin

LO-1

- It is β-lactam antibiotic
- It interferes with the synthesis of the bacterial cell wall
- Their action is usually bactericidal
- The major adverse reaction to penicillin is hypersensitivity.
- Many bacteria have developed resistance to these drugs.

LO-1



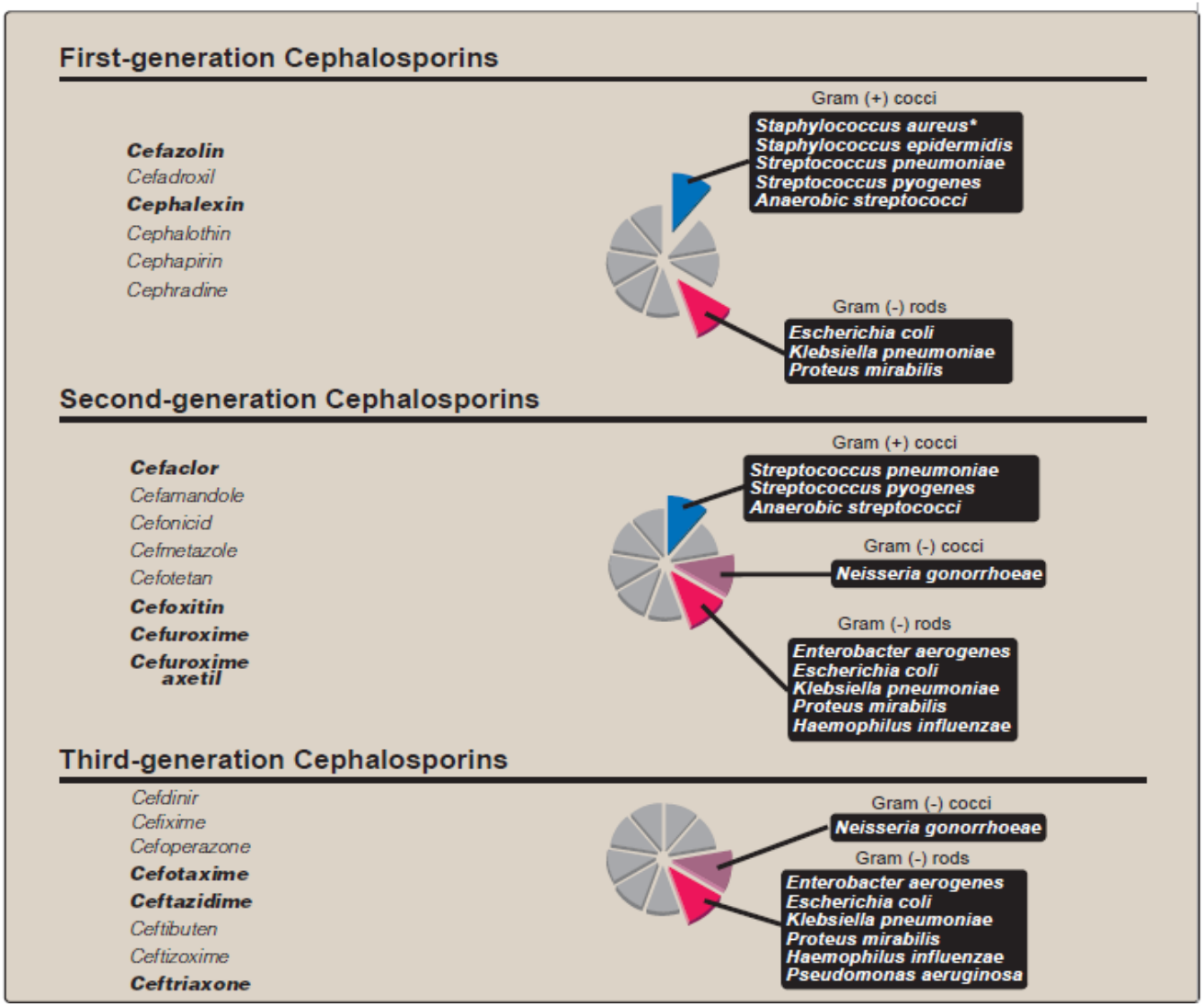
Summary of therapeutic applications of penicillin G.

2- Cephalosporins

LO-1

- Cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillin
- They are also bactericidal.
- Cephalosporins inhibit the synthesis of the bacterial cell wall
- Cephalosporins are classified as first, second, third, or fourth generation, largely on the basis of bacterial susceptibility patterns and resistance to β-lactamases.

LO-1

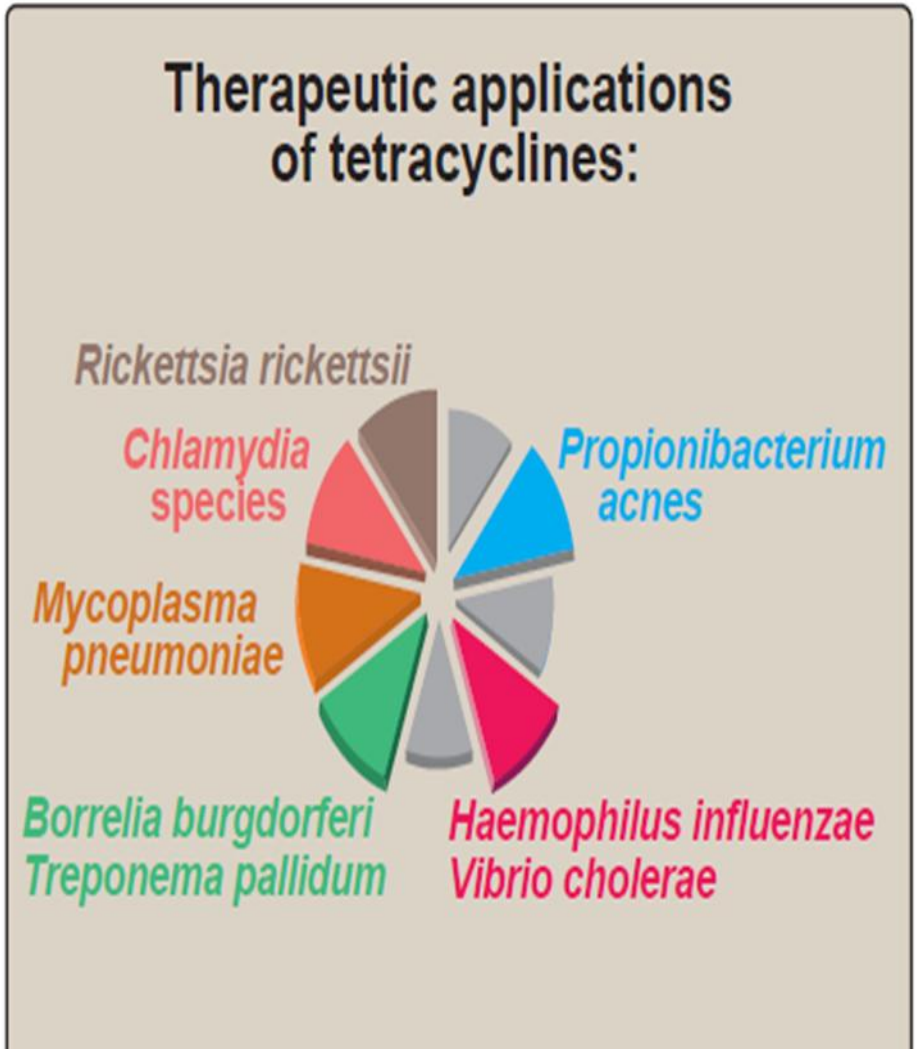


Summary of therapeutic applications of cephalosporins, with the more useful drugs shown in bold print. *Except methicillin-resistant Staphylococcus aureus.

3- Tetracyclines

LO-2

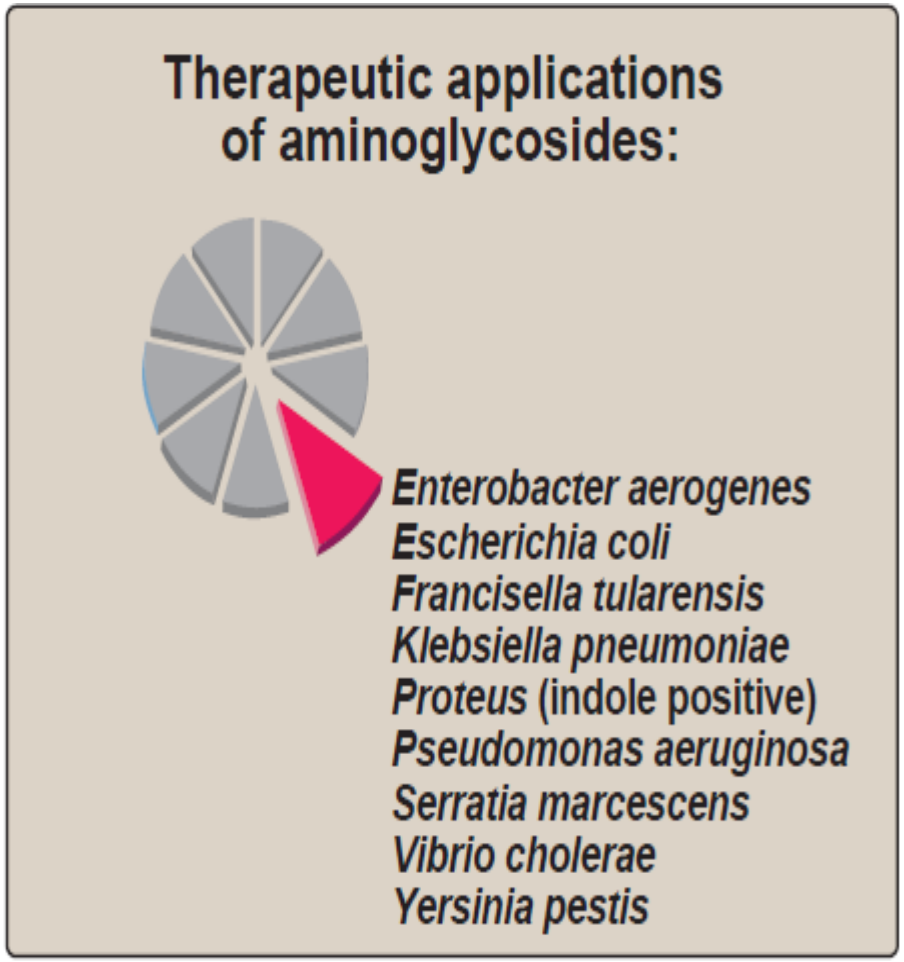
- Inhibiting bacterial protein synthesis.
- Tetracyclines are **broad-spectrum antibiotics**
- Tetracyclines are generally **bacteriostatic**



4- Aminoglycosides

LO-2

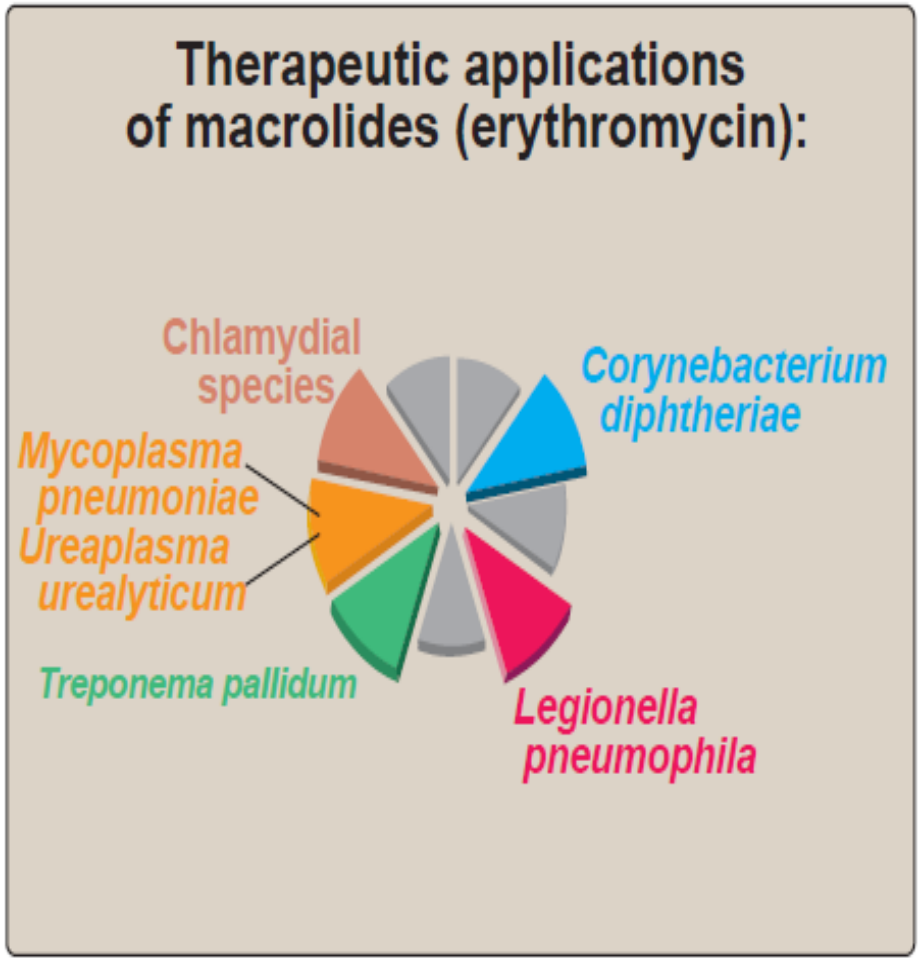
- Aminoglycosides inhibit bacterial protein synthesis.
- All aminoglycosides are **bactericidal**
- Gentamicin is example of aminoglycosides



5- Macrolides

LO-2

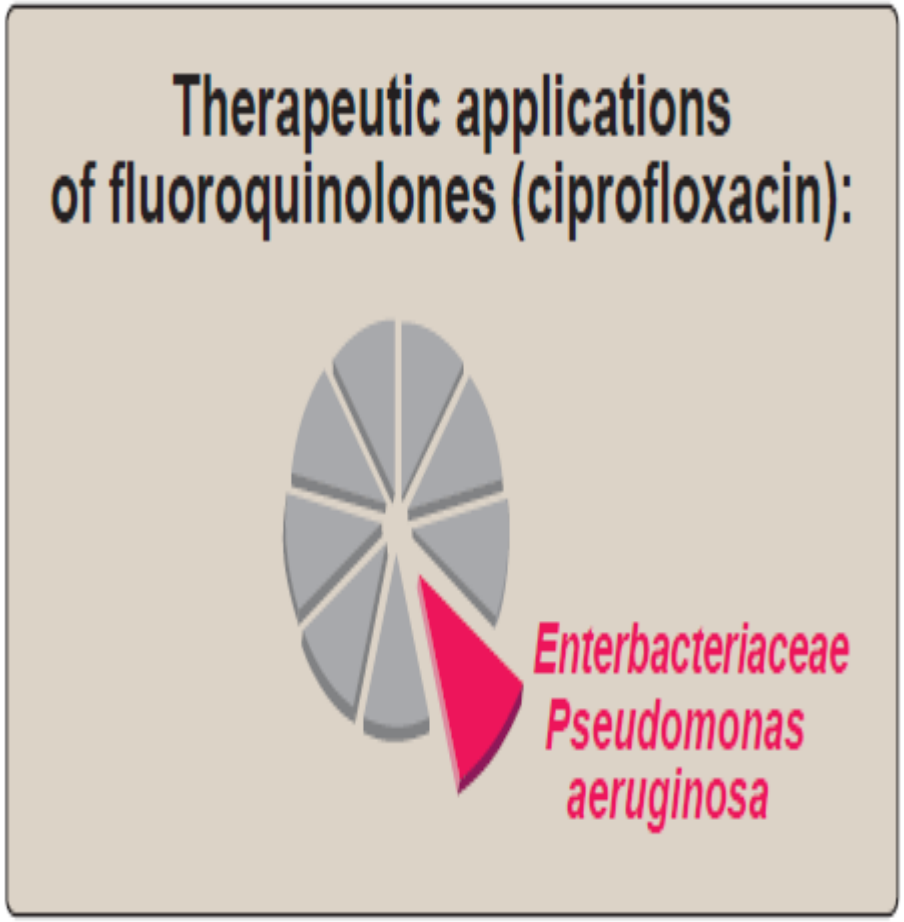
- Include Erythromycin, clarithromycin and azithromycin
- The drug of first choice, and as an alternative to penicillin in individuals who are allergic to β-lactam antibiotics.
- Macrolides inhibit bacterial protein synthesis.
- Generally considered to be bacteriostatic, they may be bactericidal at higher doses



6- Fluoroquinolones

LO-2

- Fluoroquinolones inhibit the replication of bacterial DNA.
- All of the fluoroquinolones are bactericidal.



7- Other important antibacterial agents

LO-2

A. Vancomycin: its effectiveness against multiple drug-resistant organisms, such as methicillin resistant staphylococci.

Vancomycin inhibits synthesis of bacterial cell wall.

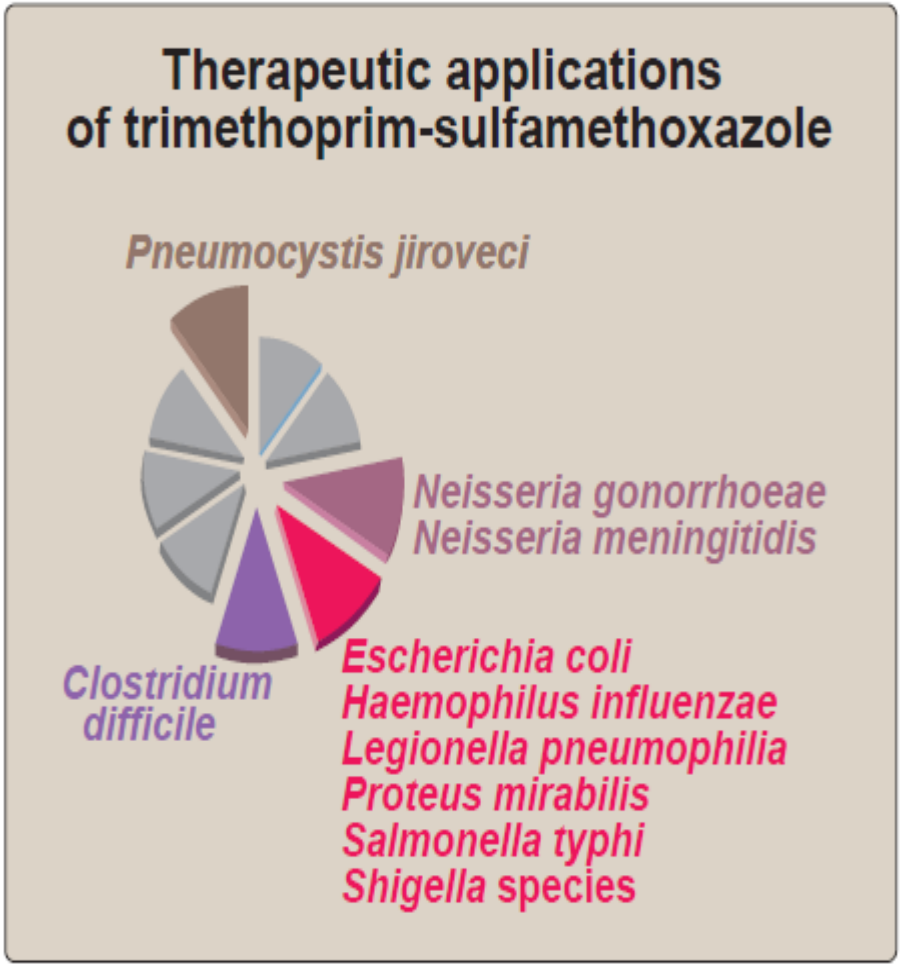
Vancomycin is useful in patients with serious allergic reactions to β-lactam antibiotics

Vancomycin is also used for potentially life-threatening antibiotic-associated colitis caused by *Clostridium difficile* or *Staphylococci*.

G. Other important antibacterial agents

LO-2

B. Trimethoprim-sulfamethoxazole, a combination called co-trimoxazole,
shows greater antimicrobial activity than equivalent quantities of either drug used alone.
The synergistic antimicrobial activity of co-trimoxazole results from its inhibition of the synthesis of tetrahydrofolic acid and preventing bacterial DNA synthesis.



LO-3

Bacterial resistance to antimicrobics

Mechanisms of Resistance

The major mechanisms of bacterial resistance are

1. Decreased uptake (or increased efflux) of antibiotic.

Pseudomonas aeruginosa has efflux pumps that expel tetracyclines and fluoroquinolones.

2. Alteration of the target site for antibiotic

MRSA alters its penicillin-binding proteins (PBPs) by change in *mecA* gene encode PBPs, leading to resistance to β-lactams.

3. Acquisition of the ability to destroy or modify the antibiotic

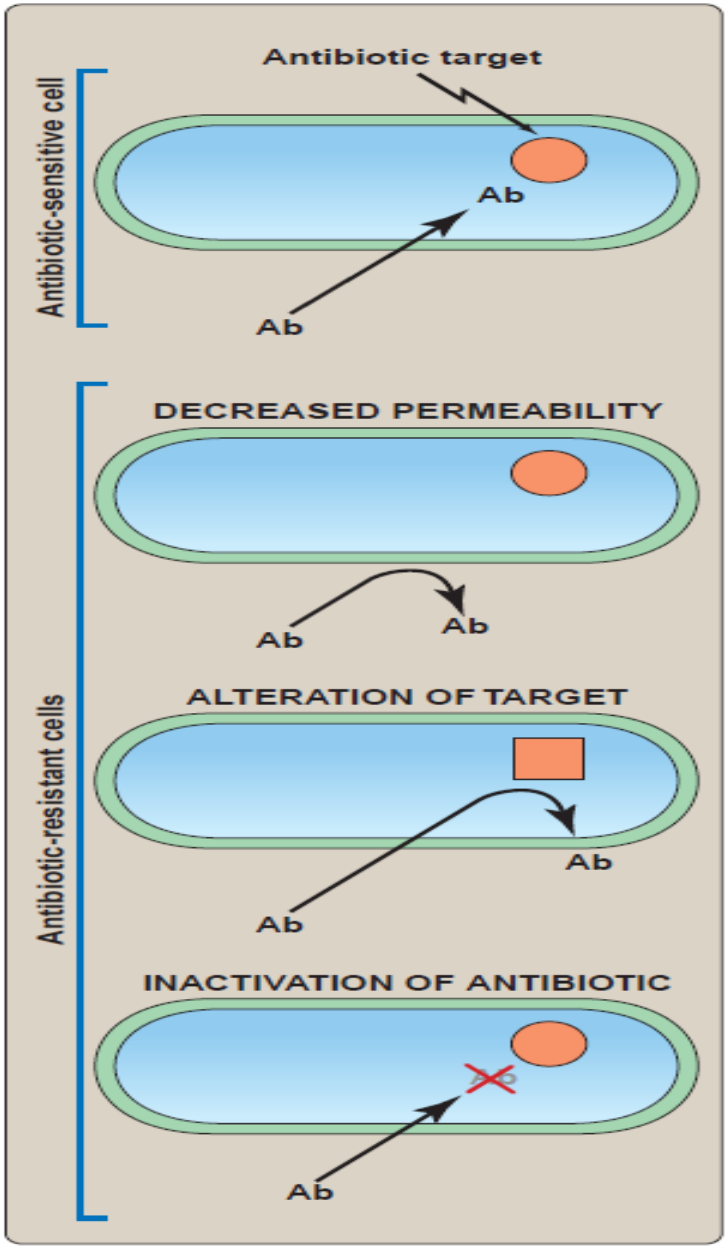
β-lactamases destroy penicillins and cephalosporins.

4. Changes in metabolic pathways can also translate into resistance in a few antimicrobic–organism combinations.

Enterococci can resist vancomycin by altering cell wall synthesis pathways.

LO-3

Common mechanisms of antibiotic resistance



LO-4

Genetics of Resistance

A- Intrinsic Resistance

For any antimicrobic, there are bacterial species that are typically within its spectrum and those which are not. The resistance of the latter group is referred to as intrinsic or chromosomal to reflect its inherent nature. The resistant species have features such as permeability barriers, a lack of susceptibility of the cell wall, or ribosomal targets that make them inherently resistance.

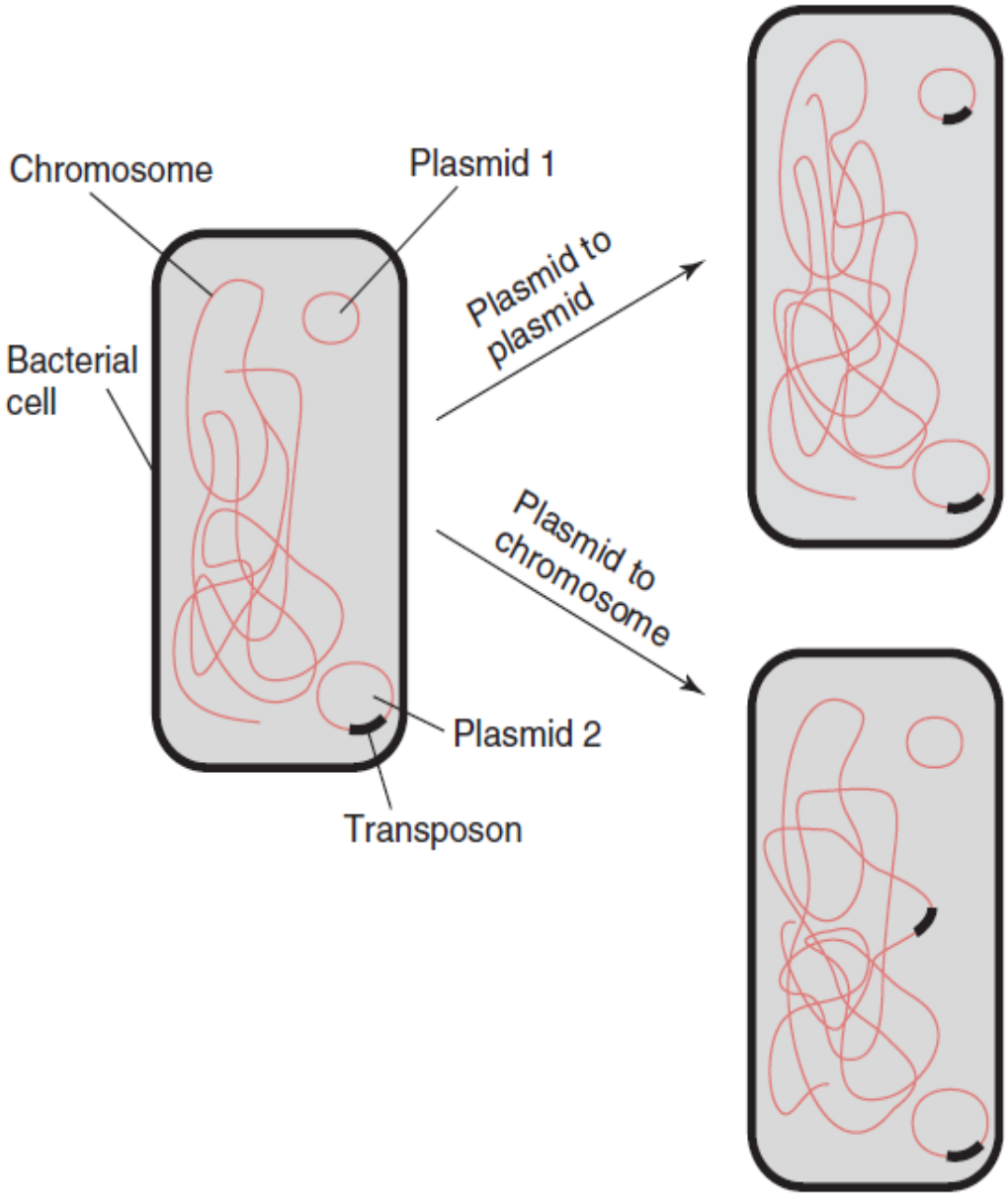
LO-4

B- Acquired Resistance

When an initially susceptible species develops resistance, such acquired resistance can be mutational or derived from another organism by the acquisition of new genes using one of the mechanisms of genetic exchange. Of these, conjugation and transposition are the most important and often work in tandem.

LO-4

Plasmids and transposons
When passed to the next generation, transposons incorporated in plasmids may be inserted in another plasmid or in the chromosome



Methods to calculate the minimal inhibitory concentration (MIC)

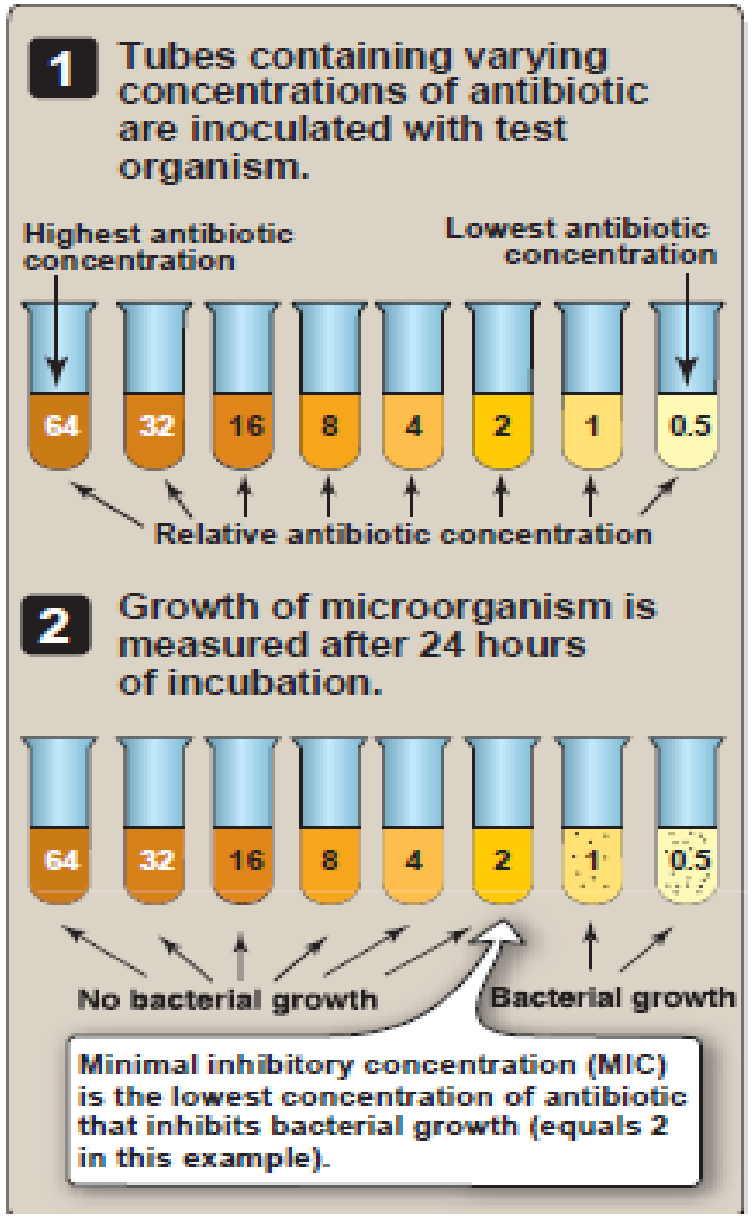
LO-5

1. Dilution Tests
2. Diffusion Tests
3. Automated Tests
4. Molecular Testing (detect resistance genes)

LO-5

Dilution Tests

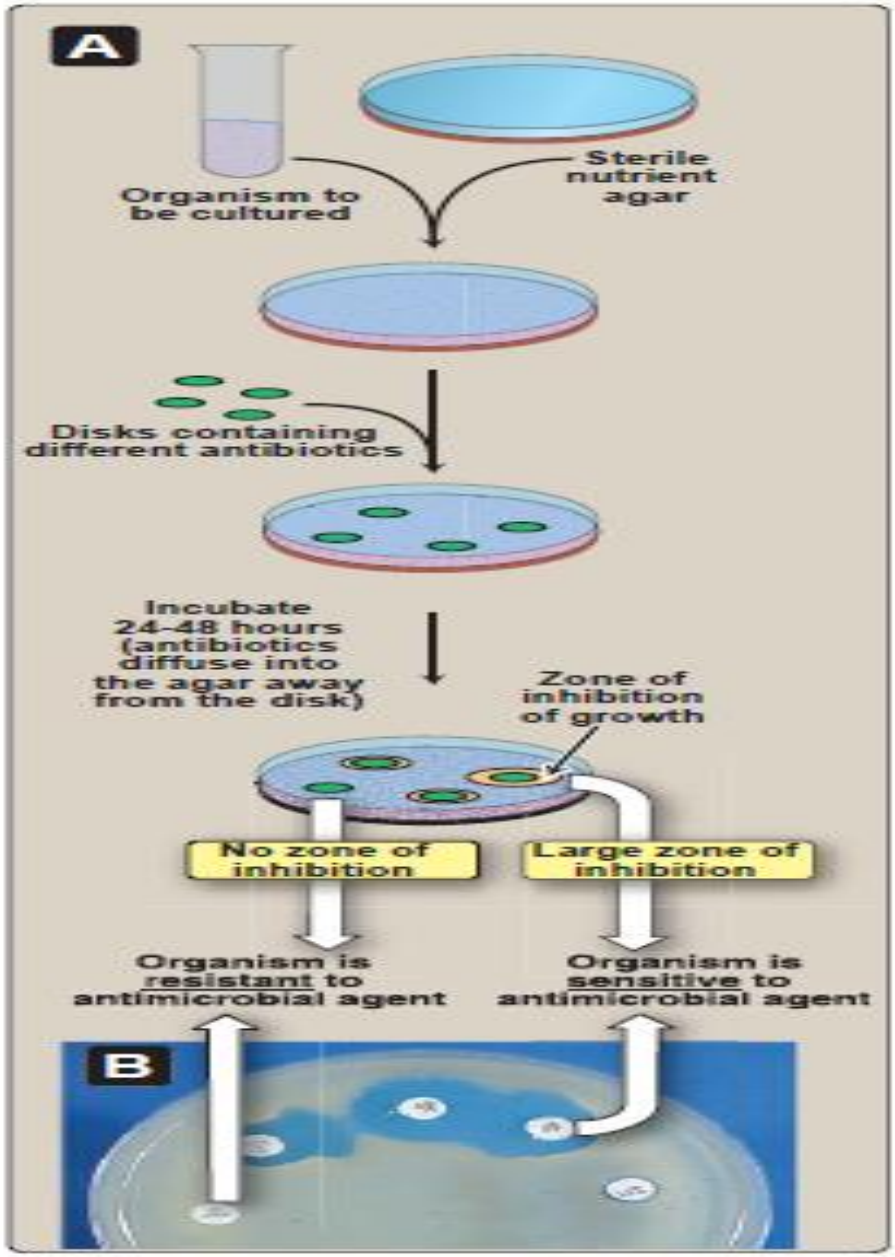
- Tubes containing serial dilutions of an antibiotic are inoculated with the microorganism is to be tested.
- The MIC of the antibiotic necessary to prevent bacterial growth



Diffusion Tests

LO-5

- The organism's growth (resistance to the drug)
- Lack of growth (sensitivity to the drug)



LO-6

Epidemiology of Resistance

- Clinical use is followed by resistance
- Predominant susceptibility can turn to resistance
- Resistance may emerge after decades of use

Control of Resistance

LO-6

1. Use antimicrobics conservatively and specifically in therapy.
2. Use an adequate dosage and duration of therapy to eliminate the infecting microorganism and reduce the risk of selecting resistant variants.
3. Select antimicrobics according to the known susceptibility of the infecting strain whenever possible.
4. Use narrow-spectrum rather than broad-spectrum antimicrobics when the specific etiology of an infection is known, if possible.
5. Use antimicrobic combinations when they are known to prevent emergence of resistant mutants.

Control of Resistance

LO-6

6. Avoid environmental contamination with antimicrobics.
7. Rigidly apply careful, aseptic and handwashing procedures to help prevent spread of resistant microorganisms.
8. Epidemiologically monitor resistant microorganisms and apply enhanced control measures.
9. Restrict the use of therapeutically valuable antimicrobics for nonmedical purposes

LO-7

Antiviral therapy

Among the unique viral events are attachment, penetration, uncoating, RNA-directed DNA synthesis (reverse transcription), and assembly and release of the intact virion.

Each of these steps may have complex elements with the potential for inhibition.

LO-7

Summary of Antiviral Agents

Mechanism of Action	Antiviral Agent	Viral Spectrum[a]
Inhibition of viral uncoating, penetration		
	Amantadine	Flu A
	Rimantadine	Flu A
Neuraminidase inhibition		
	Oseltamivir	Flu A, Flu B
	Zanamivir	Flu A, Flu B
Inhibition of viral DNA polymerase		
	Acyclovir	HSV, VZV
	Famciclovir	HSV, VZV
	Penciclovir	HSV
	Valacyclovir	HSV, VZV
	Ganciclovir	CMV, HSV, VZV
	Foscarnet	CMV, resistant HSV
	Cidofovir	CMV
	Trifluridine	HSV, VZV
Inhibition of viral reverse transcriptase		
	Zidovudine	HIV
	Dideoxyinosine	HIV
	Dideoxycytidine	HIV
	Stavudine	HIV
	Lamivudine	HIV, HBV[b]
	Nevirapine	HIV
	Delavirdine	HIV
	Efavirenz	HIV
Inhibition of viral protease		
	Saquinavir	HIV
	Indinavir	HIV
	Ritonavir	HIV
	Nelfinavir	HIV
	Lopinavir	HIV
Inhibition of viral protein synthesis		
	Interferon α	HBV, HCV, HPV
Inhibition of viral RNA polymerase		
	Ribavirin	RSV, HCV,[b] Lassa fever
Antisense inhibition of viral mRNA synthesis		
	Fomivirsen	CMV

[a] Flu A, influenza A; Flu B, influenza B; HSV, herpes simplex viruses; VZV, varicella-zoster virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RSV, respiratory syncytial virus; HPV, human papillomavirus.
[b] Used in combination with interferon.

LO-7

Inhibitors of HIV

Nucleoside Reverse Transcriptase Inhibitors, e.g., Azidothymidine (AZT)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), e.g., nevirapine, delavirdine, and efavirenz

Protease Inhibitor received approval: Ritonavir, indinavir, and nelfinavir

Feature of antifungal agents

LO-7

Agent	Mechanism of Action	Mechanism of Resistance	Route	Clinical Use
Polyenes				
Nystatin	Membrane disruption	Sterol modification	Topical	Most fungi
Amphotericin B	Membrane disruption	Sterol modification	Intravenous	Most fungi
Azoles				
Ketoconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral	*Candida, Cryptococcus,* dimorphic fungi[b]
Fluconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral, intravenous	*Candida, Cryptococcus,* dimorphic fungi
Itraconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral, intravenous	*Candida, Cryptococcus,* dimorphic fungi, invasive molds (*Aspergillus*)
Clotrimazole	Demethylase block of ergosterol synthesis	Unknown[c]	Topical	*Candida,* some other yeasts
Miconazole	Demethylase block of ergosterol synthesis	Unknown[c]	Topical	*Candida,* some other yeasts
Voriconazole	Demethylase block of ergosterol synthesis	Unknown[c]	Oral, intravenous	*Candida,* some other yeasts and molds
Allylamines				
Terbinafine	Squalene accumulation	?Active efflux	Oral	Dermatophytes, combined with azoles for *Candida, Aspergillus*
Naftifine	Squalene accumulation	Unknown	Topical	Dermatophytes
Flucytosine				
	RNA and DNA synthesis	Permease or modifying enzymes[d] absent or decreased	Oral	*Candida* and *Cryptococcus,* resistance emerges in monotherapy
Echinocandins				
Caspofungin	Block of glucan synthesis	Unknown	Intravenous	*Aspergillus, Candida*
Griseofulvin	Microtubule disruption	Unknown	Oral	Dermatophytes
Potassium iodide	Unknown	Unknown	Oral	*Sporothrix schenckii*
Tolnaftate	Unknown	Unknown	Oral	Dermatophytes

Abbreviation: 5FC, 5-flucytosine.

[a] Most work is with fluconazole and *Candida,* other azoles are to be assumed similar.

[b] Generally less absorbed and less active than fluconazole or itraconazole.

[c] Probably similar to other azoles, but resistance to the concentrations in topical preparations may differ.

[d] Cytosine deaminase and uracil phosphoribosyltransferase (the enzyme that forms 5-fluorodoxyuridine from 5FC).

Anti protozoa

LO-7

The majority of anti protozoa drugs interfere with nucleic acid synthesis or, less commonly, with carbohydrate metabolism.

Metronidazole is an example.

“ We always work together as a team ”