Chapter 44

Tetracyclines and Chloramphenicol
broad-spectrum antibiotics: tetracyclines and chloramphenicol are active against both aerobic and anaerobic G+ and G-, rickettsia, mycoplasma and chlamydia.
structure
tetracyclines

- **Natural tetracyclines**
  - Tetracycline, tetramycin, chlortetracycline, demeclocycline

- **Semisynthetic tetracyclines**
  - Metacycline, doxycycline, minocycline

- It is stable in acid solution and easily destroyed in alkaline solution.
Antibacterial property

- Their basic structures, activities, antibacterial spectrum, antibacterial mechanism and therapeutic applications are similar.
Mechanism of action

- Tetracyclines are potent inhibitors of microbial protein synthesis by binding to the 30S subunit of bacterial ribosome and inhibiting aa-tRNA into A site.
Resistance

- Completely cross-resistance among tetracycline, oxytetracycline and chlorotetracycline
- Resistant Bacterium to natural tetracycline may be sensitive to semisynthesis tetracycline.
Mechanism of resistance

- Protein gene of ribosome protection express stronger.
- OmpF of porin decrease due to Chromosome mutant of *Escherichia coli* and then impaired influx of tetracyclines.
- Efflux gene of tetracyclines
- Inactivated enzymes
tetracycline

- **Antibacterial property**: 
  - Tetracycline act on G⁻ more potently than on G⁺.
  - Antibacterial activity to G⁺ is less than β-lactam anbiotics.
  - Antibacterial activity to G⁻ is less than aminoglycosides and chloramphenicol.
  - *S.typhi, S.paratyphi, P.aeruginosa, brucellosis, cholera, plague, rickettsial infection, Eaton's pneumonia, virus*
Pharmacokinetics

- Alkalescent drug, H₂-receptor blocker and antacids can decrease tetracyclines’ solubility.
- Acidic drug such as Vit C can accelerate tetracycline absorbing.
- Tetracyclines can be Complexes with Metal ion of multivalence e.g. Mg²⁺, Ca²⁺, Al³⁺ and Fe³⁺ and absorption decrease.
- Tetracyclines are deposited in growing bones and teeth, causing staining and sometimes dental hypoplasia and bone deformities.
Therapeutic application

- **Infection of Rickettsia** (ship fever, tsutsugamushi disease, Q fever)
- **Infection of mycoplasma** (mycoplasma pneumonia, infection of the genitourinary system)
- **Infection of chlamydia** (psittacosis, trachoma and Lymphogranuloma Venereum, LGV)
- Some *spirochetes* (recurrent fever)
- **Plague, brucellosis, cholera, digestibility canker** caused by Helicobacter pylori, **groin granuloma** caused by granuloma bacilli
Adverse effect

- Gastrointestinal adverse effects
- Bone and teeth
- Liver and kidney toxicity
- Photosensitization and vestibular disturbances
- Superinfections
Superinfections

**Definition**: There is a complete microecosystem in a healthy adult. After long-term use of broad-spectrum antibiotics, sensitive bacteria growth is inhibited, non-sensitive bacteria take the chance of breeding, resulting in new infections.
Superinfections

- Mycotic infection
- Antifungal drugs
- Pseudomembranous colitis
- Vancomycin and metronidazole
Doxycycline

- The Antibacterial spectrum is the same to tetracycline.
- The effect is stronger than tetracycline.
- Resistant Staphylococcus aureus to tetracycline or oxytetracycline is still sensitive to doxycycline
- Cross-resistance
Clinical application

- Doxycycline is the first choice of tetracyclines.
- Its clinical application is the same to tetracycline.
- It is specially adapted for the Infection of Biliary system or accompanying to renal failure.
chloramphenicol
Chloramphenicol

- It is a antibiotics generated from venezuela Streptothrix.
- It can be generated a lot by chemosynthesis.
- The first synthetical antibiotics
- Its L-isomer is used in clinic.
Antibacterial spectrum

Broad-spectrum bacteriostatic

- Strong effect to $G^-$
- It is germicide to hemophilies influenzae, Diplococcus intracellularis and Streptococcus pneumoniae.
- The effect to $G^+$ is not as good as penicillin and tetracycline.
- It can repress Rickett’s organism, chlamydia and mycoplasma.
Mechanism of action

- A potent inhibitor of microbial protein synthesis
- It acts primarily by binding reversibly to the 50s subunit of the bacterial ribosome, and interferes with peptidyl transferase in the step of protein synthesis.
- A bacteriostatic antibiotic
Resistance

- Almost all microorganisms could develop resistance to chloramphenicol.
- The resistance usually is caused by a plasmid-encoded acetyltransferase that inactivates the drug.
Pharmacokinetics

- Liposolubility
- High concentration in cerebrospinal fluid
- Most of the drug binding with glucuronic acid in vivo eliminate by urine.
Clinical application

- Due to its severe adverse effects, chloramphenicol is seldom used in clinic.
- It is used only when the benefits of therapy outweigh the risks of the potential toxicity and there are no other antimicrobial agents to select.
- Typhoid fever, bacterial meningitis, anaerobic infections, rickettsial diseases, and brucellosis
Adverse effects

1. Bone marrow disturbances
   a. Reversible anemia is apparently dose-related and occurs concomitantly with period of treatment.
   b. Aplastic anemia is idiosyncratic and usually fatal, which is not related to dose and therapy.
Adverse effects

2. Gray baby syndrome
   - Chloramphenicol accumulates in newborn infants due to the lack of an effective glucuronic acid conjugation mechanism.

3. Others: dual infection, gastrointestinal adverse effects, allergic response