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PHARMACOLOGY - III

UNIT 2

TOPIC :

- c. Antibiotics- Penicillins, cephalosporins, chloramphenicol, macrolides,
  quinolones and fluoroquinolins, tetracycline and aminoglycosides

Antibiotics

→ Antibiotics are one of the most important discoveries in medical science.
→ They are widely used in the prevention and treatment of bacterial infections. Antibiotics either kill microorganisms or inhibit their growth and multiplication.
→ These drugs have greatly reduced the death rate caused by infectious diseases such as pneumonia, tuberculosis, typhoid, and wound infections.
→ Originally, antibiotics were substances produced naturally by microorganisms such as bacteria and fungi. Nowadays, many antibiotics are produced semi-synthetically or synthetically.

Definition

→ Antibiotics are chemical substances produced by microorganisms or prepared semi-synthetically/synthetically that, in low concentrations, kill or inhibit the growth of other microorganisms without causing serious damage to the host.

History of Antibiotics

- In 1928, Alexander Fleming discovered Penicillin from the fungus *Penicillium notatum*.
- Penicillin became the first successful antibiotic used in humans.
- This discovery marked the beginning of the "Antibiotic Era".

Characteristics of an Ideal Antibiotic

An ideal antibiotic should possess the following properties:

1. Selective toxicity
    - It should destroy microorganisms without harming host cells.
2. Broad-spectrum activity
    - It should act against many types of bacteria.
3. Minimal side effects
    - It should produce fewer adverse effects.
4. Good absorption and distribution
    - It should reach the site of infection effectively.
5. Low resistance development
    - Bacteria should not easily develop resistance.
6. Long duration of action
    - It should remain active for sufficient time.
7. Easy administration
    - Oral administration is preferred whenever possible.
8. Economical
    - The drug should be affordable.

Classification of Antibiotics

1. Based on Mechanism of Action

A. Cell Wall Synthesis Inhibitors

Examples:

- Penicillin
- Cephalosporin
- Vancomycin

B. Protein Synthesis Inhibitors

Examples:

- Tetracycline
- Streptomycin
- Erythromycin

C. Nucleic Acid Synthesis Inhibitors

Examples:

- Ciprofloxacin
- Rifampicin

D. Cell Membrane Disruptors

Examples:

- Polymyxin

E. Antimetabolites

Examples:

- Sulfonamides
- Trimethoprim

2. Based on Spectrum of Activity

A. Broad-Spectrum Antibiotics

Examples:

- Tetracycline
- Chloramphenicol

B. Narrow-Spectrum Antibiotics

Examples:

- Penicillin G
- Erythromycin

C. Extended-Spectrum Antibiotics

Examples:

- Amoxicillin
- Ampicillin

3. Based on Chemical Structure

A. Beta-Lactam Antibiotics

Examples:

- Penicillin
- Cephalosporin

B. Aminoglycosides

Examples:

- Gentamicin
- Streptomycin

C. Tetracyclines

Examples:

- Doxycycline
- Tetracycline

D. Macrolides

Examples:

- Azithromycin
- Erythromycin

E. Quinolones

Examples:

- Ciprofloxacin
- Levofloxacin

F. Sulfonamides

Examples:

- Sulfamethoxazole
- Sulfadiazine

4. Based on Natural Sources

A. Fungal Source Antibiotics

Examples:

- Penicillin
- Cephalosporin

B. Bacterial Source Antibiotics

Examples:

- Polymyxin

C. Actinomycetes Source Antibiotics

Examples:

- Streptomycin
- Tetracycline

D. Semi-Synthetic Antibiotics

Examples:

- Amoxicillin
- Ampicillin

E. Synthetic Antibiotics

Examples:

- Sulfonamides
- Fluoroquinolones

5. Based on Bactericidal and Bacteriostatic Action

A. Bactericidal Antibiotics

Examples:

- Penicillin
- Ciprofloxacin
- Gentamicin

B. Bacteriostatic Antibiotics

Examples:

- Tetracycline
- Erythromycin
- Chloramphenicol

Penicillins

→ Penicillins are a group of β-lactam antibiotics obtained originally from the fungus *Penicillium*.

→ They act mainly by inhibiting bacterial cell wall synthesis and are widely used against Gram-positive and some Gram-negative bacteria.

Classification of Penicillins

1. Natural Penicillins

- Penicillin G (Benzyl penicillin)
- Penicillin V

2. Penicillinase-Resistant Penicillins

(Resistant to staphylococcal β-lactamase)

- Methicillin
- Cloxacillin
- Dicloxacillin
- Oxacillin
- Nafcillin

3. Aminopenicillins (Broad Spectrum)

- Ampicillin
- Amoxicillin
- Bacampicillin

4. Antipseudomonal Penicillins

a) Carboxypenicillins

- Carbenicillin
- Ticarcillin

b) Ureidopenicillins

- Piperacillin
- Azlocillin
- Mezlocillin

5. Penicillin + β-lactamase Inhibitor Combinations

- Amoxicillin + Clavulanic acid
- Ampicillin + Sulbactam
- Piperacillin + Tazobactam

Mechanism of Action (MOA)

→ Penicillins are bactericidal drugs.

→ They inhibit bacterial cell wall synthesis by binding to Penicillin Binding Proteins (PBPs).

Steps of Action

1. Penicillin reaches bacterial cell wall.
2. Binds with PBPs (transpeptidase enzymes).
3. Inhibits cross-linking of peptidoglycan chains.
4. Weak cell wall is formed.
5. Cell wall ruptures due to osmotic pressure.
6. Bacterial cell death occurs.

Important Point

- Effective mainly against actively dividing bacteria**.**

Pharmacokinetics of Penicillins

1. Absorption

- Some penicillins are acid labile and destroyed in stomach acid.
  - Example: Penicillin G
- Some are acid stable and can be given orally.
  - Example: Penicillin V, Amoxicillin

2. Distribution

- Widely distributed in body tissues and fluids.
- Low penetration into CSF normally.
- CSF penetration increases during meningitis.

3. Metabolism

- Minimal metabolism in liver.

4. Excretion

- Mainly excreted unchanged by kidneys through:
  - Glomerular filtration
  - Tubular secretion

5. Half-life

- Generally short (about 30–60 minutes).
- Requires frequent dosing.

Uses of Penicillins

1. **Streptococcal Infections**
   - Pharyngitis
   - Pneumonia
   - Scarlet fever
2. **Staphylococcal Infections**
   - Skin infections
   - Soft tissue infections
     (Using penicillinase-resistant penicillins)
3. **Syphilis**
   - Drug of choice: Penicillin G
4. **Respiratory Tract Infections**
   - Sinusitis
   - Otitis media
   - Bronchitis
5. **Urinary Tract Infections (UTI)**
   - Mainly ampicillin or amoxicillin
6. **Meningitis**
   - Certain susceptible bacterial meningitis
7. **Endocarditis**
   - Streptococcal endocarditis
8. **Pseudomonas Infections**
   - Piperacillin and ticarcillin
9. **Dental Infections**
   - Tooth abscess
   - Gum infections

Cephalosporins

→ Cephalosporins are a group of β-lactam antibiotics derived from *Cephalosporium acremonium*.

→ They inhibit bacterial cell wall synthesis and are used against a wide range of Gram-positive and Gram-negative bacteria.

Classification of Cephalosporins

1st Generation Cephalosporins

→ Mainly active against Gram-positive bacteria.

Examples

- Cephalexin
- Cefazolin
- Cephradine

Uses

- Skin infections
- Surgical prophylaxis
- Streptococcal infections

2nd Generation Cephalosporins

→ More activity against Gram-negative bacteria.

Examples

- Cefuroxime
- Cefaclor
- Cefoxitin
- Cefotetan

Uses

- Respiratory tract infections
- Otitis media
- Sinusitis

3rd Generation Cephalosporins

→ Broad-spectrum activity with better Gram-negative coverage.

Examples

- Ceftriaxone
- Cefotaxime
- Ceftazidime

- Cefixime

Uses

- Meningitis
- Gonorrhea
- Typhoid
- Severe infections

4th Generation Cephalosporins

→ Very broad spectrum and resistant to many β-lactamases.

Examples

- Cefepime
- Cefpirome

Uses

- Hospital-acquired infections
- Severe Gram-negative infections

5th Generation Cephalosporins

→ Effective against MRSA.

Examples

- Ceftaroline
- Ceftobiprole

Uses

- MRSA infections
- Complicated skin infections

Mechanism of Action (MOA)

→ Cephalosporins are **bactericidal antibiotics**.

MOA Steps

1. Bind to **Penicillin Binding Proteins (PBPs)**.
2. Inhibit peptidoglycan cross-linking.
3. Prevent bacterial cell wall synthesis.
4. Weak cell wall causes bacterial lysis and death.

Important Point

- Effective mainly against actively dividing bacteria.

Pharmacokinetics

1. Absorption

- Some are given orally:
  - Cephalexin
  - Cefixime
- Others are given parenterally:
  - Ceftriaxone
  - Cefotaxime

2. Distribution

- Widely distributed in body tissues.
- Some cross blood-brain barrier:
  - Ceftriaxone
  - Cefotaxime

3. Metabolism

- Minimal hepatic metabolism.

4. Excretion

- Mainly excreted by kidneys.
- Ceftriaxone is partly excreted in bile.

5. Half-life

- Varies among drugs.
- Ceftriaxone has longer half-life.

Uses of Cephalosporins

1. Respiratory Tract Infections

- Pneumonia
- Bronchitis
- Sinusitis

2. Urinary Tract Infections (UTIs)

3. Skin and Soft Tissue Infections

4. Meningitis

- Ceftriaxone
- Cefotaxime

5. Gonorrhea

- Ceftriaxone is drug of choice.

Chloramphenicol

→ Chloramphenicol is a broad-spectrum antibiotic obtained originally from *Streptomyces venezuelae* and now produced synthetically.

→ It inhibits bacterial protein synthesis and is active against many Gram-positive and Gram-negative bacteria.

Classification

Chloramphenicol belongs to the class of:

- Protein synthesis inhibitors
- Amphenicol antibiotics

Related Drug

- Thiamphenicol

Mechanism of Action (MOA)

→ Chloramphenicol is mainly **bacteriostatic**.

MOA Steps

1. Enters bacterial cell by diffusion.
2. Binds to **50S ribosomal subunit**.
3. Inhibits enzyme **peptidyl transferase**.
4. Prevents peptide bond formation.
5. Protein synthesis stops.
6. Bacterial growth is inhibited.

Important Point

- May become bactericidal against some organisms like:
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*

Pharmacokinetics

1. Absorption

- Well absorbed orally.
- Also available IV and eye preparations.

2. Distribution

- Widely distributed in body tissues and fluids.
- Crosses:
  - Blood-brain barrier
  - Placenta
- Enters CSF effectively.

3. Metabolism

- Mainly metabolized in liver by glucuronidation.

4. Excretion

- Excreted through kidneys mainly as inactive metabolites.

5. Half-life

- About 1.5–4 hours in adults.
- Longer in newborns due to immature liver enzymes.

Uses of Chloramphenicol

1. Typhoid Fever

- Caused by *Salmonella typhi*

2. Bacterial Meningitis

- Especially when other drugs cannot be used.

3. Eye Infections

- Conjunctivitis
- Eye ointments and drops

4. Rickettsial Infections

- Alternative to tetracyclines

5. Anaerobic Infections

6. Brain Abscess

Macrolides

→ Macrolides are a group of **antibiotics** characterized by a large macrocyclic lactone ring**.**

→ They inhibit bacterial protein synthesis and are mainly effective against Gram-positive bacteria and atypical organisms.

Classification of Macrolides

1. Natural Macrolides

- Erythromycin

2. Semi-Synthetic Macrolides

- Azithromycin
- Clarithromycin
- Roxithromycin

3. Ketolides (Related Group)

- Telithromycin

Mechanism of Action (MOA)

Macrolides are mainly bacteriostatic**.**

MOA Steps

1. Bind to 50S ribosomal subunit of bacteria.
2. Block translocation of peptide chain.
3. Inhibit bacterial protein synthesis.
4. Stop bacterial growth and multiplication.

Important Point

- At high concentrations, may become bactericidal against some organisms.

Pharmacokinetics

1. Absorption

- Well absorbed orally.
- Erythromycin is acid labile, therefore given as enteric-coated preparations.
- Azithromycin and clarithromycin have better absorption.

2. Distribution

- Widely distributed in tissues.

- High intracellular concentration.
- Poor CSF penetration.

3. Metabolism

- Mainly metabolized in liver.

4. Excretion

- Mostly excreted through bile.
- Some drugs excreted partly by kidneys.

5. Half-life

- Azithromycin has long half-life allowing once-daily dosing.

Uses of Macrolides

1. Respiratory Tract Infections

- Pneumonia
- Bronchitis
- Pharyngitis

2. Atypical Pneumonia

Caused by:

- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella*

3. Whooping Cough (Pertussis)

4. Diphtheria

5. Skin and Soft Tissue Infections

6. Sexually Transmitted Diseases

- Chlamydial infections
- Gonorrhea (alternative therapy)

7. Helicobacter pylori Infection

- Clarithromycin used in combination therapy.

8. Penicillin Allergy

- Alternative in penicillin-allergic patients.

Quinolones

→ Quinolones are a group of synthetic broad-spectrum antibacterial drugs that inhibit bacterial DNA synthesis.

→ Fluoroquinolones are quinolones containing a fluorine atom, which increases antibacterial activity.

Classification of Quinolones

1. First Generation Quinolones

(Mainly active against Gram-negative bacteria)

Examples

- Nalidixic acid
- Cinoxacin

2. Second Generation Fluoroquinolones

(Broader spectrum)

Examples

- Ciprofloxacin
- Norfloxacin
- Ofloxacin
- Pefloxacin

3. Third Generation Fluoroquinolones

(Better activity against Gram-positive bacteria)

Examples

- Levofloxacin
- Sparfloxacin

4. Fourth Generation Fluoroquinolones

(Enhanced anaerobic coverage)

Examples

- Moxifloxacin
- Gatifloxacin

Mechanism of Action (MOA)

Quinolones are bactericidal drugs.

MOA Steps

1. Inhibit bacterial enzymes:
    - DNA gyrase (Topoisomerase II)
    - Topoisomerase IV
2. Prevent DNA replication and transcription.
3. Bacterial DNA synthesis stops.
4. Bacterial cell death occurs.

Important Point

- DNA gyrase inhibition mainly affects Gram-negative bacteria.
- Topoisomerase IV inhibition mainly affects Gram-positive bacteria.

Pharmacokinetics

1. Absorption

- Well absorbed orally.
- High oral bioavailability.

2. Distribution

- Widely distributed in tissues.
- Good penetration into:
    - Lungs
    - Kidneys
    - Prostate
    - Bone

3. Metabolism

- Some drugs metabolized in liver.

4. Excretion

- Mainly excreted through kidneys.
- Dose adjustment needed in renal impairment.

5. Half-life

- Varies with drug.
- Some allow once-daily dosing.

Uses of Quinolones

1. **Urinary Tract Infections (UTIs)**
2. **Gastrointestinal Infections**
   - Typhoid fever
   - Traveler's diarrhea
3. **Respiratory Tract Infections**
   - Pneumonia
   - Chronic bronchitis
4. **Sexually Transmitted Diseases**
   - Gonorrhea
5. **Bone and Joint Infections**
6. **Skin and Soft Tissue Infections**
7. **Anthrax**
   - Ciprofloxacin is used.
8. **Pseudomonas Infections**
   - Ciprofloxacin effective.

Fluoroquinolones

→ Fluoroquinolones are a group of synthetic broad-spectrum antibiotics containing a fluorine atom in their chemical structure.

→ They act by inhibiting bacterial DNA synthesis and are effective against many Gram-positive and Gram-negative bacteria.

Classification of Fluoroquinolones

1. Second Generation

Examples

- Ciprofloxacin
- Norfloxacin
- Ofloxacin
- Pefloxacin

Characteristics

- Strong Gram-negative activity
- Effective against *Pseudomonas*

2. Third Generation

Examples

- Levofloxacin
- Sparfloxacin

Characteristics

- Better Gram-positive coverage
- Good activity against respiratory pathogens

3. Fourth Generation

Examples

- Moxifloxacin
- Gatifloxacin

Characteristics

- Broad-spectrum activity
- Additional anaerobic coverage

Mechanism of Action (MOA)

→ Fluoroquinolones are bactericidal drugs.

MOA Steps

1. Inhibit bacterial enzymes:
    - DNA gyrase (Topoisomerase II)
    - Topoisomerase IV
2. Prevent DNA replication and transcription.
3. Stop bacterial cell division.
4. Cause bacterial cell death.

Important Point

- DNA gyrase inhibition mainly affects Gram-negative bacteria.
- Topoisomerase IV inhibition mainly affects Gram-positive bacteria.

Pharmacokinetics

1. Absorption

- Well absorbed orally.
- High oral bioavailability.

2. Distribution

- Widely distributed in tissues and body fluids.
- Good penetration into:
    - Lungs
    - Kidneys
    - Prostate
    - Bone

3. Metabolism

- Some drugs metabolized in liver.

4. Excretion

- Mainly excreted through kidneys.
- Dose adjustment required in renal impairment.

5. Half-life

- Longer half-life allows once or twice daily dosing.

Uses of Fluoroquinolones

1. **Urinary Tract Infections (UTIs)**
2. **Respiratory Tract Infections**
   - Pneumonia
   - Bronchitis
   - Sinusitis
3. **Gastrointestinal Infections**
   - Typhoid fever
   - Traveler's diarrhea
4. **Sexually Transmitted Diseases**
   - Gonorrhea
5. **Bone and Joint Infections**
6. **Skin and Soft Tissue Infections**
7. **Pseudomonas Infections**
   - Ciprofloxacin commonly used.
8. **Anthrax**
   - Ciprofloxacin used for treatment and prophylaxis.

Tetracyclines

→ Tetracyclines are a group of broad-spectrum bacteriostatic antibiotics obtained from *Streptomyces* species and also produced semisynthetically.

→ They inhibit bacterial protein synthesis and are effective against Gram-positive, Gram-negative, rickettsiae, chlamydiae, and mycoplasma organisms.

Classification of Tetracyclines

1. Short-Acting Tetracyclines

- Tetracycline
- Oxytetracycline
- Chlortetracycline

2. Intermediate-Acting Tetracyclines

- Demeclocycline
- Methacycline

3. Long-Acting Tetracyclines

- Doxycycline
- Minocycline

Mechanism of Action (MOA)

→ Tetracyclines are mainly bacteriostatic drugs**.**

MOA Steps

1. Enter bacterial cell by active transport.
2. Bind to **30S ribosomal subunit**.
3. Prevent attachment of aminoacyl-tRNA to ribosome.
4. Inhibit bacterial protein synthesis.
5. Stop bacterial growth and multiplication.

Pharmacokinetics

1. Absorption

- Well absorbed orally.
- Absorption decreases with:
  - Milk
  - Calcium
  - Iron
  - Antacids

2. Distribution

- Widely distributed in body tissues.
- Deposited in:
  - Bones
  - Teeth
- Cross placenta.

3. Metabolism

- Minimal metabolism.

4. Excretion

- Mainly excreted by kidneys.
- Doxycycline mainly excreted in bile and feces.

5. Half-life

- Doxycycline and minocycline have longer half-lives.

Uses of Tetracyclines

1. Acne

2. Cholera

3. Rickettsial Infections

- Typhus
- Rocky Mountain spotted fever

4. Chlamydial Infections

- Trachoma
- Urethritis

5. **Mycoplasma Pneumonia**
6. **Lyme Disease**
7. **Plague**

Aminoglycosides

→ Aminoglycosides are a group of bactericidal antibiotics obtained from *Streptomyces* and *Micromonospora* species.

→ They inhibit bacterial protein synthesis and are mainly effective against aerobic Gram-negative bacteria.

Classification of Aminoglycosides

1. Streptomyces Derived

- Streptomycin
- Neomycin
- Kanamycin
- Tobramycin

2. Micromonospora Derived

- Gentamicin
- Amikacin
- Netilmicin

Mechanism of Action (MOA)

Aminoglycosides are bactericidal drugs.

MOA Steps

1. Drug enters bacterial cell by oxygen-dependent transport.
2. Binds irreversibly to 30S ribosomal subunit.
3. Causes misreading of mRNA.
4. Produces abnormal proteins.
5. Inhibits protein synthesis.
6. Leads to bacterial cell death.

Important Point

- Ineffective against anaerobic bacteria because oxygen is required for drug uptake.

Pharmacokinetics

1. Absorption

- Poorly absorbed orally.
- Mostly given by:
  - Intramuscular (IM)
  - Intravenous (IV)

2. Distribution

- Distributed mainly in extracellular fluid.
- Poor penetration into:
  - CSF
  - Eye
- Cross placenta.

3. Metabolism

- Not metabolized significantly.

4. Excretion

- Excreted unchanged by kidneys through glomerular filtration.

5. Half-life

- Usually 2–3 hours.
- Increased in renal impairment.

Uses of Aminoglycosides

1. Serious Gram-negative Infections

- Septicemia
- Pneumonia
- UTIs

2. Tuberculosis

- Streptomycin used as anti-TB drug.

3. Plague and Tularemia

4. Pseudomonas Infections

- Gentamicin
- Tobramycin
- Amikacin

5. Endocarditis

- Used with penicillins or vancomycin.