Antibiotics

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Antibiotics Inhibit Cell Wall Synthesis, Protein Synthesis, Nucleic Acid Synthesis & Metabolism

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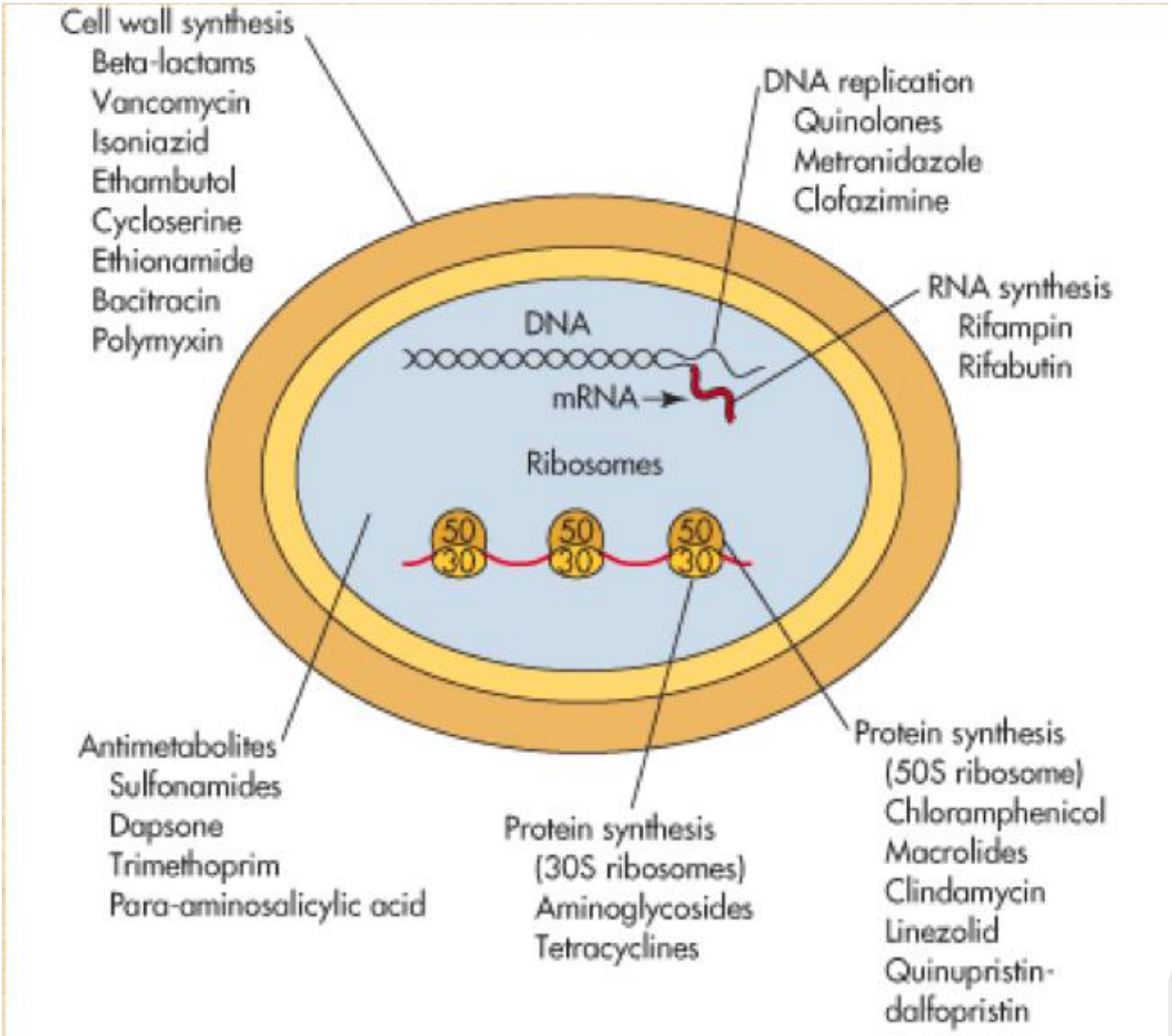


Antibiotics Inhibit Protein Synthesis

30S Ribosomal Subunit

- **Aminoglycosides**
- **Tetracyclines**

50S Ribosomal Subunit

- **Phenicols** (Chloramphenicol , Thiamphenicol Florphenicol)
- **Macrolides**(Erythromycin, Tylosin, Azithromycin)
- **Lincosamides** (Lincomycin & clindamycin)

Aminoglycoside Antibiotics

- Aminoglycosides are mostly **bactericidal** drugs.
- Share Chemical, Antimicrobial, Pharmacologic, Toxic chchs.
- **Streptomycin, Neomycin, kanamycin, Amikacin, Gentamicin, Tobramycin, Netilmicin & Paromomycin**
- **Bactericidal to treat aerob Gram – ve bacteria**
- **Anaerobic bacteria are resistant**
- All inhibit protein synthesis of bacteria by attaching to and inhibit function of 30 S ribosomal subunit .

Aminoglycosides (Aminocyclitols)

Classes:

- **Narrow-spectrum: e.g. Streptomycin, Dihydrostreptomycin**
  - Mainly active against **aerobic gram-negative bacteria.**
- **Expanded-spectrum :**

Neomycin, Framycetin , Kanamycin & Paromomycin

- Broad spectra include **gram-negative aerobic bacteria,** and **gram- positive.**

Gentamicin, Tobramycin, Amikacin, Sisomicin, Netilmicin with extended spectra include ***Pseudomonas aeruginosa*.**

- **Miscellaneous Aminogl: e.g. Apramycin & Spectinomycin**

(mechanism of action and antibacterial spectrum)

General Properties of Aminoglycosides

- Chemically, aminoglycoside characterized by Aminocyclitol gp, attached with amino sugars in glycosidic linkage.
- All aminoglycosides more active in **alkaline pH**.
- **The sulfate salt** is used for PO or parenteral administ.

Mode of Action:

- The main intracellular site of action of Ags. is the ribosome, w. **irreversibly** bound by Ags, at the 30 S.→ interfere with protein synthesis **(concentration dependent in actions)**

General Properties of Aminoglycosides

Synergism when **Ags. & β-lactam (penicillins & cephalosporins)** used in combination (The cell-wall injury induced by β-lactam allows increased uptake of Agl. by bacteria).

Ags. associated with a **Postantibiotic effect** in gram-negative (*E coli*, *Klebsiella pneumoniae*, *P aeruginosa*). The effect lasts 2–8 hr after exposure & allows for longer dosing intervals.

Once-daily dosing used to enhance both efficacy & safety.

All produce ototoxicity and nephrotoxicity.

Antibacterial Spectra

- **1- Streptomycin** & **dihydrostreptomycin** are narrow spectra.
  - **Gram-negative bacilli** [*Actinomyces bovis*, *Pasteurella* spp, *E coli*, *Brucella* spp. Salmonella spp, *Campylobacter*, *Leptospir*
  - ***Mycobacterium tuberculosis*** also sensitive to streptomycin**.**
- **2- Neomycin, framycetin, & Kanamycin have broader spectra** against gram-negative bact
{ ***Ecoli* ,*Salmonella*, *Klebsiella*, *Enterobacter*.**
- **3- Gentamicin, Tobramycin, Amikacin, Sisomicin, & Netilmicin** have **spectra include *Pseudomonas aeruginosa &*** staphylococci spp. are susceptible.
- **Anaerobic bacteria are resistant**

Pharmacokinetic features

- **Absorption:**
  - Aminoglycosides **poorly absorbed** from **healthy GI tract** (<10%), however increased in enteritis & in neonate .
  - **Rapid Absorption from IM injection sites and nearly complete (>90%).**
  - **Short dosing intervals are contraindicated for all agls → Once-daily dose indicated for safety .**

- **Distribution:**
  - **Limiting** distribution to extracellular fluids, with minimal penetration into most tissues Except **Renal cortex of kidneys & the inner ear**→ agls increasingly accumulate
  - Ags. not appreciably bound to plasma proteins (<20%).

- **Ags. excreted unchanged in urine** by glomerular filtration.
- Excessive accumulation in renal cortex → nephrotoxicity.
- Ags administered once daily → minimizing the risk of nephrotoxicity.

Therapeutic Indications:

- Ags commonly used to control local & systemic infections caused by susceptible aerobic gram-negative bacteria.
- Used topically in ears & eyes and via intrauterine to treat endometritis

Adverse Effects and Toxicity:

- **Ototoxicity, neuromuscular blockade, & nephrotoxicity .**
- Ototoxicity, manifest as either auditory or vestibular dysfunction.
- 0totoxicity is **greatest** for Gentamicin, Sisomicin, Neomycin, and **least** for **Netilmicin**.

Streptomycin (Narrow spectrum)

Source: ***Streptomyces griseus*** *i*n 1944

Dihydrostreptomycin (more toxic)→ (not use in USA)

Antibacterial Spectra:

- **Narrow spectra** with limited efficacy by bacterial resistance.
- **Bactericidal** against Gram-negative bacilli (e.g., *Actinomyces bovis, Pasteurella spp., Brucella* spp, *E.coli*, & *Salmonella* spp,
- ***Mycobacterium tuberculosis*** **also sensitive to streptomycin.**

Clinical Uses:

- **Tuberculosis for long term, used with Isoniazid**.
- **Bovine mastitis : intramammary infusion with penicillin**.
- **Bacterial enteritis : due to enter bacilli infection (E. coli).**

Streptomycin sulphate

Mode of Action :

- **Inhibit protein synthesis by prevent Amino acids polymerization → so aid in ribosomal messenger of RNA to misread the correct amino acid for peptide synthesis.**
- **Prevent amino acids polymerization → Misreading of mRNA.**
- **Poorly absorbed from GI tract .**
- **Readily absorbed After I/M adm. (Not given I/V or S/C)**
- **Rapid & complete absorption from IM site**
- **Excreted in milk→ used in combination with penicillin for mastitis**
- **Toxicity: disturbance of vestibular function & loss of balance.**
- **Affect 8th cranial nerve cause auditory impairment , deafness (irreversible)**
- **In high doses → a nephrotoxic effect.**

Neomycin - Kanamycin
Amikacin - Paromomycin

- **Constitute a chemically & biologically closely related group**
- A **broad spectrum bactericidal** antimicrobial drugs.
- With significant **nephrotoxicity** & **ototoxicity**.
- **Clinical uses:**
  - **Kanamycin** prefered for **parenteral** admin**. because less toxic than neomycin (for gram -ve urinary tract infections)**
  - Orally for **Enterobacteriaceae** & **E. coli intestinal infections.**
  - **Paromomycin** used for **intestinal amaebiasis**

Neomycin sulphate

- **Bactericidal Broad spectrum** ab.
- Act **against E coli, kelbsiella, proteus, *Staph aureus*, staph. *albus* & streptococus.**

Clinical Uses:

- **Orally: Coliform enteritis .**
- **I/M: urinary tract infections with coliforms.**
- **Topical**: ttt of **coliform mastitis (**mixed infection with **gram +ve strept , staph)** with **Cloxacillin**
- **Treatment of Abscesses** .
- **As topical oint. for wounds, ulcerative dermatitis, otitis media.**
- **Neomycin + bacitracin** used for ttt **infected burns & abscesses.**
- **Toxicity: ototoxic & nephrotoxic.**

Gentamicin
(Bactericidal Broad spectrum)

- **Act against Pseudomonas sps , Klebsiella, *E. coli* & Staph..**
- **Transmissible resistance**: Gentamicin resistant→ become resistant to Neomycin, Streptomycin, kanamycin.
- **Widely distributed, binding with plasma protein 25-35%.**
- **Excretion:** mainly in urine , selective cumulative effect in renal cells→ Nephrotoxicity.
- **Toxicity: Neuromuscular paralysis** - **Ototoxicity ,** Nephrotoxicity.
- **Not used in food producing animals.**

Tetracyclines

- **Broad-spectrum bacteriostatic antibiotics.**
- **Classes:**
  - 3 naturally occurring Tetracyclines (oxytetracycline, chlortetracycline, dimethyl chlortetracycline).
  - Semi synthetically (Tetracycline, rolitetracycline, Methacycline, Minocycline, Doxycycline, lymecycline).
- According to Elimination times:
  - **Short-acting** (Tetracycline, Oxytetracycline, Chlortetracycline).
  - **Long-acting** (doxycycline & minocycline).
  - Glycylcyclines represented by Tigecycline, is the newest class,

General Properties of Tetracycline

- Crystalline, yellowish, amphoteric subs. form salts in aqueous sol.
- Form poorly **soluble chelates** with **bivalent** & **trivalent** cations(**calcium, magnesium, aluminum, and iron)** .

Mode of action:

- Antimicrobial activity of tetracyclines due to reversible binding to the bacterial 30S ribosomal subunit, specifically at aminoacyl-tRNA acceptor ("A") site on mRNA ribosomal complex→ prevent ribosomal translation → Inhibit protein syn.

Antimicrobial Spectra

- All tetracyclines are **broad spectrum**, both **aerobic** & **anaerobic** **gram-positive** & **gram-negative bacteria**, **Mycoplasmas**, **rickettsiae, chlamydiae**, Protozoa (amebae) .
- Tetracyclines are **bacteriostatic** → responsive host-immune defense.
- **The hydrochloride is the most common salt form, Except doxycycline hyclate or monohydrate.**
- Cross-resistance among **Tetracyclines, Doxycycline, Minocycline** .

Pharmacokinetic Features

Absorption:

- **Tetracyclines absorbed in upper small intestine after oral adm. → Effective Bl. Conc. in 2–4 hr.**
- **GI** absorption impaired by **Sod bicarbonate, Aluminum hydroxide, Magnesium hydroxide, iron , calcium salts, milk & milk products.**
- **Should not be administered PO to ruminants (poorly absorbed & depress ruminal microflora activity).**
- **Tetrac. Sol. can be administered IM and IV.**
- Absorption of oxytetracycline from **IM sites** produce **a long-acting effect** (delayed) .

Distribution

- **Tetracyclines distribute rapidly in all tissues and body fluids after parenteral adm. → high conc. in kidneys, liver, bile, lungs, spleen, bone**
- **Deposited in growing bones & teeth of young animals because Tetracycline irreversibly chelate calcium ions.**
- **Doxycycline & Minocycline (The more lipid-soluble tetracyclines) penetrate the blood-brain barrier, and CSF.**
- **Doxycycline is the most extensively distributed.**
- **Bound to plasma proteins (30%, oxytetracycline, 60% tetracycline, and 90% doxycycline).**

Biotransformation

- Biotransformation of tetracyclines is limited .
- About one-third of a given dose excreted unchanged.
- Doxycycline and minocycline more extensively biotransformed than other tetracyclines .

Excretion:

- Tetracyc. excreted via the **kidneys** 50–80% (glomerular filtration) and the **GI tract** (biliary elimination) ~10–20%
- Doxycycline eliminated in feaces.
- Tetracyc. eliminated in **milk**; peak conc 6 hr after parenteral dose & still present up to 48 hr later.
- Concentrations in milk ~50%–60% of plasma conc .
- Tetracyc also excreted in saliva and tears.

Therapeutic Indications

- **Tetracyclines used to treat both systemic & local infections as respiratory infections, CRD (mycoplasma), Coryza. Mastitis, Pasteurellosis. Coliform-salmonella (white scour).**
- **Topically for foot.-Rot.**
- **Specific conditions include infectious keratoconjunctivitis in cattle, Chlamydiosis, actinomycosis & Anaplasmosis, ehrlichiosis(doxycycline).**
- Minocycline & doxycycline effective against **staph. aureus.**
- Administered PO **bid-tid (every 12–24 hr. for** doxycycline, minocycline.

Tetracyclines used for other purposes

- Chlortetracycline serve as growth promoters in animal feeds**.**
- used to **delineate tumors** by **fluorescence** because of its affinity for bones & teeth.
- used to reduce risk of adverse effects & to enhance killing of adult **heartworms** and/or **microfilaria** before adulticide ttt.

Adverse Effects &Toxicity:

- Superinfection by non-susceptible pathogens(fungi, yeasts) →
- **GI disturbances after either PO or parenteral adm.**
- **Severe & fatal diarrhea in horses receiving tetracy.**
- Doses administered **PO** to ruminants disrupt microflora activity.
- Monogastric animals reduces the synthesis of **vitamins B , K.**
- **Rapid IV inj.** → **hypotension & collapse(**chelate calcium).
- Cause **yellowish** then **brownish** discoloration in Teeth .
- **Hepatotoxic effects.**

Antibiotics that bind to 50 S ribosomal subunit

Chloramphenicol & Macrolides

- **Chloramphenicol**
- **Source: From 1949 completely synthetic antibiotic**
- **Broad spectrum- Bacteriostatic against gram(+) ve & (-) ve aerobic bacteria and rickettsia.**
- Inhibit protein synthesis By binding to **50S** ribosomal subunit
- Rapidly & completely absorbed after oral adm,
- For parentral inj. widely distributed to all B. fluids(CNS, CSF.)
- used for treatment of CNS infections.
- Drug of choice in ttt of Typhoid fever, paratyphoid (Salmonellosis
- **Toxicity: Bone** marrow depression (anaemia - Aplastic anaemia

Phenicols

Chloramphenicol - Thiamphenicol- Florfenicol

- **Chloramphenicol is a highly effective broad-spectrum antibiotic.**
- **Prohibited for use in food-producing animals (USA & Canada).**
- **Thiamphenicol is less effective but safer than chloramphenicol**
- **Florfenicol, a thiamphenicol derivative & significantly more active**
- **Florfenicol approved for use in cattle.**

- **Mode of Action:**
  - **inhibit microbial protein synthesis by binding to the 50S subunit of the 70S ribosome & impairing peptidyl transferase activity. bacteriostatic effect**
- **Antimicrobial Spectra:**
  - **Gram +ve & gram-ve bacteria, anaerobes (*Bacteroides fragilis)*, *Rickettsia* & *Chlamydia* spp. Efficacy against Salmonella spp.**

Pharmacokinetic Features

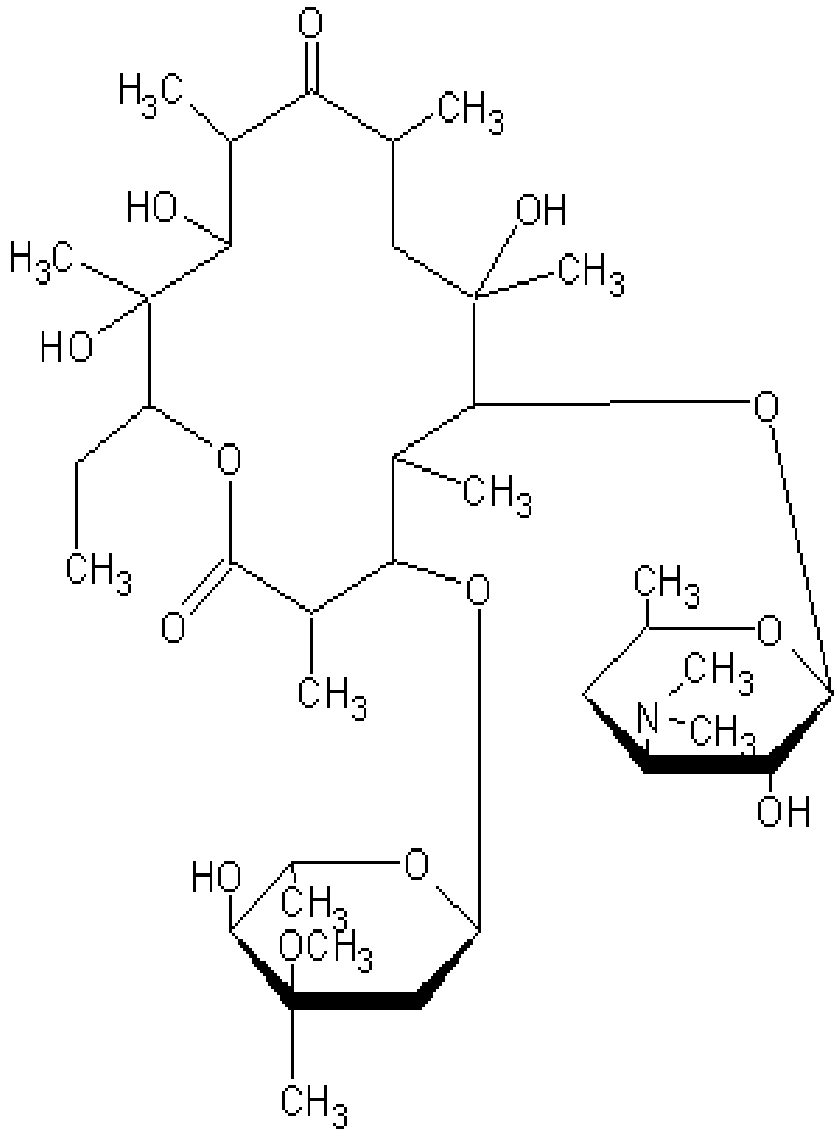
- Thiamphenicol is a derivative of Chloramphenicol less active (1-2 less)
- Thiamph. Not induce irreversible bone marrow depression in human.
- Rapidly Absorption from upper GIT after PO adm. to non - ruminant a
- Because ruminal microflora reduce the nitro gp →chloram inactivated in ruminoreticulum and is **not available for absorption**.
- Diffuses into all tissues (including brain); highest conc in kidneys, liver, bile & body fluids (CSF) . bound to plasma albumin (60%).
- Milk conc ~50% those of plasma but higher in mastitis.
- undergo extensive hepatic metabolism ; by glucuronide conjugation.
- Excreted in urine. Enterohepatic cycling prolong Bl. conc. in herbivores.

Florfenicol (Veterinary—Systemic)

- **Florfenicol is an analogue of Thiamphenicol**
- **A broad-spectrum, bacteriostatic antibiotic active against *Mannheimia (Pasteurella) haemolytica, P. multocida- Haemophilus – Enterobacter, E. coli, Klebsiella pneumoniae, Salmonella typhi, & Shigella dysenteriae.***
- **the fluorine molecule reduces bacterial resistance(prevents acetylation→ enhancing the efficacy).**
- **Available as injectable sol. intended for IM use.**
- **Rapidly absorbed after PO adm.**
- **Penetrate the milk of lactating cows.**
- **Eliminated by the kidneys**.
- Treat both systemic & local infections. Salmonellosis & *Bacteroides* sepsis .
- Approved for treatment of **bovine respiratory disease**(Pneumonia in cattle).
- **Withdrawal time for florf.= 28 days→ should not be used in dairy cattle**
- **Do not induce irreversible bone marrow aplasia in humans**
- Thiamphenicol & Florfenicol cause reversible bone marrow depression.

Macrolide Antibiotics

- **Macrolide ch. by macrocyclic lactone ring + attached deoxy sugars**
- **Erythromycin → prodrug 1952**
- **Erythromycin,** clarithromycin, azithromycin,
- **oleandomycin**, spiramycin, & **tylosin**
- **Lincosamides:** lincomycin, & clindamycin



Macrolides have a large lactone ring in structure.

More effective against gram-+ve than gram - ve bacteria.

Active against Mycoplasmas & rickettsia.

- **Classes**
- Macrolides 3 classes, depending **size of macrocyclic lactone ring**.
- **1- Erythromycin, oleandomycin & troleandomycin** → belong to **the 14-membered ring gp.**

  2-Azithromycin (synthesized from erythromycin) & **Gamithromycin** are the **15-ring members → (azalides)** .

  3-**Spiramycin, Josamycin, Tylosin & Tilmicosin** (synthesized from tylosin) are Of the **16-membered ring gp.**

  Tulathromycin contains 3 amine rings & classified as **a triamilide.**

Macrolides General Properties

- **Colorless, crystalline subs. , poorly water soluble, dissolve in organic solvents.**
- **MOA: interfere with bacterial protein synthesis by inhibiting 50S subunit of the ribosome.**
- **The effect** confined to **rapidly dividing bacteria** & **mycoplasmas**.
- **Bacteriostatic** but **bactericidal** at high conc.
- **More active at higher pH ranges (7.8–8).**
- **Time dependent** in antimicrobial efficacy.
- **Immunomodulatory effects to treat respiratory infections.**
- **A Prokinetic effect (increase motility of upper gut).**
- **Cross Resistance with other Macrolides.**

Antimicrobial Spectra

- **Macrolides active against aerobic & anaerobic gram-positive bacteria.**
- **In general, macrolides not active against gram-negative bacteria, Except**
- **Tilmicosin, Gamithromycin, Tulathromycin, have broader spectra include *Mannheimia haemolytica, Pasteurella multocida*, *Haemophilus, Neisseria* spp & *also Helicobacter.***
- **Azithromycin** include *Bordetella* in spectra
- ***Bacteroides fragilis* also susceptible .**
- **Macrolides** active against **Mycobacterium, , *Mycoplasma*, *Chlamydia*,and *Rickettsia* sp**
- **Macrolide not against protozoa or fungi.**

Pharmacokinetic Features

- **Absorption:**
- Macrolides absorbed from the GI tract.
- Enteric-coated oral preparations , or stable salts or esters (stearate, propionate) used.
- Erythromycin & tylosin administered IV or IM. , except in swine, oral tilmicosin preparation available.
- Rapid Absorption after injection , but pain & swelling at inj. sites.
- **Distribution:**
- Macrolides widely distributed in tissues (spleen, liver, kidneys, and particularly the lungs).
- Accumulate within cells, macrophages(≥20 times plasma conc.).
- concentrate in bile & milk.
- Up to 75% of dose is bound to plasma proteins.
- **Excreted** mainly in bile & undergo enterohepatic cycling.

Therapeutic Indications

- **Macrolides regarded as alternatives to penicillins for treatment of streptococcal & staphylococcal infections.**
- **For upper respiratory tract infections, bronchopneumonia, bacterial enteritis, metritis, pyodermatitis, urinary tract infections,& arthritis.**
- **For treatment of *Rhodococcus* respiratory tract infections in foals.**
- **Formulations to treat mastitis have advantage of a short withholding time for milk (conc. in milk is greater several times than in plasma, in mastitis.**
- **Tilmicosin, gamithromycin, & tulathromycin approved for bovine respiratory diseases associated with *Mannheimia haemolytica*,& *Pasteurel multocida*.**
- **In swine, Tilmicosin added to feed or water for control of swine respiratory d.**
- **Horses are sensitive macrolide-induced GI disturbances that serious & fatal.**
- **Tilmicosin characterized by cardiac toxicity. Cattle died after IV inj.**

Adverse Effects and Toxicity

- **Oleandomycin with streptomycin for mastitis.**
- **Spiramycin: for mycoplasmosis .**
- **Tilmicosin: long-acting for use in bovine respiratory diseases due to Pasteurella haemolytica & mycoplasma.**
- **Tilmicosin characterized by a 28-day withdrawal time & should not be used in any species other than adult cattle .**
- **Not approved for use in lactating cattle, .**
- **Erythromycin estolate be hepatotoxic & cause cholestasis → induce vomiting & diarrhea.**
- **Macrolides should not used with chloramph. or lincosamides, [compete for the same 50S ribosomal binding site],**

Tylosin

- **Tylosin has a wide safety margin in all animal species.**
- **Stable for 3 months**
- **Against gram(+)ve & effective against PPLO, spirochetes and some gram(-)ve bacteria**
- **Administered in drinking water ,S/C or I/M.**
- **Cross resistance with erythromycin.**
- **Used for treatment of pneumonia, upper respiratory tract infections , foot rot and metritis.**

Lincosamides

Llincomycin & clindamycin

- **Bacteriostatic against gram (+) ve , mycoplasma & anaerobic bact.**
- **MOA: Lincomycin & clindamycin bind to the 50S subunit of bacterial ribosomes and suppress protein synthesis.**
- **Most gram (-)ve bacteria are resistant .**
- **Clindamycin: more active for anaerobes (***Bacteroides* spp **).**
- **Lincomycin** incompletely absorbed from GIT, **Absorption from IM inj.**
- **Lincosamides** widely distributed in fluids and tissues, including bone **.**
- **clindamycin bound to plasma proteins(90%).**
- **Excreted** in bile , urine and **Milk ; important excretory route.**

Therapeutic Indications

- **Lincosamides indicated for infections caused by gram-positive bacteria (strept,& staph., and for anaerobic pathogens.**
- **Clindamycin approved for treatment of infected wounds, abscesses, and dental infections in cats & dogs .**
- **Clindamycin used to treat toxoplasmosis.**
- **No organ toxicity , but GI disturbances occur.**
- **Clindamycin-induced pseudomembranous enterocolitis or disruption of GI flora .**
- **clindamycin is contraindicated for use in horses(severe & even fatal colitis) and ruminants.**

Polypeptide Antibiotics
Polymexins B (Colistin)

- **Polymexins** narrow spectrum antibiotic
- Produced by bacillus polymaxima (stable)
- **Bactericidal** effect on **Gram-negative bacilli,** especially on **pseudomonas** - E.**coli-** and **Klebsilla**
- **MOA:** disrupt the structure of bacterial cell membrane by interacting with its phospholipids
- Not absorbed from GIT but absorption after s/c or I/M
- Polymyxins highly neurotoxic and nephrotoxic,

Polypeptide Antibiotics
Polymexins

Bactericidal narrow spectrum include polymyxin B & polymyxin E, or colistin.

used topically, or PO for treatment of intestinal infections due to toxicity.

MOA: interact with phospholipids in bacterial cell membranes → disrupt permeability & function.

Effective against gram-negative bacteria [*Enterobacter*, *E. coli*, *Klebsiella*, *Salmonella*, *Pasteurella*, *Bordetella*, *Shigella*, and *Pseudomonas* spp.] .

Reduce the activity of endotoxins → used for endotoxemia.

Act synergistically with potentiated sulfonamides , tetracyclines,

Polymexins (B)
Colistin

Polymyxins not absorbed after PO or topical administration.

polymixins undergo renal elimination .

Nephrotoxic and neurotoxic → systemic therapy avoided.

Polymyxins used PO against susceptible intestinal infections.

Anti-endotoxin binding activity → additional therapy .

Topical application is common, eg, for otitis externa.

The main indication for parenteral use is life-threatening infection due to gram –(ve) b. or resistant *Pseudomonas* spp .

Polymyxin B is a potent histamine releaser.

Bacitracin

Bacitracin A is the main active component of commercial Bacitracin

Bacitracin used either topically or PO.

Bactericidal interfere with cell membrane function by preventing the formation of peptidoglycan strands.

Bactericidal activity require the presence of divalent cations as **zinc.**

Bacitracins broad spectrum but used to treat gram-positive infections.

Resistance is rare.

Bacitracin used in combination with **neomycin** and **polymyxins** to enhance the antibacterial spectrum.

Not absorbed from the GI tract & not used systemically (nephrotoxicity.

used locally in wound powders and ointments, dermatologic preparations, eye and ear ointments,

used as feed additives in swine & poultry rations for growth promotion.