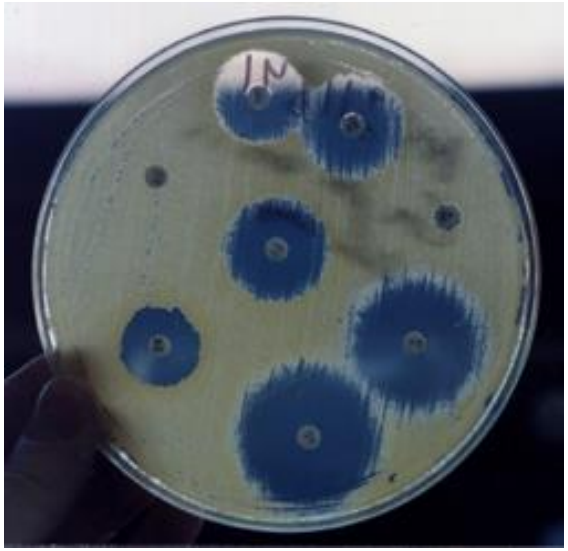
MICROORGANISM AND CHEMOTHERAPEIC MATERIALS



- Chemotherapeutic substances are antimicrobials derived from chemical substances.

- Antibiotics are antimicrobials obtained from bacteria or fungi

- CHEMOTHERAPYTIC MATTER
- In very small quantities (treatment doses), the harmful effects on the microorganisms (parasitic effect) are large, whereas the effects on the organism (organotrophic effect) are very small or not, are the chemical substances used for the treatment of infectious diseases.

- Damaging effect on microorganism (parasitic effect)

- Damaging effect on the organism (organotrophic effect)

- In the treatment doses of the chemotherapeutic agent, to be the parasitic effect is large and the organotrope effect is not present or very small is called "SELECTIVE TOXIC EFFECT".
- The selective toxic effect is due to differences in structure and biochemical mechanisms between the microorganism cell and the mammalian cell.
- Selective toxicity is the most important difference between chemotherapeutics and antiseptics.

- Therapeutic index: The therapeutic dose is the toxic dose rate. The higher the therapeutic index, the more effective the antibiotic is.

- The variety of microorganisms susceptible to an antimicrobial agent is called the "antimicrobial spectrum".

- Antimicrobial agents effective against one or several microorganism strains are called "narrow spectrum".

- Antimicrobial agents effective against a large number of microorganism strains are called "broad spectrum".

- ANTIBIOTIC: It is a substance that is formed in some breeding environments by some microorganisms in the form of bacteria or fungi and which is used for microbiostatic or microbicide for the treatment of microbial infection.

- They can be obtained natural, synthetic or semi-synthetic.

- Generally, each chemotherapeutic agent is microbiostatic at the beginning and microbicide effect at higher concentrations. They can be obtained natural, synthetic or semi-synthetic.

- The important point is the effect on therapeutic doses that do not harm the organism.

Classification of antibiotics according to their influence forces

- 1. Bactericides · Penicillins · Cephalosporins · Aminoglycosides Vancomycin · Teikoplanin · Fluoroquinolones Polymyxins · Rifampicin

- 2. Bacteriostatics · Tetracyclines · Chloramphenicol Sulfonamides Erythromycin · Clindamycin Miconazole Etambutol

- IMPACT MECHANISMS OF CHEMOTHERAPEUTIC MATERIALS
- 1.) Influence of Cell Wall Synthesis
- It is based on the blocking of transpeptidase and carboxypeptidase enzymes which play a role in peptidoglycan formation. (Bactericid is active during the active reproductive period, bactericidal ones are effective)

- Beta-lactam group Antibiotics - Penicillins - Cephalosporins - Carbapenems (imipenem, meropenem) - Monobactams (aztreonam) - Beta lactamase inhibitors (clavulanic acid, sulbactam, tazobactam)

- Beta-lactam ring free antibiotics -Glycopeptides Teicoplanin Vancomycin - Cycloserine - Simple. - Phosphomycin

- 2.) Effect on Cell Membrane;
- They degrade the selective permeability of the cytoplasmic membrane. By reacting with phospholipids in the cytoplasmic membrane, it increases cell permeability and destroys osmotic integrity (substance breaks down, creates a bactericidal effect, this group also kills the bacteria that have completed development).
- - Polymyxins
- - Nystatin and Amphotericin B
- - Azol Derivatives (Mikanozol, Ketoconazole, Itraconazole, Fluconazole)

- 3.) Affecting Protein Synthesis;
- Chemotherapeutic agents of this type often have broad spectrum and bacteriostatic effects.
- Tetracyclines inhibit the binding of t-RNA to ribosomes.
- Chloramphenicol blocks peptidyl transferase.
- Macrolide: Erythromycin blocks translocation (separation of tRNA from ribosomes).
- Linkozamides: Clindamycin inhibits the formation of peptide bonds.

- Aminoglycoside antibiotics bind to 30 S. 2 mechanisms.
- 1)inhibition of transfer of tRNA from region A to region P
- 2) leads to misreading of the message from DNA and / or premature termination of protein synthetesis. The resulting missing proteins enter the cytoplasmic membrane, altering permeability, and causing more of the aminoglycoside to enter the cell, leading to increased antibacterial activity.
- Because of this, aminoglycosides differ from other protein synthesis inhibitors by bactericidal action.

- The function of Ribozomun 30 S subunit disrupts function
- Tetracyclines (Tetracycline, Oxytetracycline, Chortetracycline, Democlocclin, Doxycycline, Minocycline): The tRNA is prevented from binding to ribosomes.
- Aminoglycosides (Streptomycin, Neomycin, Kanamycin, Gentamycin, Tobramycin, Amikacin, Netilmicin): They are bactericidal.

- The function of Ribozomun 50 S subunit disrupts function
- Macrolides (Erythromycin, Oleomindicine, Spiramycin, Clarithromycin, Roxytromycin, Azithromycin): prevent the tRNA from separating from the ribosome.
- Chloramphenicol binds reversibly to the thiamphenicol: peptidyltransferase region, inhibiting transpeptidation, resulting in bacteriostatic action.
- Linkosamides Linkomycin, Clindamycin: prevents peptide binding.

Act on nucleic acids

- - Quinolones: inhibit the activity of two separate topoisomerases in the bacterial cell by binding both to DNA and to enzymes. DNA gyrase (Topoisomerase II: supersamal formation), Topoisomerase I: supersameric expansion. The end result of inhibition of topoisomerase activity; DNA replication and repair, transcription and DNA-related cell functions are inhibited, and bactericidal action occurs. Quinolones: Chloroquinoline, novobiocin, cinnoxine Fluoroquinolones: ofloxacin, ciprofloxacin, norfloxacin, pefloxasin

- Disrupting the Function of mRNA; (Rifamycin, Rifampicin, Etambutol): Inhibits the synthesis of mRNA from genetic material by inhibiting the enzyme of RNA polymerase.

- 5.) Similarities in Chemical Structures Hence, Bacterial Metabolism by Destroying Those Affecting (Antimetabolite effect)
- The ability of enzymes to provide DNA synthesis and protein synthesis in a cell, to synthesize purines and pyrimidines depends on the presence of folic acid.
- Human cells take this from the outside.
- Bacterists synthesize themselves.
- Because folic acid can not absorb from the environment they are in.

- The folic acid precursor is converted to folic acid by a series of reactions with para amino benzoic acid (PABA) enzymes. The chemical structures of PABA and sulphonamides are very similar.
- With this similarity, sulphonamides replace PABA in the bacterial cell. The dihydropteroate synthetase enzyme, which acts in the first step of folic acid synthesis, binds not to PABA but to sulfonamide and stops folic acid synthesis.

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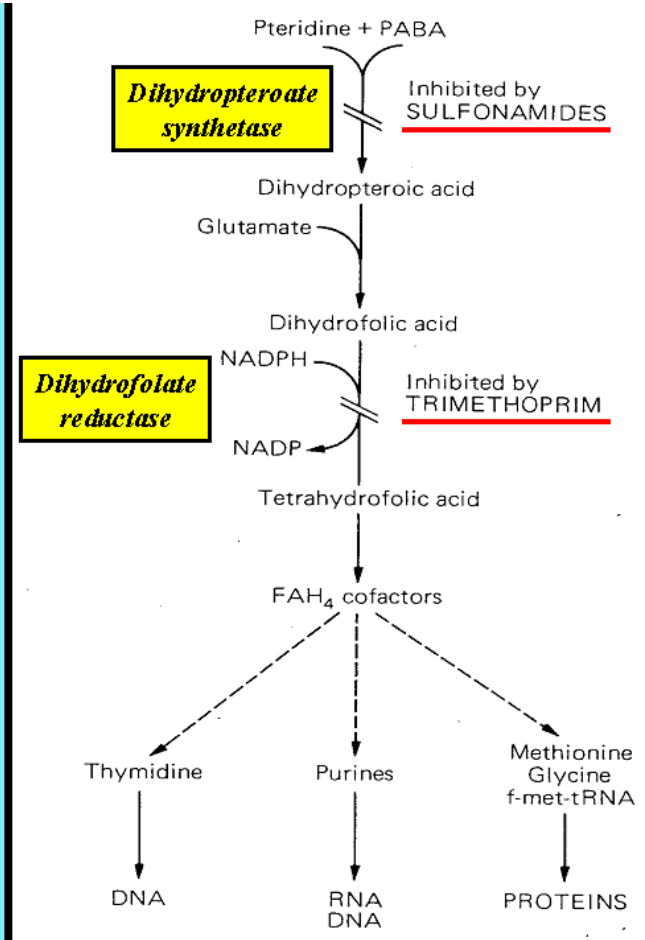
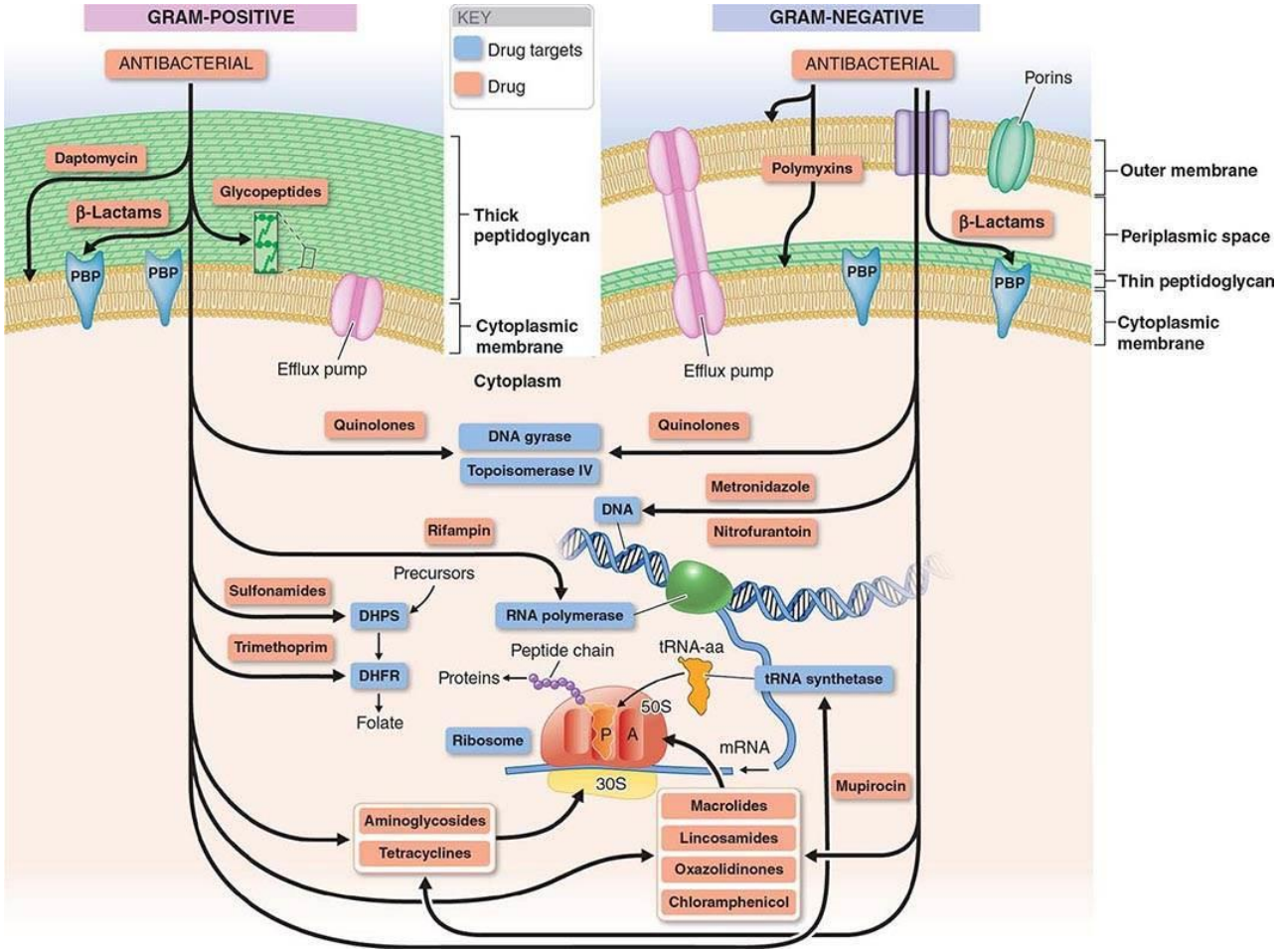
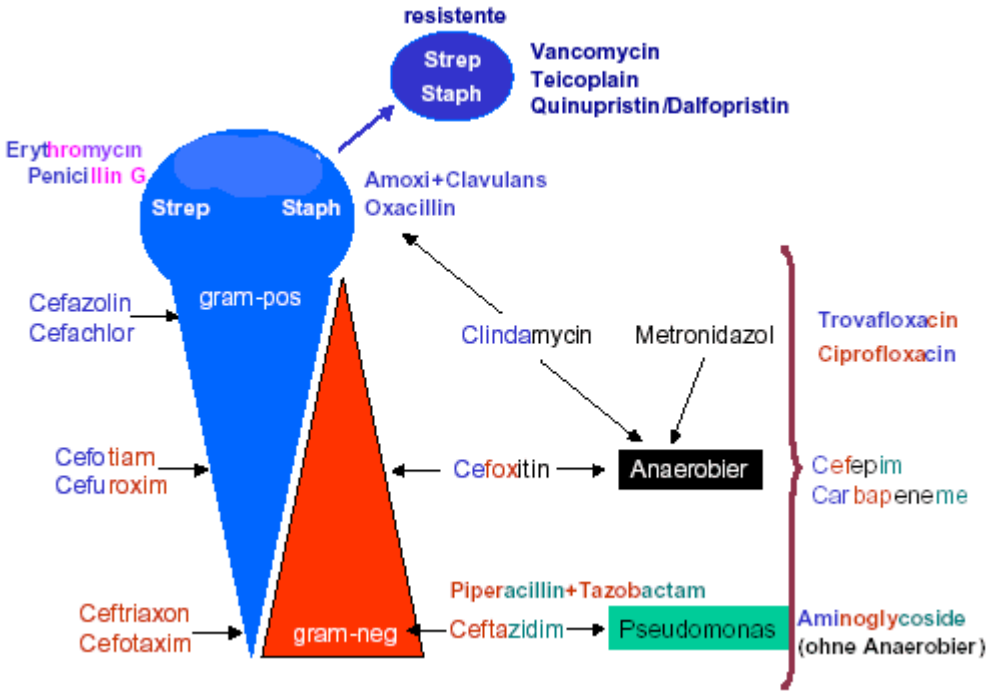

Pteridine + PABA
Dihydropteroate synthetase
Inhibited by SULFONAMIDES
Dihydropteroic acid
Glutamate
Dihydrofolic acid
NADPH
Dihydrofolate reductase
Inhibited by TRIMETHOPRIM
NADP
Tetrahydrofolic acid
FAH4 cofactors
Thymidine
Purines
Methionine
Glycine
f-met-tRNA
DNA
RNA
DNA
PROTEINS

- As a result, the purines and pyrimidines necessary for DNA synthesis can not be synthesized and bacterial replication is prevented.
- Sulfonamides and trimethoprim-sulfamethoxazole are in this group.


GRAM-POSITIVE
KEY
Drug targets
Drug
GRAM-NEGATIVE
ANTIBACTERIAL
ANTIBACTERIAL
Porins
Daptomycin
Glycopeptides
β-Lactams
Thick peptidoglycan
Cytoplasmic membrane
PBP
PBP
Polymyxins
β-Lactams
Outer membrane
Periplasmic space
Thin peptidoglycan
Cytoplasmic membrane
PBP
PBP
Efflux pump
Cytoplasm
Efflux pump
Quinolones
DNA gyrase
Topoisomerase IV
Quinolones
Metronidazole
DNA
Nitrofurantoin
Rifampin
Precursors
Sulfonamides
DHPS
RNA polymerase
Trimethoprim
DHFR
Peptide chain
tRNA-aa
Proteins
tRNA synthetase
Folate
50S
Ribosome
P
A
mRNA
30S
Mupirocin
Aminoglycosides
Tetracyclines
Macrolides
Lincosamides
Oxazolidinones
Chloramphenicol


resistente
Strep
Staph
Vancomycin
Teicoplain
Quinupristin/Dalfopristin
Erythromycin
Penicillin G
Strep
Staph
Amoxi+Clavulans
Oxacillin
gram-pos
Cefazolin
Cefachlor
Clindamycin
Metronidazol
Trovafloxacin
Ciprofloxacin
Cefotiam
Cefuroxim
Cefoxitin
Anaerobier
Cefepim
Carbapeneme
Piperacillin+Tazobactam
Ceftriaxon
Cefotaxim
gram-neg
Ceftazidim
Pseudomonas
Aminoglycoside
(ohne Anaerobier)

- QUALIFICATION RESOURCES
- 1) Non-Genetic Resistance Depending on the conditions in which the bacteria are found, it is the persistent resistance, which disappears if these conditions are not met. L-forms of bacteria are not affected by antibiotics that inhibit cell wall synthesis

- Genetically Dependent Resistance
- A) Natural Resistance: Chromosomal resistance naturally found in all strains of a bacterium. Enterococci beta lactam is resistant to antibiotics and especially cephalosporins. Bacteria of the genus Enterococcus show weak affinity to PBPs

- B) Acquired Resistance: This persistent resistance occurs either chromosomally or extracromosomally.
- Resistance to antimicrobials develops due to mutations in the genes that are located on the bacterial chromosome as a result of mutation or recombination. In this way, the bacterium gains chromosomal resistance, for example by synthesizing enzymes that it can not synthesize in advance or by altering the molecules targeted by antimicrobials.

- Extrachromosomal resistance occurs with plasmids and transposons.

- C) Cross-resistance: A resistance to an antibiotic is acquired by resistance to another effective antibiotic by a similar mechanism. Tetracyclines

Resistance formation mechanisms

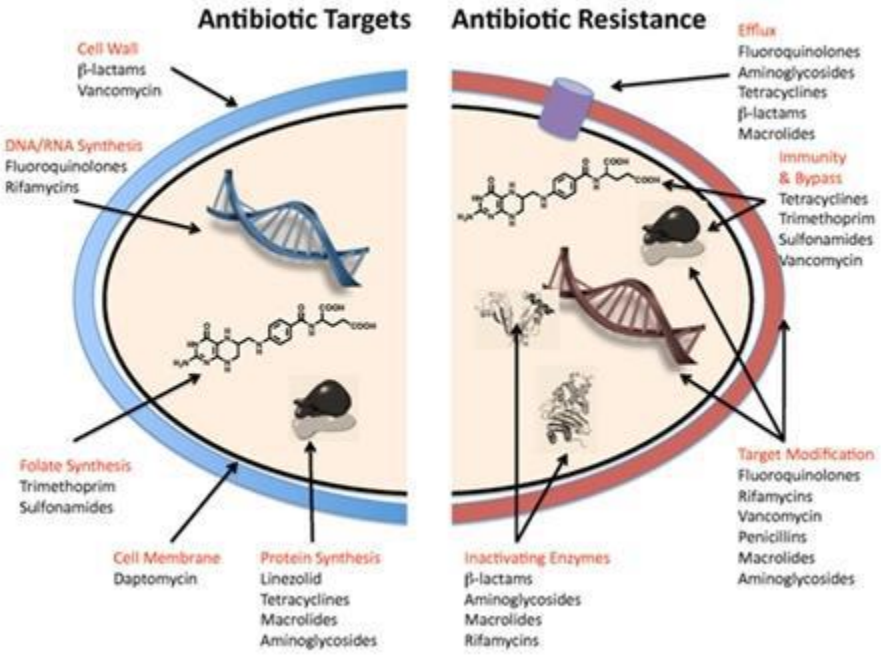
- 1- Target molecule change: When the structure of the molecule that the antibiotic binds in the cell changes with the chromosomal mutation, the molecular suitability of the antibiotic decreases and disappears. For example, a change in the structure of PBPs bound by beta lactam antibiotics causes the antibiotic not to bind to PBPs. Methicillin-resistant S. aureus By altering 12 S proteins in the 30S subunits of the ribosomes of some bacteria, streptomycin is metabolized to chloramphenicol by a change in the 50S subunits Resistance to rifampicin by alteration in beta subgroups of the enzyme of RNA polymerase

- 2- Prevention of Entry into Bacterial Cell In Gram negative bacteria, the passage of beta lactam antibiotics to the cytoplasmic membrane occurs due to porin proteins present in the cell wall. The change in the genes encoding the porin proteins causes the structure of these proteins to change. As a result, beta-lactam antibiotics can not reach the target molecules in the cell and gain bacterial resistance. Resistance to carbapenems in Pseudomonas aeruginosa Group 3 enzyme encoded by plasmids against aminoglycosides; Acetyltransferase, phosphoryltransferase, adenyltransferase Acetylation of amino groups of aminoglycosides, modification of hydroxyl groups by phosphorylation and adenylation (Inhibition of cytoplasmic membrane passage)

- 3- Synthesis of enzymes that inactivate bacteriin antibiotics Examples of such resistance are beta lactamase enzymes that inactivate Beta lactam antibiotics.
- Penicillins → Penicillinase
- Cephalosporins → Cephalosporinase
- Beta lactamases hydrolyze a ligand in the beta-lactam ring present in all beta lactam antibiotics, causing the ring to break down and the antibiotic to become ineffective.
- Acetylation of hydroxylamines of chloramphenicol with acetyltransferase produced by Gram (+) and (-) bacteria prevents binding of the ribosome to the 50S subunit

- 4-Active extracellular breakthrough

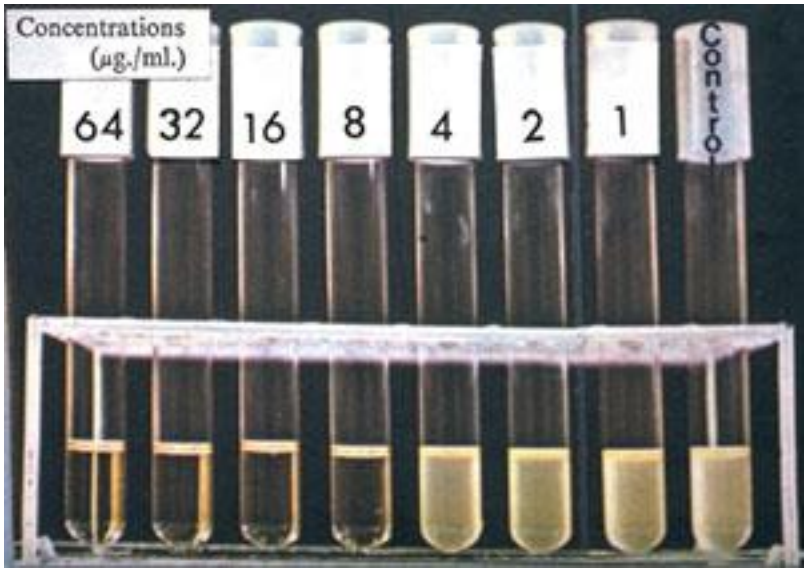
- In this type of resistance encoded by chromosomes or plasmids, antimicrobial agents are extracellularly excreted by the bacteria. Multiple antibiotics are called 'multiple drug discharge pumps'.
- This is the case for a resistance to quinolone in S. aureus, P. aeruginosa and E. coli.


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

- ANTIBIOTIC SENSITIVITY TESTS
- - Disc diffusion test in agar
- - Agar dilution (dilution in solid medium) test
- - Broth dilution (dilution in liquid medium) test
- - Microbial dilution (dilution in very small amount of liquid medium) test
- Disc diffusion test in agar
- An agar is spread homogeneously on a plate at a specific density. Paper discs containing antibiotics are placed on the agar surface. The agar plate is incubated at 37 ºC for 18-24 hours.

- Agar dilution (dilution in solid medium) test Different concentrations of a single chemotherapeutic agent are added to the agar plates.
- Microorganisms to be tested are planted on these agar plates. Agar plates are incubated at 37 ºC for 18-24 hours. Considering the amount of chemotherapeutic agent (MIC) that microorganisms do not produce at the end of the period, there is a minimal amount of inhibitory concentration.

- Broth dilution (dilution in liquid medium) test In this method, microorganisms to be tested in liquid medium containing different concentrations of chemotherapeutic agent are inoculated and incubated.
- The MIC (minimal inhibition concentration) value of the last tube (where the medium is clear) and the MBC (minimal bacteriocidal concentration) are the concentrations at which the bacterium does not reproduce when cultured from solid tuber to clear medium.


Concentrations
(μg./ml.)
64
32
16
8
4
2
1
Control