PHARMACOLOGY OF ANTIMICROBIAL DRUGS:
ANTISEPTICS AND DISINFECTANTS.
PHARMACOLOGY OF ANTIBIOTICS.

Antiseptics and disinfectants are both widely used to control infections. They kill microorganisms such as bacteria, viruses, and fungi using chemicals called biocides.
Antiseptics are chemical substances which inhibit the growth or kill microorganisms on living surfaces such as skin & mucous membrane.
Disinfectants are destruct or inhibit growth of all pathogenic organisms (bacteria, viruses, fungii) on non- living surfaces.
Antiseptics and disinfectants should possess a broad spectrum of activity against bacteria, viruses, protozoa and fungi. They should have a short latent period, high activity in in the presence of biological substances. Properties of good antiseptic/ disinfectant:
1.Bactericidal 2. Non staining & good odour 3. Active against all pathogens 4. Active in presence of pus, blood & exudates 5. Rapid acting 6. Non irritating to tissues / non corrosive 7. Non absorbable 8. Non sensitizing
Phenol coefficient (the ratio between the concentrations of phenol and the antiseptic under test, in which both substances provides equal antimicrobial effect) in common measure of antiseptic activity.
The mechanism of action of different antiseptics and disinfectants vary. They may include protein denaturation, impairment of plasma membrane permeability and inhibition of the enzymes which are required for the vital activity of microbes.

According to chemical structure A@D are classified:
1.Detergents: Cerigel Roccal Degmecid Green soap
2.Nitrofuranes: Furacilin Furaplast Lifuzol Klefurin
3. Biguanides: Chlorhexidine
4. Phenols and related compounds: Phenol Rezorcine Ferezol Trikrezol
5. Dyes: Methylene blue Brilliant green Aethacridine lactate
6. Halogens and halogen containing compounds:
Chlorine: Chloramine B Chlorhexidine Pantothenatecide
Iodine: Iodine alcohol solution Lugol solution Iodophore Iodinole
7. Oxidizing agents: Hydrogen peroxide Potassium permanganate Hydroperite
8. Aldehydes and Alcohols: Formaldehyde Lizoform Hexamethylene tetramine Ethanol
9. Heavy metals:
Mercury: Mercury bichloride Mercury monochloride Lead plaster
Silver: Silver nitrate Protargole Collargole
Zinc: Zinc sulfate
Bismuth: Xeroform Dermatol
10. Acids and alkalis:
Boric acid Salicylic acid Benzoic acid Solutio Ammonii caustici 10%
10. Mineral oil, synthetic balms, preparations of sulfur and pitch:
Pitch (Pix liquide) Naphthalan ointment Viniline

11. Natural medicines: Sodium uncinate Evcalimin Marigolds bloom (Flores Calendulae officinalis) Tinctire Saphorae yaponicae

Antimicrobial is a general term can be classified according to the type of microorganisms that they act on. There are 5 groups of drugs: 1. Antibacterial 2. Antiviral 3. Antifungal 4. Antiprotozoal 5. Anthelminthic drugs

Antimicrobial drugs can be also classified into: 1. Bacteriostatic: This results in arresting the division and multiplication of bacteria 2. Bactericidal: These types of antimicrobial drugs kill the bacteria (such as penicillins, and cephalosporins).

Antimicrobial drugs unlike antiseptics and disinfectants are more selective against certain kinds of microorganisms, they have a specific spectrum of antimicrobial activity and low toxic for people and animals/

ANTIBIOTICS

Antibiotics are chemical compounds of biological origin that have a selective damaging or destructive effect on microorganisms. Antibiotics used in medical practice are produced by actinomycetes (ray fungi), molds, and some kinds of bacteria. This group of drugs also includes synthetic analogues and derivatives of natural antibiotics.

Ideal characteristics of antibiotics

- ✓ selective toxicity with minimal side effects to host
- ✓ easy to tolerate without a complex drug regimen
- ✓ bactericidal rather than bacteriostatic
- ✓ narrow spectrum rather than broad
- ✓ low cost of production & for consumer
- ✓ stable (shelf-life)
- ✓ adequate bioavailability: drug must reach adequate concentrations in relevant tissues or body sites

Classification according to:
1.Sourses: Natural a. Fungi (penicillin) b. Bacteria (polymixin, tetracycline, chloramphenicol 2. Semi-synthetics

2. Antimicrobial activity: bactericidal, bacteriostatic

3. Spectrum of activity: narrow spectrum, broad spectrum
4. Mechanism of action: a. inhibition of cell wall synthesis
b. Alteration of cell membrane permeability
c. Inhibition of bacterial protein synthesis
d. Inhibition of nucleic acid synthesis

Classification of antibacterial drugs:

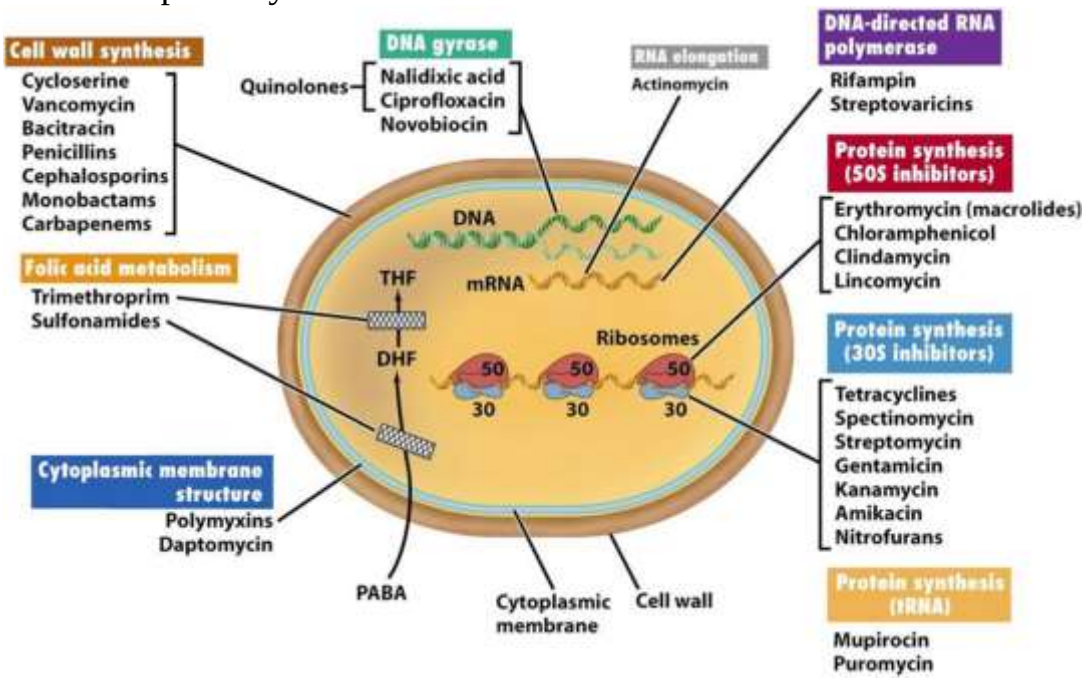
1. Inhibition of cell wall synthesis:

This group of drugs has selectivity in interfering with the synthesis of the cell wall of the bacteria, the structure of which is sufficiently different from mammalian cells. The cell wall of microorganisms contains pepidoglycan (a polymer); which is joined together by transpeptidaion. A. Beta-Lactams a. penicillins b. Cephalosporins c. Carbapenem d. Monobactam B. Other inhibitors of cell wall synthesis Vancomycin

2. Inhibition of protein synthesis a. Aminoglycosides b. Tetracycline c. Macrolides (erythromycin, clindamycin d. Others (chloramphenicol)

3. Inhibition of nucleic acid synthesis: a. Sulphonamides b. Quinolones (e.g. ciprofloxacin) c. Azoles (e.g. metronidazole)

Mechanism of antimicrobial action of some antibiotics
Antimicrobial agents can be divided into groups based on the mechanism of antimicrobial activity.
The main groups are: agents that inhibit cell wall synthesis, depolarize the cell membrane, inhibit protein synthesis, inhibit nuclei acid synthesis, and inhibit metabolic pathways in bacteria.



Classification of antibacterial drugs according mechanism of action:
1. Inhibition of cell wall synthesis: these drugs interfere with the ability of the bacteria to resist osmotic pressure so it swollen and burst. Example: Penicillins, Cephalosporins, and vancomycin.

02. Inhibition of cytoplasmic membrane: Example: Nystatin, amphotericin, miconazole and other antifungal drugs.
3. Inhibition of protein synthesis: These drugs interfere with the synthesis of peptide chain of the ribosoms of the organisms. These include chloramphenicol, erythromycin, and aminoglycosides.
4. Nucleic acid inhibitors: Drugs may interfere directly with microbial DNA or its replication, an example: quinolons, metronidazole, or with RNA such as rifampicin. Indirect inhibitors of nucleic acid synthesis occur with sulphonamides and trimethoprim.

Antibiotic resistance mechanisms

1. **STOP THE ANTIBIOTIC FROM REACHING ITS TARGET**

Pump the antibiotic out from the bacterial cell. Bacteria can produce pumps that sit in their membrane or cell wall. These so-called efflux pumps are very common in bacteria and can transport a variety of compounds such as signal molecules and nutrients. Some of these pumps can also transport antibiotics out from the bacterium, in this way lowering the antibiotic concentration inside the bacterial cell. In some cases mutations in the bacterial DNA can make the bacteria produce more of a certain pump, which in turn increases resistance.

Decrease permeability of the membrane that surrounds the bacterial cell. Certain changes in the bacterial membrane make it more difficult to pass through. In this way, less of the antibiotic gets into the bacteria.

Destroy the antibiotic. There are bacterial enzymes that can inactivate antibiotics. One example is β-lactamase that destroys the active component (the β-lactam ring) of penicillins, extremely important antibiotics for treating human infections. In later years, bacteria that produce extended-spectrum β-lactamases, so called ESBL-producing bacteria, have become a major problem. They can degrade a wide spectrum of β-lactam antibiotics, sometimes also the last resort drugs available for infections with these bacteria.

Modify the antibiotic. Bacteria can sometimes produce enzymes that are capable of adding different chemical groups to antibiotics. This in turn prohibits binding between the antibiotic and its target in the bacterial cell.

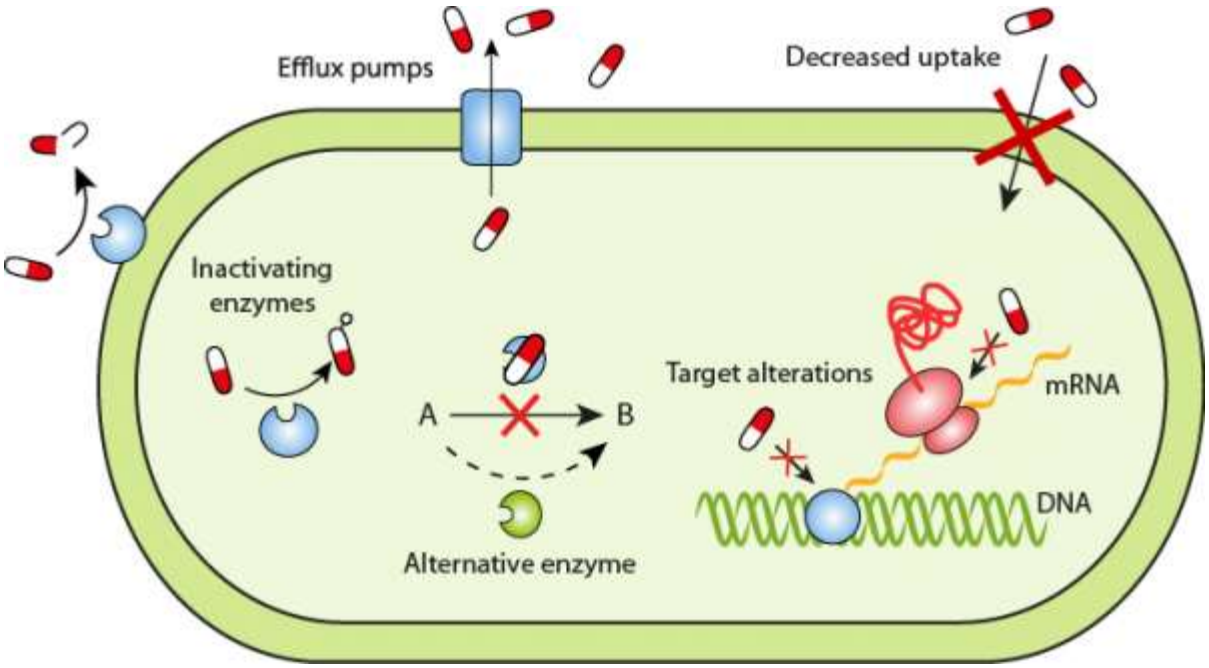


Figure 1. Antibiotic resistance strategies in bacteria.

2. MODIFY OR BYPASS THE TARGET OF THE ANTIBIOTIC:

Camouflage the target. Changes in the composition or structure of the target in the bacterium (resulting from mutations in the bacterial DNA) can stop the antibiotic from interacting with the target. Alternatively, the bacteria can add different chemical groups to the target structure, in this way shielding it from the antibiotic.

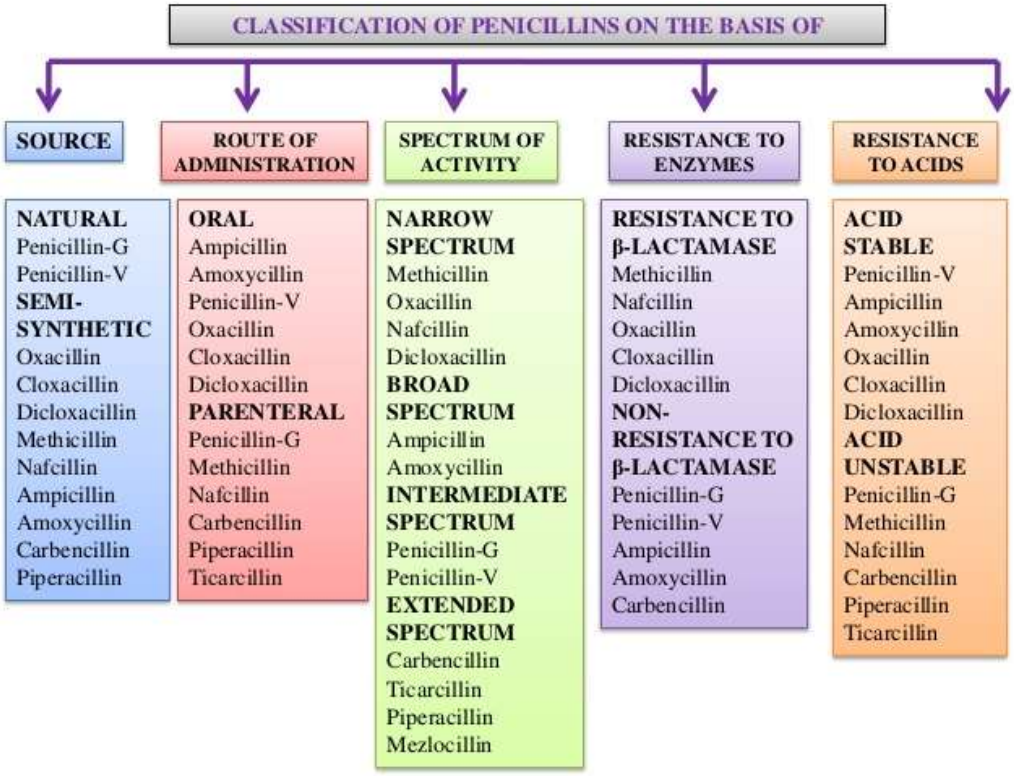
Express alternative proteins. Some bacteria are able to produce alternative proteins that can be used instead of the ones that are inhibited by the antibiotic. For example, the bacterium *Staphylococcus aureus* can acquire the resistance gene *mecA* and produce a new penicillin-binding protein. These proteins are needed for bacterial cell wall synthesis and are the targets of β-lactam antibiotics. The new penicillin-binding protein has low affinity to β-lactam antibiotics and is thus resistant to the drugs, and the bacteria survive treatment. This type of resistance is the basis in MRSA (methicillin-resistant *Staphylococcus aureus*).

- **Reprogram target.** Sometimes bacteria can produce a different variant of a structure it needs. For example, Vancomycin-resistant bacteria make a different cell wall compared to susceptible bacteria. The antibiotic is not able to interact as well with this type of cell wall.

I. Beta-Lactams antibiotics A. Penicillins:

Classification of penicillins: Penicillins can be classified as follows: 1. Natural penicillins 2. Antistaphylococcal penicillins 3. Antipseudomonal penicillins: (carboxypenicillin and Ureidopenicillin) 4. Extended-spectrum penicillins: Ampicillin and Amoxicillin

Natural penicillins: 1. Penicillin G (benzyl penicillin, crystalline penicillin) (for IM, IV) 2. Phenoxymethylpenicillin (for oral use) 3. Procaine Penicillin (for IM use only) 4. Benzathin Penicillin (long acting, for IM use only)



PENICILLINS AND CEPHALOSPORINS are the major antibiotics that inhibit bacterial cell wall synthesis. The beta-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections. Vancomycin, fosfomycin, and bacitracin also inhibit cell wall synthesis but are not nearly

All penicillins are derivatives of 6-aminopenicillanic acid and contain a beta-lactam ring structure that is essential for antibacterial activity.

Procaine and benzathine forms of penicillin G are administered intramuscularly and have long plasma half-lives because the active drug is released very slowly into the bloodstream. Most penicillins cross the blood-brain barrier only when the meninges are inflamed.

Penicillins are bactericidal drugs. They act to inhibit cell wall synthesis by the following steps :

(1) binding of the drug to specific enzymes (penicillin-binding proteins [PBPs]) located in the bacterial cytoplasmic membrane;

(2) inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan chain constituents of the cell wall; and (3) activation of autolytic enzymes that cause lesions in the bacterial cell wall.

Resistance

1.Enzymatic hydrolysis of the beta-lactam ring results in loss of antibacterial activity. The formation of beta-lactamases (penicillinases) by most staphylococci and many gram-negative organisms is a major mechanism of

bacterial resistance. Inhibitors of these bacterial enzymes (eg, clavulanic acid, sulbactam, tazobactam) are often used in combination with penicillins to prevent their inactivation.

2.Structural change in target PBPs is another mechanism of resistance

Clinical Uses

1. Narrow-spectrum penicillinase-susceptible agents— Penicillin G is the prototype of a subclass of penicillins that have a limited spectrum of antibacterial activity and are susceptible to beta-lactamases.

2. Very-narrow-spectrum penicillinase-resistant drugs—This subclass of penicillins includes methicillin (the prototype, but rarely used owing to its nephrotoxic potential), nafcillin, and oxacillin. Their primary use is in the treatment of known or suspected staphylococcal infections.

3. Wider-spectrum penicillinase-susceptible drugs

a. Ampicillin and amoxicillin—These drugs make up a penicillin subgroup that has a wider spectrum of antibacterial activity and used in combination with inhibitors of penicillinases (eg, clavulanic acid), their antibacterial activity is often enhanced. In enterococcal and listerial infections, ampicillin is synergistic with aminoglycosides.

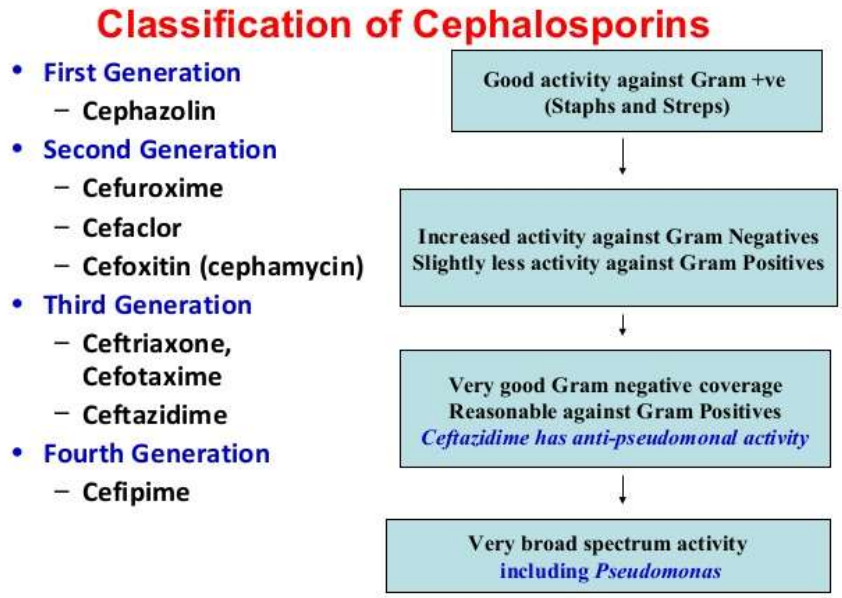
b. Piperacillin and ticarcillin—These drugs have activity against several gram-negative rods, including *Pseudomonas*, *Enterobacter*, and in some cases *Klebsiella* species. Most drugs in this subgroup have synergistic actions with aminoglycosides against such organisms. Piperacillin and ticarcillin are susceptible to penicillinases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

CEFALOSPORINES

A. Classification

Cephalosporins are beta-lactam antimicrobials used to manage a wide range of infections from gram-positive and gram-negative bacteria. The five generations of cephalosporins are useful against skin infection, resistant bacteria, meningitis, and other infections. This activity describes the indications, contraindications, and possible adverse effects of cephalosporins and will highlight the mechanism of action, adverse event profile, monitoring, route of administration, as well as other key factors.

The cephalosporins are derivatives of 7-aminocephalosporanic acid and contain the beta-lactam ring structure. Many members of this group are in clinical use. They vary in their antibacterial activity and are designated first-, second-, third-, fourth or fifth generation drugs according to the order of their introduction into clinical use.



Fifth-generation cephalosporins include ceftaroline. Ceftaroline is also a broad-spectrum antimicrobial and thus can cover susceptible gram-positive and gram-negative organisms. However, what makes it unique from the rest of the cephalosporins is that it has coverage against methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline can also
cover *Listeria monocytogenes* and *Enterococcus faecalis*. However, ceftaroline does not cover *Pseudomonas aeruginosa*.

B. Pharmacokinetics

Several cephalosporins are available for oral use, but most are administered parenterally. Cephalosporins may undergo hepatic metabolism, but the major elimination mechanism is renal excretion via active tubular secretion. Cefoperazone and ceftriaxone are excreted mainly inthe bile. Most first- and second-generation cephalosporins do not enter the BBB.

C. Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. Cephalosporins are bactericidal against susceptible organisms.

Structural differences from penicillins render cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of other betalactamases that can inactivate cephalosporins. Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs. Methicillin-resistant staphylococci are also resistant to cephalosporins.

D. Clinical Uses

1. First-generation drugs—Cefazolin (parenteral) and cephalexin (oral) are examples of this subgroup. They are active against gram-positive cocci, including

staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive.

2. Second-generation drugs—Drugs in this subgroup usually have slightly less activity against gram-positive organisms than the first-generation drugs but have an extended gram-negative coverage.

Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses include infections caused by the anaerobe *Bacteroides fragilis* (cefotetan, cefoxitin) and sinus, ear, and respiratory infections caused by *H influenzae* or *M catarrhalis* (cefamandole, cefuroxime, cefaclor).

3. Third-generation drugs—Characteristic features of third generation drugs (eg, ceftazidime, cefoperazone, cefotaxime) include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier (except cefoperazone and cefixime). Most are active against *Providencia, Serratia marcescens,* and beta-lactamase producing strains of *H influenzae* and *Neisseria*; they are less active against *Enterobacter* strains that produce extended-spectrum

4. Fourth-generation drugs—Cefepime is more resistant to beta-lactamases produced by gram-negative organisms, including *Enterobacter, Haemophilus, Neisseria*, and some penicillinresistant pneumococci. Cefepime combines the gram-positive activity of first-generation agents with the wider gram-negative spectrum of third-generation cephalosporins. Ceftaroline has activity in infections caused by methicillin-resistant staphylococci.

5. Fifth-generation drug - Ceftaroline injection is used to treat some types of skin infections caused by certain bacteria in adults, children, and infants, including newborns. Ceftaroline injection is used to treat some types of pneumonia (lung infection) caused by bacteria in adults, children, and infants 2 months of age and older

E. Toxicity

1. Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur less frequently with cephalosporins than with penicillins. . However, patients with a history of *anaphylaxis* to penicillins should not be treated with a cephalosporin.

2. Other adverse effects—Cephalosporins may cause pain at intramuscular injection sites and phlebitis after intravenous administration. They may increase the nephrotoxicity of aminoglycosides when the two are administered together. Drugs containing a methylthiotetrazole group (eg, cefamandole, cefoperazone, cefotetan) may cause hypoprothrombinemia and disulfiram-like reactions with ethanol

Monobactams

A. Aztreonam

Aztreonam is a monobactam that is resistant to beta-lactamases produced by certain gram-negative rods, including *Klebsiella*, *Pseudomonas*, and *Serratia*. The drug has no activity against gramnegative bacteria or anaerobes. It is an inhibitor of cell wall synthesis, preferentially binding to a specific penicillin-binding protein (PBP3), and is synergistic with aminoglycosides. Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure.

Adverse effects include gastrointestinal upset with possible superinfection, vertigo and headache, and rarely hepatotoxicity. Although skin rash may occur, there is no cross-allergenicity with penicillins.

Carbapenems

B. Imipenem, Doripenem, Meropenem, and Ertapenem

These drugs are carbapenems (chemically different from penicillins but retaining the beta-lactam ring structure) with low susceptibility to beta-lactamases. They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes. With the exception of ertapenem, the carbapenems are active against *P aeruginosa* and *Acinetobacter* species. For pseudomonal infections, they are often used in combination with an aminoglycoside. The carbapenems are administered parenterally and are useful for infections caused by organisms resistant to other antibiotics. . Imipenem is rapidly inactivated by renal dehydropeptidase I and is administered in fixed combination with cilastatin, an inhibitor of this enzyme. Cilastatin increases the plasma halflife of imipenem and inhibits the formation of a potentially nephrotoxic metabolite. The other carbapenems are not significantly degraded by the kidney.

Adverse effects of imipenem-cilastatin include gastrointestinal distress, skin rash, and, at very high plasma levels, CNS toxicity (confusion, encephalopathy, seizures). There is partial cross allergenicity with the penicillins. Meropenem is similar to imipenem except that it is not metabolized by renal dehydropeptidases and is less likely to cause seizures.

C. Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins. They are most active against plasmid-encoded beta-lactamases such as those produced by gonococci, streptococci, *E coli*, and *H influenzae*. They are not good inhibitors of inducible chromosomal beta-lactamases formed by *Enterobacter, Pseudomonas*, and *Serratia*.

Glycopeptides

Vancomycin is a bactericidal glycoprotein that binds to the d-Ala-d-Ala terminal of the nascent peptidoglycan pentapeptide side chain and inhibits transglycosylation. This action prevents elongation of the peptidoglycan chain and interferes with crosslinking. Vancomycin has a narrow spectrum of activity and is used for serious infections caused by drug-resistant gram-positive organisms, including methicillin-resistant staphylococci (MRSA), and in combination with a third-generation cephalosporin such as ceftriaxone for treatment of infections due

to penicillin-resistant pneumococci (PRSP). Vancomycin is also a backup drug for treatment of infections caused by *Clostridium difficile*.
Teicoplanin and telavancin, other glycopeptide derivatives, have similar characteristics.
Vancomycin is not absorbed from the gastrointestinal tract and may be given orally for bacterial enterocolitis. When given parenterally, vancomycin penetrates most tissues and is eliminated unchanged in the urine. Toxic effects of vancomycin include chills, fever, phlebitis, ototoxicity, and nephrotoxicity. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome") from histamine release.

CHLORAMPHENICOL

A. Classification and Pharmacokinetics

It is effective orally as well as parenterally and is widely distributed, readily crossing the placental and blood-brain barriers. Chloramphenicol undergoes enterohepatic cycling, and a small fraction of the dose is excreted in the urine unchanged. Most of the drug is inactivated by a hepatic glucuronosyltransferase.

B. Antimicrobial Activity

Chloramphenicol has a wide spectrum of antimicrobial activity and is usually bacteriostatic. Some strains of *Haemophilus influenzae, Neisseria meningitidis*, and *Bacteroides* are highly susceptible, and for these organisms chloramphenicol may be bactericidal. It is not active against *Chlamydia* species. Resistance to chloramphenicol, which is plasmid-mediated, occurs through the formation of acetyltransferases that inactivate the drug.

C. Clinical Uses

Because of its toxicity, chloramphenicol has very few uses as a systemic drug. It is a backup drug for severe infections causedby *Salmonella* species and for the treatment of pneumococcaland meningococcal meningitis in beta-lactam-sensitive persons.Chloramphenicol is sometimes used for rickettsial diseases and for infections caused by anaerobes such as *Bacteroides fragilis*. The drug is commonly used as a topical antimicrobial agent

D. Toxicity

1. Gastrointestinal disturbances—These conditions may occur from direct irritation and from superinfections, especially candidiasis.
2. Bone marrow—Inhibition of red cell maturation leads to a decrease in circulating erythrocytes. This action is dose-dependent and reversible. Aplastic anemia is a rare idiosyncratic reaction (approximately 1 case in 25,000–40,000 patients treated). It is usually irreversible and may be fatal.
3. Gray baby syndrome—This syndrome occurs in infants andis characterized by decreased red blood cells, cyanosis, and cardiovascular collapse. Neonates, especially those who are premature, are deficient in hepatic glucuronosyltransferase and are sensitive to doses of chloramphenicol that would be tolerated in older infants.

4. Drug interactions—Chloramphenicol inhibits hepatic drug metabolizing enzymes, thus increasing the elimination half-lives of drugs including phenytoin, tolbutamide and warfarin.

TETRACYCLINES

A. Classification

Drugs in this class are broad-spectrum bacteriostatic antibiotics

B. Pharmacokinetics

Oral absorption is variable, especially for the older drugs, and may be impaired by foods and multivalent cations (calcium, iron,aluminum). Tetracyclines have a wide tissue distribution and cross the placental barrier. All the tetracyclines undergo enterohepatic cycling.

Doxycycline is excreted mainly in feces; the other drugs are eliminated primarily in the urine. The half-lives of doxycycline and minocycline are longer than those of other tetracyclines. Tigecycline, formulated only for IV use, is eliminated in the bile and has a half-life of 30–36 h.

C. Antibacterial Activity

Tetracyclines are broad-spectrum antibiotics with activity against gram-positive and gram-negative bacteria, species of *Rickettsia*, *Chlamydia*, *Mycoplasma*, and some protozoa.

Resistance mechanisms include the development of mechanisms (efflux pumps) for active extrusion of tetracyclines and the formation of ribosomal protection proteins that interfere with tetracycline binding.

D. Clinical Uses

1. Primary uses—Tetracyclines are recommended in the treatment of infections caused by *Mycoplasma pneumoniae* (in adults), chlamydiae, rickettsiae, vibrios, and some spirochetes.

2. Secondary uses—Tetracyclines are alternative drugs in the treatment of syphilis. They are also used in the treatment of respiratory infections caused by susceptible organisms, for prophylaxis against infection in chronic bronchitis

3. Selective uses—Specific tetracyclines are used in the treatment of gastrointestinal ulcers caused by *Helicobacter pylori* (tetracycline), Doxycycline is also used for the prevention of malaria and in the treatment of amebiasis , Demeclocycline
inhibits the renal actions of antidiuretic hormone (ADH)
and is used in the management of patients with ADH-secreting
tumors
,

E. Toxicity

1. Gastrointestinal disturbances—Effects on the gastrointestinal system range from mild nausea and diarrhea to severe, possibly life-threatening enterocolitis. Disturbances in the normal flora may lead to candidiasis (oral and vaginal) and, more rarely, to bacterial superinfections with *S aureus* or *Clostridium difficile*.

2. Bony structures and teeth—Fetal exposure to tetracyclines may lead to tooth enamel dysplasia and irregularities in bone growth

3. Hepatic toxicity—High doses of tetracyclines, especially in pregnant patients and those with preexisting hepatic disease, may impair liver function and lead to hepatic necrosis.
4. Renal toxicity—One form of renal tubular acidosis, Fanconi's syndrome, has been attributed to the use of outdated tetracyclines.
5. Photosensitivity—Tetracyclines, especially demeclocycline, may cause enhanced skin sensitivity to ultraviolet light.
6. Vestibular toxicity—Dose-dependent reversible dizziness and vertigo have been reported with doxycycline and minocycline.

MACROLIDES

A. Classification and Pharmacokinetics

The macrolide antibiotics (erythromycin, azithromycin, and clarithromycin) are large cyclic lactone ring structures with attached sugars.

B. Antibacterial Activity

Erythromycin has activity against many species *Chlamydia, Mycoplasma, Legionella*, gram-positive cocci, and some gram-negative organisms. The spectra of activity of azithromycin and clarithromycin are similar but include greater activity against species of *Chlamydia*, *Mycobacterium avium* complex, and *Toxoplasma*. Azithromycin is also effective in gonorrhea, as an alternative to ceftriaxone and in syphilis, as an alternative to penicillin G.

C. Resistance to the macrolides in gram-positive organisms involves efflux pump mechanisms and the production of a methylase that adds a methyl group to the ribosomal binding site.

D. Adverse effects, especially with erythromycin, include gastrointestinal irritation (common) via stimulation of motolin receptors, skin rashes, and eosinophilia. Erythromycin inhibits several forms of hepatic cytochrome P450 and can increase the plasma levels of many drugs, including anticoagulants, carbamazepine, cisapride, digoxin, and theophylline. Azithromycin does not inhibit hepatic cytochrome P450.

LINCOZAMIDES

CLINDAMYCIN

A. Classification and Pharmacokinetics

Clindamycin inhibits bacterial protein synthesis via a mechanism similar to that of the macrolides, although it is not chemically related. Mechanisms of resistance include methylation of the binding site on the 50S ribosomal subunit and enzymatic inactivation. Gram-negative aerobes are intrinsically resistant because of poor penetration of clindamycin through the outer membrane.

B. Clinical Use and Toxicity

The main use of clindamycin is in the treatment of severe infections caused by certain anaerobes such as *Bacteroides*. Clindamycin has been used as a backup drug against gram-positive cocci (it is active against community-acquired strains

of methicillin-resistant *S aureus)* and is recommended for prophylaxis of endocarditis in valvular disease patients who are allergic to penicillin. The drug is also active against *Pneumocystis jirovecii* and is used in combination with pyrimethamine for AIDS-related toxoplasmosis. The toxicity of clindamycin includes gastrointestinal irritation, skin
rashes, neutropenia, hepatic dysfunction, and possible superinfections such as *C difficile* pseudomembranous colitis.

STREPTOGRAMINS

Quinupristin-dalfopristin, a combination of 2 streptogramins, is bactericidal . Antibacterial activity includes penicillin-resistant pneumococci, methicillin-resistant (MRSA) and vancomycin-resistant staphylococci (VRSA), and resistant *E faecium; E faecalis* is intrinsically resistant via an efflux transport system. Administered intravenously, the combination product may cause pain and an arthralgia-myalgia syndrome. Streptogramins are potent inhibitors of CYP3A4 and increase plasma levels of many drugs, including astemizole, cisapride, cyclosporine, diazepam, nonnucleoside reverse transcriptase inhibitors, and warfarin.

LINEZOLID

The first of a novel class of antibiotics (oxazolidinones), linezolid is active against drug-resistant gram-positive cocci, including strains resistant to penicillins (eg, MRSA, PRSP)and vancomycin (eg, VRE). The drug is also active against *L monocytogenes* and corynebacteria. Linezolid binds to a unique site located on the 23S ribosomal RNA of the 50S ribosomal subunit, and there is currently no cross-resistance with other protein synthesis inhibitors. Resistance (rare to date) involves a decreased affinity of linezolid for its binding site. Linezolid is available in both oral and parenteral formulations and should be reserved for treatment of infections caused by multidrugresistant gram-positive bacteria. The drug is metabolized by the liver and has an elimination half-life of 4–6 h. Thrombocytopenia and neutropenia occur, most commonly in immunosuppressed patients. Linezolid has been implicated in the serotonin syndrome when used in patients taking selective serotonin reuptake inhibitors (SSRIs).

AMINOGLYCOSIDES

Aminoglycosides have a hexose ring, to which various amino sugars are attached by glycosidic linkages. They are water-soluble, stable in solution, and more active at alkaline than at acid pH. Aminoglycosides have polar groups in their molecules and do not absorb in GIT, must be given intramuscularly or intravenously for systemic effect. They have limited tissue penetration and do not readily cross the blood-brain barrier. Glomerular filtration is the major mode of excretion, and plasma levels of these drugs are greatly affected by changes in renal function. Excretion of aminoglycosides is directly proportional to creatinine clearance.

Aminoglycosides are bactericidal inhibitors of protein synthesis.Their penetration through the bacterial cell envelope is partlydependent on oxygen-dependent active transport, and they have minimal activity against strict anaerobes. Aminoglycoside entry can be enhanced by cell wall synthesis inhibitors, which may be the basis of antimicrobial synergism. Inside the cell, aminoglycosides bind to the 30S ribosomal subunit and interfere with protein synthesis in at least 3 ways:
1. they block formation of the initiation complex;
2. they cause misreading of the code on the mRNA template;
3. and (3) they inhibit translocation .
Ehe primary mechanism of resistance to aminoglycosides, especially in gram-negative bacteria, involves the plasmid-mediated formation of inactivating enzymes. These enzymes are group transferases that catalyze the acetylation of amine functions and the transfer of phosphoryl or adenylyl groups tothe oxygen atoms of hydroxyl groups on the aminoglycoside. In addition, resistance appears to be due to changes inthe ribosomal binding site. Drugs for the treatment of serious infections causedby aerobic gram-negative bacteria, including *Escherichia coli* and*Enterobacter, Klebsiella, Proteus, Providencia, Pseudomonas*, and *Serratia* species. These aminoglycosides also have activity against strains of *Haemophilus influenzae, Moraxella catarrhalis*, and *Shigella* species, In most cases, aminoglycosides are used in combination with a beta-lactam antibiotic. When used alone, aminoglycosides are not reliably effective in the treatment of infections caused by gram-positive cocci. Antibacterial synergy may occur when aminoglycosides are used in combination withcell wall synthesis inhibitors

TOXICITY
A. Ototoxicity
Auditory or vestibular damage (or both) may occur with anyaminoglycoside and may be irreversible. Auditory impairmentis more likely with amikacin and kanamycin; vestibulardysfunction is more likely with gentamicin and tobramycin. Ototoxicity risk is proportional to the plasma levels and thus is especially high if dosage is not appropriately modified in a patient with renal dysfunction. Ototoxicity may be increased by the use of loop diuretics. Because ototoxicity has been reported after fetal exposure, the aminoglycosides are contraindicated in pregnancy unless their potential benefits are judged to outweigh risk.
B. Nephrotoxicity
Renal toxicity usually takes the form of acute tubular necrosis. This adverse effect, which is often reversible, is more common in elderly patients and in those concurrently receiving amphotericin B, cephalosporins, or vancomycin. Gentamicin and tobramycin are the most nephrotoxic.
C. Neuromuscular Blockade
Though rare, a curare-like block may occur at high doses of aminoglycosides and may result in respiratory paralysis. It is usually reversible by treatment with calcium and neostigmine, but ventilator support may be required.
D. Skin Reactions Allergic skin reactions may occur in patients, and contact dermatitis may occur in personnel handling the drug.