Pharmacology Lecture 1 Dr.Siham .A .Wadee.

General Principles of Antimicrobial Therapy.

Antimicrobial chemotherapy .

Antimicrobial Agents: Chemical substances that can kill or suppress the growth of microorganism.

Microorganisms of medical importance fall into 4 categories:(1) bacteria, (2) viruses, (3) fungi, and(4) parasites.

Likewise, antibiotics are broadly classified as (1) antibacterial, (2) antiviral, (3) antifungal, and (4) antiparasitic agents.

Minimum inhibitory concentration (MIC): the lowest concentration of antibiotic that inhibits bacterial growth.

Minimum bactericidal concentration(MBC):is the lowest concentration of antimicrobial agent that results in a99.9 percent decline in colony count after overnight broth dilution incubations.

There are six selection questions that are helpful to use routinely to aid selection:

1. Is an antimicrobial agent required—is there an infection that will respond to your treatment?

2. Where is the infection (which organ/tissue)—what are the access problems to be overcome?

3. Which pathogen(s) are usually found at the location of the infection?

4. Which antimicrobial agent has the necessary pharmacokinetic properties to get to the location and also will get there at a concentration above the MIC so that the MIC is below the breakpoint?

5. What dose and route is necessary to achieve the desired effect?

6. How long should the treatment be for?

There are 4 additional factors to help the selection:

1. A bactericidal compound is preferable to a bacteriostatic compound.

2. Toxicity and cost limit the selection of an antimicrobial drug.

3. In food-producing animals, residues in milk and meat requiring the need for withdrawal times before slaughter (pre slaughter withdrawal times) are very important and limit the use of specific antimicrobial drugs.

Animals must not be slaughtered. for meat or their milk used within the pre slaughter period .

4. It should be appreciated that the plasma concentration governs the dose intervals on a treatment regimen but it is the tissue residence times that govern the pr eslaughter withdrawal times in production animals.

Resistance to antimicrobials:-

1. Mechanisms by which bacteria manifest resistance:

a. Organisms may produce enzymes, constitutive or inducible, which inactivate the drug.

b. The permeability to or uptake of the drug by organisms may be decreased or transport out of the cell may be increased.

c. Alteration of the drug receptor or binding site may result in reduced drug affinity at target loci.

d. The organism may develop alternate metabolic or synthetic pathways to bypass or repair the effects of the antimicrobial.

2. Mechanisms by which bacteria develop resistance

a. Mutation. Within a large population of bacteria, chromosomal mutations may occur, Mutation is a random event .

Antimicrobials do not induce mutations but may exert a selecting out of

resistant strains by suppression of susceptible bacteria.

b. Conjugation. Certain Gram(–) bacteria undergo conjugation, a type of reproduction in which genetic material is transferred from cell to cell via a

pilus that is encoded by a resistance transfer factor (RTF) on a plasmid. Resistance factors (Rfactors) from plasmid DNA and/or chromosomal DNA may encode for resistance to multiple drugs and may be rapidly transferred to the bacterial population.

c. Transduction. The process of transference of drug resistant genes by bacteriophage is termed transduction. It may be important in the development of resistant strains of Staphylococcus aureus.

d. Transformation. Bacteria may incorporate DNA encoding for drug resistance from their environment after its secretion or release by resistant organisms. Acquisition of resistance by this mechanism is relatively infrequent.

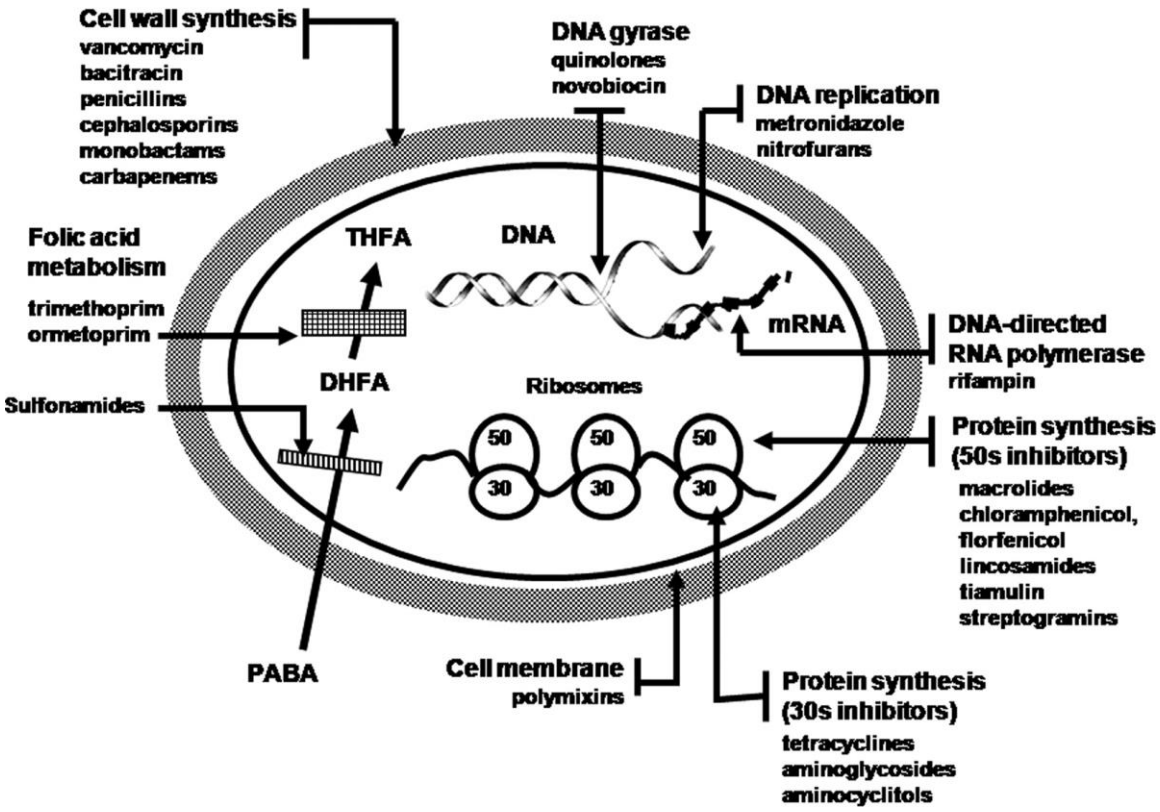

Figure 1:-**Mechanisms of action of antibacterial drugs.**

The five general mechanisms are:-

(1) inhibit synthesis of cell wall, (2) damage outer membrane, (3) modify nucleic acid/DNA synthesis, (4) modify protein synthesis, and (5) modify energy metabolism in the cytoplasm (at folate cycle).

PENICILLINS

Mechanism of action:-

Penicillins bind to and inhibit the transpeptidase involved in the cross-linking of the bacterial cell wall, the third and final step in cell-wall synthesis.

The weakened cell wall ruptures, resulting in lysis and cell death. Penicillins also inhibit other peptidases (penicillin-binding proteins) involved in cell wall synthesis and block the inhibition of autolysins. Rapidly growing bacteria are most susceptible to the bactericidal effect of penicillin.

The penicillins are primarily effective against Gram(+) aerobes and anaerobes. The broad-spectrum, semisynthetic penicillins are also effective against some Gram(–) pathogens.

Therapeutic uses

1. Natural penicillins

a. Penicillin G (benzylpenicillin) is used in all species for the treatment of infections caused by Gram(+).

b. Penicillin V now used infrequently for long-term oral therapy of Gram(+) bacterial infections in dogs, cats, and horses.

2. Penicillinase-resistant penicillins include methicillin, oxacillin, and cloxacillin. Their use is suited for severe staphylococcal infections caused by β-lactamase-producing organisms (some bovine mastitis) but they are less effective against Streptococcus than the natural penicillins.

3.Broad-spectrum penicillins

a. **Aminopenicillins. Ampicillin and amoxicillin** are active against many Gram(–)aerobes (E. coli, Proteus, Haemophilus spp.) as well as Gram(+) pathogens.

They are used in all species for the treatment of susceptible infections. They are acid stable but are not penicillinase stable. GI absorption of amoxicillin is better than ampicillin.

b. **Carbenicillin and ticarcillin** are carboxypenicillins that have antipseudomonal actions when used alone or in combination with or gentamicin or tobramycin.
They are useful for ear and skin infections in dogs caused by Pseudomonas spp.

c. **Piperacillin is an ureidopenicillin** that has an extended Gram(–) spectrum including Pseudomonas, Enterobacter, and Klebsiella spp. Cost limits its use to the treatment of severe Gram(–) bacterial infections in dogs and cats.

4. **Potentiated penicillins. Clavulanic acid** has minimal antibacterial action but it inhibits many of the β-lactamases produced by penicillin-resistant organisms.
It is combined with amoxicillin or ticarcillin in commercial preparations. **Sulbactam** has an action similar to clavulanic acid and is combined with ampicillin.
The potentiated penicillins are used in small animals for extended spectrum antimicrobial action.
Tazobactam is another β-lactamase inhibitor.

Adverse effects.
1-Allergic reactions to penicillin may occur in animals, especially cattle. Signs include skin eruptions, angioedema, and anaphylaxis.
2-Procaine salts of penicillin should not be used in birds, snakes, turtles, guinea pigs, or chinchillas because these species are sensitive to procaine.
3-Procaine penicillin G should not be used in race horses 30 days before racing . . Release of procaine due to high levels of plasma esterases in horses may produce CNS effects. Hyperkalemia and cardiac arrhythmias may result from IV administration of potassium penicillin in all species.

CEPHALOSPORINS:-

Mechanism of action.

Cephalosporins inhibit the third stage of bacterial cell wall synthesis—the cross-linking of the peptidoglycan chain, by the same mechanism as the penicillins .

Cephalosporins are bactericidal.

1. **First generation cephalosporins** include cephalexin (oral), cefadroxil (oral), cephapirin (parenteral), and cephalothin (parenteral). They are effective against Gram(+) aerobes.

2**. Second-generation cephalosporins** include cefaclor (oral) and cefoxitin (parenteral).
Their antibacterial spectrum is broader than that of first-generation cephalosporins and includes some Gram(–) pathogens.

3. **Third-generation cephalosporins** include ceftiofur, cefoperazone, cefotaxime, cefixime, and cefpodoxime (Simplicef R).
They have an extended spectrum of action against Gram(–) organisms, are resistant to β-lactamases cephalosporinases), and penetrate the blood–brain barrier. Ceftiofur is used in the treatment of respiratory disease in cattle, horses, sheep, and swine following IM injection and for intramammary treatment of mastitis in cattle.
It is also used for treating urinary tract infections and soft tissue infections in dogs and cats.
Cefoperazone is used in dogs to treat soft tissue infections and Gram(–) bacteremia.
Cefotaxime is used in dogs, cats, and foals to treat Gram(–) sepsis, soft tissue infections meningitis, and CNS infections.
Cefpodoxime proxetil is the prodrug marketed for use in the treatment of skin infections in dogs and cats.
Cefixime is used in the treatment of urinary tract infections and respiratory infections in dogs and cats and for bacterial endocarditis in dogs.

4. **Fourth-Generation cephalosporins** include cefepime and cefquinone and have more activity against bacteria, particularly Pseudomonas, showing resistance to other cephalosporins.
Some manufacturers have implied incorrectly that their third generation cephalosporins are fourth generation.

Resistance. Bacterial β-lactamase production may confer resistance, although cephalosporins tend to retain efficacy in contrast to the penicillins.

Adverse effects.

Side effects are rare and cephaolsporins are considered to be among the safest antimicrobials in use.
Prolonged treatment or high doses may produce hemopoietic effects with anemia and bone marrow depression.
Hypersensitivity and allergic reactions may occur.

CARBAPENEMS

Mechanism of action.

is similar to other β-lactam antimicrobial drugs but the carbapenems bind to more penicillin-binding proteins so that they have a very broad spectrum of action, one of the widest spectrum antimicrobials .

Therapeutic uses.

The carbapenems are used to treat very serious infections like peritonitis associated with ruptured GI tract or intestinal spillage during surgery. They are effective against Gram(+) and Gram(–) aerobic and anaerobic bacteria including Pseudomonas and Enterobacteriaciae.

Pharmacokinetics.

Oral administration is not possible because of acid hydrolysis and poor absorption. Imipenem is given IV over a period of 15–30 minutes and elimination in humans is governed by a t 1/2 of 2 hours where 75% is eliminated by renal filtration and metabolism in the renal tubules.
No information on t 1/2 is available for animals.
Imipenem undergoes extensive metabolism by the kidney dehydropeptidase(DHP-1) in the brush border of the proximal tubule.

The metabolite is nephrotoxic and exhibits antimicrobial action in the urine. Imepenem is used with a DHP-1 inhibitor, illastatin,to decrease toxicity and increase elimination t 1/2 .

Meropenem is a more recent derivative that is more DHP-1 stable that does not need cilastatin to inhibit kidney metabolism .

Adverse effects.

Side effects may include GIT (anorexia, vomiting, and diarrhea), CNS toxicity including seizures and tremors; and

a hypersensitivity reactions including pruritis, fever, and rarely, anaphylaxis.

MONOBACTAMS

Chemistry.

Monobactams have a β-lactam ring but the adjacent thiazolidine ring has been replaced.

B. Mechanism of action. Aztreonem binds to penicillin binding proteins present in Gram(–) aerobic bacteria and disrupt cell wall synthesis .

It is stable to most β-lactamases.

Therapeutic uses.

Aztreonem is used in humans to replace aminoglycosides, which are more toxic when used with macrolides and lincosamides. It may be used as a reserve antibiotic in veterinary medicine to treat severe Gram(–) infections .

Pharmacokinetics.

When given parenterally, aztreonem has a similar distribution to penicillin G. Penetration of CSF is good. It is excreted by the kidneys with an elimination

t 1/2 of 1.2 hours in humans. No other information is available for animals.

E. Adverse effects. Hypersensitivity reactions may occur but cross-allergy with penicillins or cephalosporins has not beeserved.

. **Vancomycin**

Mechanism of action.

Vancomycin blocks the second step of bacterial cell wall synthesis by by inhibiting polymer release from the cell membrane .It is bactericidal for Gram(+) organisms.

Therapeutic uses.

Vancomycin is a reserve antibiotic administered IV over 30–60 minutes every 6–8 hours for methicillin-resistant staphylococcal infections of bone and soft tissue in dogs and cats .

It is administered orally every 6–8 hours in dogs for the treatment of multidrug-resistant enteric infection.

Pharmacokinetics.

Vancomycin is not absorbed orally. It distributes to the ECF and transcellular fluids and is excreted unchanged by glomerular filtration. It has a plasma t 1/2 of 2 hours.

Adverse effects.

Ototoxicity and nephrotoxicity occur with large or prolonged dosage.

Bacitracin

Mechanism of action.

acitracin inhibits the second step of cell wall synthesis .

It is bactericidal for Gram(+) bacteria and Spirochetes.

Therapeutic uses.

Bacitracin is used in topical ointments and solutions and is frequently combined with polymixin B and/or neomycin in these preparations. It is also added to swine and poultry rations for the prevention and treatment of clostridial enteritis and as a growth promotant

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Pharmacokinetics.

Bacitracin is not absorbed orally. It is too nephrotoxic for systemic use.

Adverse effects.

Systemic toxicity does not occur with topical or oral administration of bacitracin.

Polymyxin B.

Mechanism of action.

Polymyxin B interacts with phospholipids in the bacterial cell membrane to produce a detergent-like effect and membrane disruption .

It is rapidly bactericidal to Gram(–) organisms.

2. **Therapeutic uses**.

Polymyxin B is used topically to treat Gram(–) bacterial infections of the skin ,eye ,and ear in all

of the skin, eye, and ear in all species. It is usually combined with bacitracin

for broad-spectrum antibacterial effects. Polymyxin B is administered orally to cattle

and swine for the treatment of Gram(–) enteric infections.

3. Pharmacokinetics. Polymyxin B is not absorbed orally. It is too nephrotoxic for parenteral use.

4-Adverse effects. Polymyxin B does not produce systemic toxicity when administered topically or orally, since it is not absorbed systemically using these routes of administration.

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