Antibiotics

Group [C-11]

- Supervised by:
  Dr. Seri Sawaqed

- Anas Adnan
- Alaa Al-Matrouk
- Saeed Bydoon
- Muhammad Al-Adwan

Topics

- Antimicrobial Resistance
- Bacterial Review
- Penicillin
- Cephalosporin
- Carbapenems
- Vancomycin
- Tetracyclines
- Glycylcyclines
- Aminoglycosides
- Macrolides
- Chloramphenicol
- Clindamycin
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- Streptogramins
- Fluoroquinolones
- Folate Antagonists
- Chemoprophylaxis

Antimicrobial Resistance

- Antimicrobial resistance is an urgent global public health threat, killing at least **1.27 million people worldwide**.

- In the U.S., more than **2.8 million** antimicrobial-resistant infections occur each year.
  More than 35,000 people die as a result.

- The estimated national cost to treat infections caused by six multidrug-resistant germs frequently found in health care can be substantial—more than **$4.6 billion annually**

-MRSA: methicillin-resistant Staphylococcus aureus
-VRE: vancomycin-resistant Enterococcus
-ESBL: extended-spectrum β-lactamase
-CRE: carbapenem-resistant Enterobacteriaceae
-CRA: carbapenem- resistant Acinetobacter baumannii
-MDRA: multidrug-resistant Pseudomonas aeruginosa

To Whom?
For What?
How Much?
How Long?

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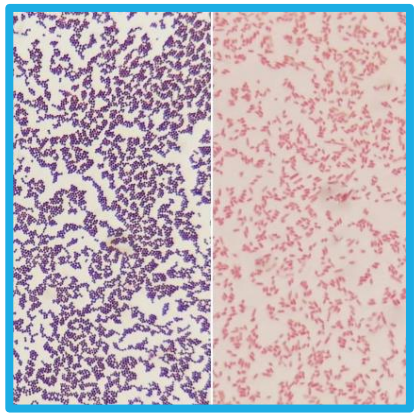
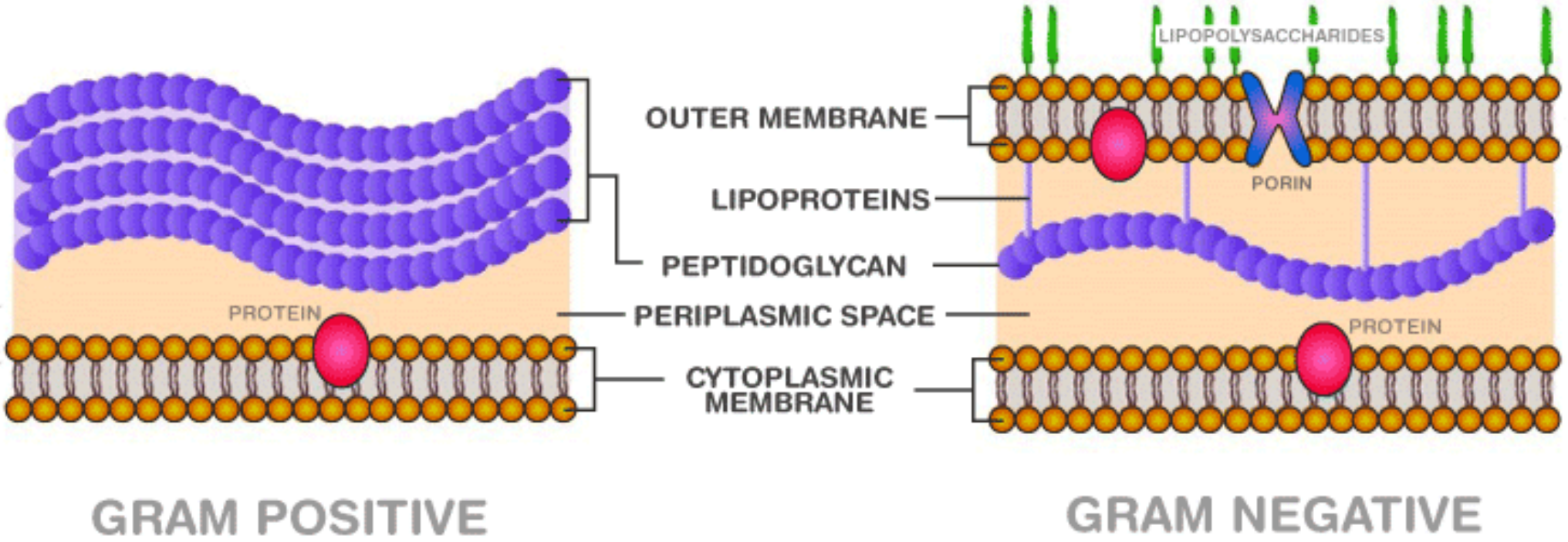
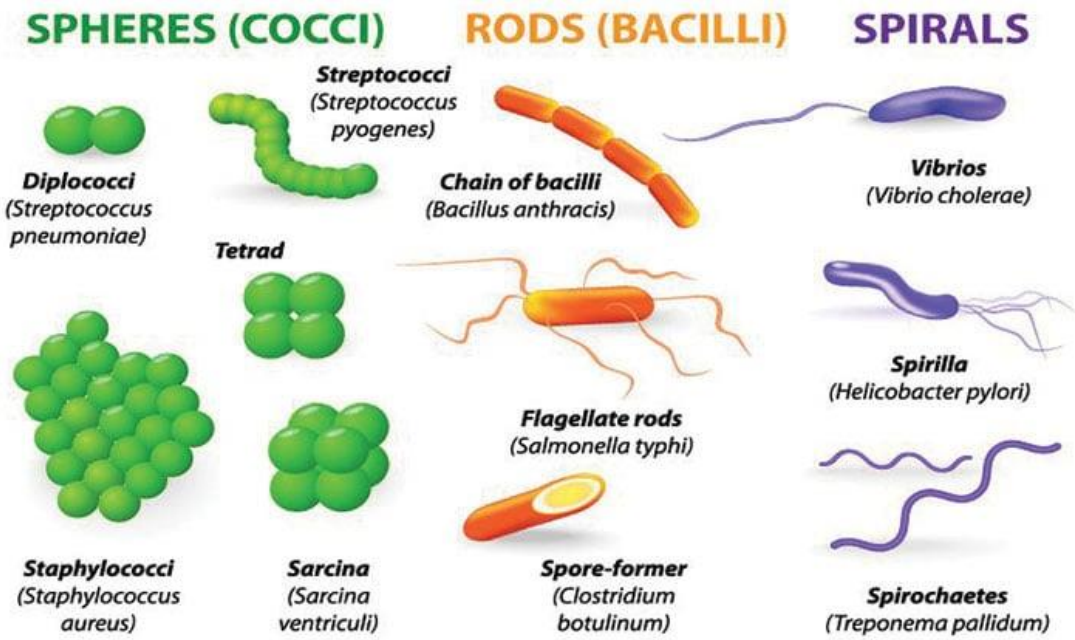
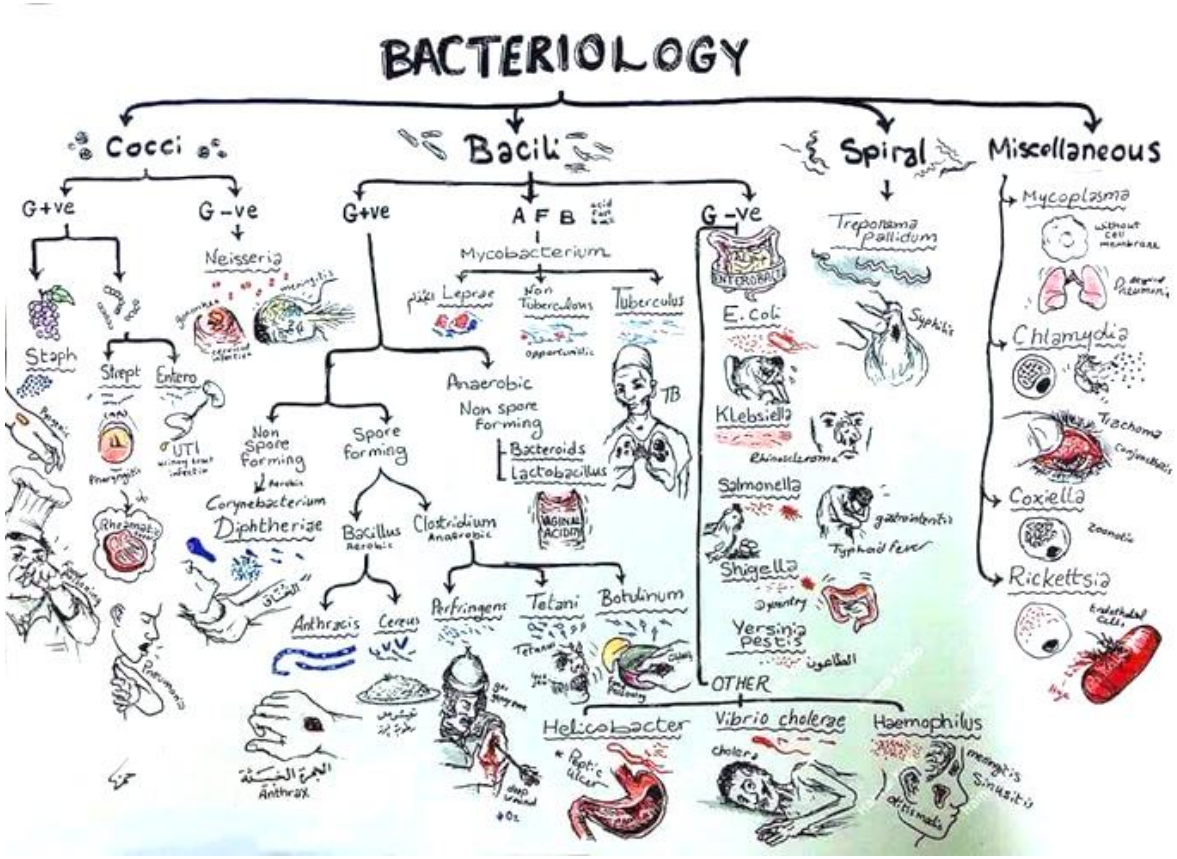
Bacterial Anatomy



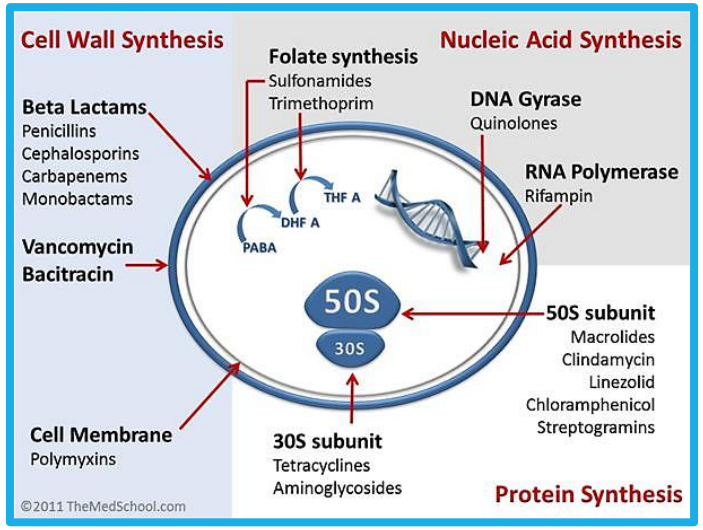


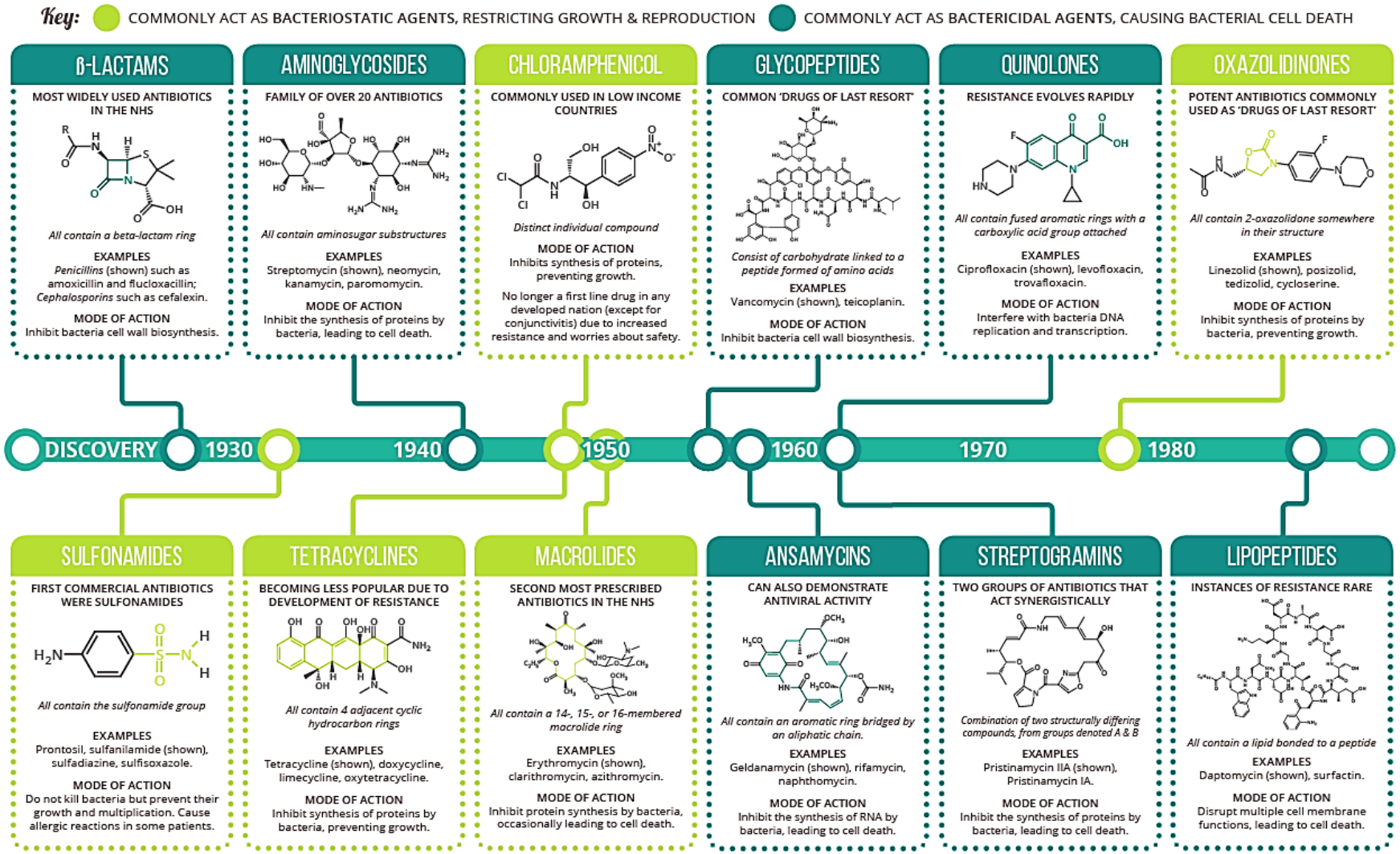
Bacterial Classification



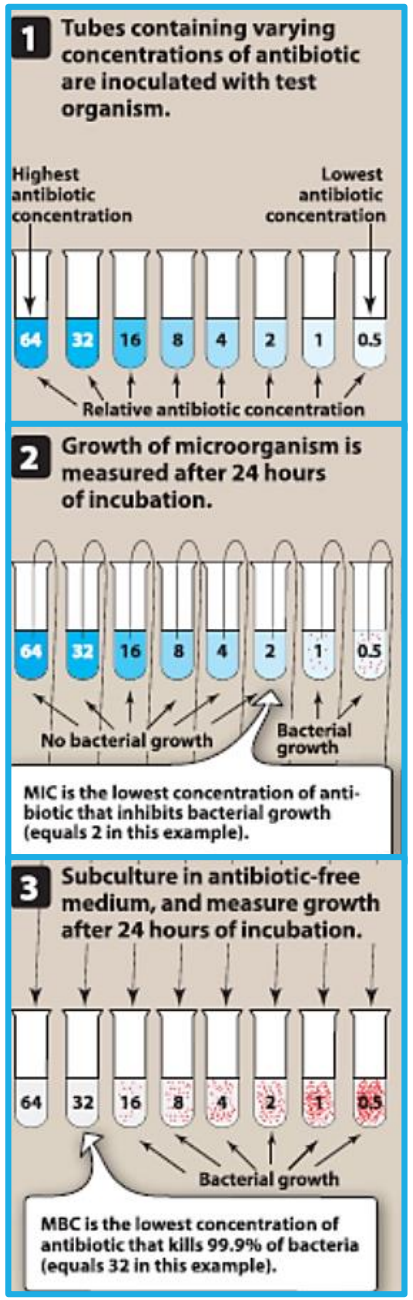


Antibiotics Classes



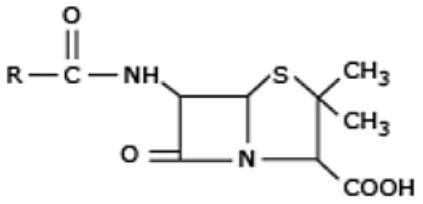


Bactericidal	Bacteriostatic
Kills the bacteria.	Prevents bacterial growth.
Inhibit cell wall formation.	Inhibit DNA replication and protein synthesis.
Irreversible action.	Reversible action.
Don’t work with the immune system of the host.	Work with the immune system of the host to prevent growth and reproduction of bacteria.
Minimal Bactericidal Concentration (MBC): drug concentration required to kill 99.99% of the bacterial population.	Minimal Inhibitory Concentration (MIC): minimum drug concentration which inhibits bacterial growth.
Ex: Beta lactams, Aminoglycosides, Quinolones .	**Ex:** Tetracyclines, Macrolides, Chloramphenicol.

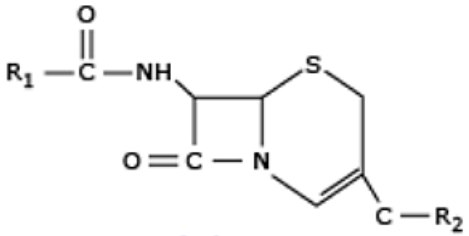


Beta-lactam antibiotics

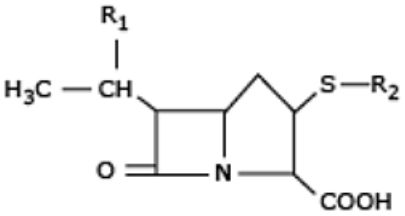
- Beta-lactam antibiotics are among the most commonly prescribed drugs. Grouped together based upon a shared structural feature, the **beta-lactam ring**.
- Generally are **bactericidal**, they inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane.
- The most common antibiotics to cause **anaphylaxis**.



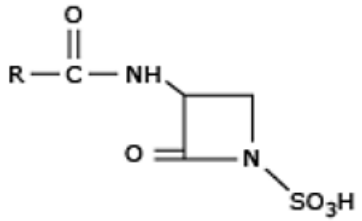
Penicillins



Cephalosporins



Carbapenems



Monobactams

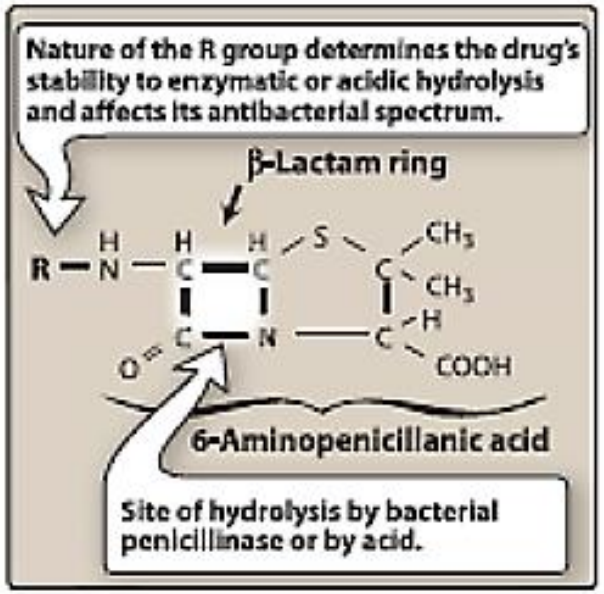


Figure 29.2
Structure of β-lactam antibiotics.

Penicillin

- The most widely effective and least toxic antibiotic.
- **Mechanism Of Action**
  Inhibits bacterial cell wall synthesis by binding to transpeptidase which interferes with cross-linkage of peptidoglycan cell wall.
- **Antibacterial Spectrum**
  The antibacterial spectrum of penicillins is determined by their ability to cross the bacterial peptidoglycan cell wall to reach the penicillin binding proteins in the periplasmic space.

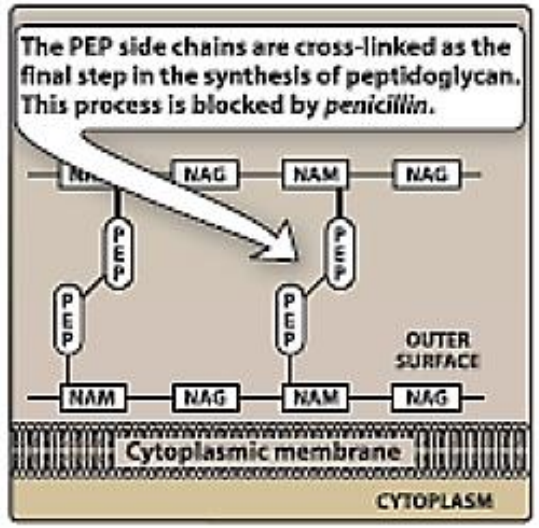


Figure 29.3
Bacterial cell wall of gram-positive bacteria. NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.

CLASSIFICATION

Natural penicillins: (from Penicillium chrysogenum fungus) penicillin G and V

- highly active against most gram-positive cocci, gram-positive rods, gram-negative cocci, anaerobes, and spirochetes.
- The drug of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum).

Semisynthetic penicillins:

- Extended spectrum penicillins (Ampicillin and amoxicillin): active against the majority of strains of gram – negative rods (Escherichia coli, Proteus mirabilis, Salmonella, Shigella, and Haemophilus influenzae).
- When you add beta-lactamase inhibitor: (ampicillin and sulbactam, amoxicillin and clavulonic acid) that will extend to more gram negative, anaerobes and MSSA.

CLASSIFICATION

Anti-staphylococcal penicillins:

- Methicillin, Nafcillin, Oxacillin, and Dicloxacillin are lactamase (penicillinase)-resistant penicillins. Their use is restricted for penicillinase-producing staphylococci (**Ex:** MSSA.)
- Minimal to no activity against gram-negative infections.

Anti-pseudomonal penicillins:

- Piperacillin, Carbenicillin, and ticarcillinis are used for gram-negative rods (Pseudomonas aeruginosa).
- Formulation of piperacillin with tazobactam extends the antimicrobial spectrum to include penicillinase-producing organisms (**Ex:** most Enterobacteriaceae and Bacteroides species).

Pharmacokinetics

The Route of administration is determined by:

- The stability of the drug to gastric acid.
- The severity of infection.

Route of administration:

- Ampicillin w/ sulbactam, piperacillin w/ tazobactam, and the antistaphylococcal penicillins: nafcillin and oxacillin → (**IM**) or (**IV**).
- Penicillin V, amoxicillin, and dicloxacillin → (**PO**).
- Others are effective by the → **oral**, **IV**, or **IM** routes.

Absorption:

- Most drugs are incompletely absorbed orally and reach the intestine in sufficient amounts to affect the intestinal flora.
- Administered on an empty stomach (acidity and food(↑gastric emptying)= ↓absorption).

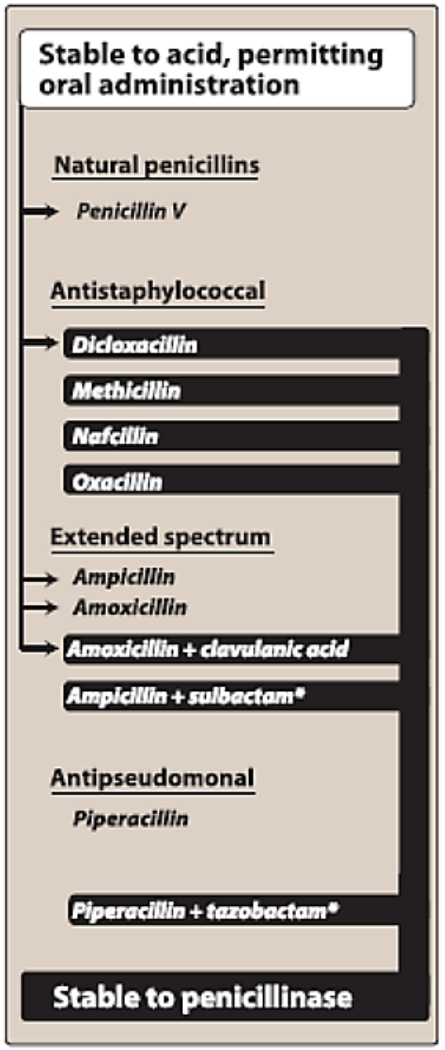


Figure 29.6
Stability of the penicillins to acid or the action of penicillinase. *Available only as parenteral preparation.

Pharmacokinetics

Distribution:

- The B-lactam antibiotics distribute well throughout the body.
- All cross the placental barrier but no teratogenic effects have been shown.
- Penetration into bone or CSF is insufficient for therapy unless inflamed.
- Penicillin amounts in prostate are insufficient to be effective against infections

Metabolism:

- Host metabolism of B-lactam antibiotics is usually insignificant, but some metabolism of penicillin G may occur in patients with impaired renal function.

Excretion:

- All excreted **renally** except nafcillin and oxacillin(metabolized in the **liver**).
- They are also excreted in breast milk.

Resistance to penicillin occurs due to:

- β-Lactamase production
- Decreased permeability to the drug (Decreased penetration to the target site through porins)
  P. aeruginosa (lacking high permeability porins) and K. pneumoniae (efflux pump)
- Altered penicillin-binding proteins (PBPs) (Inactivation by a bacterial enzyme)
  MRSA (lower affinity PBP)

Adverse Effects:

- Penicillins are among the safest drugs.

Contraindications:

- Hypersensitivity reactions
- Serious skin reactions (ex: Stevens-Johnson syndrome)

CEPHALOSPORIN

Mechanism of action:-

-Cephalosporins have the same mode of action as penicillins, and are affected by the same resistance mechanisms.

-The β-lactam ring confers bactericidal activity

-They are more resistant than penicillins to certain b-lactamases.

Antibacterial spectrum coverage

. Cephalosporins have been classified into first, second, third, and fourth generation based on:
1-Bacterial susceptibility patterns
2-Resistance to B-lactamases.

However, commercially available penicillins are ineffective against MRSA, L.monocytogenes, C.difficile and the enterococci.
-most of the available cephalosporin are semi-synthetic derivatives of cephalosporin C, a compound with antibacterial activity produced by the fungus cephalosporin.

-1st -generation cephalosporins

generally serve as substitutes for penicillin, and also have coverage against Proteus, Klebsiella, and E. coli, and MSSA.

*Cefazolin is the only parenteral first-generation cephalosporin available in the United States

-2nd -generation cephalosporins

have more gram-negative activity and less gram-positive activity than first-generation cephalosporins. They are used to treat gram- negatives :H. influenzae, Neisseria gonorrhoeae, and Enterobacter spp.

-3rd -generation cephalosporins

have even more gram-negative activity, less gram-positive activity, and are able to cross the blood–brain barrier. Ceftazidime is effective against P.aeruginosa.

1st and 2nd generation cephalosporins do not penetrate the CSF and should not be used to treat infections of the central nervous system.

- 4th -generation cephalosporins are the most broad-spectrum, including **(Cefepime)** Effective against:-

- Streptococci and staphylococci

-Aerobic gram negative organisms

-against Pseudomonas, Neisseria, and methicillin-sensitive Staphylococcus aureus, as well as most of the above-mentioned organisms. * It has better staphylococcal coverage than third-generation drugs

- 5th -generation cephalosporins are a new class of drugs which show high activity against MRSA

(Ceftaroline)

- Broad spectrum gram positive and gram negative unlike the other generations.
- It covers MRSA and Enterococcus faecalis
- It doesn't cover pseudomonads

-All cephalosporins (every generation) will cover viridans group streptococci, group A, B, and C streptococci, E. coli, Klebsiella, Proteus mirabilis.

-Third- and fourth-generation cephalosporins are not useful for treating infections due to gram-positive cocci (except for Streptococcus species) or Acinetobacter.

-All cephalosporins cross the placenta. Cephalosporins are excreted renally except ceftriaxone.(It is excreted through the bile into the feces).

Administration:

Many cephalosporins must be administered IV or IM due to their poor oral absorption. Exceptions are:

1. First generation: Cephalexin, Cefadroxil.
2. Second generation: Cefuroxime.
3. Third generation: Cefdinir, cefixime, ceftibuten.

Side effects :-

Cephalosporins are well tolerated,however patients who has:
-Steven-Johnson syndrome
-Or toxic epidermal necrolysis to penicillins should not receive cephalosporins.
-The most common adverse effects include: nausea/vomiting/lack of appetite, and abdominal pain
-The highest allergic cross sensitivity is between penicillin and first generation cephalosporins.
-Certain cephalosporins (especially the second generation) can promote a bleeding diathesis, which is reversible with vitamin K, but this is rare.

Contraindications:-

1-allerigic patients or had an anaphylactic reaction to pencillin or other B-lactam antimicrobials.

2-ceftriaxone in neonates with hyperbilirubinemia ,it displaces bilirubin from albumin by increasing the free bilirubin concentration and increase the risk of jaundice.

3-ceftriaxone reacts to calcium containing solution, and it can precipitate in the lungs and kidney of infants less than 28 days old, which could be life threatening.

Mechanism of resistance

Cephalosporins , like other beta lactams, bind to the bacterial pencillin binding proteins.

Resistance arise when the PBP and in particular , the trans peptidases are modified, or when they are protected by b-lactamases, or permeability barriers.

Target mediated cephalosporin resistance can either involve reduced affinity of an existing PBP component , or the acquisition of a supplementary beta-lactam insensitive PBP.

Carbapenems

The carbapenems are semisynthetic β-lactams and include imipenem, meropenem, doripenem and ertapenem.
They are currently the broadest spectrum of antibiotics, being active against the majority of Gram-positive and Gram-negative as well as anaerobic bacterial pathogens.

Mechanism of action:

-CARBAPENEMS act as a mechanism based inhibitors of the peptidase domain of PBPs.

-A key factor of the efficacy of Carbapenems is their ability to bind to multiple different PBPs.

-They work by penetrating the cell wall bacteria, binding with PBPs , and result in the inactivation of intracellular auotolytic inhibitor enzymes, ultimately killing the bacterial cell.

Indication:-

They are used for serious nosocomial infections when multiple-resistant Gram-negative bacilli or mixed aerobe and anaerobe infections are suspected.

Toxicity :-

This is similar to that of β-lactam antibiotics. Nausea, vomiting and diarrhoea occur in less than 5% of cases, pruritis and rashes, and it sometimes may cause neutopenia. Imipenem may cause seizures and should not be used to treat meningitis; meropenem is safe for this indication.

Contraindication:

It is contraindicated in those who are hypersensitive to them, and in increased risk of seizures in pediatric patients with central nervous system infections.

Mechanism Of Resistance:-

Resistance to Carbapenems may be attributed to three major mechanisms :

Porin mediated resistance to reduce uptake of Carbapenems

Efflux pumps, which pump the Carbapenems outside of the cells

Enzyme mediated resistance with is mediated by the acquisition of carbapemens genes.

Vancomycin

-Vancomycin is a miscellaneous cell wall inhibitors, Inhibits cell wall synthesis by interfering with cross-linkage of peptidoglycan chains , and alters bacterial cell membrane permeability and RNA synthesis.
-It is given intravenously for meticillin-resistant Staph. aureus and other multiresistant Gram-positive organisms.

Indications:
It is also used for treatment and prophylaxis against Gram-positive infections in penicillin-allergic patients, pseudomembranous colitits, and enterococcus faecium.
It is used for Strep. pneumoniae meningitis when caused by penicillin-resistant strains.
It is also used for the treatment of septicemia, infective endocarditis, peritonitis, skin infections, bone infections, and lower respiratory tract infection.
-Oral vancomycin is effective to treat C. difficile infections of the bowel Acts synergistically with aminoglycosides to treat enterococcal infections.

Adverse reactions:-

include fever, nephrotoxicity, ototoxicity, and “red man syndrome” (flushing due to infusion-induced histamine release).

Treat red man syndrome by slowing the infusion and giving antihistamines (i.e., diphenhydramine)

Serum levels must be followed up in prolonged therapy, and doses must be adjusted for renal insufficiency.

Mechanism of resistance:

Vancomycin resistance is an emerging, ominous phenomenon caused by an altered peptidoglycan terminus , resulting in reduced vancomycin binding and failure to prevent cell wall synthesis. Many enterococci have developed resistance to vancomycin creating vancomycin resistant enterococci (VRE), resistance in vancomycin-intermediate S. aureus and glycopeptide-intermediate S. aureus.

Contraindications:

Vancomycin should not be used with patients who are hypersensitive to this antibiotic and during pregnancy unless benefits outweigh the risk of medication, and needs close monitor of maternal blood to reduce the risk of ototoxicity and nephrotoxicity in the fetus.

Tetracyclines

Mechanism of action:
Reversible binding to 30S subunit of bacterial ribosome, inhibiting protein synthesis

Antimicrobial coverage:
Bacteriostatic against Gram +ve (Staphylococcus Aureus, Streptococcus pneumonia, Bacillus anthracis),Gram -ve (Brucella, H.Pylori, Vibrio cholerae),Mycoplasma (M. Pneumonia),Chlamydia ,anaerobes (Clostridium perfringens and tetani) and spirochetes.

Examples:

- Demeclocycline
- Doxycycline
- Minocycline
- Tetracycline

Indications:

- Pneumonia
- Rocky mountain spotted fever
- Chlamydia trachomatis
- Cholera
- Peptic Ulcer Disease
- Lyme disease
- Acne

Adverse effects:

- Epigastric discomfort
- Teeth discoloration and hypoplasia
- Hepatotoxicity
- Phototoxicity
- Vestibular (Dizziness,Vertigo,Tinnitus)
- Pseudotumor cerebri(Increased ICP)
- C/I in pregnant women and children <8 years old

Glycylcyclines

Mechanism of action:
Same as Tetracyclines.

Antimicrobial coverage:
Broad spectrum against MRSA, VRE, Actinobacter, multidrug resistant streptococci.

Indications:

- Skin and soft tissue infections
- Intra-abdominal infections
- Community acquired Pneumonia

Examples:

- Tigecycline

Adverse Effects:

- Nausea/Vomiting
- Acute pancreatitis
- Elevated KFT and LFT
- Same as tetracycline

Aminoglycosides

Mechanism of action:
Bind to 30S ribosomal subunit of bacteria interfering with assembly of functional apparatus.

Antimicrobial coverage:
Gram -ve bacilli (Pseudomonas aeruginosa, Klebsiella pneumoniae and Enterobacter), if combined with a Beta Lactam it is effective against Enterococcus Faecalis and Faecium

Indications:
Infective endocarditis

Examples:

- Gentamicin
- Neomycin
- Streptomycin
- Tobramycin

Adverse Effects:

- Ototoxicity
- Nephrotoxicity
- Neuromuscular paralysis
- Allergic reaction

Macrolides

Mechanism of action:
Irreversible binding to 50S subunit of bacterial ribosome, inhibiting protein synthesis.

Antimicrobial coverage:
H.Influenza, Chlamydia, Legionella, Moraxella, Ureaplasma, H. Pylori, Streptococcus pneumonia.

Indications:

- Diphtheriae
- Chlamydial infection
- Legionellosis
- Mycoplasma pneumonia

Examples:

- Azithromycin
- Clarithromycin
- Erythromycin

Adverse Effects:

- GI upset
- Cholestatic Jaundice
- Ototoxicity
- QT prolongation

Contraindication:

- in hepatic dysfunction

Chloramphenicol

Mechanism of action:
Bactericidal/static, binds reversibly to 50S subunit of bacterial ribosome, inhibiting protein synthesis.

Antimicrobial coverage:
Chlamydiae, Rickettsiae, Spirochetes and anaerobes

Indications:

- Meningitis
- Rocky mountain spotted fever

Adverse effects:

- Grey baby syndrome
- Anemia (Hemolytic)

Clindamycin

Mechanism of action:
Similar to macrolides

Antimicrobial coverage:
Gram +ve (MRSA) , streptococcus and anaerobes

Indications:

- Aspiration pneumonia
- Strep. Pharyngitis
- Bacterial Vaginosis
- Septicemia
- LRT infections
- Intra-abdominal infections

Adverse effects:

- Skin Rash
- Diarrhea

Linezolid

Mechanism of action:
Preventing formation of 70S initiation complex.

Antimicrobial coverage:
Gram +ve (Staphylococcus, Streptococcus, Enterococci, Cornybacterium, Listeria)

Indications:

- VRE
- Bacterial pneumonia
- Skin infections

Adverse effects:

- GI upset/Nausea/Diarrhea
- Headache and Rash
- Thrombocytopenia
- Optic neuritis

Streptogramins

Quinupristin / Dalfopristin

Mechanism of action:

They are a mixture of two streptogramins in a ratio of 30 to 70.

Each of the components binds to a different site on the 50S bacterial ribosome. Disrupting the elongation of the peptide chain. Thus, they work synergistically to interrupt protein synthesis.

Indication:

They are active primarily against gram-positive cocci, including those resistant to other antibiotics.

They are normally reserved for the treatment of severe E. faecium infections, including vancomycin-resistant Enterococcus VRE strains.

Side effects: (severe)

Venous irritation, Hyperbilirubinemia, Arthralgia and myalgia

Fluoroquinolones

FLUOROQUINOLONES
Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY

Mechanism of action:

Following cell wall entry through porin channels, fluoroquinolones

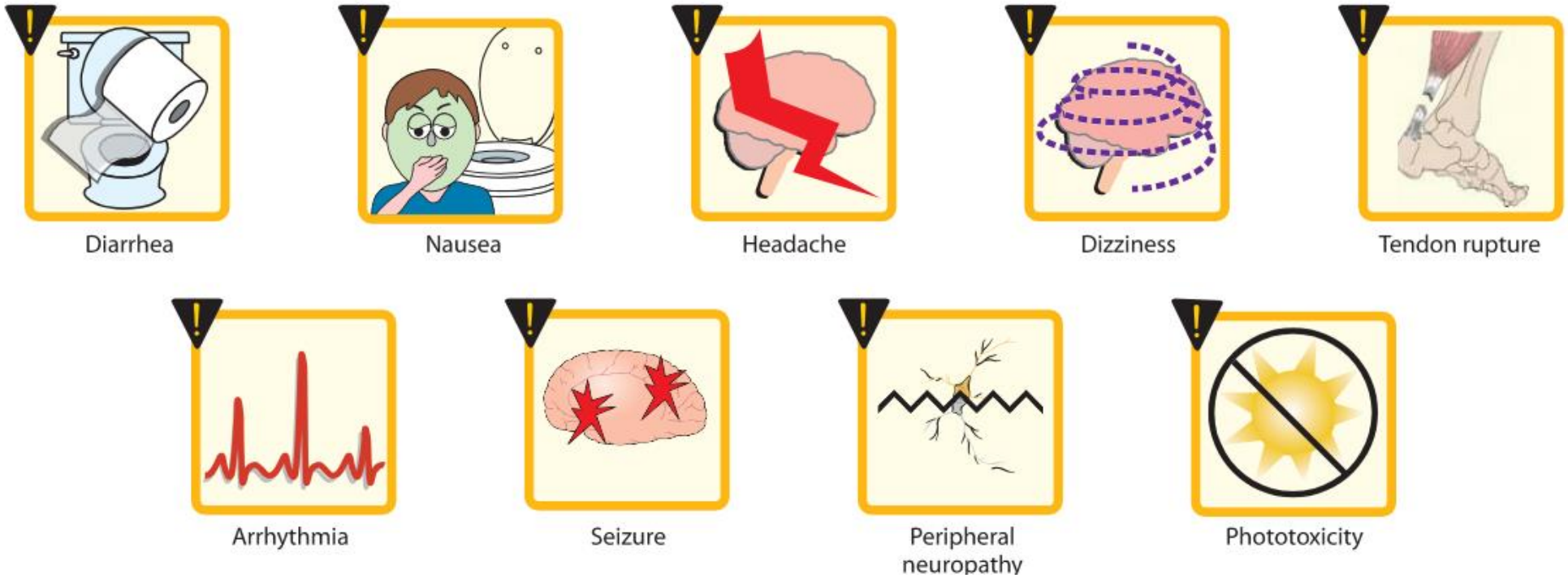
bind to two distinct enzymes DNA gyrase, and topoisomerase IV and interfere with DNA ligation.

This interference increases the number of permanent chromosomal breaks, triggering cell lysis.

Antimicrobial coverage:

- **First-generation compounds** (Ex: nalidixic acid)
  were narrow spectrum agents with activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae.
- **Second-generation compounds** (Ex: ciprofloxacin)
  exhibit broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp.
- **Third-generation compounds** (Ex: levofloxacin)
  maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp.
- **Fourth generation compounds** (Ex: moxifloxacin, gemifloxacin, and delafloxacin)
  have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp.

Adverse effects:



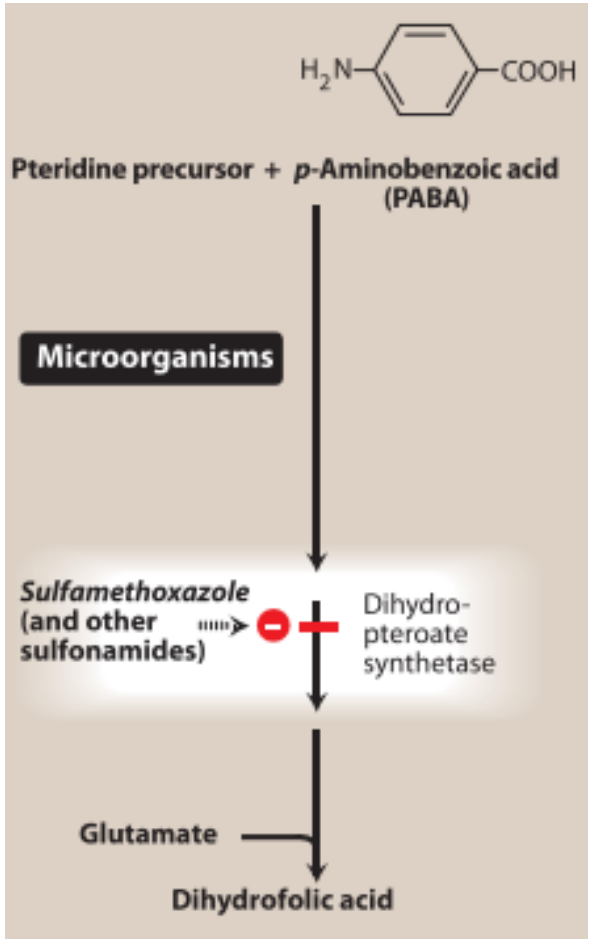
Folate Antagonists

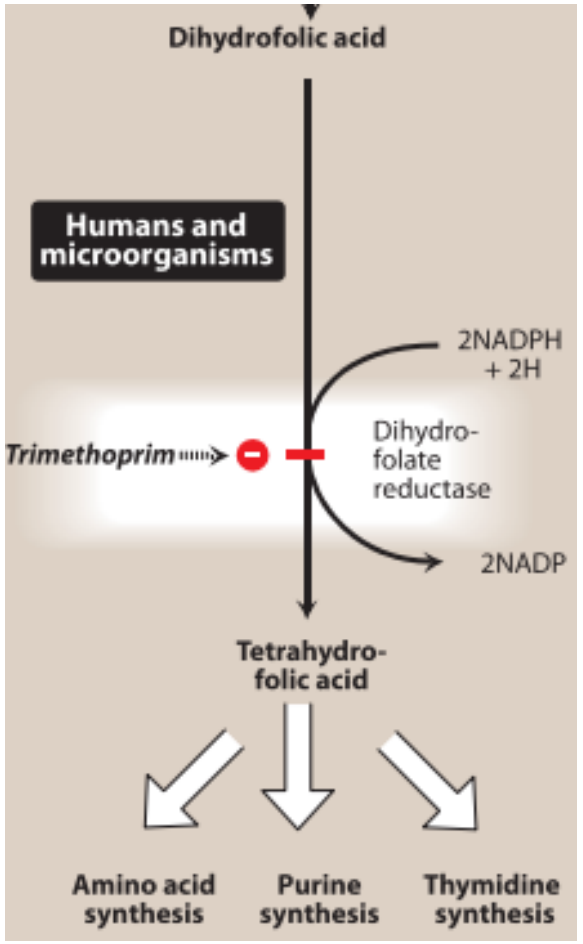
Sulfonamides, trimethoprim, Cotrimoxazole

Folic acid is a coenzyme essential in the synthesis of RNA, DNA, and certain amino acids.
In the absence of folate, cells cannot grow or divide.

Mechanism of action:
-**Sulfonamides** (sulfa drugs) are a family of antibiotics that inhibit incorporation of PABA into dihydrofolic.

-**Trimethoprim,** prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid.





Antimicrobial coverage:

Sulfa drugs have in vitro activity against gram-negative and gram positive organisms. Common organisms include Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia.

Trimethoprim's is similar to that of sulfamethoxazole.
However, trimethoprim is 20- to 50-fold more potent than the sulfonamides.

Adverse effects:

Sulfa drugs	Trimethoprem
Crystalluria	megaloblastic anemia
Hypersensitivity	leukopenia
Kernicterus	granulocytopenia
Hemolytic anemia	hyperkalemia

Cotrimoxazole

The combination of trimethoprim with sulfamethoxazole is called cotrimoxazole.
It shows greater antimicrobial activity than equivalent quantities of either drug used alone.
The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

Mechanism of action:
-Inhibits incorporation of PABA into dihydrofolic
-Inhibits reduction of dihydrofolic acid to tetrahydrofolic acid.

Antimicrobial coverage:
Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone.
-It is effective in treating UTis and respiratory tract infections, as well as Pneumocystis jirovecii, toxoplasmosis, Listeria monocytogenes, and Salmonella infections.

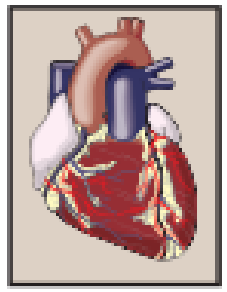
Adverse effects:
Adverse reactions and drug interactions related to cotrimoxazole are similar to those expected with each of the individual components.

Prophylaxis

Certain clinical situations require the use of antibiotics for the prevention rather than for the treatment of infections

1

Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

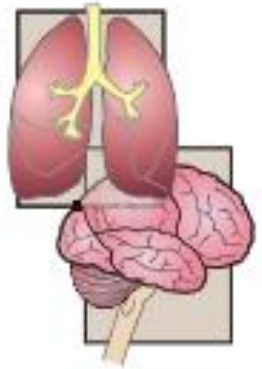


2

Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.

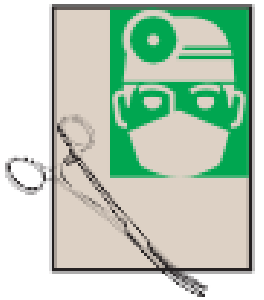
3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.

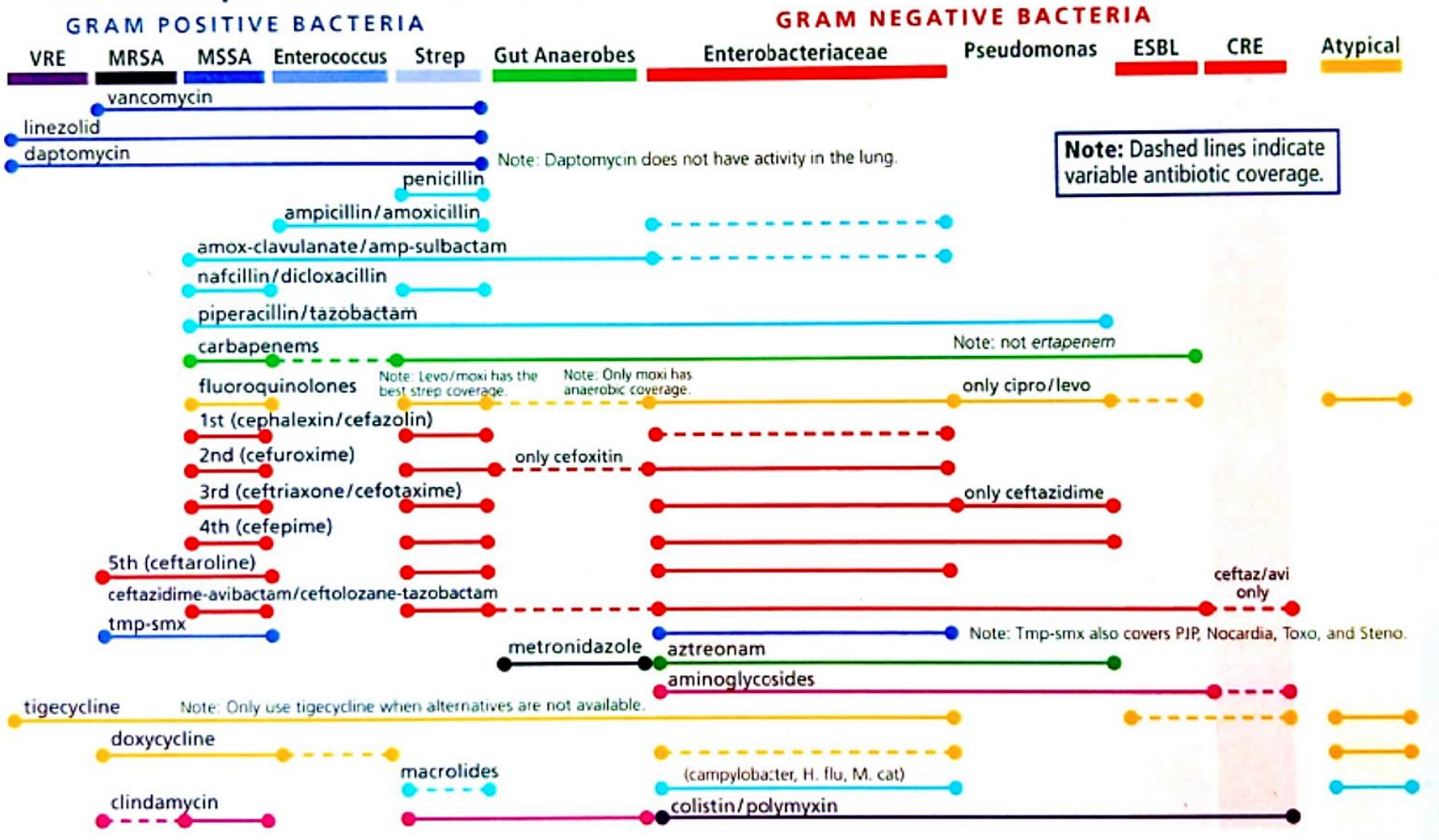


4

Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



General Spectrum of Antibiotics



Thank You

Resources

-Lippincott Pharmacology 7th Edition