Antimicrobial drugs

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Introduction

- The use of antimicrobial drugs is successfully control the majority of bacterial, parasitical, fungal infections which affect human and animals.

- **Sulphonamide** 1934, **Penicillin G** 1941 obtained from *Penicillium notatum*. **Aminoglycosides** (*Streptomycin, Kanamycin*) 1946. Obtained from Soil Bacteria *Actinomyctes* group.

- At present about 100 antimicrobial drugs of different classes are available for use in humans.

- Clinically effective antimicrobial agents should exhibit selective toxicity toward the bacterium not the host. Few Side Effects. Good pharmacokinetics
General Antimicrobial Effects

• Drugs kill only actively growing microorganisms are termed **bactericidal**. Penicillins, Aminoglycosides

• Drugs that only inhibit the growth of microorganisms are termed **bacteriostatic**. Sulfonamides, Chloramphenicol, Tetracyclines

• The decision to use a bactericidal / bacteriostatic drug to treat infection depends entirely upon the type & body site of infection, patients age, kidney–Liver functions.. acute or chronic infection.

• Ultimate elimination of the organisms is dependent upon host immune defense.. **phagocytic activity & specific antibodies**
**Antibiotic Targets**

- **Cell Wall**
  - β-lactams
  - Vancomycin

- **DNA/RNA Synthesis**
  - Fluoroquinolones
  - Rifamycins

- **Folate Synthesis**
  - Trimethoprim
  - Sulfonamides

- **Cell Membrane**
  - Daptomycin

- **Protein Synthesis**
  - Linezolid
  - Tetracyclines
  - Macrolides
  - Aminoglycosides

**Antibiotic Resistance**

- **Efflux**
  - Fluoroquinolones
  - Aminoglycosides
  - Tetracyclines
  - β-lactams
  - Macrolides

- **Immunity & Bypass**
  - Trimethoprim
  - Sulfonamides
  - Vancomycin

- **Target Modification**
  - Fluoroquinolones
  - Rifamycins
  - Vancomycin
  - Penicillins
  - Macrolides
  - Aminoglycosides

- **Inactivating Enzymes**
  - β-lactams
  - Aminoglycosides
  - Rifamycins
Action of Antimicrobial Drugs on Bacteria

- **Antimicrobials are classified:** Range of activity/spectrum.
  - Narrow (Vancomycin, Penicillin, Antimycobacterial drugs),
  - moderate-Broad (Gram-ve/Gram+ve) Ampicillin, Amoxicillin, **Broad spectrum** Tetracylines, Chloramphenicol

- **Antimicrobials affect specific or various bacterial cellular targets.** cell wall, plasma membrane, nucleic acids, proteins synthesis.

1- **Inhibition Cell Wall Synthesis:** Group of 6-Amino penicillanic acid include all Beta-Lactam drugs. Bactericidal. They differs only by the presence of an amino/carboxyl group. helps the drug penetrate the outer membrane of gram-negative bacteria.
Inhibition Cell Wall-1

- **All Beta-Lactam Drugs** attached to Penicillin Binding Proteins (PBPs) inhibit *transpeptidases* peptide cross-linking of growing peptidoglycan. Stop cell wall synthesis. Activation cell autolysins.


- **2- Broad spectrum**. Ampicillin, Amoxacillin. Developed 1960s. G+ve/G-negative. All these B-lactam drugs susceptible to Penicillinases/ß-Lactamases actions.
Beta-Lactam Structures
Benzylpenicillin (5-Thiazolidine Ring)
Cephalosporins (6-Dihydrothiazine Ring)
Inhibition Cell Wall-2

• **3- Penicillinase-R drugs:**
  - Oxacillin, flucloxacillin, Methicillin (1970s) used only against Staph-R to Penicillins-Ampicillin. Methicillin-R Staph. aureus (MRSA) in Jordan up 70%, Worldwide distribution. Serious Infections.

• **Amoxacillin+Clavulinic Acid** (B-lactamase inhibitor) compound)/ Broad Spectrum.. Against Penicillinase-R

• **Carbencillin, Piperacillin** (1970s) Carboxyl Penicillin group. used mainly against G-ve Pseudomonas spp.

• **Monobactam:** Aztreonam.. G-ve Enteric bacteria

• **Carbapenem:** imipenem & meropenem (200o) Broad Spectrum, some penicillinase-R bacteria, against Serious Nosocomial Infection, Enteric bacilli., *P. aeruginosa*, *Acinetobacter* spp. due to Develop of extended beta-lactamases.
Inhibition Cell Wall-3

- **4- Cephalosporins**: 4 Generations..1965-1990s..Oral, IV, IM.
  - 1\(^{\text{th}}\) (1960) *Cephalexin, Cephradine*, Broad spectrum..
  - 2\(^{\text{th}}\) (70s) *Cefoxitin, Cefuroxime*, Broad spectrum..
  - 3\(^{\text{th}}\) (80s) *Ceftriaxone, Cefotaxime*.. mainly G-ve Enteric bacteria..but effective against some G+Ve bacteria *Strept.pneumoniae*
  - 4\(^{\text{th}}\) (90s) *Cefepime*.. mainly G-ve Enteric bacteria
    - UTI, RTI, Intestinal, Blood sepsis, CSF infections.. Not used against anaerobes.. Increased resistance Enterococcus group (E.fecalis) in human intestinal
Inhibition Cell Wall-4

• **Resistance Development:**

• All G-ve enteric bacteria especially *E.coli*, *Klebsiella/Enterobacter spp.*, *P.aeruginos* & *Acinetobacter spp.* develop rapidly resistance by **mutation & Plasmid transfer** β-lactamases genes. **Extended β-lactamases** (> 60 types).. Altered Penicillin Binding Proteins.. inactive β-lactam ring..spread mostly in hospitalized patients.

• **Methicillin resistance** in *S. aureus* is mediated by the *mecA* gene..production PBP-2a

• **Side Effects:** Sensitization, Penicillin Allergy, Fever, Serum Sickness, Nephritis, Anaphylactic Shock
Inhibition Cell Wall-5

• **Glycopeptides:** *Vancomycin*, *Teicoplanin*
  large polycyclic peptides..interfere with the synthesis of the bacterial cell wall G+ve bacteria ..different mechanism than the beta-lactams.. Prevent formation the cross-linking.

• Treatment *Methicillin-R Staphylococcus spp.*, *Multi-R Enterococci* (E. fecalis).. High doses/ long period cause toxic effects ..*Vacomycin-R* is still not detected or very rare in the world.
2- Inhibition of membrane integrity

- Polyenes: **Colistin /Polymixen E**: Large circular molecule consisting of a hydrophobic and hydrophilic region. Complex Cyclic Polypeptides. Bactericidal, used mostly against G-ve, Topical & Intravenous Drug. Wounds, systemic. against **Multiresistant Pathogens**. **Acinetobacter & Pseudomonas**. Nephrotoxic

- Polypeptides: **Bacitracin**. Affects cell membrane-bound phospholipid carrier. Bactericidal, Toxic only **topical use** against G+ve bacteria.
1- Vancomycin-Glycopeptide
2-Polyenes -Colistin /Polymixen
3-Inhibition Protein Synthesis

- Bacterial Ribosomes composed **30s+50s=70s**

**Aminoglycosides:** Inhibit protein synthesis by binding to the **30S ribosomal subunits**.. prevent formation complex polypeptides with messenger RNA.. Increase cell membrane leakage.

- **Bactericidal, Broad-spectrum** of activity, Mainly used against G-ve.. Not Anaerobes.. Serious Infection, .. Hospital ..IV, IM, **Streptomycin, Neomycin, Amikacin, Gentamicin, Tobramicin, Netilmicin,**

- **Side Effects:** Otototoxicity.. Nephrotoxicity.. Ototoxicity - 8th cranial nerve- hearing loss.. blood-level monitoring .

- **Resistance:** Production Acetylate, Phosphorylate, adenylate Enzymes..when the drug passes cell membrane..chromosomal & plasmid resistance
Aminoglycoside-Tetracycline
3-Inhibition Protein Synthesis

- **Tetracyclines:** Mid1950s: Bacteriostatic, Broad Spectrum, Accumulate in cytoplasmic membrane.. inhibit essential enzymes.. prevent attachment of the amino-acyl tRNA to 30S ribosome complex.. Side effect.. over growth of yeast (Candida spp.) .. develop of resistance by reduced active transport.

- **Doxycycline, Minocycline**.. Cholera, Respiratory & Genital Infection.. *Mycoplasma, Chlamydia, Legionella* infections.. New introduced Tigecycline

- **Chloramphenicol, Mid1950s**: Bacteriostatic ..Acts by binding to the 50S ribosomal subunit and blocking the formation of the peptide bond .. Broad Spectrum.. Intracellular bacteria.. Meningitis, Septicemia, Tyhoid fever, highly Toxic.
Chloramphenicol-Ciprofloxacin - Structures
Macrolides

- **Large lactone** ring structure ranged between 14- or 16-membered rings.. binds to the **50S ribosomal subunit** .. inhibits either peptid transferase activity or translocation of peptide to mRNA.

- Most widely used Macrolides .. **Erythromycin, Clarithromycin, Azithromycin** (*Long acting-12 hours*) Oral

- Relatively non-toxic drugs, mostly active against Gram-positive/Intracellular bacteria.. Respiratory Infections.. G+ve Pneumonia, Diphtheria.., **B-H-Streptococci- Staphylococcal Mycoplasma, Chlamydia, Legionella pneumophila** Infections.

B) **Lincosamides/Clindamycin, Lincomycin**: **Staphylococcus**.. Streptococci.. Bones, Oral cavity.. Anaerobic Infections..

* Common Cause **Pseudomembranous colitis**.. Bloody diarrhea.. Increase Growth **Clostridium difficile** in Intestine..
Inhibition Nucleic Acid Synthesis-4

- **Nalidixic acid (Quinolone):** Inhibit DNA Gyrase/Replication. Bactericidal. **Nitrofurantoin:** Damage DNA. Both synthetic drugs. Active against G-ve enteric bacteria. *E.coli* used in Urinary tract infection.


- **Fusidic acid:** A steroid antibiotic used in treat Gram-positive infections. Affects attachment to tRNA Ribosome.
5-Inhibition Synthesis of Essential Metabolites

• **Sulfa drugs / Sulfonamides**: Structure analogue to PABA. Compete with it. **Block folic acid synthesis**. Essential for nucleic acid synthesis. Mammals don’t need PABA or its analogs.

• **Bacteriostatic**. Now Rare used alone, Rapid develop Resistance by altered binds PABA.

• **Sulfamethoxazole-trimethoprim** / (Cotrimoxazole). Combined effects/Synergism. Broad Spectrum, UTI, RTI

• **Antituberculosis Drugs**: Inhibition **Mycolic acid**. Part of Mycobacterial Cell Wall. *Mycobacterium tuberculosis*.

• **Isoniazid (INH), Ethambutol, Cycloserine, Rifampin, Streptomycin**, 6- months treatment. Rapid Resistance if used alone. Treatment of R-tuberculosis 1-2 years.

• **Metronidazol**: Anti-protozoa & Most Anaerobic Bacteria.
Inhibition Folic acid synthesis

Para-aminobenzoic Acid (PABA)  Sulfanilamide
Antibiotic Susceptibility Tests

- **Laboratory Antibiotic Susceptibility Tests:**
- Culture, Isolation, Identification of Bacteria from clinical specimen as pure E. coli, S. aureus,
- Testing of only one pure fresh bacteria culture on Mueller-Hinton Broth & Agar. Disk Diffusion test. Measure inhibition zone after 24 hrs incubation at 37°C
- **Minimal Inhibitory Concentration (MIC/ug/ml)** E-test consists of a strip containing an exponential gradient of one antibiotic (1-2-4-8-16-32-64-128-256) ug/ml
- **Lab Report:** Susceptible isolates (S). Intermediate susceptible (IS). Resistant (R)
- Multi-resistant. Resistance to ≥2 antibiotic classes.
Antibiotic Disc - Test
Antibiotic E-test (MIC-mg/ml)
Antimicrobial Resistance

- **Resistance** is becoming a serious problem Worldwide.. more commensal/pathogenic microorganisms (Bacteria, Yeast, Viruses) are become untreatable with commonly used antimicrobials.. *Acinetobacter spp., Pseudomonas spp., MR-staphylococci* (MRSA), Va-R Enterococcus, MR-*Mycobacteria spp... High Mortality & High Treatment Cost*.

- This problem is due to **over use/ misuse** of antimicrobials in medicine & agriculture and misuse by **general population**.

- **Antibacterial resistance** including β-lactamases, efflux pumps, porin mutations, modifying enzymes and binding site mutations. horizontal transfer of combined resistance by plasmids.. Develop multidrug resistance.. **Mostly Not Reversible.**

- Antibiotics selective Pressure..Human, Animals, Environment.