Antimicrobial drugs

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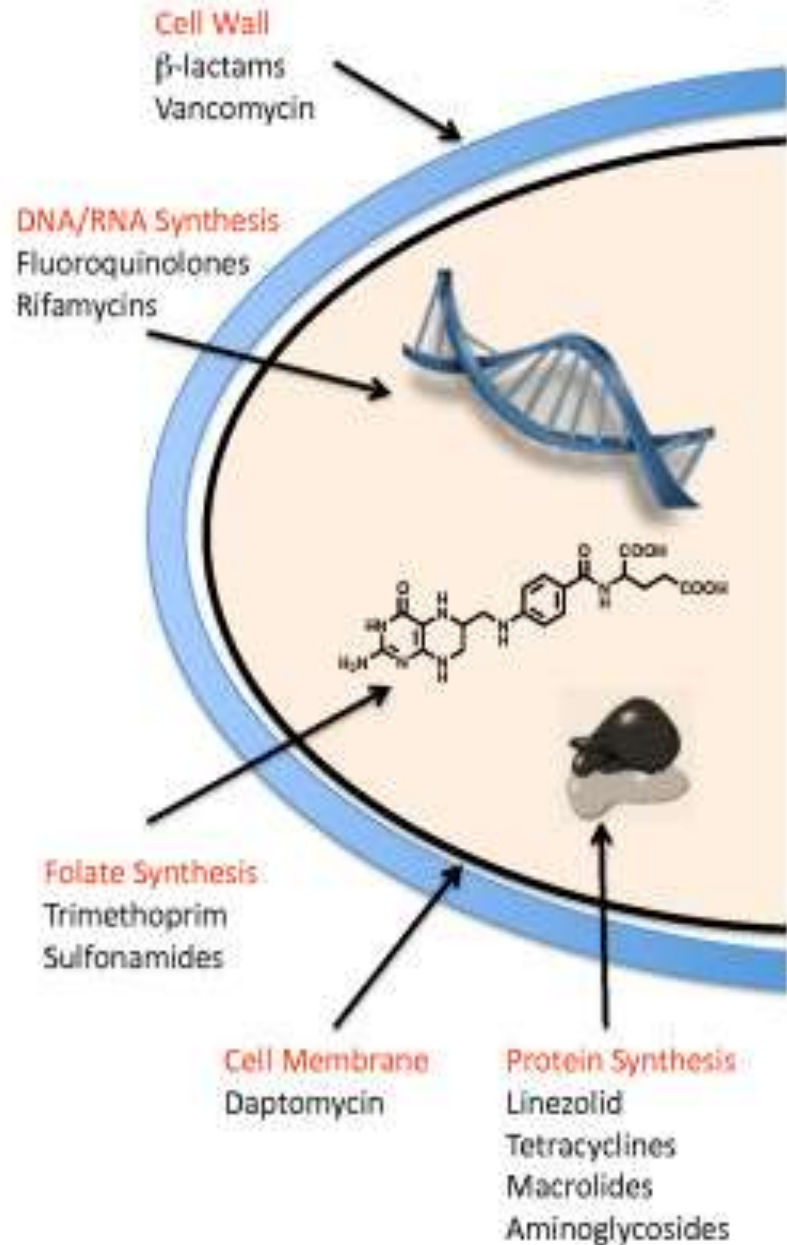
University of Jordan

Introduction

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

- **Sulfonamide** 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
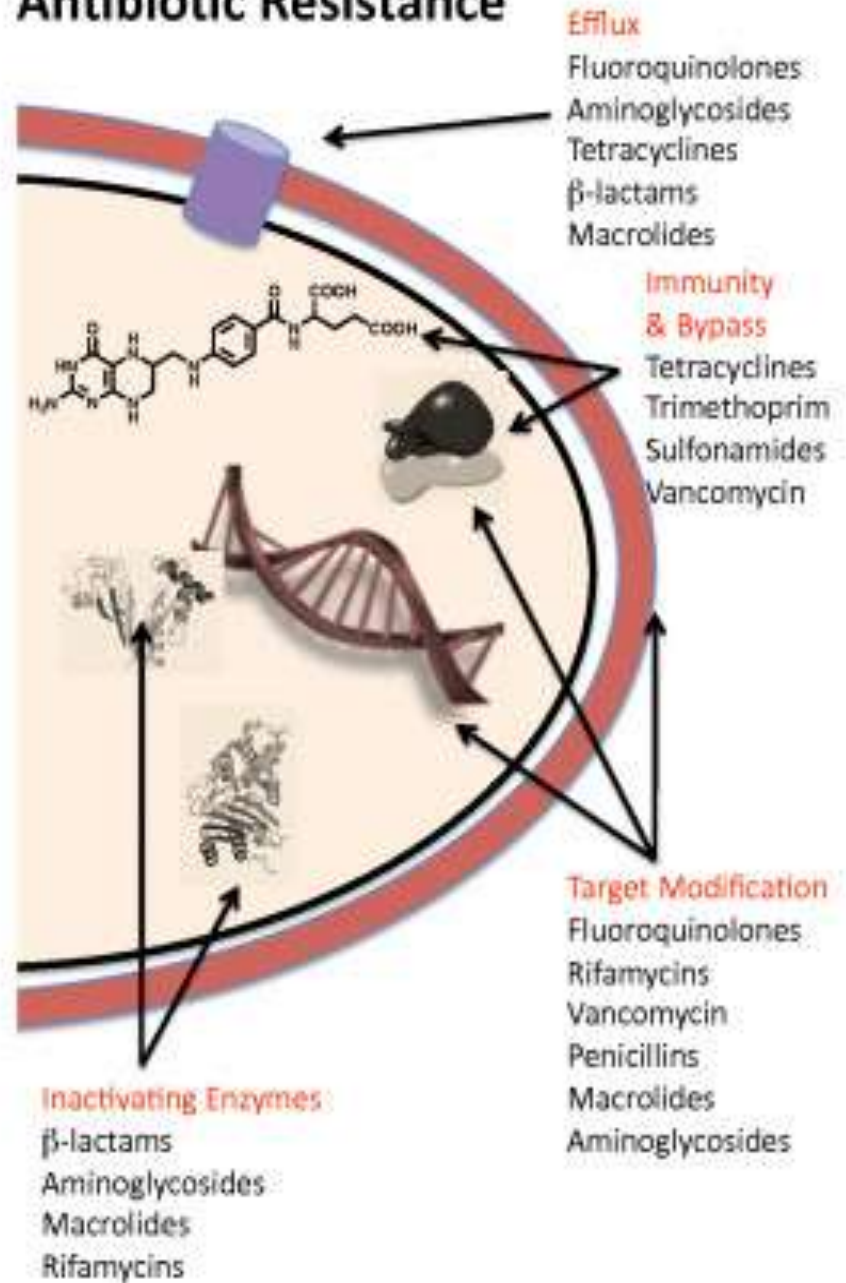
General Antimicrobial Effects

- 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
Tetracyclines
Trimethoprim
Sulfonamides
Vancomycin

Target Modification
Fluoroquinolones
Rifamycins
Vancomycin
Penicillins
Macrolides
Aminoglycosides

Inactivating Enzymes
β-lactams
Aminoglycosides
Macrolides
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.
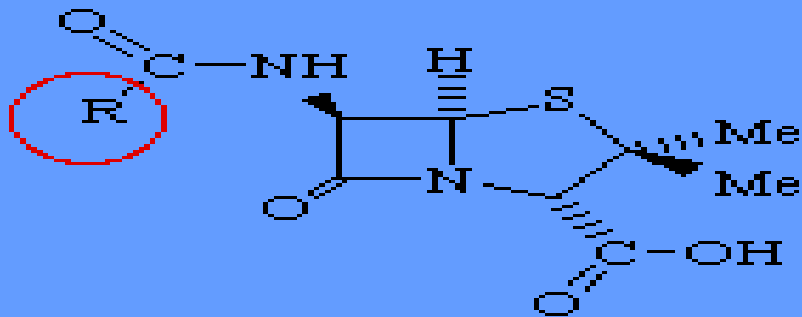
Inhibition Cell Wall-1

- 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.

- 1- Narrow- moderate.. Penicillin G, V .. affects mainly G+e & G-ve aerobic & anaerobic bacteria.. Less G-ve Facultative aerobic.. *Streptococci, Staphylococci, Bacateriodes ,*

- 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
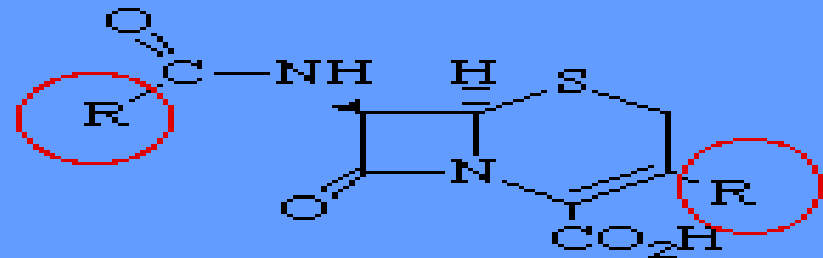# Benzylpenicillin (5-Thazolidine Ring)
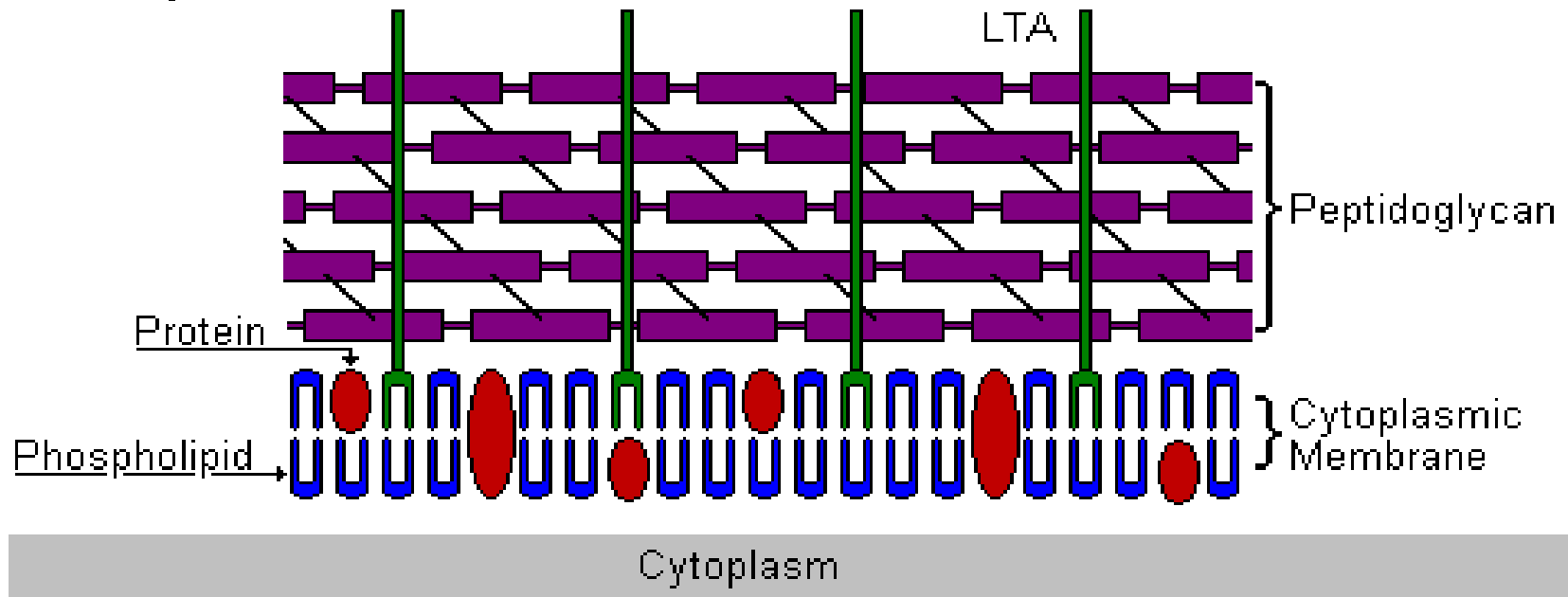
Cepalosporins (6-Dihydrothiazine Ring)

Gram-positive Cell Wall

LTA

Peptidoglycan

Protein

Phospholipid

Cytoplasmic Membrane

Cytoplasm

Gram-negative Cell Wall

Protein

LPS

Porins

Lipoprotein

Peptidoglycan

Phospholipid

Outer Membrane

Periplasmic Space

Inner Membrane

Cytoplasm
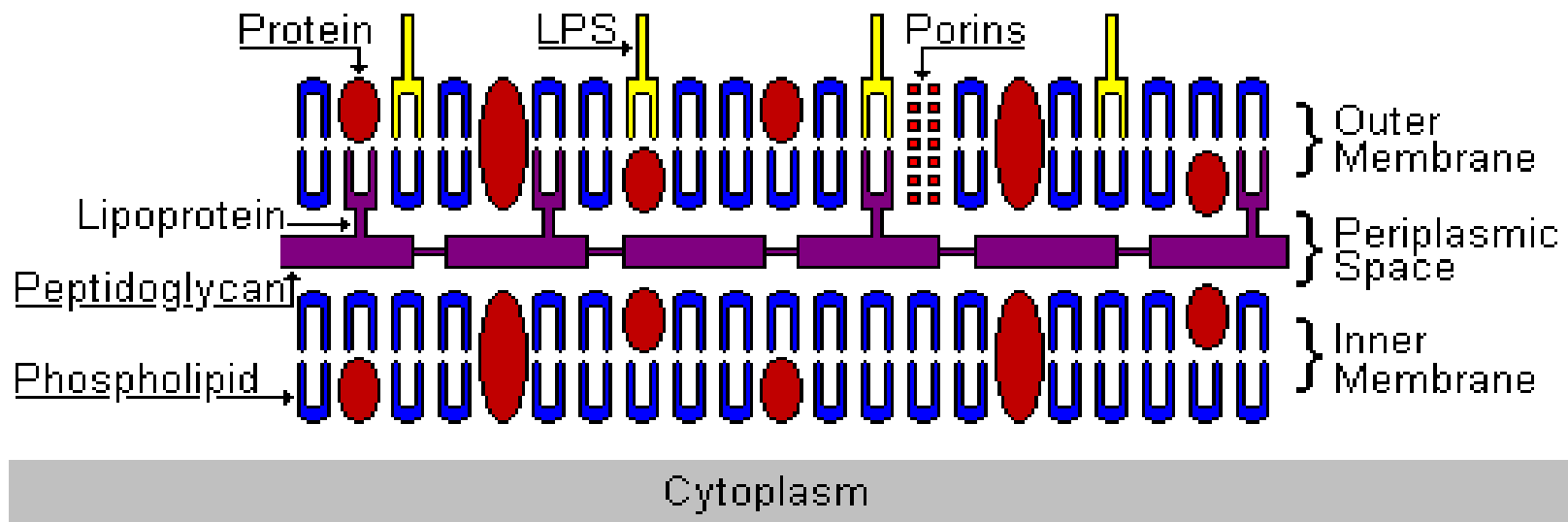
Inhibition Cell Wall-2

- **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.

- 1th (1960) *Cephalexin, Cephradine,* Broad spectrum..

- 2th (70s) *Cefoxitin, Cefuroxime,* Broad spectrum..

- 3th (80s) *Ceftriaxone, Cefotaxime..* mainly G-ve Enteric bacteria..but effective against some G+Ve

  bacteria *Strept.pneumoniae*

- 4th (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** ß-lactamases genes.. Extended ß-lactamases (> 60 types).. Altered Penicillin Binding Proteins.. inactive ß-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.. <u>Prevent formation the cross-linking</u>.

- 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
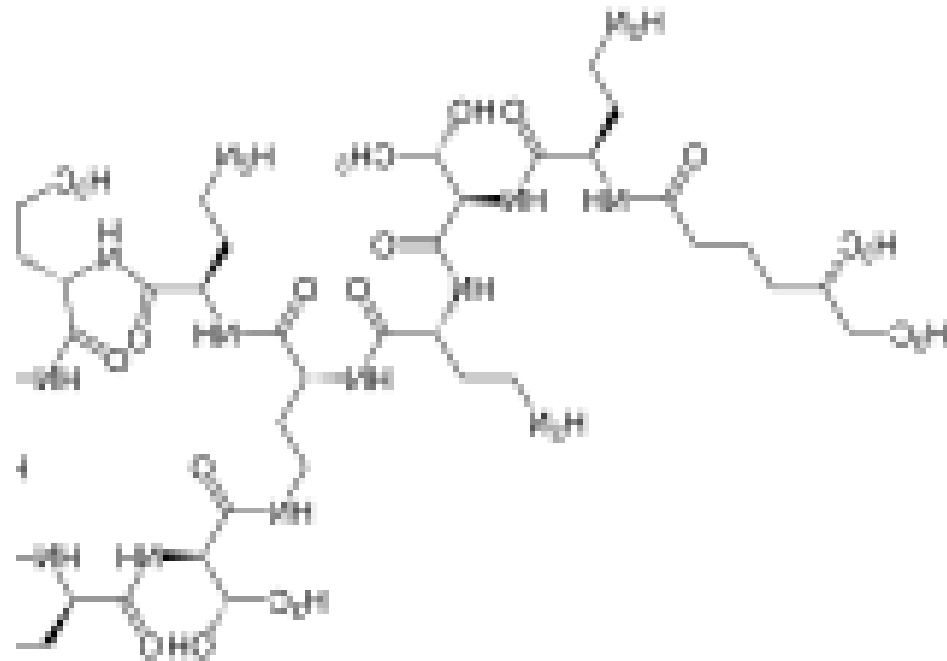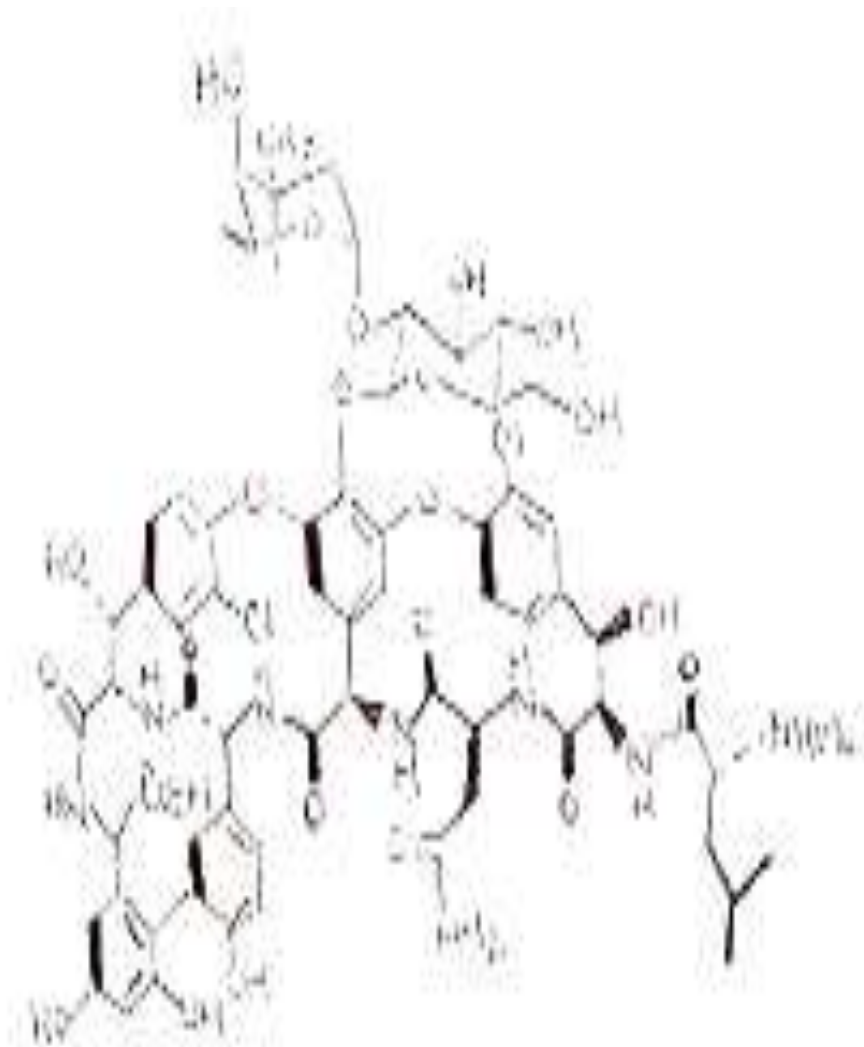
3-Inhibition Protein Synthesis

- 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
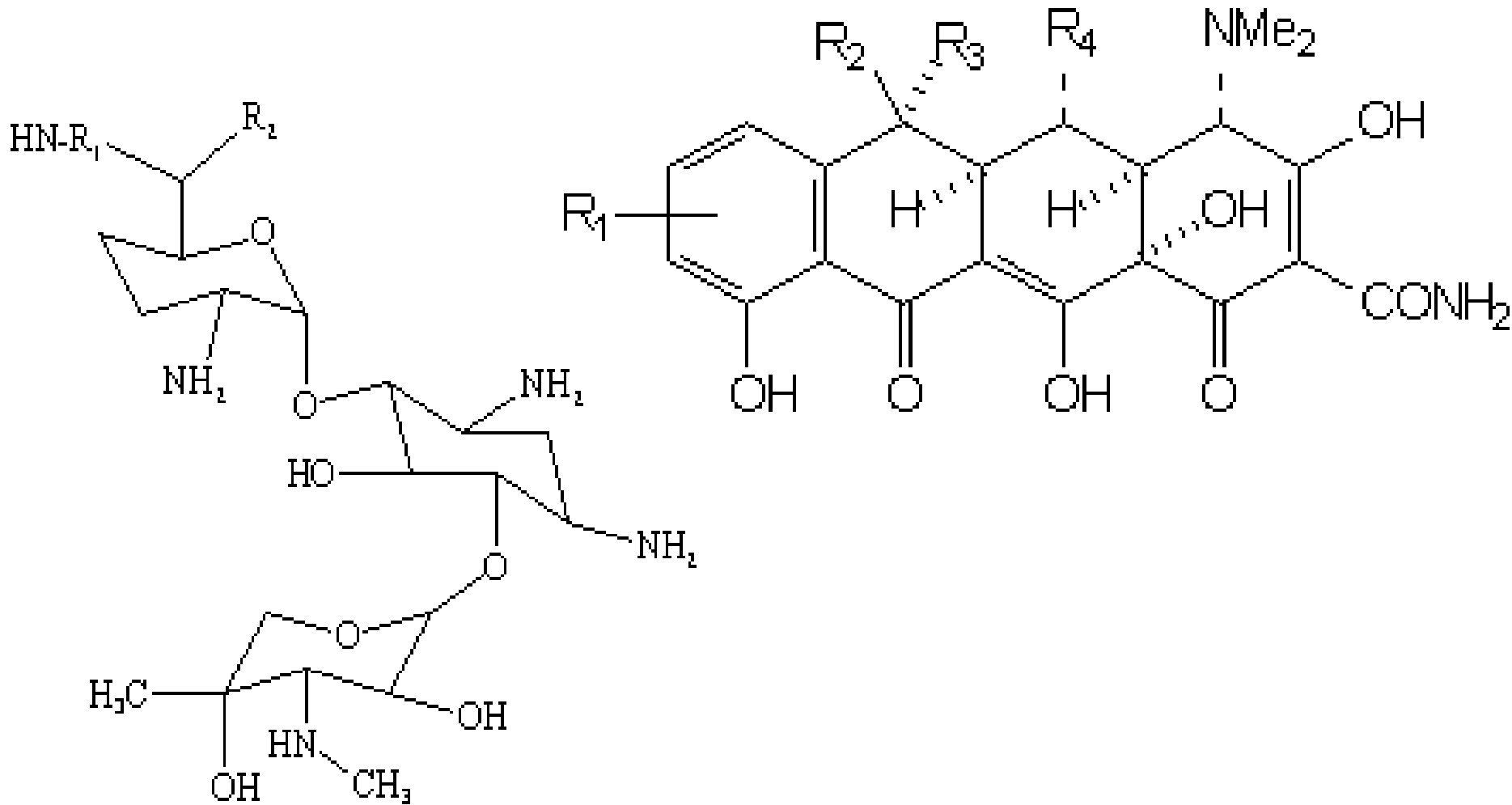
3-Inhibition Protein Synthesis

- **Tetracyclines**: <u>**Mid1950s**</u> : 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.

- <u>**Doxcycline, Minocycline**</u>.. Cholera, Respiratory & Genital Infection.. *Mycoplasma, Chlamydia, Legionella* infections.. New introduced **Tigecycline**

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

Chloramphenicol-Ciprofloxacin -Structures
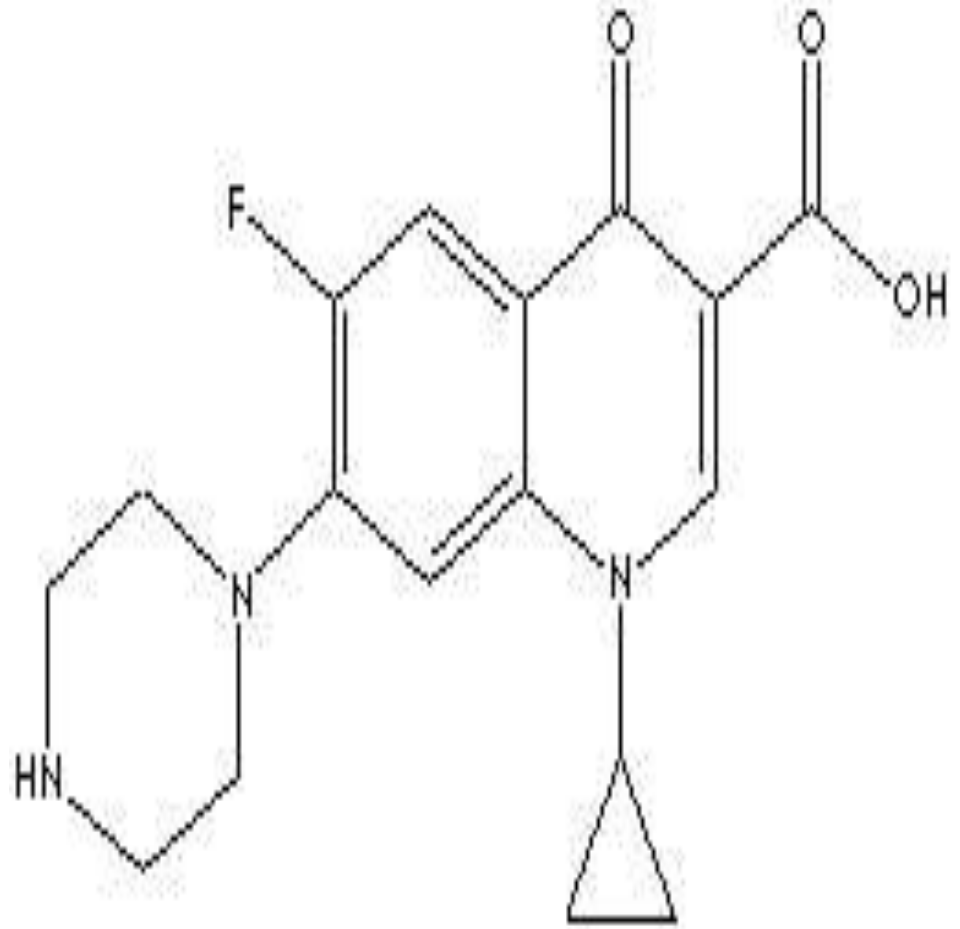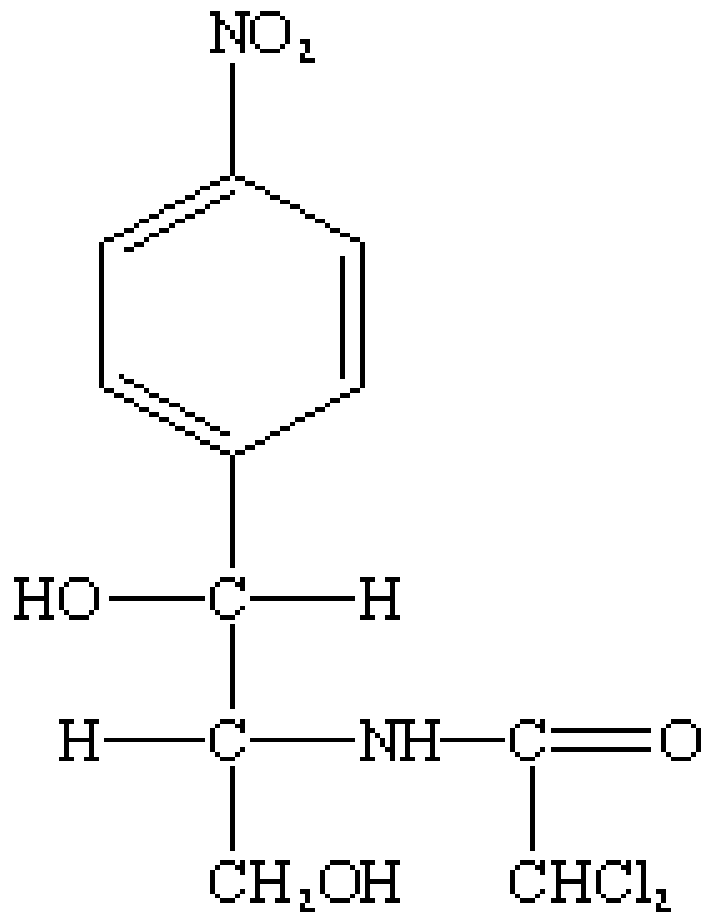
Macrolides

- **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.. Bactericidial. **Nitrofurantoin**..*Damage* DNA.. Both synthetic drugs..Active against G-ve enteric bacteria..*E.coli..* used in Urinary tract Infection.

- **Floroquinolones:** (1980s-2000s).. inhibit **DNA Gyrase** & **transcription**. **Bactericidal**, Norfloxacin, Ciprofloxacin, Levofloxacin , Ofloxacin..Broad spectrum.. More G-ve than G+e Infections.. intracellular pathogens, Urinary Tract, Pneumonia, Septicemia.. Resistance by altered DNA gyrase.. Develop due to mutation during treatment.

- **Rifamycin /Rifampin**: binds to the **RNA polymerase..** Prevent its transcription from DNA .. **Bactericidal**, *Mycobacteria*.. Intracellular bacteria.. *Chlamydia, Brucella*, Resistance due to change in RNA polymerase ß-subunit .

- **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.
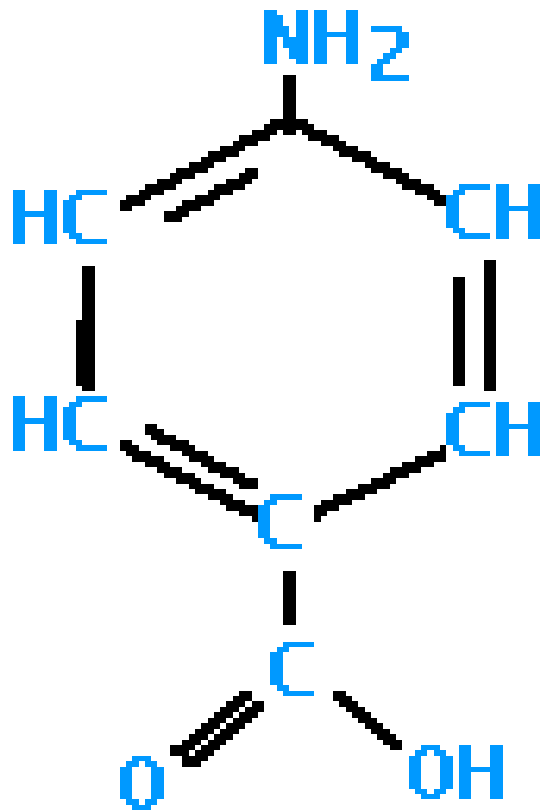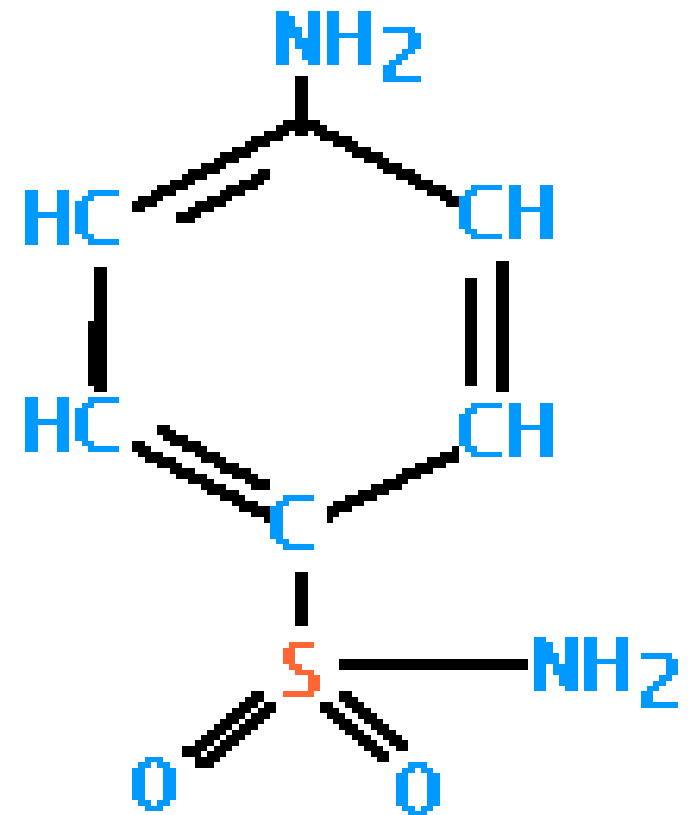
Antibiotic Susceptibility Tests

- 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 37^oC
- 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 $\geq$2 antibiotic classes.

Antibiotic Disc -Test
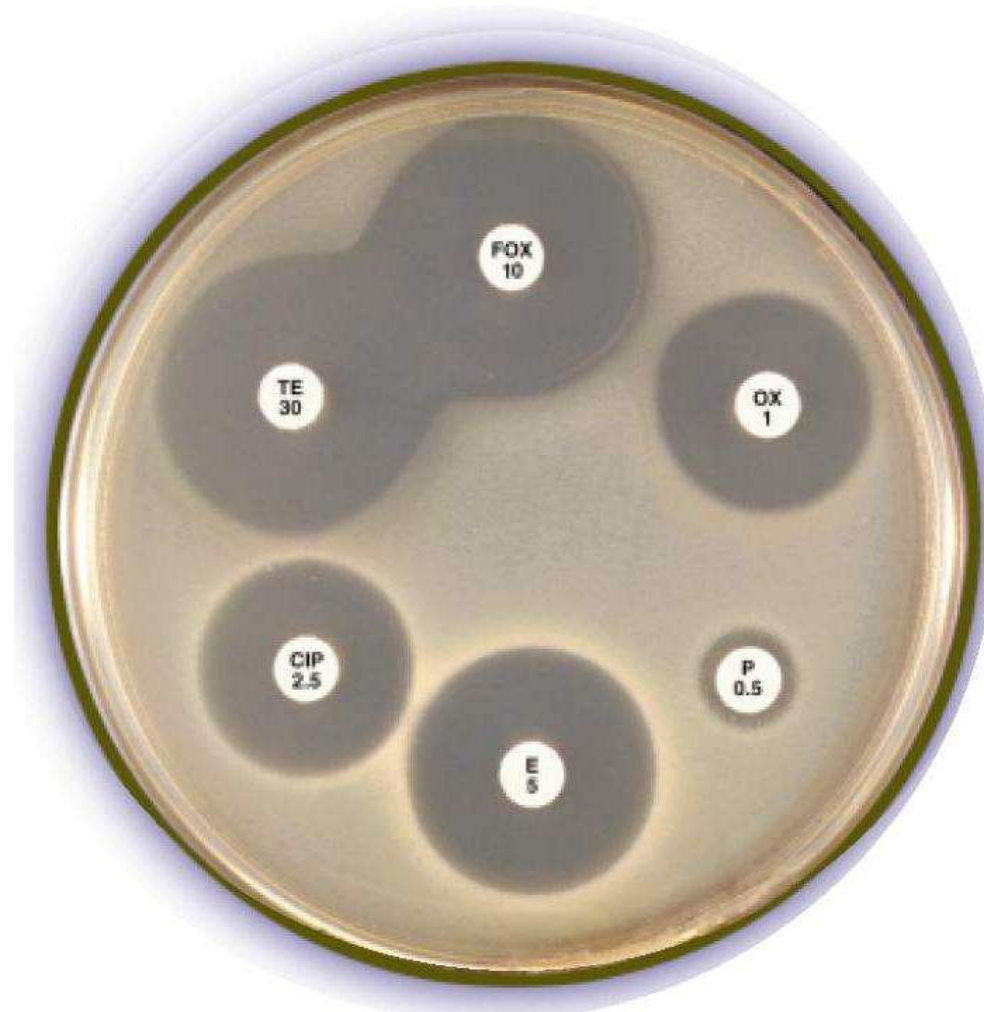
Antibiotic E-test (MIC-mg/ml)

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 <u>over use/ misuse</u> of antimicrobials in medicine & agriculture and misuse by <u>general population</u>.

- **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.