Chemotherapeutic Agents
Antimicrobial Drugs

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Introduction

- ***Antimicrobial drugs***: *are effective in the treatment of infections because of their selective toxicity (the ability to kill an invading M.O without harming the cells of the host).*

- ***Antibacterial & antimicrobial***:
- **Antimicrobial** *are substances that inhibit the growth or kill bacteria or other M.O like bacteria, viruses, fungi & protozoa. While antibacterial are substances that inhibit the growth or kill bacteria.*

- ***Antibiotics***: *refers to chemicals that are produced by one kind of M.O that inhibits the growth of or kill another.*

Selection of Antimicrobial Agents

Selection of the most appropriate antimicrobial agent requires knowledge of:

1) the identity of the organism,

2) The susceptibility of the organism to a particular agent,

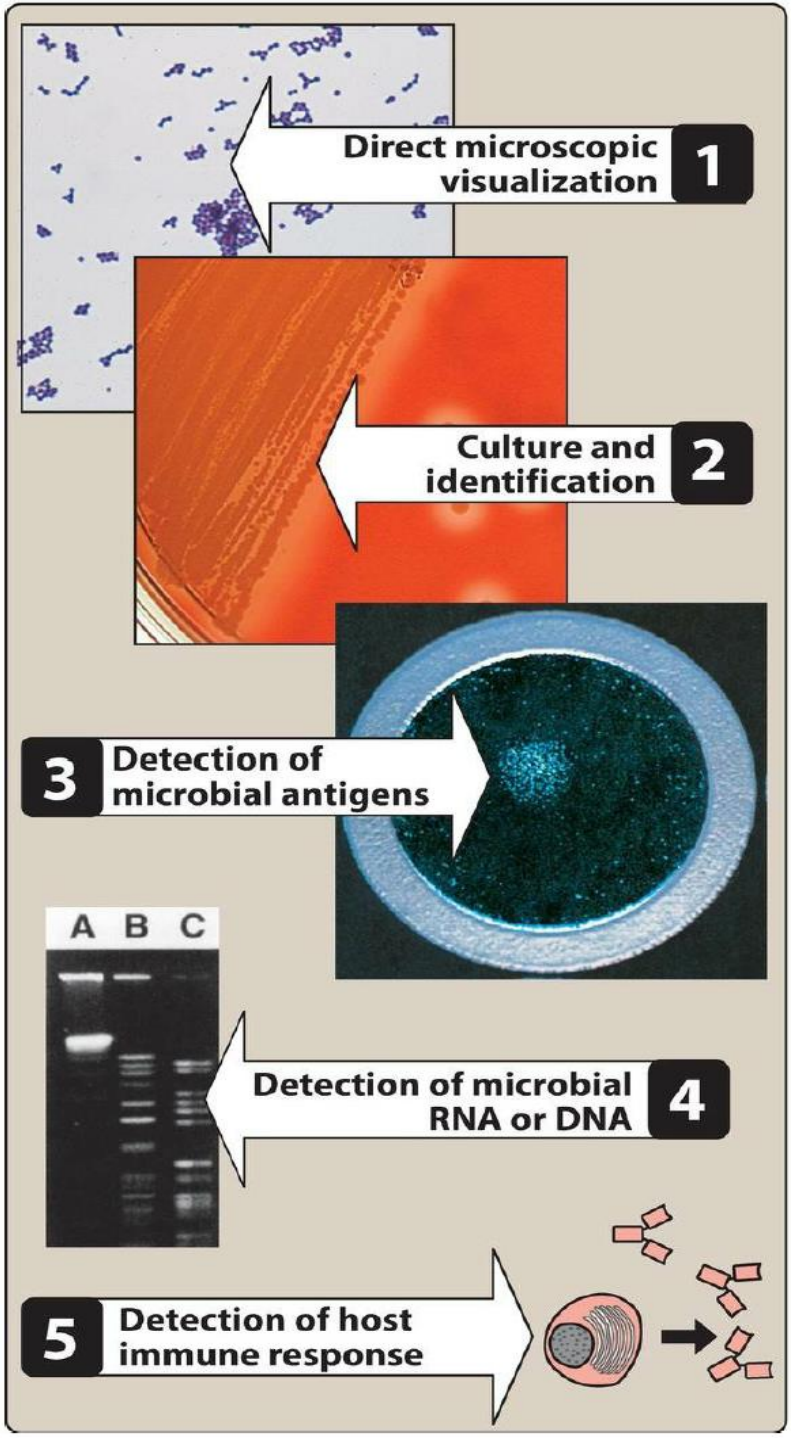
3) the site of the infection,

4) patient factors,

5) the safety and efficacy of the agent, and

6) the cost of therapy.

Identification of the infecting organism



Empiric antimicrobial therapy

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its susceptibility to antimicrobial agents established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

1. Timing: If possible, therapy should be initiated after specimens for laboratory analysis have been obtained but before the results of the culture and sensitivity are available.

2. Selecting a drug

Drug choice in the absence of susceptibility data is influenced by the site of infection, the patient history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, whether the infection was hospital- or community-acquired), and local susceptibility data. Broad-spectrum therapy may be indicated initially when the organism is unknown or polymicrobial infections are likely.

Determination of antimicrobial susceptibility

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in selection of antimicrobial therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy.

1-Bacteriostatic versus bactericidal drugs (not important clinically)

2- Minimum inhibitory concentration (MIC) which is the lowest antimicrobial concentration that prevents visible growth of an organism after 24 hours of incubation. This serves as a quantitative measure of in vitro susceptibility and is commonly used in practice to streamline therapy.

3- Minimum bactericidal concentration (MBC): rarely used in clinical practice due to time and labor requirement.

Bacteriostatic versus bactericidal drugs

Antimicrobial drugs are commonly classified as either bacteriostatic or bactericidal. Historically, bacteriostatic drugs were thought to only arrest the growth and replication of bacteria at drug levels achievable in the patient, whereas bactericidal drugs were able to effectively kill ≥ 99.9% within 18 to 24 hours of incubation under specific laboratory conditions. Note that the rate of in vitro killing is greater with bactericidal agents, but both agents are able to effectively kill the organism. It is also possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, linezolid is bacteriostatic against Staphylococcus aureus and enterococci, but is bactericidal against most strains of S. pneumoniae. Also, bactericidal and bacteriostatic agents have similar efficacy for treating common clinical infections.

Effect of the site of infection on therapy: the blood–brain barrier

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta. Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:

1. **Lipid solubility:** Only lipid soluble drug can penetrate. Except in meningitis water soluble drug (eg. Pencilline can penetrate the inflamed meningies.)
2. **Molecular weight:** vancomycin penetrate BBB poorly, even in the presence of meningeal inflammation.
3. **Protein binding:** A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

4. **Susceptibility to transporters or efflux pumps:.** Antibiotics that have an affinity for transporter mechanisms or do not have an affinity for efflux pumps have better CNS penetration

Patient factors

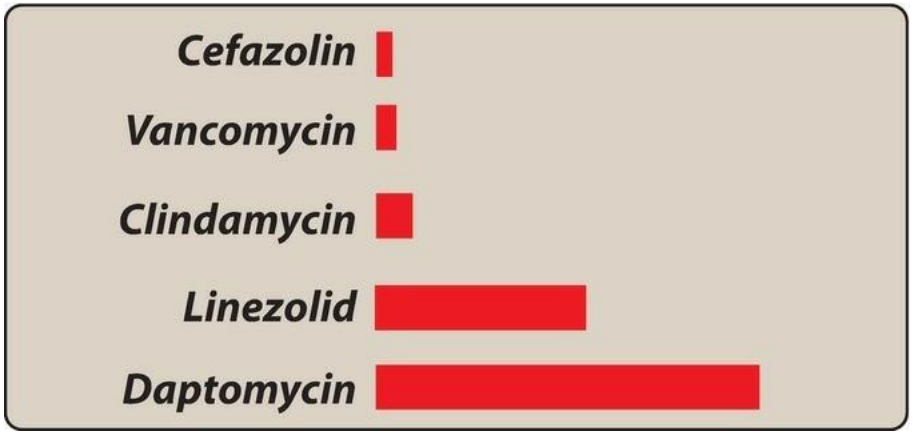
1. **Immune system**:Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, and immunosuppressive drugs can affect immunocompetence. High doses of bactericidal agents or longer courses of treatment may be required to eliminate infective organisms in these individuals.
2. **Renal dysfunction:** Poor kidney function may cause accumulation of certain antibiotics. Dosage adjustment prevents drug accumulation and adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.
3. **Hepatic dysfunction :** AB Metabolized in liver must be use with caution in hepatic disease (like erythromycin and doxycycline)

Patient factors

4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that site of infection, making it more difficult to treat. Decreased perfusion of the gastrointestinal tract may result in reduced absorption, making attainment of therapeutic concentrations more difficult with enteral routes.
5. **Age:** Chloramphenicol and sulphonamide C.I in newborn and Tetracycline and ciprofloxacin C.I in young children, elderly show decrease in renal and hepatic function so effect on pharmacokinetic of the drug).
6. **Pregnancy and lactation** (Tetracyclin is contraindicated during pregnancy and lactation)
7. Risk factors for multidrug-resistant organisms
8. **Safety of the agent:** Penicillin least toxic while chloramphenicol has large toxicity.

Cost of therapy

Although choice of therapy usually centers on the site of infection, severity of the illness, and ability to take oral medications, it is also important to consider cost of the medication. The following figure illustrates the relative cost of commonly used drugs for staphylococcal infections.



Route of Administration

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections who require maintenance of higher serum concentrations of antimicrobial agents. In hospitalized patients requiring intravenous (IV) therapy, the switch to oral agents should occur as soon as possible. Switching patients from IV to oral therapy when clinically stable has been shown to decrease health care costs, shorten length of stay, and decrease complications from IV catheters. However, some antibiotics, such as *vancomycin* and aminoglycosides, are poorly absorbed from the gastrointestinal (GI) tract and do not achieve adequate serum levels via oral administration.

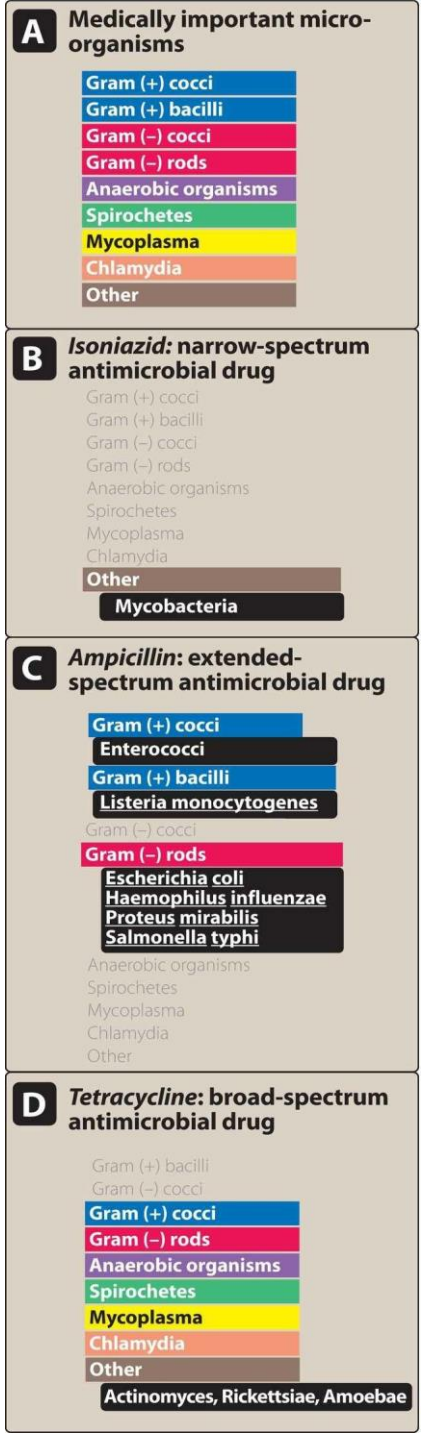
Determinants of Rational Dosing

Rational dosing of antimicrobial agents is based on pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism, and elimination of the drug). Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent (concentration-independent) killing, and postantibiotic effect (PAE). Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

- **Example on antibiotic shows Concentration-dependent killing:** aminoglycosides and daptomycin.
- **Example on antibiotic shows time-dependent killing:** β-lactams, glycopeptides, macrolides, clindamycin, and linezolid.
- **Example on antibiotic shows postantibioitic effect:** aminoglycosides and fluoroquinolones

Chemotherapeutic spectra

- The chemotherapeutic spectrum of a particular drug refers to the species of organisms affected by that drug.
- ***A-Narrow spectrum*** → chemical agents acting only on a single or limited group of M.O.. For e.g. Isoniazid is active only against Mycobacteria.
- ***B-Extended spectrum*** → Effective against gram positive organism and also against a significant number of gram negative organism, for e.g.:
- Ampicillin and amoxicillin
- ***C-Broad spectrum*** → drugs such as tetracycline and chloramphenicol affect a wide variety of microbial species and are referred to as broad spectrum antibiotics.



Combination of antimicrobial drugs

Advantages

- Combination of antimicrobial agents should only be used in special situation such as:
- 1-when mixed infection occur
- 2-In treatment of enterococcal endocarditis
- 3-when there is a risk of developing resistant organisms
- 4-Infection of unknown origin
- 5-When there are organisms with variable sensitivity, such as when treating tuberculosis.
- Example on combination antibiotics that show synergism are β-lactams and aminoglycosides, show synergism (Ampicillin and gentamycin)

Disadvantages of drug combinations

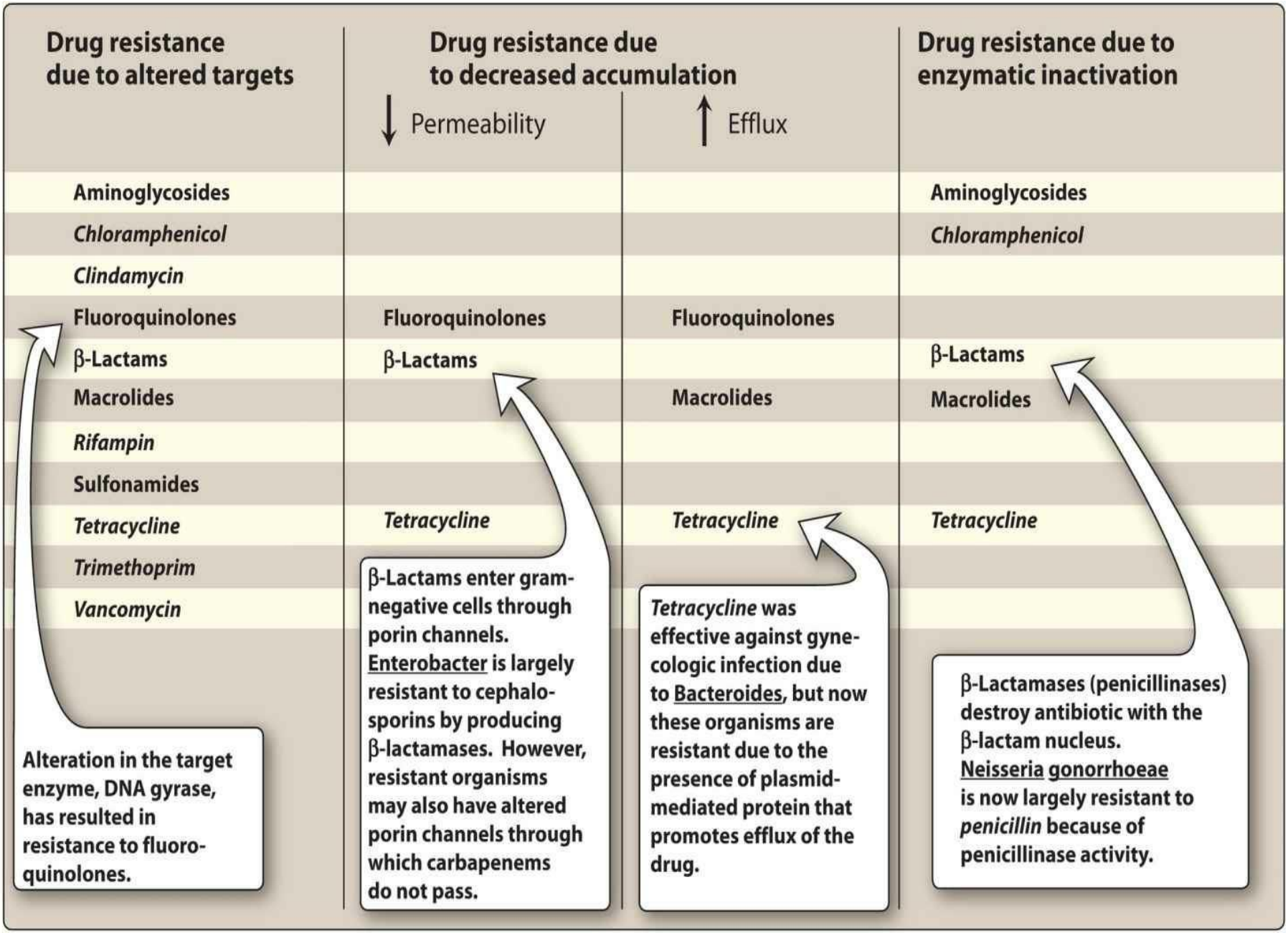
1. *Development of antibiotic resistance by giving unnecessary combination therapy.*
2. *Bacteriostatic should not be combined with bactericidal For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins.*

Resistance to antibacterial

- Bacteria may be sensitive or resistant to certain antibacterial.
- If it is sensitive to the drug, the organism is inhibited or destroyed.
- If bacteria is resistant to an antibacterial, the organism continues to grow despite administration of that antibacterial drug.
- Bacterial resistance may be→ naturally (inherent) or it may be→ acquired.
- *A natural, or inherent resistance* occurs without previous exposure to the antibacterial drug for e.g: the gm-ve pseudomonas aeruginosa is resistant to penicillin G.
- *An acquired resistance* is caused by prior exposure to antibacterial, for e.g: Although staph aureus was once sensitive to penicillin G, previous exposure have caused this organism to become resistant to penicillin G.
- Penicillinase (betalactamase), an enzyme produced by the organism is responsible for causing penicillin resistance.

Genetic alterations leading to drug resistance

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another


Drug resistance due to altered targets
Drug resistance due to decreased accumulation
↓ Permeability
↑ Efflux
Drug resistance due to enzymatic inactivation
Aminoglycosides
Chloramphenicol
Clindamycin
Fluoroquinolones
β-Lactams
Macrolides
Rifampin
Sulfonamides
Tetracycline
Trimethoprim
Vancomycin
Fluoroquinolones
β-Lactams
Tetracycline
Fluoroquinolones
Macrolides
Tetracycline
Aminoglycosides
Chloramphenicol
β-Lactams
Macrolides
Tetracycline
Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoroquinolones.
β-Lactams 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 carbapenems do not pass.
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.
β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.

Prophylactic antibiotics

Are used in certain clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely controlled to prevent the unnecessary development of antibiotic resistance. such as:

1. Pretreatment may prevent streptococcal infection in patients with a history of rheumatic heart disease.
2. Pretreatment of patients undergoing dental extractions who have implanted prosthetic devices.
3. Pretreatment may prevent T.B or meningitis among individuals who are in close contact with infected patients.
4. Treatment prior to most surgical procedure can decrease the incidence of infection afterwards.
5. Protect the fetus in the case of an HIV – infected, pregnant woman.

Complications of Antibiotic Therapy

1-Hypersensitivity: example penicillin cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock. Vancomycin cause red man syndrome during rapid infusion and Stevens-Johnson syndrome or toxic epidermal necrolysis reaction (a severe sloughing of skin and mucus membranes).

2-Direct toxicity when given in high dose: For example, aminoglycosides can cause ototoxicity. Chloramphenicol may leading to bone marrow suppression. Fluoroquinolones can have effects on cartilage and tendons, and tetracycline have direct effect on bone .

3- Superinfections: Broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections usually require secondary treatments using specific anti-infective agents.

Classification of antimicrobial agents

1-According to their chemical structure like [β-lactams, Aminoglycosides]

2-According to the mechanism of action [cell walls synthesis inhibitors]

3-According to the activity against particular type of organisms [bacteria, fungi, ……..]

Classification of some antimicrobial agents by their sites of action.

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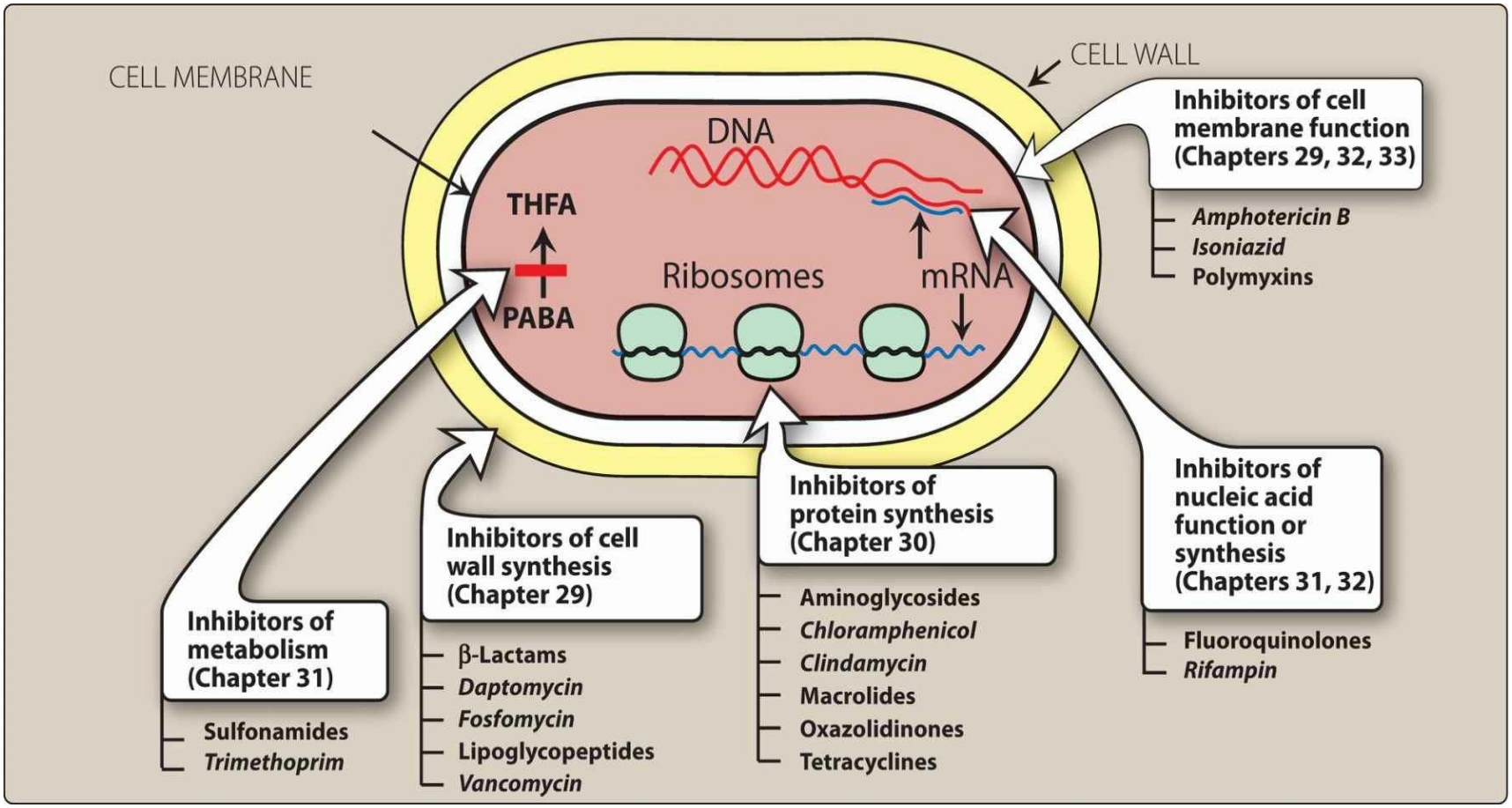
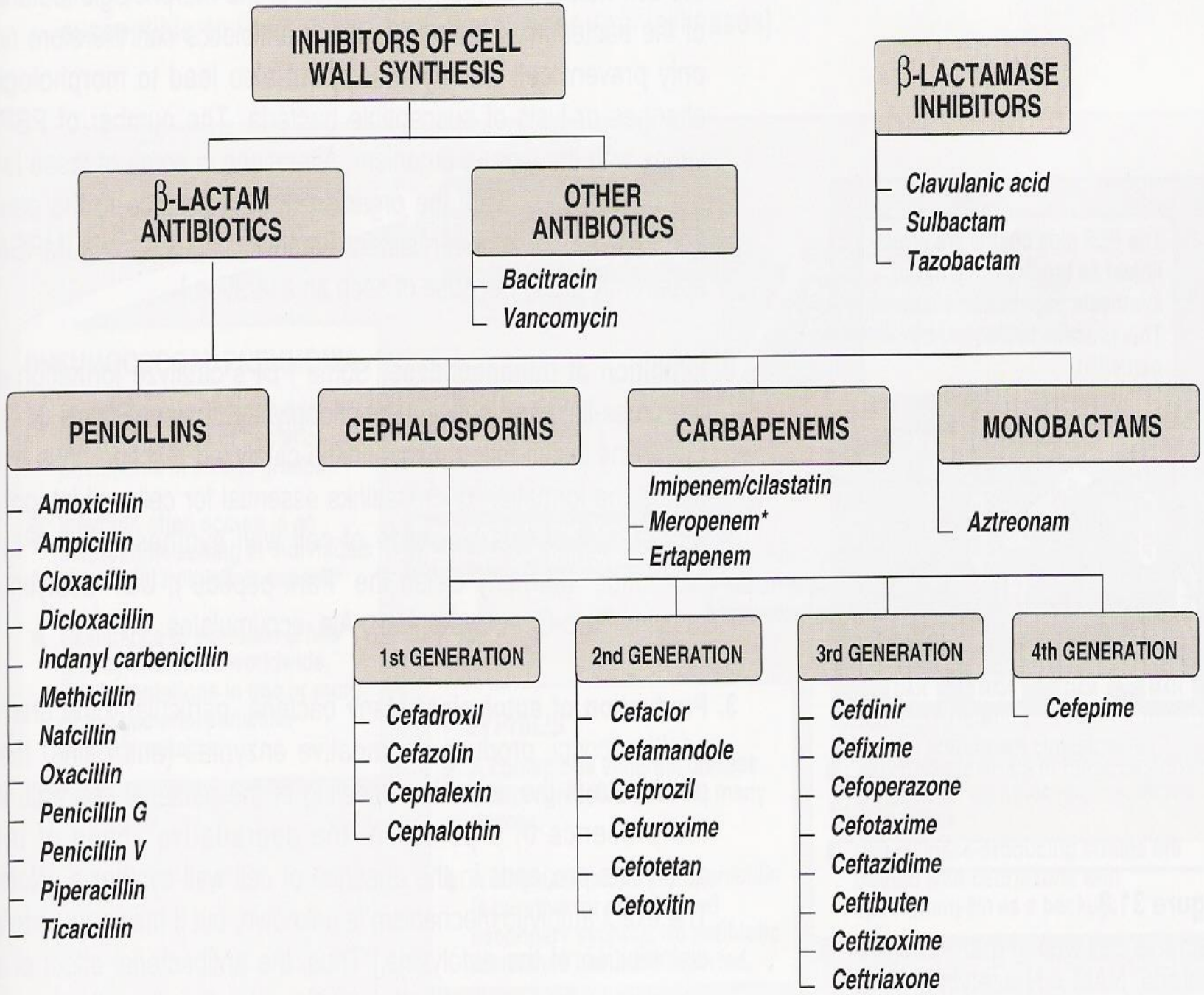


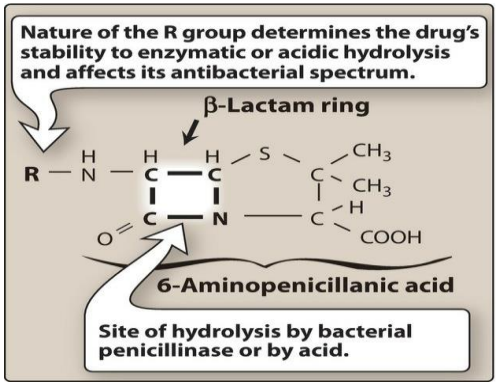
THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.

Cell wall inhibitors
β-lactam antibiotics

- A no. of antibiotics produced by fungi of genous celphalosporium have been identified penicillin genus→ give penicillins. These antibiotics called Cephalosporin's contain, in common with the penicillin, a B-lactam ring.
- In addition to the numerous penicillin's and cephalosporin's in use, two other classes of B-lactam antibiotics are available for clinical use.
- These are *Carbapenem, and Monobactams*. All B-lactam antibiotics have the same bactericidal mechanism of action. They block a critical step in bacterial cell wall synthesis.


INHIBITORS OF CELL WALL SYNTHESIS
β-LACTAM ANTIBIOTICS
OTHER ANTIBIOTICS
Bacitracin
Vancomycin
β-LACTAMASE INHIBITORS
Clavulanic acid
Sulbactam
Tazobactam
PENICILLINS
Amoxicillin
Ampicillin
Cloxacillin
Dicloxacillin
Indanyl carbenicillin
Methicillin
Nafcillin
Oxacillin
Penicillin G
Penicillin V
Piperacillin
Ticarcillin
CEPHALOSPORINS
1st GENERATION
Cefadroxil
Cefazolin
Cephalexin
Cephalothin
2nd GENERATION
Cefaclor
Cefamandole
Cefprozil
Cefuroxime
Cefotetan
Cefoxitin
3rd GENERATION
Cefdinir
Cefixime
Cefoperazone
Cefotaxime
Ceftazidime
Ceftibuten
Ceftizoxime
Ceftriaxone
4th GENERATION
Cefepime
CARBAPENEMS
Imipenem/cilastatin
Meropenem*
Ertapenem
MONOBACTAMS
Aztreonam

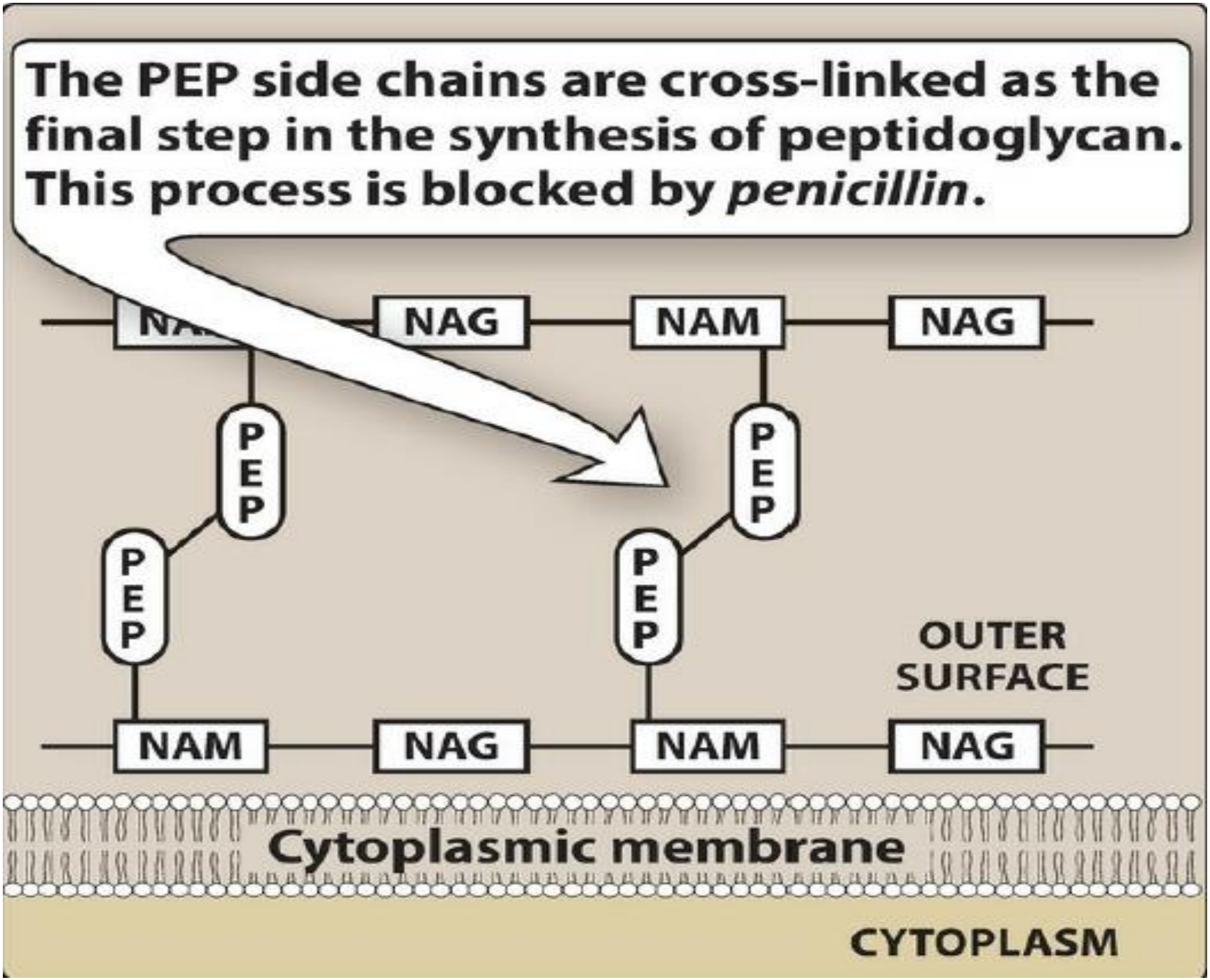
penicillin's



- The penicillin's are a large group of bacterial compounds. They can be subdivided and classified by their chemical structure and spectrum of activity.
- The antimicrobial activity of penicillin exist in in the β -lactam ring.
- Splitting of B-lactam ring by either acid hydrolysis or β -lactamases results in the formation of penicillin acid, a product without antibiotic activity.
- Addition of various side chain (R) to the basic penicillin mol. creates classes of compounds with the same mechanism of action as penicillin but with different chemical and biological properties.

Mechanism of action of pencillin's

Penicillins interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation. Since penicillin's structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called penicillin-binding proteins (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall. The result is the formation of a weakened cell wall and ultimately cell death. For this reason, penicillins are regarded as bactericidal and work in a time-dependent fashion.


The PEP side chains are cross-linked as the final step in the synthesis of peptidoglycan. This process is blocked by *penicillin*.
NAG
NAM
NAG
PEP
PEP
PEP
PEP
OUTER SURFACE
NAM
NAG
NAM
NAG
Cytoplasmic membrane
CYTOPLASM

Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors determining PBP susceptibility to these antibiotics include size, charge, and hydrophobicity of the particular β-lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins, and, therefore, in the absence of resistance, they are susceptible to these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry.

Antibacterial spectrum
And classification of pencillin antibiotics

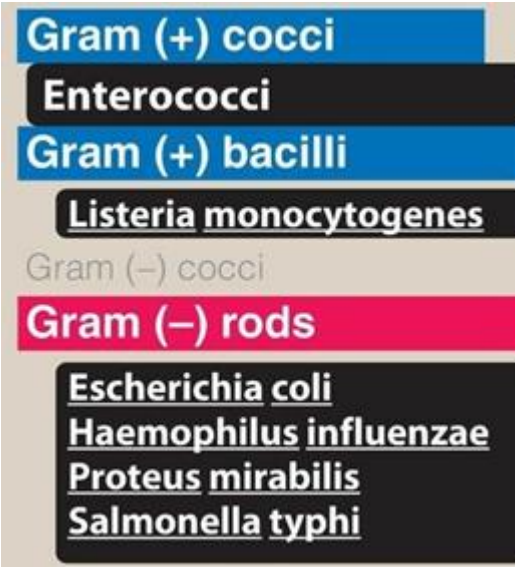
1- Natural penicillins

- *Penicillin G* and *penicillin V* are obtained from fermentations of the fungus Penicillium chrysogenum.
- *Penicillin G* (*benzylpenicillin*) available as injection and has activity against a variety of gram-positive organisms, gram-negative organisms, and spirochetes *penicillin* remains the drug of choice for the treatment of gas gangrene (Clostridium perfringens) ; syphilis (Treponema pallidum) and pneumococcal infection.
- *Penicillin V*, only available in oral formulation, has a spectrum similar to that of *penicillin G*, but it is not used for treatment of severe infections because of its limited oral absorption.
- *Penicillin V* is more acid stable than is *penicillin G* and is the oral agent employed in the treatment of less severe infections.

2- Semisynthetic penicillins

- *Ampicillin* and *amoxicillin* (also known as aminopenicillins or extendedspectrum penicillins) are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus.
- *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible enterococcal species.
- These drugs are coformulated with β-lactamase inhibitors, such as *clavulanic acid* or *sulbactam*, to combat infections caused by β-lactamase–producing organisms.

Antimicrobial spectrum of Ampicillin



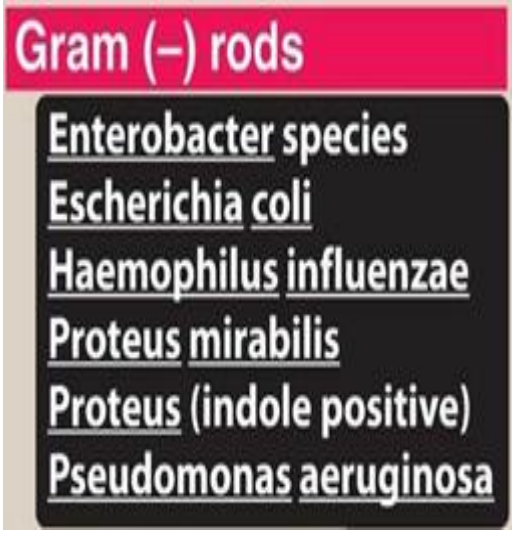
3-Antistaphylococcal penicillins

- *Methicillin*, *nafcillin* , *oxacillin*, and *dicloxacillin* are β-lactamase (penicillinase)-resistant penicillins.
- Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including MSSA.
- Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically.
- The penicillinase-resistant penicillins have minimal to no activity against gram-negative infections.

4-Antipseudomonal penicillin

- *Piperacillin* is also referred to as an antipseudomonal penicillin because of its activity against Pseudomonas aeruginosa .
- Formulation of *piperacillin* with *tazobactam* extends the antimicrobial spectrum to include penicillinase-producing organisms (for example, most Enterobacteriaceae and Bacteroides species).
- Carbenicillin is an antipseudomonal penicillin formulated for oral administration. This drug used to treat urinary tract infections caused by P. aeruginosa, Proteus spp. and E.Coli.

Antimicrobial spectrum of piperacillin



5- β-lactamase inhibitor combinations·

- ***Ampicillin-sulbactum [parenteral formulation]***
- ***Ticarcillin-clavulanic acid [parenteral formulation]***
- ***Piperacillin-tazobactam [parenteral formulation]***
- ***Amoxicillin-clavulanic acid [oral bioavailability]***
- require dose adjustments in patients with renal insufficiency.
- The addition of the β -lactamase inhibitor significantly broadens the spectrum of antibacterial activity against β -lactamase-producing organisms.
- These drugs have clinical use in treating infections with known or suspected mixed bacterial flora, such as biliary infections, diabetic foot ulcers, endomyometritis and peritonitis.

Example on penicillin stable to acid, permitting oral use

1. Natural penicillin's (penicillin V)
2. Anitstaphylococcal (Dicloxacillin)
3. Extended spectrum (Ampicillin, Amoxicillin, Amoxicillin +clavulanic acid)
4. Antipseudomonal (carbenicillin)

Example on penicillin drug stable to pencillinase (mean we can give to kill bacteria that release pencillinase enzyme.)

1. Antistaphyllococcal (Dicloxacillin, methicillin, nafcillin and oxacillin)
2. Extended spectrum (Amoxicillin +clavulanic acid, Ampicillin + sulbactum)
3. Antipeudomonal (pipracillin + Tazobactum)

Mechanism of resistance

- A number of M.O has evolved mechanism to overcome the inhibitory actions of the B-lactam antibiotics.
- There are four major mechanism of resistance:

1-Inactivation of β-lactam ring by B-lactamases.

2-Alteration of penicillin-binding proteins [PBPs]

3-Reduction of antibiotic access to PBPs

4-Elaboration of antibiotic efflex mechanism

- The most important mechanism of resistance is hydrolysis of the B-lactam ring by B-lactamases (Penicillinases or Cephalosporinases).
- Many bacteria (*staphylococcus aureus, Neisseria gonorrhoeae, Enterobactericeae, Haemophilus influenza and Bacteroides spp*.) possess B-lactamases that hydrolyze penicillins and cephalosporins.

Pharmacokinetics of pencillin's

1- Administration: The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

2- Routes of administration: The combination of *ampicillin* with *sulbactam*, *piperacillin* with *tazobactam*, and the antistaphylococcal penicillins *nafcillin* and *oxacillin* must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V*, *amoxicillin*, and *dicloxacillin* are available only as oral preparations. Others are effective by the oral, IV, or IM routes. [Note: The combination of *amoxicillin* with *clavulanic acid is available as oral*]

3- Depot forms: *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms.

4- Absorption: Acid in the stomach destroyed some of pencillin like pencillin G so can not given orally. Food decreases the absorption of the penicillinase-resistant penicillin dicloxacillin because as gastric emptying time increases, the drug is destroyed by stomach acid. Therefore, it should be taken on an empty stomach. Conversely, amoxicillin is stable in acid and is readily absorbed from GIT.

Pharmacokinetics of pencillin's

5- Distribution: The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed

6-Metabolism

Some metabolism of *penicillin G* may occur in patients with impaired renal function. *Nafcillin* and *oxacillin* are primarily metabolized in the liver.

7-Excretion

The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Because *nafcillin* and *oxacillin* are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in breast milk.

Adverse reactions

1- Hypersensitivity

Approximately 10% of patients show allergy to penicillin. Reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the βlactam antibiotics.

2. Diarrhea

Caused by a disruption of the normal balance of intestinal microorganisms. Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

3. Nephritis

Methicillin, have the potential to cause acute interstitial nephritis. That is why methicillin not used clinically.

4. Neurotoxicity

The penicillins are irritating to neuronal tissue. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

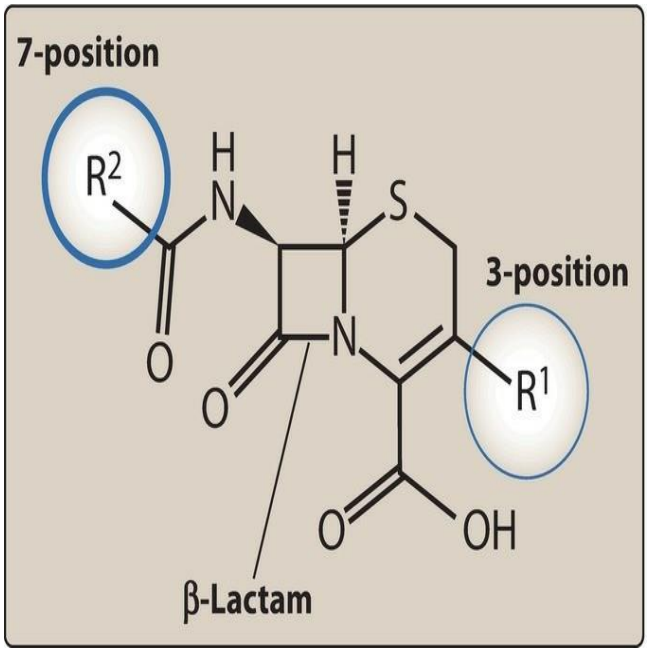
5. Hematologic toxicities

Decreased coagulation may be observed with high doses of piperacillin and nafcillin. Cytopenias have been associated with therapy of greater than 2 weeks.

Cephalosporins

cephalosporins

- They are β-lactam antibiotics closely related both structurally and functionally to penicillins.
- Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.
- Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain β-lactamases.



Antibacterial spectrum

Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases.

First-generation cephalosporins

Gram (+) cocci

- Staphylococcus aureus*
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) rods

- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis

Second-generation cephalosporins

Gram (+) cocci

- Staphylococcus aureus*
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis

Anaerobic organisms**

Third-generation cephalosporins

Gram (+) cocci

- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa†
- Serratia marcescens

Fourth-generation cephalosporins

Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

Advanced generation

Ceftaroline which is active against MERSA

1-First generation

- They are resistant to the staphylococcal penicillinase (that is, they cover MSSA).
- They Gover gram positive and gram rod negative bacteria.
- Isolates of S. pneumoniae resistant to *penicillin* are also resistant to first generation cephalosporins.
- Agents in this generation also have modest activity against Proteus mirabilis, E. coli, and K. pneumoniae.
- Most oral cavity anaerobes like Peptostreptococcus are sensitive, but the Bacteroides fragilis group is resistant.
- Example on 1st generation **(cefazolin, cephalexin).**

2- Second generation

- Display greater activity against gram-negative organisms, whereas activity against gram-positive organisms is weaker.
- Cefotetan and cefoxitin act also on anaerobes (for example, Bacteroides fragilis).
- They are the only cephalosporins commercially available with appreciable activity against gram-negative anaerobic bacteria. However, neither drug is first line because of the increasing prevalence of resistance among B. fragilis.
- Example cefuroxime sodium and cefuroxime exitel.

3-Third generation

- They are less potent than first-generation cephalosporins against MSSA.
- They have enhanced activity against gram-negative bacilli, including β-lactamase producing strains of H. influenzae and Neisseria gonorrhoeae.
- The spectrum of activity of this class includes enteric organisms, such as Serratia marcescens and Providencia species.
- *Example: Ceftriaxone* and *cefotaxime* have become agents of choice in the treatment of meningitis. *Ceftazidime* has activity against P. aeruginosa.
- Must be used with caution, as they are associated with significant "collateral damage," including the induction of antimicrobial resistance and development of Clostridium difficile infection.

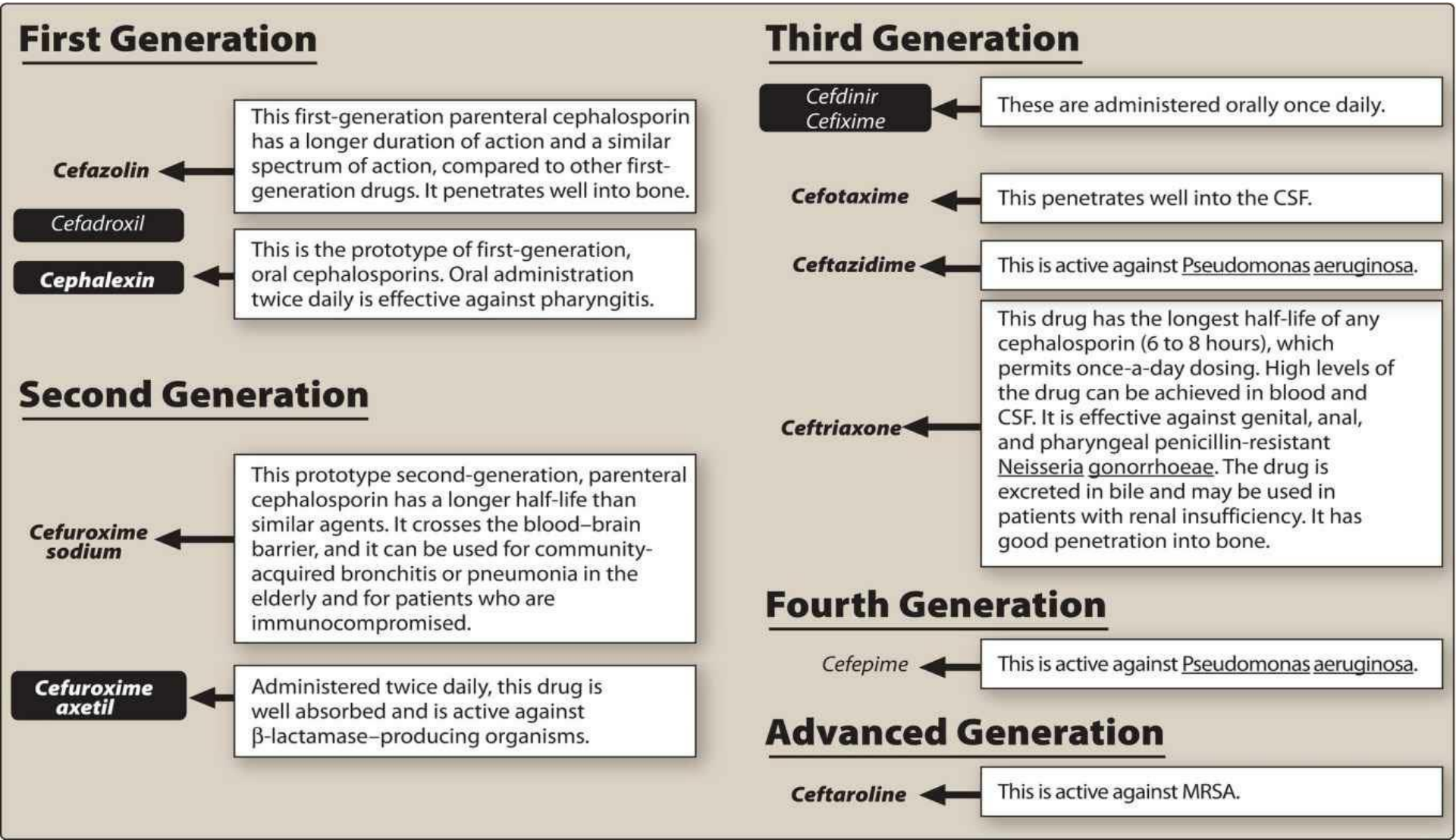
4- Fourth generation

- *Cefepime* is classified as a fourth-generation cephalosporin and must be administered parenterally.
- *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible).
- *Cefepime* is also effective against aerobic gram-negative organisms and P. aeruginosa.

5- Advanced generation

- *Ceftaroline is a broad-spectrum, advanced-generation cephalosporin.*
- *It is the only β-lactam in the United States with activity against MRSA*
- *It is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia.*
- *It also has similar gram-negative activity to the third-generation cephalosporin ceftriaxone.*
- *The twice-daily dosing regimen also limits use outside of an institutional setting.*

Therapeutic uses of Cephalosporin



Pharmacokinetics

- **Administration**

Many of the cephalosporins must be administered IV or IM because of their poor oral absorption.

- **Distribution**

All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins. For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood meningitis. *Cefazolin* is commonly used for surgical prophylaxis due to its activity against penicillinase-producing S. aureus, along with its good tissue and fluid penetration.

- **Elimination**

Cephalosporins are eliminated through tubular secretion and/or glomerular filtration (need dose adjustment in renal failure). *Ceftriaxone*, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

Adverse effects of cephalosporin

1. Allergic reactions. Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins.
2. They should be avoided or used with caution in individuals with penicillin allergy because there is highest rate of allergic cross-sensitivity is between *penicillin* and first-generation cephalosporins.

Resistance to cephalosporin

IT is either due to the hydrolysis of the beta-lactam ring by β-lactamases or reduced affinity for PBPs.


Thanks