TETRACYCLINES
&
CHLORAMPHENICOL

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TETRACYCLINES

Tetracyclines

- A group of drugs with common basic chemical structure (4 ringed structure), antimicrobial activity and pharmacologic properties.
- **Short acting:** Chlortetracycline, Tetracycline, Oxytetracycline.
- **Intermediate acting:** Demeclocycline, Methacycline.
- **Long acting:** Doxycycline and Minocycline.

Antimicrobial activity

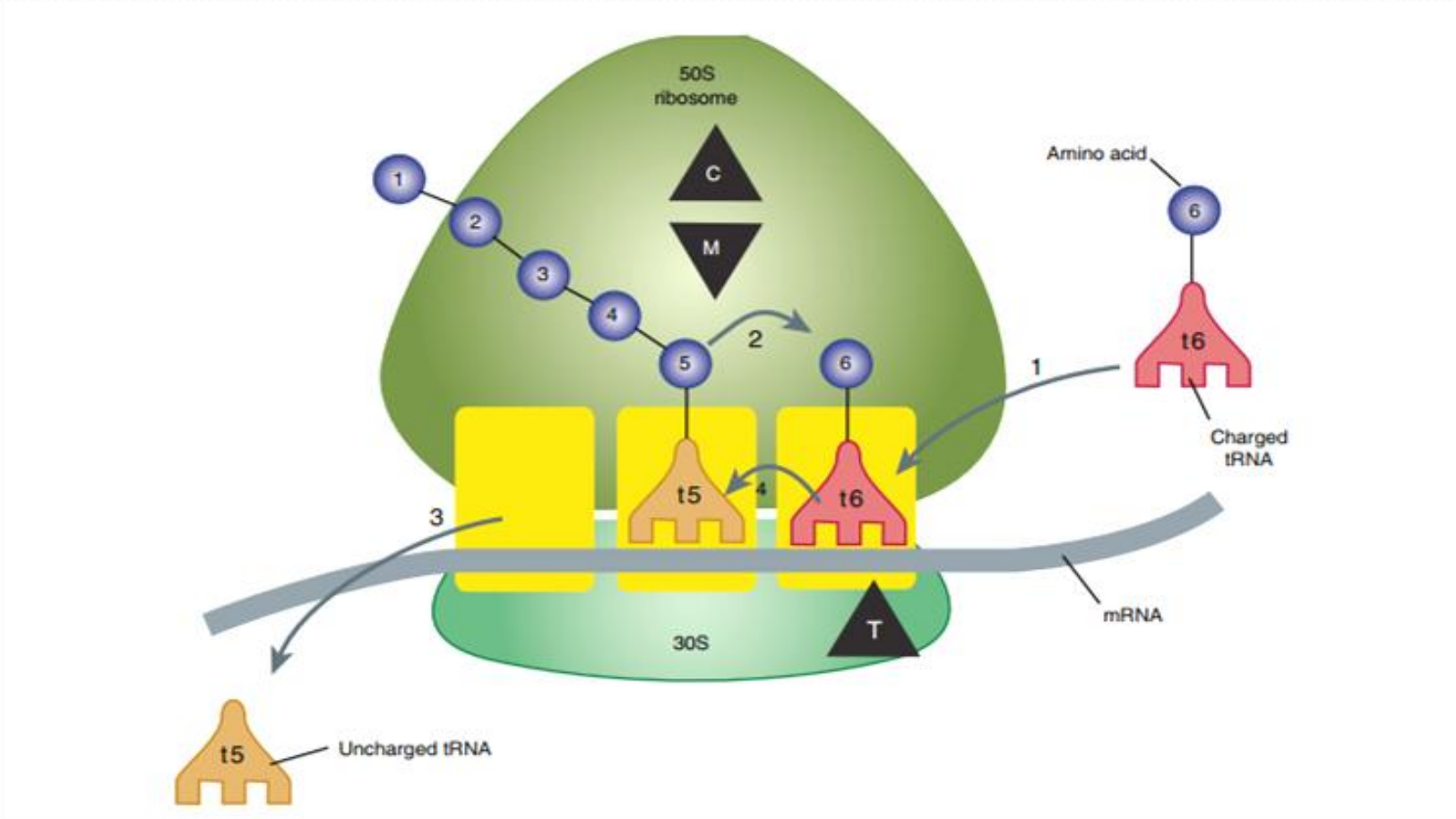
- Tetracyclines are **broad-spectrum antibiotics**.
- Against both **aerobic** and **anaerobic. gram-positive** and **gram-negative** bacteria including *Rickettsiae, Chlamydiae, Mycoplasmae, Legionalla.* They are also active against some **protozoa** (ameba)
- Tetracyclines are more active against gram-positive than gram-negative microorganisms.
- However, these agents are rarely indicated for infections caused by gram-positive bacteria because of the problem of **resistance** and the **availability of superior antibiotics**.

Mechanism of action

- Tetracyclines are bacteriostatic.
- They **inhibit protein synthesis** in susceptible organisms by binding to 30 S ribosomal subunits., they prevent access of aminoacyl- tRNA to the acceptor site on mRNA- ribosome complex and prevent the addition of new amino acids to the growing peptide chain.
- **To reach the ribosomes, the transport of tetracyclines requires two processes:**

1. Passive diffusion.
2. Active-energy dependant process.

Steps in bacterial protein synthesis and target of several antibiotics:



Resistance

- The main resistance **mechanisms** include:

1. **Decreased accumulation** of tetracyclines as a result of decreased influx of the antibiotic or increased efflux of the drug via an energy-dependent pathway.
2. Decreased access of tetracyclines to the ribosome because of the presence of **ribosome protection proteins** (interfere with tetracyclines binding to ribosome) .
3. **Enzymatic inactivation of tetracyclines**.

Pharmacokinetic

Absorption:

- Most of tetracyclines are adequately but incompletely absorbed from the GIT.
- Absorption is impaired by food, by dairy products and antacids which contain multivalent cations and iron salts.
- Tetracyclines ***chelate metal ions*** (Ca^{+2}, Mg^{+2} , Al^{+3} and Fe^{+2}) forming non absorbable complexes (As aresult of chelation tetracyclines are bound to and damage growing bones and teeth) .

Distribution:

- Tetracyclines have wide distribution, entering most fluid compartments, crossing placenta to fetus and appearing in milk.
- **Minocycline** in unique among tetracyclines in that it reaches a high concentration in tears and saliva sufficient to eradicate the meningococcal carrier state.

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Excretion :

- Excretion of most tetracyclines **is-by-two** routes, one via biliary enterohepatic circulation then feces and the other via kidney by glomerular filtration.
- Most of tetracyclines will accumulate if renal function is impaired.
- **Doxycycline** is an exception as it is excreted only via the **biliary system** in feces and therefore does not require dose adjustment in renal failure.

Adverse effects

1- GIT:

- Irritation of GIT following oral administration.
- Epigastric distress, abdominal discomfort; nausea, vomiting, diarrhea may occur.
- In severe cases tetracyclines suppress enteric flora; this leads to overgrowth of **Clostridium difficile** and gives rise to ***psendomembranous colitis*** a potentially life-threatening complication.

2- Phototoxicity:

- Demeclocycline, doxycycline may produce mild to severe reactions in the skin exposed to sunlight.

3-Hepatotoxicity:

- Occurs only with **high doses**.
- Jaundice appears first followed by azotemia, acidosis and irreversible shock.
- Oxytetracycline and tetracycline appear to be the least hepatotoxic of these agents.
- Pregnant women susceptible to severe tetracycline induced hepatic damage.

4-Renal toxicity:

- Tetracyclines may aggravate uremia in patients with renal disease.
- Outdated (expired) tetracyclines may cause a form of the ***Fanconi syndrome*** (damage of proximal renal tubules) characterized by nausea, vomiting, polyuria, polydipsia, proteinuria, glycosuria, aminoaciduria and acidosis.

5- Effects on calcified tissues:

- Because they chelate calcium, they are deposited in growing bones and teeth causing *staining (***teeth discoloration***)*, sometimes ***dental hypoplasia*** *and* ***bone deformities****.*
- Thus they should never be given to children below 8 years, pregnant women or nursing mothers.

6- Pseudotumor cerebri:

- Oucur in young infants the tetracyclines may cause increased intracranial pressure and tense bulging of fontanelles.

7- Vestibular distrubances:

- Minocycline (dizziness, ataxia , nausea and vomiting).

Clinical uses

1-Rikettsial infections:

Tetracyclines are effective in treatment of **Rocky Mountain spotted fever**, **epidemic typhus**, **murine typhus**, **scrub typhus** and **Q fever**.

2-Mycoplasma infections:

Either a tetracycline or an erythromycin is effective in treatment of pneumonia caused by ***M .pneumoniae***.

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3- Chlamydia infections:

lymphogranulbma venereum, **chlamydia pneumonia**, **inclusion conjunctivitis**, **trachoma** and **non-specific urethritis**. .

4- Bacillary infections:

As **brucellosis**, **tularemia** and **cholera**.

5- Treatment of acne, exacerbation of bronchitis, community-acquired pnemonia

6- Combination regimens to treat gastric and duodenal ulcer caused by *H. pylori*.

7- Some times used in treatment of protozoal infection:

E. Histolytica and ***P. Falciparum.***

CHLORAMPHENICOL

The first completely synthetic anti-bacterial agents to be produced commercially for clinical uses.

Mechanism of action:

- Chloramphenicol is a potent **inhibitor of microbial protein synthesis**.
- It binds **reversibly** to **50 S ribosomal subunit at the peptidyl transferase site and inhibits the transpeptidation reaction** (protein chain elongation by inhibiting peptide bond formation between adjacent a. a).
- Chloramphenicol binds to the 50 S ribosomal subunit near the site of action of clindamycin and the macrolide antibiotics and binding by one of these antibiotics to the ribosome may inhibit the interaction of the other. There is no clinical indication for the concurrent use of these antibiotics.
- Chloramphenicol can also inhibit mitochondrial protein synthesis in mammalian cells and erythropoietic cells seem to be particularly sensitive to the drug.

Antibacterial activity

- Chloramphenicol has wide spectrum of **bacteriostatic** activity against both aerobic and anaerobic. gram-negative and gram-positive organisms.
- It is active also against **Rickettsiae** but **not Chlamydiae**.
- *H influenzae*, *N. meningitidis* and *S. pneumoniae* are highly susceptible, and for these organisms, chloramphenicol may be **bactericidal**.

Resistance

- Due to the presence of specific **acetyltransferase** that inactivates the drug.
- Decreased permeability of the microorganisms.

Pharmacokinetic

- Chloramphenicol is rapidly and compeletly **absorbed** after oral administration.
- Reaches maximum plasma concentration within 2 hours; it can also be given parenterally.
- Widely **distributed** throughout the tissues and body fluids including the brain and CSF.
- Most of the drug is **inactivated** in the liver mainly by conjugation with glucuronic acid.
- About 10% is **excreted** unchanged in urine.

Adverse effects

1. Depression of the bone marrow:

The most important adverse effect, this effect may occur in two ways:

- **Dose related toxic effect:** as anemia, leukopenia or thrombocytopenia.
- **Idiosyncratic response:** (not dose related) manifested by aplastic anemia leading in many cases to fatal pancytopema.
  - The incidence of this reaction is low, approximately 1 in 30,000 of those on chloramphenicol.
  - If the aplasia is severe, result in death.
  - Patients who recover have a high risk of acute leukemia.
- *This unwanted effect of bone marrow depression seems to be related to the p-NO_2 group of Chloramphenicol. Thiamphenicol, a related compound in whicn the p-NO_2 group of chlormphenicol is replaced by SO_2CH_3 not to have this undesirable effect on bone marrow.*

2. Gray baby syndrome:

- It is seen in neonates especially premature babies who have been given relatively large doses of chloramphenicol.
- The illness usually begins 2-9 days after treatment is started and is manifested by **vomiting**, **flaccidity**, **cyanosis**, **respiratory irregularities**, **vasomotor collapse**, **hypothermia**, **abdominal distension**, **loose green stools** and **very pale gray color**.
- **The condition is due to increased blood concentration of chloramphenicol resulting from:**
  - Inadequate metabolic activity with failure of drug conjugation.
  - Inadequate exceretion of unconjugated drug.
- In the newborn both the metabolic and excretory powers are not well developed.

3. G I T irritation:

Nausea, **vomiting** and **diarrhea**.

4. Hypersensitivity reactions:

Skin rash, **fever**, **angioneurotic edema** have been described but are relatively uncommon.

Therapeutic Uses

Due to its potential toxicity, the risk of aplastic anemia cloramphenicol should not be used except in infections that cannot be treated with other antimicrobial drugs.

1- Bacterial meningitis:

Chloramphenicol, ampicillin and cephalosporins produce excellent results in ***H. influenzae*** **meningitis** (although cephalosporins are preferred).

Similar response can be obtained also in **meningitis** caused by ***N. meningitidis*** and ***S. pneumoniae***.

2- Anaerobic or mixed infections:

In **brain abscesses**, **intraabdominal** or **pelvic abscesses**, (chloramphenicol + penicillin **or** aminoglycoside).

In **brain abscesses** some recommend the use of (penicillin + metronidazole).

3-Rickettsial diseases:

Tetracyclines are preferred, chloramphenicol can be used as an alternative when tetracyclines are contraindicated.

4-Typhoid fever:

- Many strains of *Salmonella* are **now resistant** to chloramphenicol.
- **Third generation cephalosporins** and **quinolones** are the drugs of choice.

5- Chloramphenicol is used topically in the treatment of eye infections (broad spectrum activity and penetration of ocular tissues and aqueous humor)

- **It is ineffective in Chlamydia infections.**