Chemotherapy of microbial disease

• ***Antibiotics are chemical substances or drugs that is produced by microorganisms like bacteria and*** fungi that destroy or inhibit the growth of other microorganisms like bacteria and fungi’’

•***Antibacterial agents are chemical substances that kills or*** inhibits the growth of bacterial microorganisms .

- ***Antimicrobial drugs are chemical substances or drugs that kill or inhibit the growth of a variety of*** microorganisms like bacteria, viruses, fungi, and parasites .

- ***Sub-therapeutic use or Non-therapeutic use is ‘‘any use of antibiotics/antibacterial drugs as a feed or*** water additive in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, and weight gain.

Medicines with an antimicrobial activity are divided into two groups:

1 – non-selective antimicrobial agents, causes most destructive effect on the *majority of microorganisms* (***antiseptics and disinfectants***).

2 - selective antimicrobial drugs (***chemotherapeutic agents***).

Features of Antimicrobial Drugs

- Antimicrobial action
  - Drugs may kill or inhibit bacterial growth
    - Inhibit = bacteriostatic
    - Kill = bacteriocidal
  - Bacteriostatic drugs rely on host immunity to eliminate pathogen
  - Bacteriocidal drugs are useful in situations when host defenses cannot be relied upon to control pathogen

Cont…

- Type of action

Primaily bacteriostatic

- Sulfonamides
- Tetracyclines
- Chloramphenicol
- Erythromycin
- Ethambutol
- Clindamycin

Primarily bacteriocidal

- Penicillins
- Aminoglycosides
- Polypeptides
- Rifampin
- Isoniazid
- CephalosPorins

Features of Antimicrobial Drugs

- Selective toxicity
  - Antibiotics cause greater harm to microorganisms than to human host
  - Toxicity of drug is expressed as therapeutic index
    - Lowest dose toxic to patient divided by dose typically used for treatment
      - High therapeutic index = less toxic to patient
      - Narrow therapeutic index = more toxic, monitor closely

Features of Antimicrobial Drugs

- Spectrum of activity
  - Antimicrobials vary with respect to range of organisms controlled
    - Narrow spectrum
      - Work on narrow range of organisms
        - » Gram-positive only OR Gram-negative only
      - Advantage: affects pathogen only
      - Disadvantage: requires identification of pathogen
    - Broad spectrum
      - Advantage: Work on broad range of organisms
      - Disadvantage : disruption of normal flora

Features of Antimicrobial Drugs

- Tissue distribution, metabolism and excretion
  - Drugs differ in how they are distributed, metabolized and excreted
  - Half-life: Rate of elimination of drug from body
    - Time it takes for the body to eliminate one half the original dose in serum
    - Half-life dictates frequency of dosage
  - Patients with liver or kidney damage tend to excrete drugs more slowly

Features of Antimicrobial Drugs

Adverse Effects

1. Allergic Reactions: some animal develop hypersensitivities to antimicrobials
2. Toxic Effects: some antimicrobials toxic at high concentrations or cause adverse effects
3. Suppression of normal flora: when normal flora killed, other pathogens may be able to grow to high number
4. Antimicrobial resistance: unresponsiveness of m.o to antimicrobial agents. Microorganisms have innate or adaptive resistance to antibiotics

Features of Antimicrobial Drugs

- Antimicrobial drug combination

Indication

1)Severe infection of unknown etiology

2)Mixed infection

3)Decreased toxicity

4)Inhanced action(e.g penicilline &aminoglycosides

CONT…

- Disadvantage of antimicrobial agents combination

A) Increase risk of allergy

B) Antagonism of antimicrobial effects

C) Increase risk of superinfection

D) Increased cost

Features of Antimicrobial Drugs

- Misuse of antimicrobial drugs

A. Attempted treatment of untreated infection

B. Improper dosage –too low or too high

C. Treatment in the absence of adequate bacteriological information

D. Omission of surgical drainage –have limited efficiency in presence of foreign material, necrotic tissue, or

Antiseptics and disinfectants

The terms antiseptic and disinfectant are an agent which inhibits or kills microbes on contact.

Antiseptics -. This is a group of medicines that are used to eliminate pathogens on living surfaces (skin, mucous membranes). Causes bacteriocidal or bacteriostatic effect depending on the concentration.

Disinfectants - used to eliminate pathogens on inanimate objects like medical instruments, utensils, facilities, equipment, etc.

Disinfection - a complex of measures aimed at prevention of infection in the wound (in the body as a whole) or to prevent the spread of infection.

There is considerable overlap as many agents are used in either way.

However, there is difference between 'disinfection‘ and'sterilization'. Sterilization means complete killing of all forms of microorganisms, disinfection refers to reduction in the number of viable pathogenic microbes to a level that they do not pose a risk to individuals with normal host defence. Thus, in ordinary usage, disinfection do not eliminate all microbes.

- Spectrum of activity of majority of antiseptic and disinfectants is wide, reflecting non selectivity of action.
- Mechanisms of action of germicides are varied, but can be grouped into:

(a)Oxidation of bacterial protoplasm.

e.g Halogen,oxidizing agent

(b) Denaturation of bacterial proteins including

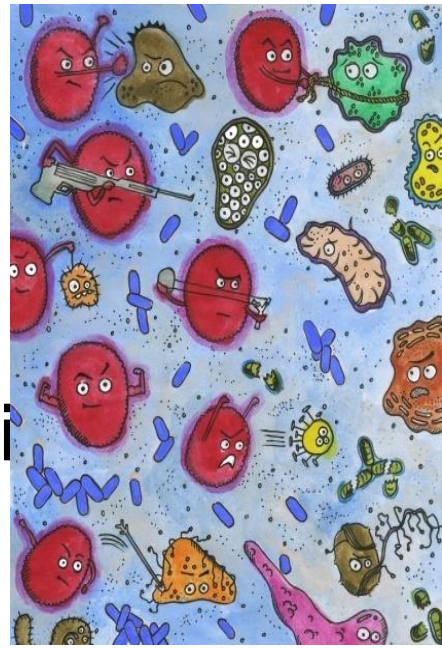
enzymes. e.g Alcohols, aldehyde, acids

(c) Detergent like action increasing permeability

of bacterial membrane.

e.g Soaps, quaternary ammonium

Requirements for antiseptics and disinfectants.



- Have a broad spectrum of action;
- Rapid onset of action;
- Cidal and not merely static, , destroyi spores as well.
- High availability and low cost;
- Lack of local irritant or allergic effects on tissues;
- Low toxicity.
- Active even in the presence of blood, pus, exudates and excreta

Factors which modify the activity of germicides are:

(i) Period of contact with the microorganism.
(ii) Nature of microbe involved.
(iii) Size of innoculum,
(iv) Presence of blood, pus or other organic matter.

Relative resistance of microbes

- **Highest resistance**
  - Bacterial endospores
- **Moderate resistance**
  - *Pseudomonas sp.*
  - *Mycobacterium tuberculosis*
  - *Staphylococcus aureus*
  - Protozoan cysts
- **Least resistance**
  - most vegetative cells
  - Fungal spores
  - enveloped viruses
  - Yeast
  - Protozoan trophozoites

Classification of Antiseptics and Disinfectants

1. Halogens:

- Chlorine
- Iodine

2. Oxidizing agents:

- Hydrogen peroxide
- Potassium permanganate

3.Quaternary ammonium

- Cetrimide

4. Acids

- Boric acid

5. Alcochols:

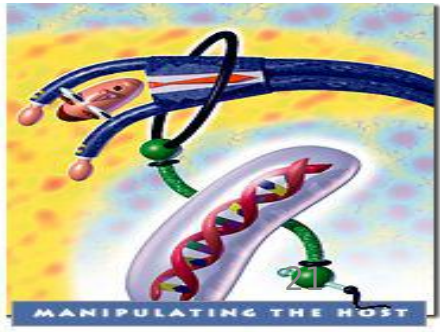
- (Ethyl alcohol)

6.Aldehydes:

- Formaldehyde (Formalin)

7. Soaps

8. Biguanide



1. HALOGENS

lodine It is a rapidly acting, broad-spectrum (bacteria, fungi, viruses, spores, T.B.)

- skin antiseptic

-Active bactericidal element

-Acts by oxidizing microbial protoplasm.

-Even bacterial spores are killed with higher concentrations/ longer contact. Organic matter retards but does not abolish its germicidal action.

-Solid iodine is corrosive, stronger solutions (> 5%) cause burning and blistering of skin.

Tincture iodine (2% in alcohol)

-It is used on cuts, for degerming skin before surgery and to treat ring worm, etc.

-Disinfection of instrument like thermometer.

Chlorine

- disinfectant in the form of gas

- wide spectrum (fungi & viruses)

- high-level (high concentration)---kill T.B.& spores

-active bactericidal element

- It is used to disinfect urban water supplies.

-Chlorine is more active in acidic or neutral medium.

2.QUATERNARY AMMONIUM

(CATIONTC) detergents

ϖThese are detergents; cidal to bacteria, fungi and viruses. However, many gram-negative bacteria (especially Pseudomonas) M. tuberculosis and bacterial spores are relatively resistant.

ϖThey act by altering permeability of cell membranes and denaturing of bacterial proteins.

ϖSoaps, being anionic, neutralize their action, while alcohol potentiates. They spread through oil and grease, have cleansing properties.

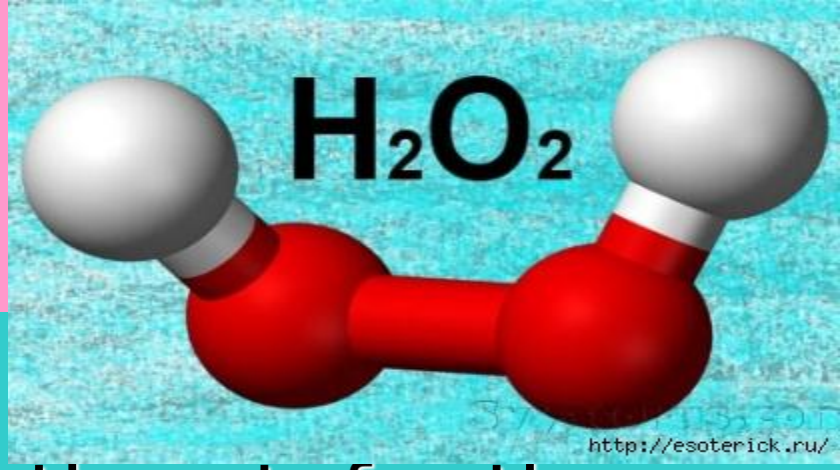
ϖThey are nonirritating and mildly keratolytic. However, the germicidal action is rather slow.

ϖPus, debris and porous material like cotton, polyethylene reduce their activity

3.OXIDIZING AGENT

- **HYDROGEN PEROXIDE**
- It is available as 30% and 3% solution. More common 3% solutions is used.
- $H_2O_2 = 2H + \mathbf{O_2}$
- Act by oxidizing bacterial protoplasm

Hydrogen peroxide



Indications:

- rinsing the mouth and throat, for the treatment of wounds that are infected with anaerobic pathogens. Concentrated solutions (20-30%) is indicated for the treatment of warts.

Side effects:

- burn mucosa. Not used in deep wounds, and not introduced into a body cavity - **may cause embolism.**

Potassium permanganate

- Act by oxidizes bacterial protoplasm.
- Higher concentrations cause burns and blistering.
- It promotes rusting.
- Used for Gargling, irrigating cavities, and wounds.
- In a 2-5% solution is used for burns, bites of mosquitoes and snakes, for quick healing of wounds.
- Disinfection of water.



4. ACIDS

Boric acid It is bacteriostatic and a very weak antiseptic. But being nonirritating even to delicate structures.

used for irrigating eyes, mouth wash, etc.

-Involve in enzyme inactivation or disruption

5. ALCOHOLS

Disinfectant & antiseptic

Ethanol It is an effective antiseptic and cleansing agent at 40-90% concentration.

Bactericidal activity starts with alcohol 20% and increases with concentration.

They are not sporocidal

virucidal---enveloped viruses

It acts by denaturing bacterial proteins. A cotton swab soaked in70% ethanol rubbed on the skin kills 90% bacteria in 2 min.; has been used before hypodermic injection.

6. ALDEHYDES

Formaldehyde It is a pungent gas-sometimes used for fumigation.

It is effective against bacteria, virus ,fungus and spores

A 37% aqueous solution called Formalin used for hardening and preserving dead tissues.

It denatures proteins

acts slowly.

A broad-spectrum germicide, but use as antiseptic is restricted by its irritating nature and pungent odour.

7.SOAPS

-Soaps are anionic detergents; weak antiseptics

-Affect only gram-positive bacteria. Their usefulness primarily resides in their cleansing action.

Washing with soap and warm water is one of the most effective methods of preventing transmission of infection by removing/diluting pathogenic bacteria

8. BIGUANIDE

Chlorhexidine(Savlon) nonirritating, cationic antiseptic that disrupts bacterial cell membrane &denaturating bacterial.

- cannot kill spores or T.B. , limited antifungal activity.
- It is relatively more active against gram-positive bacteria. Extensively used for surgical scrub, neonatal bath, mouthwash, obstetrics and as general skin antiseptic.

classification of antimicrobial drug

1. Antibacterial
2. Antifungal
3. Antiviral
4. Antiparasites

ANTIBACTERIAL AGENTS

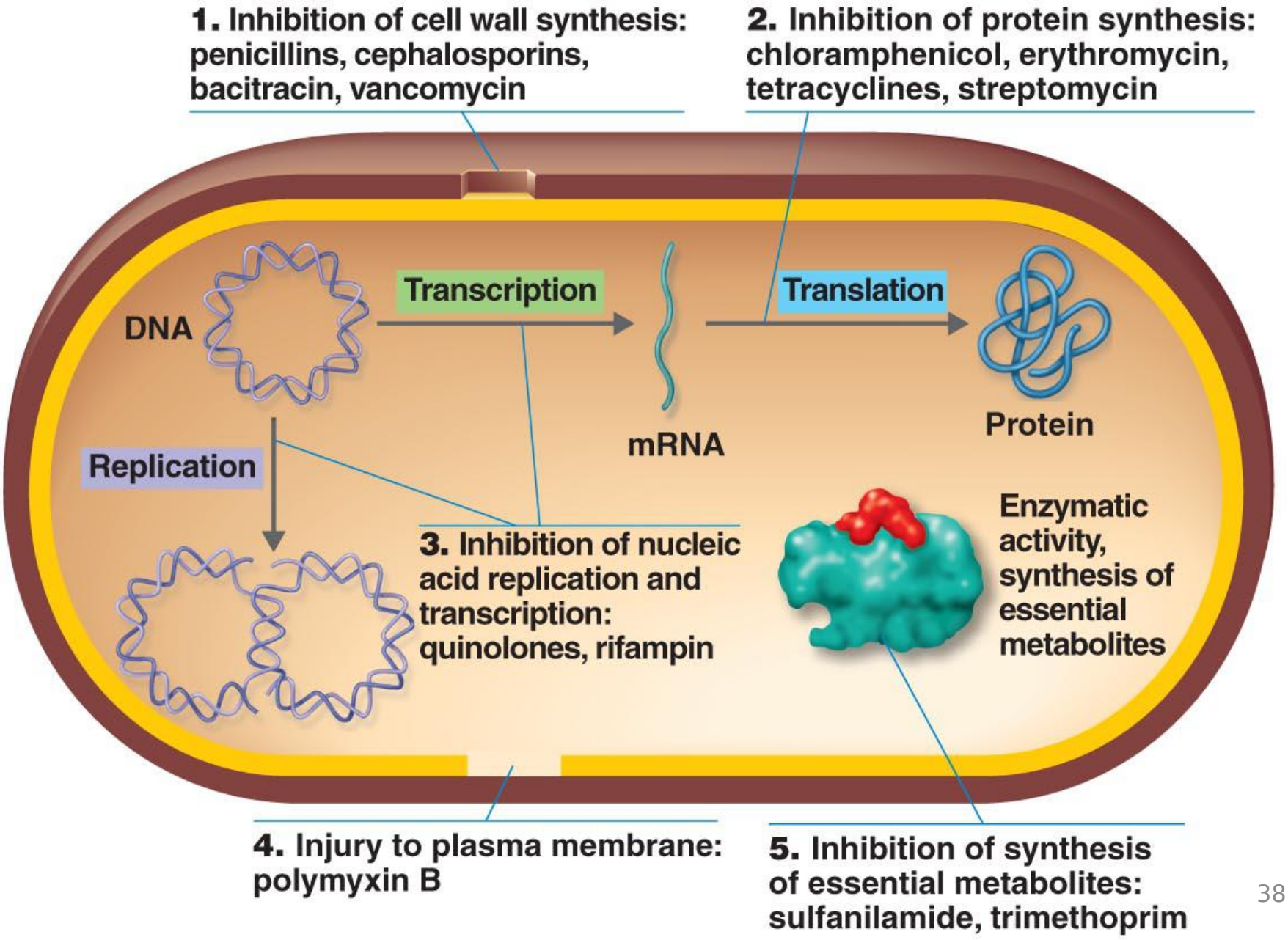
What is the Ideal Antibacterial?

- Selective target – target unique
- Bactericidal – kills
- Narrow spectrum – does not kill normal flora
- High therapeutic index – ratio of toxic level to therapeutic level
- Few adverse reactions – toxicity, allergy
- Various routes of administration – IV, IM, oral
- Good absorption

Mechanisms of Action of Antibacterial Drugs

1) Inhibition of cell wall synthesis
   - Penicillins, Cephalosporins, Vancomycin, carbapens
2) Inhibition of protein synthesis
   - Aminoglycosides, tetracyclines, macrolides, chloramphenicol, lincosamides
3) Inhibition of nucleic acid synthesis
   - Fluoroquinolones, rifamycins
4) Inhibition of metabolic pathways
   - Sulfonamides, trimethoprim
5) Interference with cell membrane integrity

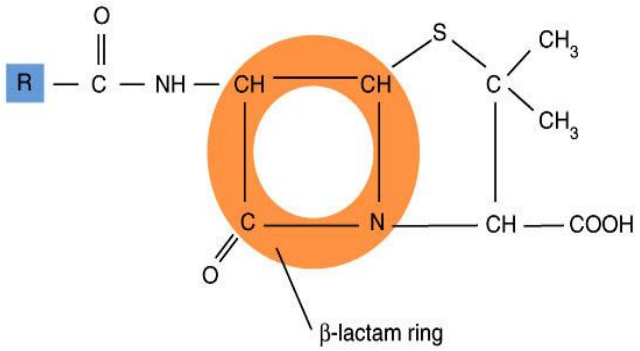
The Action of Antimicrobial Drugs



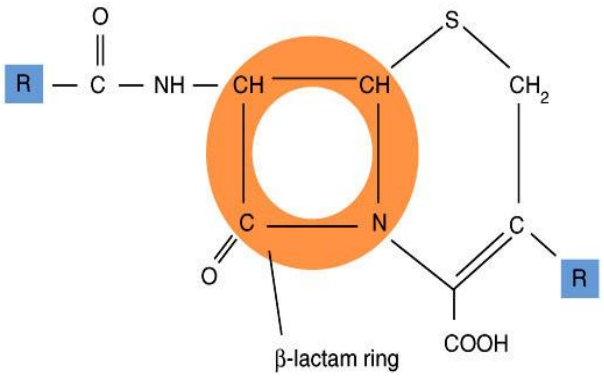
Mechanisms of Action: Cell Wall Synthesis

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(a) Penicillin

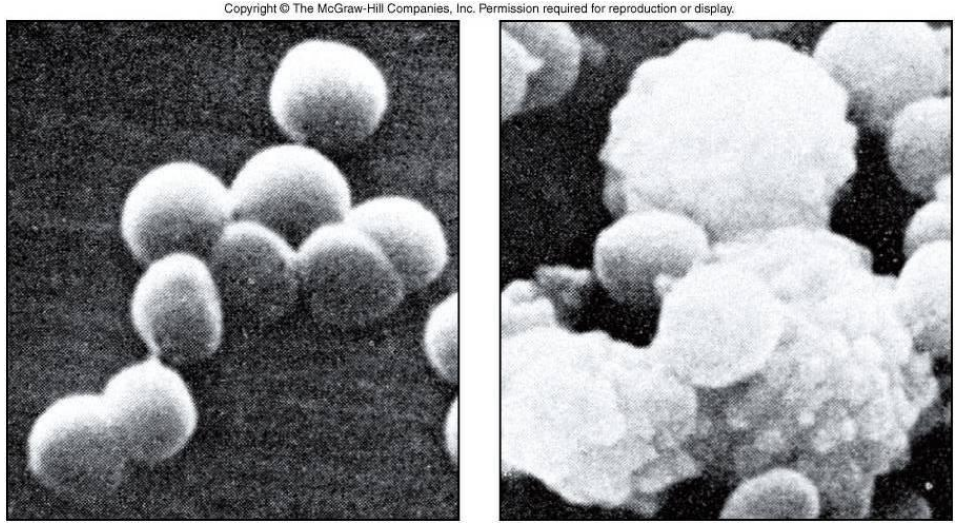


(b) Cephalosporin



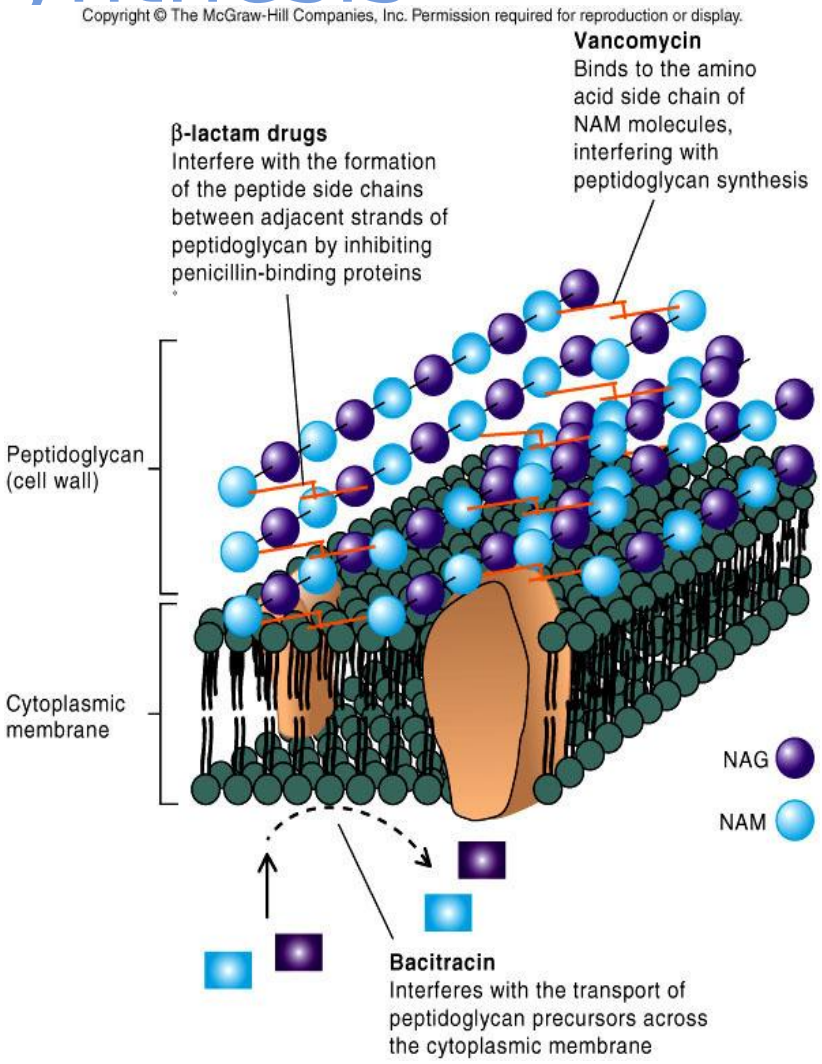
- Drugs vary in spectrum
  - Some more active against Gram (+)
  - Some more active against Gram (-)
  - Resistance through production of β-lactamase enzyme
  - Penicillins + β lactamase inhibitor
    - Augmentin = amoxicillin + clavulanic acid

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Mechanisms of Action: Cell Wall Synthesis

- Inhibition of cell wall synthesis
  - Antimicrobials that interfere with the synthesis of peptidoglycan
  - These drugs have very high therapeutic index
  - Antimicrobials of this class include
    - β lactam drugs (penicillin, cephalosporin)
    - Vancomycin
    - Bacitracin



Beta lactam antibiotics and other inhibitors of Cell Wall Synthesis

- Cell Wall Synthesis Inhibitors
  - ϖ Beta lactam antibiotics
  - ϖ Other antibiotics
- Beta lactam antibiotics

ϖ Penicillins, Cephalosporins, monobactam, carbapens

- Other antibiotics

ϖ Vancomycin,bacitracin

Beta lactam antibiotics

Mechanism of action

- ϖ Inhibition of cell wall synthesis
- ϖ Interferance with the last step of bacterial cell wall synthesis.
- ϖ Inhibition of transpeptidase
- ϖ Resulting in exposure of the osmotically less stable membrane.
- ϖ Cell lysis can then occur, either through osmotic pressure or through the activation of autolysis.
- All beta-lactams are subject to inactivation by bacterial-produced enzymes called beta-lactamases.
- They are all bactericidal

Beta lactam antibiotics

Penicillin



- **It has broad bacterial activity against Gram negative and gram positive bacteria.**
- **It is susceptible to betalactamase** producing organisms, which may account for resistance in organisms such as Staphylococci and certain

Inhibitors of Cell Wall Synthesis

Beta-lactams - Penicillins

- Spectrum of Action

1. Natural penicillins

- **Penicillin G: Active against Gram-positive organisms that do not** produce beta-lactamases, *Neisseria and some anaerobes*

2. Penicillinase-resistant penicillins

- **Penicillin M: Active against penicillinase-producing *Staphylococci***

Methicillin,Cloxacillin

3. Extended-spectrum penicillins

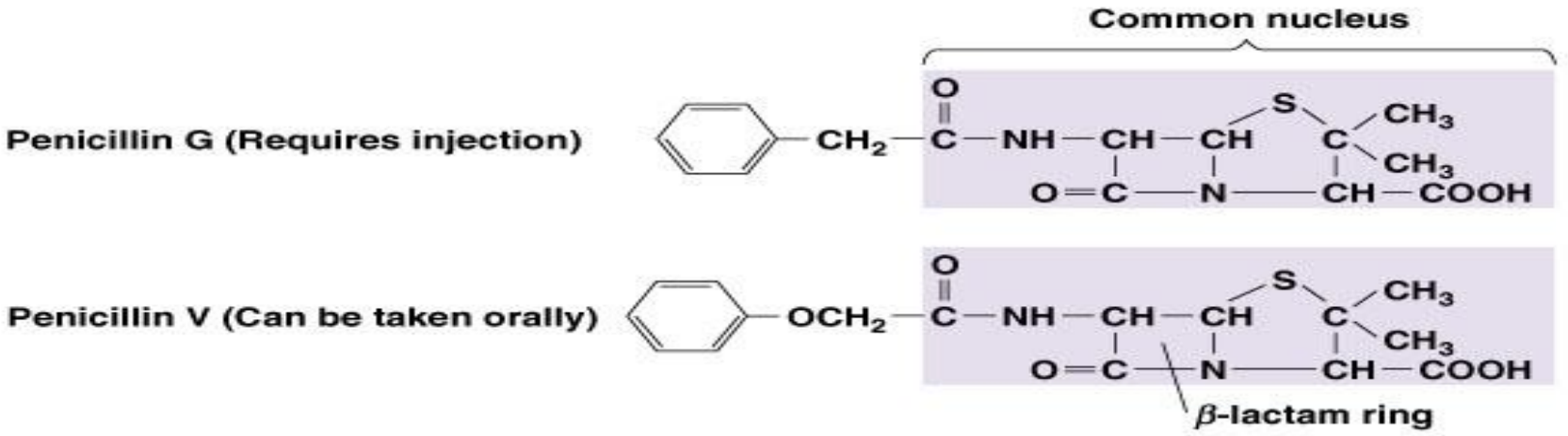
• **Aminopenicillins: Slightly less active than Penicillin G against**

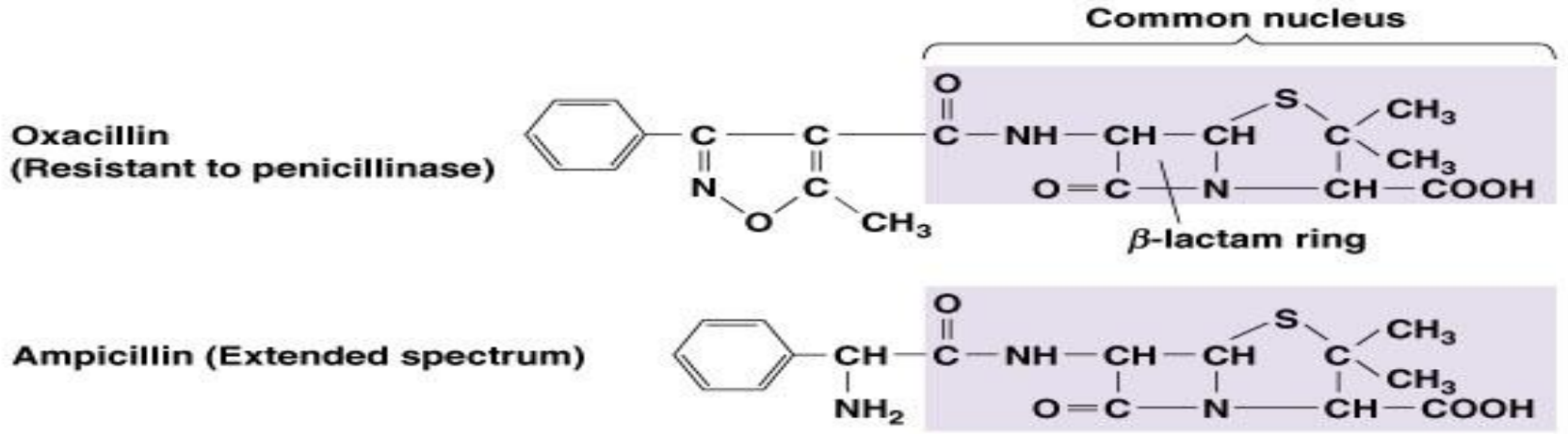
Pneumococci, Streptococci and Meningococci, but active against many strains of *Salmonella, and Shigella.*

Ampicillin, Amoxicillin.

4. Co-Drugs (Beta-lactam + beta-lactamase inhibitor)

• **ß-lactamase inhibitors (BLI) combinations:** Additional activity


Common nucleus
Penicillin G (Requires injection)
Penicillin V (Can be taken orally)
β-lactam ring
(a) Natural (antibiotic) penicillins


Common nucleus
Oxacillin
(Resistant to penicillinase)
β-lactam ring
Ampicillin (Extended spectrum)
(b) Semisynthetic penicillins

Cont...

- **Pharmacokinetics:** Absorption of most orally administered penecillins takes place in the stomach and small intestine. Most injected penicilins are absorbed rapidly at the injection site and are distributed rapidly through most tissue.
- The kidneys are the primary organ for excretion of penicillins, although the liver methabolizes penicillins. Withdrawal times for dairy cows must be adhered to because penicillins are excreted

Cont…

- Access to mammalian tissue is generally adequate to combat bacterial infections with exception of intraocular and intracerebral sites.
- It is particularly useful in urinary tract infection since the intact parent drug is eliminated in the kidneys via tubular secretion. This drug is very safe since Penicillins affect a process in bacterial cell walls, which are not present in mammalian cells.

Cont…

- **Pharmacodynamics**: penicillins bind reversibly with enzymes outside , the bacterial cytoplasmic membrane. These enzymes called penicilline - binding protein(PBPs) are involved in cellwall synthesis and cell division;when this binding occurs, it increases internal osmotic pressure and ruptures the cell. Some bacteria produce beta lactamase (penicillinase) which increases the resistance of bacteria by converting penicillin to

Cont…

- **Indications:**

  For the treatment of soft tissue and genito-urinary tract infections caused by susceptible bacteria.

- **Contraindications:**

- Not to be used with animals who are allergic to the Penicillins,
- In animals with impaired renal function, the dosage of the drug should be decreased with the extent to which renal function is impaired.

Cont…

- **Side Effects:**

⎫ Gastrointestinal upsets – Vomiting /Diarrhea

⎫ Allergic Reaction (Animals sensitive to Penicillins) : From rashes to anaphylaxis

- **Drug Interactions:**

It is generally recommended that Penicillins not be used with bacteriostatic (i.e. tetracycline) antibiotics since these drugs impair bacterial wall synthesis.

Inhibitors of Cell Wall Synthesis

Beta-lactamase Inhibitors (BLI)

Aim: to block β-lactamases

These enzymatic inhibitors have weak or poor antibacterial activity alone, but a strong affinity for β- lactamases:

Clavulanic Acid

Sulbactam

Tazobactam

Combination β-lactams - β-lactamase inhibitor:

- Amoxicillin + Clavulanic Acid
- Ampicillin + Sulbactam
- Ticarcillin + Clavulanic Acid
- Piperacillin + Tazobactam

Beta lactam antibiotics

Cephalosporin



- Antibacterial activity is accomplished by an inhibition of bacterial cell wall synthesis.
- It is particularly effective against gram positive bacteria and has relative poor activity against gram negative organisms. Beta lactamase (cephalosporinase)-producing bacteria are generally resistant to the antibiotic.

cont...

- Cephalosporins are used primarily in small animal medicine. However,afew have been developed for use in large animal medicine. this group of drug is classified into generations according to spectrum of activity.

Beta-lactams - Cephalosporin

Spectrum of Action

- **1st generation cephalosporins (C1G): Narrow spectrum; good**

Gram-positive activity and relatively lowest Gram-negative activity. Inactivated by Gram-neg beta-lactamases

(Derived from *Cephalosporium acremonium).* ***e.g*** **Cefazolin**

- **2nd generation cephalosporins (C2G): Better Gram-negative**

coverage (more beta-lactamase stability), but less

• **3rd generation cephalosporins (C3G): Wider spectrum of action** when compared to C1G and C2G. Less active than narrow spectrum agents against Gram-positive cocci, but much more active against the *Enterobacteriaceae and Pseudomonas aeruginosa (better betalactamase* stability). **E.g Cefotaxime**

• **4th generation cephalosporins (C4G): Broadest spectrum of**

action. Active against high level cephalosporinases of

Cont…

- Metabolism occur In liver and elimination of the intact drug is primarily via the kidney (by tubular secretion and glomerular filtration). Overall, Cephalosporins, such as Cfazolin, are remarkably safe drugs since they affect a process in bacterial cell walls, which is not important in mammalian metabolism.

Cont…

- **Pharmacokinetics:**

  This drug is not absorbed from the gastrointestinal tract, and must be given by parental routes. Cephalosporins are distributed to tissues and fluids, with the exception of the central nervous system (CNS). Some cephalosporins are absorbed into the cerebrospinal fluid, but this absorption is limited.

Cont…

- **Pharmacodynamics**

  Similar to penicillin , cephalosporine intrerfere with cell wall synthesis by binding to the bacterial enzymes(P BPs).

  The spectrum of activity of cephalosporine is reveled by the drug ability to penetrate the bacterial cell wall and bind with protein with in the cytoplasmic membrane.

  Another similarity between cephalosporins and penicillins is the susceptibility of cephalosporins to beta-lactamases (cephalosporinases), which

Cont…

- **Clinical use**

  Cephalosporine are used to treat cystitis, skin and soft tissue infections in the dogs and cats, bovine mastitis, shipping fever, and other respiratory infections in cattle,horse,sheep,and swine.

Contraindications:

- Not to be used with animals who are allergic to the Cephalosporins
- In animals with impaired renal function, the dosage of the drug should be decreased with the extent to which

Cont...

Side Effects:

- superinfection
- Allergic Reaction
- Bleeding tendency
- Local effects:thrombophilibitis from i.v injection

Forms of Drug:

- **Cefazolin**
- **Cephamycin**
- **Cefotaxime**
- **Cefepime**

Drug Interactions:

- Cephalosporins may enhance nephrotoxicity of **Aminoglycosides.**

Beta-lactams: Monobactams

Spectrum of Action

- **Aztreonam: Gram-negatives**

(*Enterobacteriaceae and Pseudomonas). Not hydrolyzed by most commonly occurring* plasmid and chromosomally mediated ß-lactamases, and does not induce the production of these enzymes.

Beta-lactams: Penems

Slightly different structure than the other ß-lactams, make the Penems much more resistant to beta-lactamase hydrolysis.

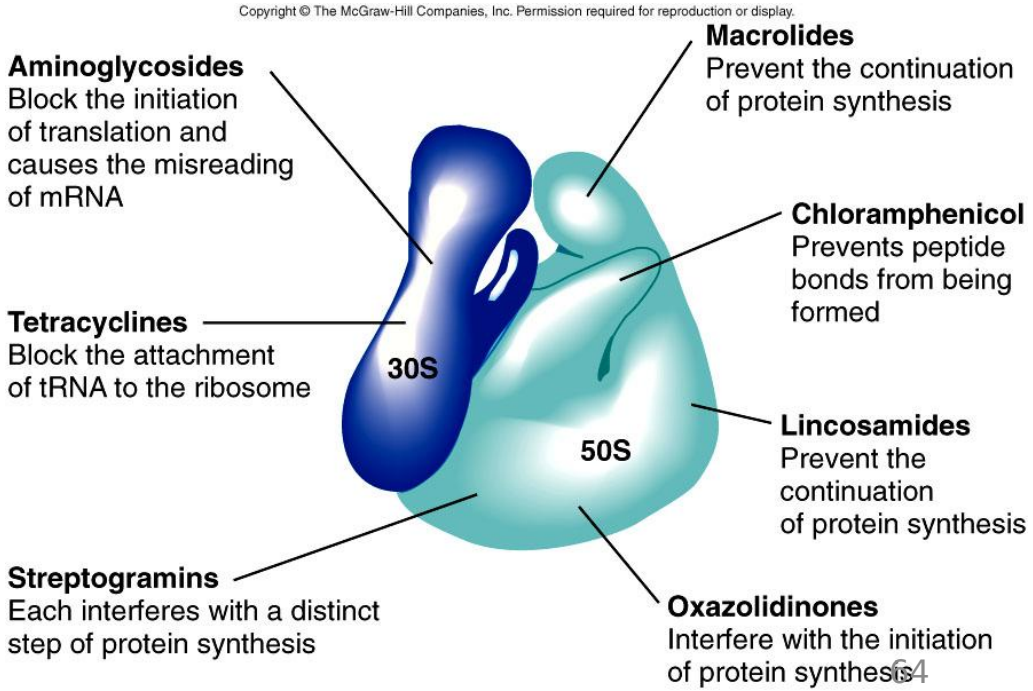
Spectrum of Action

• **Carbapenems: ß-lactams with a broad spectrum of action. Gram positives,** except MRSA. Gram-negatives, *Ps. aeruginosa (except* Ertapenem) and anaerobes. Very efficient against high level cephalosporinase and ESBL. Wide diffusion in the body, especially in the cerebrospinal fluid.

Oral. Primarily for respiratory tract infections.

Mechanisms of Action: Protein Synthesis

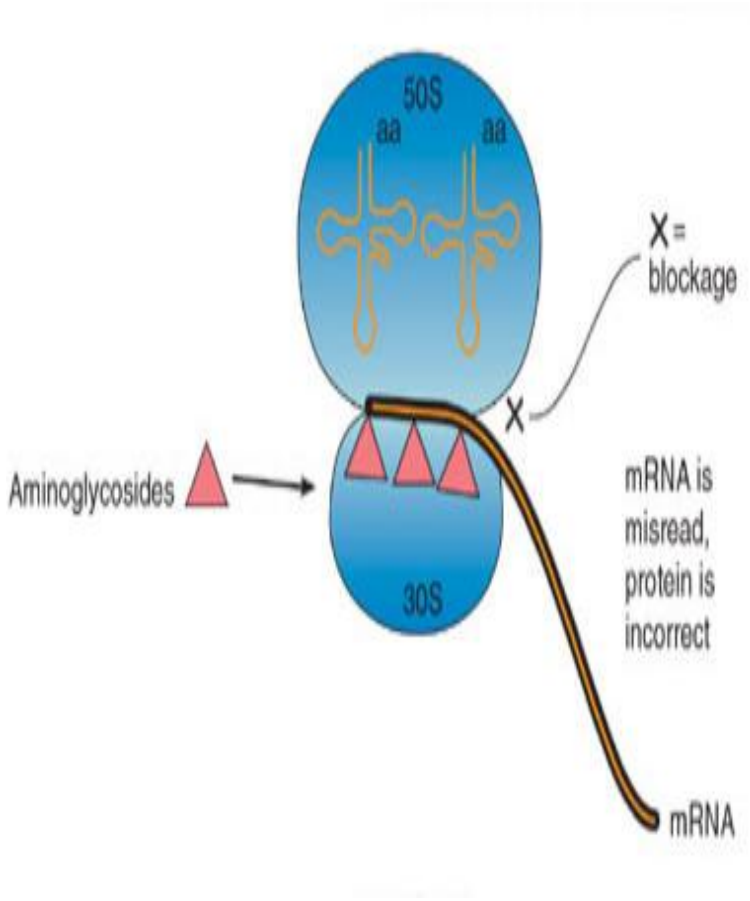
- Inhibition of protein synthesis
  - Structure of prokaryotic ribosome acts as target for many antimicrobials of this class
  - Drugs of this class include
    - Aminoglycosides
    - Tetracyclins
    - Macrolids
    - Chloramphenicol
    - Lincosamides



Mechanisms of Action: Protein Synthesis

Aminoglycosides

- Irreversibly binds to 30S ribosomal subunit
  - Blocks initiation complex of peptide formation
  - Causes/induce misreading of mRNA
- Not effective against anaerobes, enterococci and streptococci
- Often used in synergistic combination with β-lactam drugs
- Examples include
  - Gentamicin, streptomycin, kanamycin ,amikacin and others
- All are bactericidal and more



Cont…

Antimicrobial spectrum

- Aerobic gram negative organism

Pharmacokinetics

- Absorbed very poorly from intact GIT (IM&IV)
- Distributed limited to ECF
  - Bind to renal tissue =nephrotoxicity
  - Peneterate to perilymph &endolymph of inner ear=ototoxicity
- Eliminated primarily by the kidney

Pharmacodynamics

- Aminoglycosides work similarly to tetracyclines by inhibiting protein synthesis and impeding bacterial cell division.

PRECAUTIONSA ND INTERACTIONS

1. Avoid aminoglycosides during pregnancy: risk of foetal ototoxicity.
2. Avoid concurrent use of other ototoxic drugs,e.g. high ceiling diuretics, minocycline.
3. Avoid concurrent use of other nephrotoxic drugs, e.g. amphotericin B, vancomycin, Cephalosporins and cisplatin.
4. Cautious use inpatients with kidney damage.
5. Cautious use of muscle relaxants in patients receiving an aminoglycoside.

Cont…

- Clinical use

  Are used to treat patients with pneumonia, endometritis, urinary tract infection, bacterial enteritis, conjunctivitis, and skin and soft tissue infection caused by aminoglycoside susceptible organisms.

- Dosage form

1. Amikacin
2. Gentamicin
3. Kanamycin
4. Neomycin
5. Streptomycin

- **Adverse effect of aminoglycoside**

1)ototoxicity

A)cochlear toxicity:high frequency hearing loss

Neomycin,kanamycin,amikacin

B)Vestibular toxicity:ataxia,loss of balance

streptomycin and gentamicin

Toxicity is minimized by:

- Short duration of therapy
- Periodic assessment of renal function
- Avoiding concurrent use of ototoxic drugs

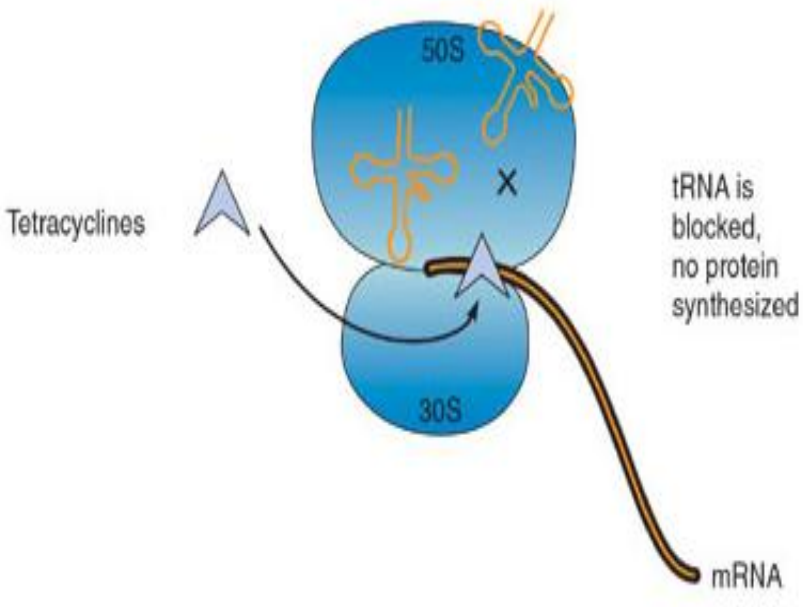
2)Nephrotoxicity

Bacteriostatic inhibitors of protein synthesis

- Tetracyclines
- Macrolides
- Chloramphenicol
- Lincosamides

Mechanisms of Action: Protein Synthesis

- **Tetracyclins**
  - Reversibly bind 30S ribosomal subunit
    - Blocks attachment of tRNA to ribosome
      - Prevents continuation of protein synthesis



Tetracycline

- A semisynthetic tetracycline antimicrobial drug
- **Tetracycline c**an be administered parentrally or orally.
- Gram +ve&-ve aerobic &anaerobic bacteria
- Spirochetes,mycoplasma,rikettsia,chlamydia &some protozoa.



Cont...

- **Pharmacokinetics**

  When tetracyclines are administered quickly distributed throughout the tissue and sometimes penetrate in the CNS. Decreased metabolism occurs with most tetracyclines; then they are eliminated from the body in active form. Elimination occurs most often by glomerular filtration but sometimes may be achieved through bilary excretion routes.

- **Phrmacodynamics**

  Acts by an inhibition of microbial protein synthesis. There by impeding bacterial cell division. Affects a broad spectrum of gram positive and gram positive bacteria and other pathogens including Mycoplasma, Chlamydia, and Rickettsia species. As a group, tetracyclines affect

Cont....

Forms of Drug:

- Doxycycline
- Tetracycline
- Oxytetracycline

Clinical use

- Tetracycline are used to treat respiratory tract infection, bacterial enteritis ,and urinary tract infection caused by tetracycline-susceptible microorganisms. Tetracyclines also are used to treat rickettsial diseases.

Cont...

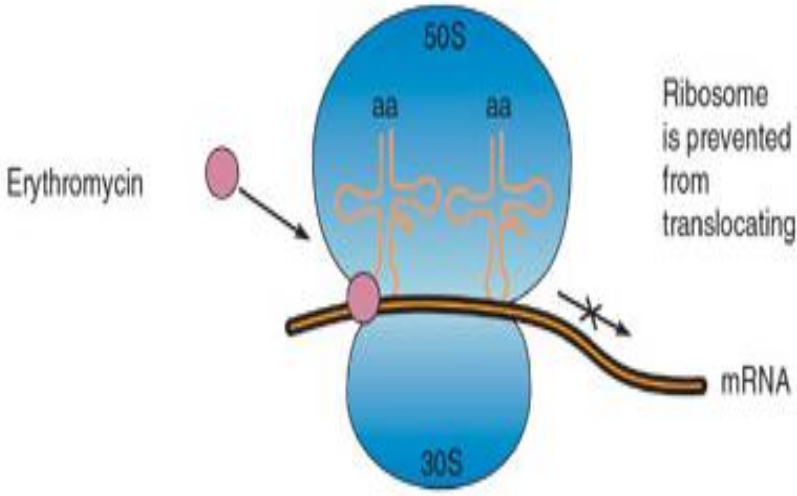
Side Effects: Side effects are rare but can include:

- Gastrointestinal upsets (i.e. Vomiting /Diarrhea)
- Fevers - Hyperthermia (Cats) - Cats are more sensitive to Tetracyclines and may have aberrant increases in body temperature. (Rare)
- Rashes or irritations of mucus membranes (Photosensitization) – Causing lesions on the skin and mucocutaneous tissue when exposed to ultraviolet light. (Rare)
- Affect formation of bone and teeth(cause staining of teeth)in young animals.
- some hepatotoxicity may occur at increased doses;

Mechanisms of Action: Protein Synthesis

Macrolids

- Reversibly binds to 50S ribosome
  - Prevents continuation of protein synthesis
- Effective against variety of Gram (+) organisms
- Often drug of choice for patients allergic to penicillin
- Macrolides most commonly used in



Cont…

- Clinical use

  Macrolides are used to treat patients with upper respiratory tract infection, mastitis, metritis, and foot rot caused by microorganisms susceptible to macrolides.

Cont…

Erythromycin

Mechanism

- Inhibition of aminoacyl translocation reaction and formation of intiation complex=inhibition of protein synthesis via binding to 50s ribosomal RNA;
- bacteriostatic.

Pharmacokinetics

- Decreased by stomach acid

Adminstration

Oral ,topical,parentral

Cont...

- **Adverse side effects**

  These include diarrhea, vomiting and anorexia in small animals after oral administration of erythromycin and tylosin. severe diarrhea may result from oral administration of erythromycin and tylosin to ruminants and horses. Intramuscular injection to erythromycin and tylosin is very painful. Adverse side effects are uncommon in cattle after subcutaneous injection.

Mechanisms of Action: Protein Synthesis

- Lincosamides: clindamycin
  - Binds to 50S ribosomal subunit
    - Prevents continuation of protein synthesis
  - Inhibits variety of Gram (+) and few Gram (-) organisms

Cont…

-**Therapeutic use**

- -Penicillin resistant anaerobic bacteria
- Incombination with aminoglycosides/cephalosporins to treat penetrating wounds of the abdomen

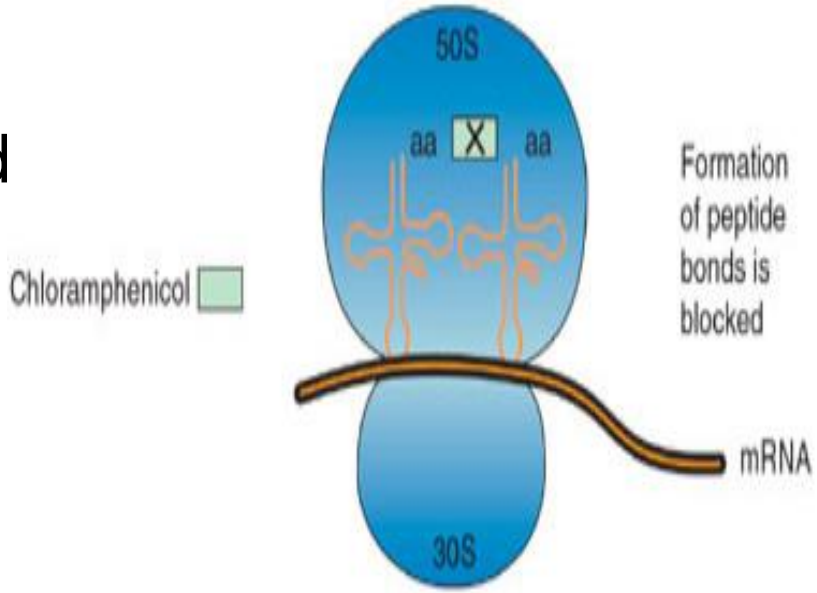
Cont…

Adverse effect

- Nausea, diarrhea & skin rash
- Clindamycin associated colitis

Mechanisms of Action: Protein Synthesis

- **Chloramphenicol**
  - Binds to 50S ribosomal subunit
    - Prevents peptide bond formation
    - bacteriostatic
  - Antimicrobial spectrum: Wide spectrum
- Both aerobic & anaerobic G+ve &G-ve,rickettesiae,*Mycoplasmas, and Chlamydia. It has an excellent therapeutic*



Pharmacokinetics:

- Following oral administration, chloramphenicol is rapidly absorbed
- The drug becomes widely distributed in the tissues including those of the eye.
- The drug is widely metabolized in the liver.

Cont…

Adverse effect

A)GI disturbance

B) bone marrow depression

- Suppression of RBC production : dose related
  - Aplastic anemia

C) superinfection

Mechanisms of Action: Inhibition of nucleic acid synthesis



- **Fluoroquinolone** is bactericidal and affects a wide spectrum of gram negative and gram positive aerobic bacterial pathogens. It is ineffective against anaerobic bacteria and has variable effectiveness against Streptococci.

Cont…

- **Pharmacokinetics:** Fluoroquinolones are available for oral and parentral administration. After administration they are readily absorbed in to tissue and body fluids. Metabolism occurs in the liver ,and elimination occurs via the kidneys in to urine or through bile in to the intestine.
- high tissue penetrability: concentration in lung, muscle, bone and prostate, but CSF is lower.

Cont…

- **Pharmacodynamics**:The broad spectrum of activity offered by the floroquinolones is bactericidal against many different pathogens .The effect of floroquinolones is achived through inhibition of or interference with the bacterial enzyme DNA –gyrase

Cont...

- **Indications:**

Penetration into mammalian cells makes it effective for infections at intracellular sites (Chlamydia, Mycoplasma, Mycobacterium).

Treatment of genitourinary tract infections.

Cont…

- **Contraindications:**

- Not to be used in skeletally immature animals (Including pregnant females) since drug administration may cause microscopic cartilage lesions leading to lameness in weight bearing joints or the body.
- High doses of fluoroquinolones may promote seizure activity. This tendency may be enhanced in epileptics and in animals with structural CNS disease.

Fluoroquinolone

- **Side Effects:**

- Gastrointestinal upsets – Vomiting /Diarrhea
- Retinal Lesions have been seen to occur when doses exceed 2.5-5 mg / kg / day.

Cont...

- **Drug Interactions:**

- sucralfate, magnesium and aluminum containing antacids, and calcium and iron containing dietary supplements decrease oral absorption of Enrofloxacin.
- Simultaneous administration with Chloramphenical may decrease Enrofloxacin efficacy.
- Fluoroquinolones may inhibit Theophyilline metabolism leading to accumulation of toxic (CNS stimulatory) levels of the latter drug.

Mechanisms of Action: Inhibition of Metabolic Pathways

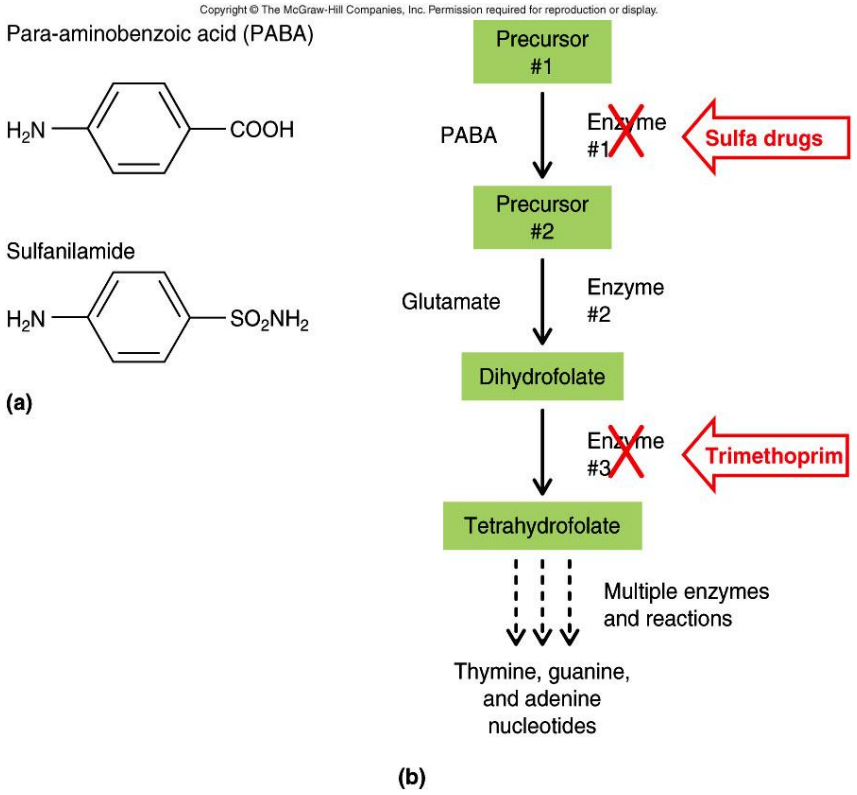
Folate inhibitors

Mode of actions to inhibit the production of folic acid

Mimic PABA

› Antimicrobials in this class include

- Sulfonamides
- Trimethoprim



Sulfonamides

- Sulfonamides or sulfa drugs were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections.
- Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria.
- The most common sulfonamides used in veterinary medicine are sulfadiazine, sulfamethoxazole and sulfadimethoxine.
- Trimethoprim, pyrimethamine,and ormetoprim are commonly combined with sulfonamides to enhance their effect.

Cont...

Pharmacokinetics

- Sulfonamides are rapidly absorbed from GIT. Extent of plasma protein binding differs considerably (10-95%) among different members. The highly protein bound members are longer acting.
- Sulfonamides are widely distributed in the body—enter serous cavities easily. The free form of sulfadiazine attains the same concentration in CSF as in plasma .They cross placenta freely.

Cont…

Clinical use

- sulfonamides are used to treat patients with acute urinary tract infection, respiratory tract infection, wound infection, coccidiosis and foot rot.

Trimethoprim

- Generally exerts a bactericidal action.
- The drug has a relatively broad spectrum of antibacterial activity against gram negative and gram-positive bacteria and generally has a greater effect against aerobic than anaerobic organisms.
- A specific drug in this family (i.e. **Tribrissen)** also inhibits the growth of protozoa (e.g., Coccidia.



Cont…

Form of the drug:

- **Trimethoprim /Sulfadiazine (Tribrissen)**
- **Trimethoprim / sulfamethoxazole (Bactrim)**
- **Ormetoprim / sulfadimethoxine (Primor)**

Route of Administration: Most of this family comes in oral medication; however

Trimethoprim

Precautions / Contraindications:

- **Organ Disease:** Caution should be used in animals with

  extensive liver or kidney disease cautiously.

- **Breed sensitivity:** The drug should be avoided in animals

  with breed susceptibilities and in animals with ocular disorders.

- **Pregnancy:** Caution should be used with

Cont..

Side Effects:

- **Gastrointestinal upsets** (anorexia, vomiting, diarrhea) may result from flora alterations.
- **Anaphylaxis**: Too rapid intravenous administration may lead to a shock-like state with weakness, tremors and collapse.
- **Dry Eye**: Keratoconjunctivitis sicca is a side effect of sulfonamide therapy in dogs.

Interference with cell membrane integrity

POLYPEPTIDE ANTIBIOTICS

- These are low molecular weight cationic polypeptide antibiotics. All are powerful bactericidal agents, but not used systemically due to toxicity .

Clinically used ones are:

- Polymyxin B
- Colistin

Cont…

- They are active against gram negative bacteria only; all except Serratia and Neisseria are inhibited .Both have very similar range of activity, but colistin is more potent on Pseudomonas, Salmonella and Shigella.

Uses

Topically usually in combination with other antimicrobials for skin infections, burns, otitis externa, conjunctivitis, corneal ulcer-

Cont…

- **Mechanism of action**

- They are rapidly acting bactericidal agents; have a detergent-like action on the cell membrane. They have high affinity for phospholipids: gram-negative bacterial cell membrane causing membrane distortion. As a result ions, amino acids, etc. leak out .They may also inactivate the bacterial endotoxin.

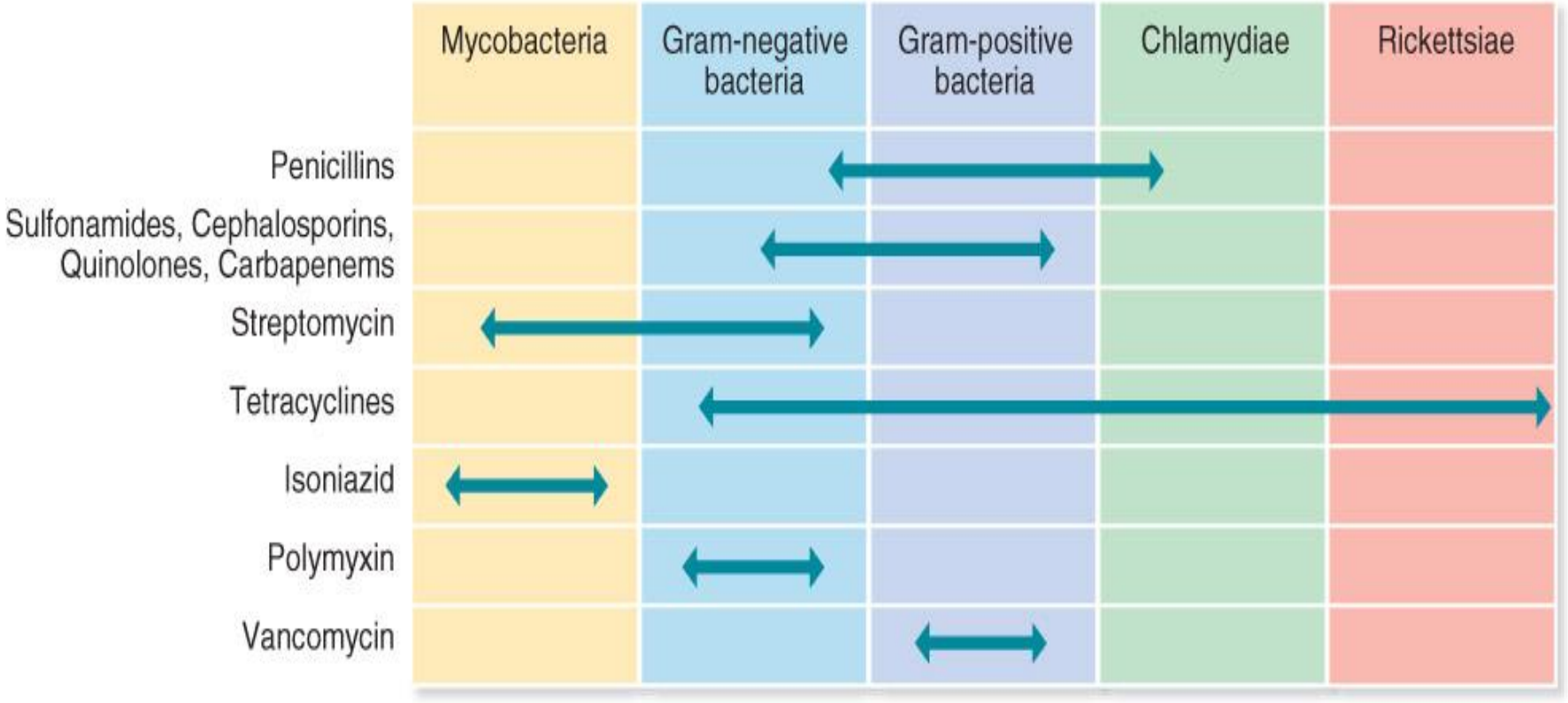
- They exhibit synergism with many other AMAs

Cont…

Adverse effects

- They are safe-no systemic effect or sensitization occurs. A rash is rare.
- Systemic toxicity of these drugs (when injected) is high: marked kidney damage, neurological disturbances, neuromuscular blockade.

Antibiotic spectrum of activity



MECHANISMS OF ANTIBIOTIC RESISTANCE

Definition

- Definition:-Relative or complete lack of effect of antibiotic against a previously susceptible microbe.

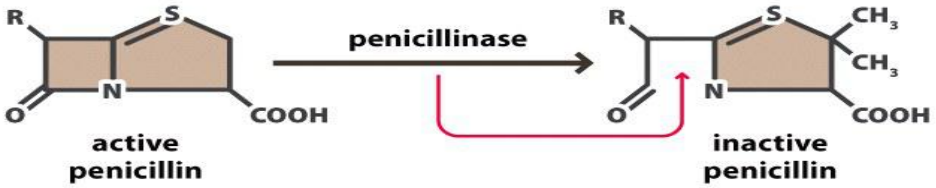
It refers to unresponsiveness of a microorganism
to an AMA .

MECHANISMS FOR ACQUIRING RESISTANCE

- Bacteria use several mechanisms to become antibiotic-resistant:
  - Inactivation of the antibiotic
  - Efflux pumping of the antibiotic
  - Modification of the antibiotic target
  - Alteration of the pathway

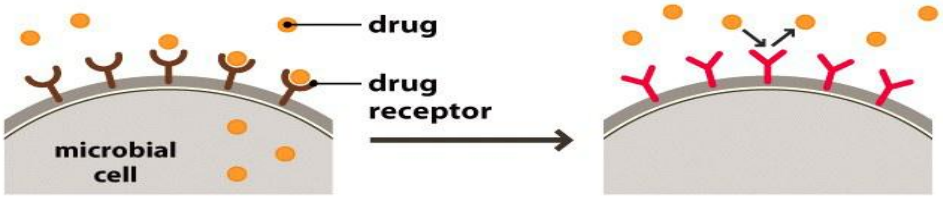
MECHANISMS FOR ACQUIRING RESISTANCE

(a) drug inactivation



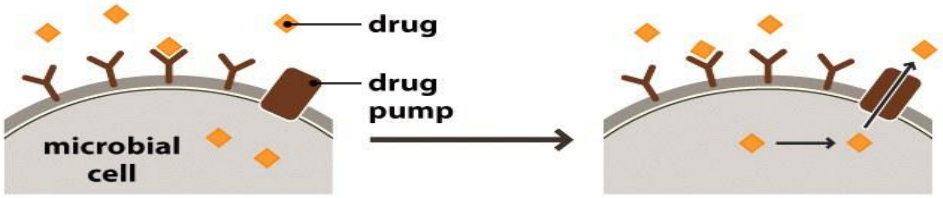
an enzyme (in this case penicillinase) cleaves a portion of the antibiotic molecule and renders it inactive

(b) decreased permeability/change in shape of receptor



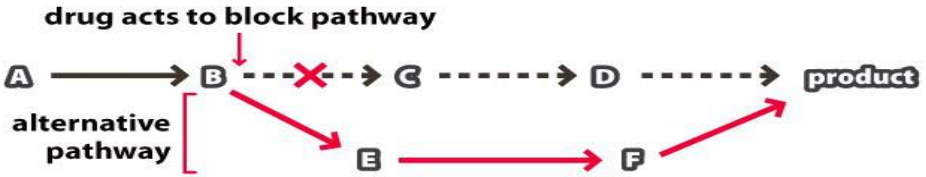
mutations can alter the receptor that transports the drug, so that the drug cannot enter the cell

(c) activation of drug pumps



specialized membrane proteins are activated and continually pump the drug out of the cell

(d) use of alternative metabolic pathway



some drugs block the usual metabolic pathway, organisms can circumvent this by using an alternative, unblocked pathway that produces the required product

Figure 20.2 Microbiology: A Clinical Approach (© Garland Science)

INACTIVATION OF ANTIBIOTIC

- Inactivation involves enzymatic breakdown of antibiotic molecules.
- A good example is β-lactamase:
  - Secreted into the bacterial periplasmic space
  - Attacks the antibiotic as it approaches its target
  - There are more than 190 forms of β-lactamase.
  - E.g of lactamase activity in *E.coli* and *S. aureus*

EFFLUX PUMPING OF ANTIBIOTIC

Efflux pumping is an active transport mechanism.

- It requires ATP.

Efflux pumps are found in:

- The bacterial plasma membrane
- The outer layer of gram-negative organisms

Pumping keeps the concentration of antibiotic below levels that would destroy the cell

OTHER MECHANISMS OF KEEPING ANTIBIOTICS OUT

- Some bacteria reduce the permeability of their membranes as a way of keeping antibiotics out.
  - They turn off production of porin and other membrane channel proteins.
  - Seen in resistance to streptomycin, tetracycline, and sulfa drugs.

MODIFICATION OF ANTIBIOTIC TARGET

- Bacteria can modify the antibiotic's target to escape its activity
- Bacteria must change structure of the target but the modified target must still be able to function. This can be achieved in two ways:
  - Mutation of the gene coding for the target protein
  - Importing a gene that codes for a modified target

..MODIFICATION OF ANTIBIOTIC TARGET

- Bacteria have PBPs in their plasma membranes.
  - These proteins are targets for penicillin.
- MRSA has acquired a gene (*mec A*) that codes for a different PBP.
  - It has a different three-dimensional structure.
  - MRSA less sensitive to penicillins.

..MODIFICATION OF ANTIBIOTIC TARGET

- MRSA is resistant to all β-lactam antibiotics, cephalosporins, and carbapenems.
  - It is a very dangerous pathogen
- *Streptococcus pneumoniae* also modifies PBP.
  - It can make as many as five different types of PBP.
  - It does this by rearranging, or shuffling, the genes.
    - Referred to as genetic plasticity

MODIFICATION OF TARGET RIBOSOMES

- Bacterial ribosomes are a primary target for antibiotics
  - Different antibiotics affect them in different ways.
- Resistance can be the result of modification of ribosomal RNA so it is no longer sensitive.
- Some organisms use target modification in conjunction with efflux pumps.
  - Resistance is even more effective

ALTERATION OF A PATHWAY

- Some drugs competitively inhibit metabolic pathways.
- Bacteria can overcome this method by using an alternative pathway.

Factors promoting drug resistance

Exposure to sub-optimal levels of antimicrobial

Exposure to microbes carrying resistance genes

Inappropriate drug use

- Inadequate surveillance or defective susceptibility assays
- Use of antibiotics in foods-Antibiotics are used in animal feeds and sprayed on plants to prevent infection.

ANTIFUNGAL THERAPY

Anti Fungal Drugs

θ **Fungal Infections:** are termed **mycoses** and divided in to two.

- **Superficial infections** (affecting skin, nails, scalp or mucous membranes)
  - classified in to dermatomycosis and candidiasis.
    - **Dermatomycosis-** skin, hair and nails.
    - **Superficial candidiasis-** yeast like organism infects the mucous membranes of the mouth, vagina or skin.

- **Systemic infections** (affecting deeper tissues and

Drugs used for the treatment of fungal infections

- The antifungal, or antimycotic drugs are divided in to four classes;

1) polyene

2) azoles

3) antimetabolic and

4) superficial agents

1.Polyene antifungal agents

The polyene antibiotics bind with sterols in the fungal cell membrane, principally ergosterol. This causes the cell's contents to leak out and the cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible.

- AMPHOTERICIN B

Mechanism of action

-Binding to ergosterol present in the membranes of fungal cells

Formation of “pores” in the membrane

Leaking of small molecules (mainly K+) from the cells

-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on drug concentration.

Cont…

- **Clinical uses**
- These drugs are used to treat dogs and cats with systemic mycotic infection. Effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans and many strains of Aspergillus.

Cont…

- **Pharmacokinetics**

It gets widely distributed in the body, but penetration in CSF is poor. It binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods. About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile.

Adverse effects: has a low therapeutic index

- Fever and chills
- Renal toxicity
- Hypotension accompanied by hypokalemia

Cont...

Drug Interactions

- Flucytosine has supra additive action with AMB in the case of fungi sensitive to both (AMB increases the penetration of 5-Fc into the fungus). Rifampin and minocycline potentiate AMB action .
- Aminoglycosides, vancomycin, cyclosporine and other nephrotoxic drugs enhance the renal impairment caused by AMB .

Nystatin

- Nystatin is a polyene antibiotic much like amphotericin B.
- It is too toxic for parenteral administration and is only used topically.
- Available in creams, ointments, suppositories, and other forms for application to skin and mucous membranes.
- It is not absorbed to a significant degree from skin, mucous membranes, or the GIT.
- As a result, nystatin has little toxicity, although

Cont…

NYSTATIN

Nystatin may be fungistatic or fungicidal. It often combined with other drug such as neomycine and thiostrepton.

- **Clinical use**

Nystatin is used to treat dogs and cats with candidiasis infection of the skin mucous membranes.

- **Adverse side effects**

Adverse side effects are uncommon

2. AZOLES

- Synthetic fungistatic agents with broad spectrum
- Divided in to two
  - Imidazoles: ketoconazole, miconazole, and clotrimazole
  - Triazoles: itraconazole, fluconazole, voriconazole, and posaconazole.
- MOA:
  - Inhibit C-14 α-demethylase (CYP450 enzyme), thereby blocking the demethylation of lanosterol to ergosterol
  - Inhibition of ergosterol biosynthesis disrupts membrane structure and function

Ketoconazole

- Clinical uses
- These include the treatment of some systemic mycotic infections and some dermatophytosis,as well as candidia infection in dogs and cats.
  - It is distinguished from triazoles by its greater tendency to inhibit mammalian cytochrome P450 enzymes; that is, it is less selective for fungal P450 than are the newer azoles → decline in systemic use
  - Agents that increase gastric pH

Ketoconazole cont'd...

- **Adverse effects**

  Liver toxicity, GI disturbance and pruritis.

  Endocrine effects: decrease libido

- **C/I:** hepatic impairment.

- Drug Interaction

  -H2 blockers, proton pump inhibitiors and antacids decrease the oral absorption by reducing gastric acidity .

Miconazole

- Given orally for infections of the GIT including oropharyngeal candidiasis.
- Most commonly prepared for topical use

Adverse effect

- Miconazole may produce tachycardia, arrhythemia, fever and nausea.

Itraconazole

-Itraconazole is the most recently available triazole for use in vet.medicine.

-Available in both oral and IV formulations

Clinical uses

Itraconazole is used to treat dogs and cats with systemic mycotic infection.

Itraconazole

- Drug absorption is increased by food and by low gastric pH
- Interacts with hepatic microsomal enzymes (lesser degree than ketoconazole)
- Penetrates poorly into the CSF

Adverse effects: GI disturbance, headache, dizziness.

Drug interactions: Oral absorption of itraconazole is reduced by antacids, H2 blockers and proton pump inhibitors

Fluconazole

- good CSF penetration.
- Has the least effect of all the azoles on hepatic microsomal enzymes
- Available in both oral and intravenous formulations
- Lacks the endocrine side effects of ketoconazole.
- Use:
  - Fungal meningitis.
  - Rx of mucocutaneous candidiasis
- Unwanted effects: nausea, headache and skin rashes

3.Antimetabolic antifungal agents

- Flucytosine (5-FC): is a water-soluble pyrimidine analogue
- Has narrow spectrum of action than amphotericin B.
- MOA
  - Flucytosine is taken up by fungal cells via the enzyme cytosine permease.
  - Converted intracellularly to 5-fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP), which inhibit DNA and RNA synthesis, respectively.
  - Human cells are unable to convert the parent drug to its active metabolites
- Has Synergy with amphotericin B

Flucytosine cont...

- Antifungal spectrum:
  - 5-FC is fungistatic
  - Not used as a single agent because of its demonstrated synergy with other agents and to avoid the development of secondary resistance.
  - Its activity is restricted to cryptococcal infection, some Candida spp
- Adverse side effect

These include bone marrow depression, anemia, leucopenia, and thrombocytopenia

4.Superficial antifungal agents

- Griseofulvin
- Narrow spectrum antifungal obtained from Penicillium griseofulvum.
  - Fungistatic.
- MOA:
  - Causes disruption of the mitotic spindle and inhibition of fungal mitosis
  - Therapy must be continued until normal tissue replaced infective tissue.

Griseofulvin cont....

- Poorly soluble in water
- Absorption is enhanced when it is administered along with fatty meal.
- It is a potent liver enzyme inducer.
- Use: Used for the treatment of dermatophyte infections of the skin , nails and scalp.
- Adverse effects-Liver toxicity, GI upset headache, photosensitivity, nausea, vomiting, rashes and hypersensitivity reactions.
- CI: liver failure, pregnancy and hypersensitivity

Cont…

- Griseofulvin is used primarily in dogs and cats and horse as an antifungal. It is administered orally in the form of tablet or powder.
- **Clinical use**

  Griseofulvin is used to treat dermatophytosis.

- **Adverse side effect**

Adverse side effects are uncommon.

Cont…

- Other antifungal Agents

Several agents that have other uses are also affective as topical antifungal drugs. A topical preparation often is used in conjunction with systemic antifungal drugs.

commonly used topically preparations include chlorhexidine, iodine, benzoic acid, salicylic acid, and thiabendazole.

Antiviral drugs

- Antiviral drugs are used to treat patients with viral infection.
- At present, only one antiviral compound has been licensed for use in veterinary medicine: feline interferon-omega
- (IFN-ω), which has a yet undefined mechanism of activity that most probably combines immunostimulatory activity with antiviral activity . human approved antiviral agents are used.
- Despite this, several antivirals licensed for use in human medicine are currently used with the

Cont...

- **Example**
- **Acyclovir**

  -cats with feline herpesvirus 1 (FeHV-1)

  ocular infection
- **Zidovudine** against feline immunodeficiency virus (FIV)

Adverse side effects

Adverse side effects include leucopenia and anemia in treated cats.

Cont…

- **Interferon Alfa-2A,Human Recombinant**

Clinical uses

In vet.medicine, Interferon Alfa-2A is administered orally to treat cats with nonneoplastic FeLV disease.

Adverse side effects

No adverse side effects have been