Antibiotics and chemotherapeutics

definition
mechanism of action
type of action
toxicity and undesirable actions
types of antibiotics, rational therapy
ANTIBIOTICS (ATB)

- Selectively inhibit or kill microbes in concentrations that are not toxic for macroorganism
- not like desinfections and antiseptics, ATB can be used inside human body
- Antibiotics (ATB), antimicrobial (ATM) agents are also chemotherapeutics with antimicrobial activity that have
  - source in the nature
  - been produced artificially
CHEMOTHERAPEUTIC AGENTS

FOLIC ACID
PTERIDINE
PABA
GLUTAMIC ACID

SYNTHESIS OF FOLIC ACID

SYNTHETASE

SULFANILAMIDE DERIVATIVE

INFECTION S. AUREUS

BLOCKED FOLIC ACID SYNTHESIS: COMPETITIVE INHIBITION
ATB according to their source:

Producers can be:

1. actinomycetes - aminoglycosides, tetracyclines, macrolides
2. other bacteria (mostly *Bacillus sp.*) - bacitracin, polymyxin
3. microscopic fungi (*penicilium, aspergilum*) - penicilíny

ATB can be derived also from plants - fytoncides
- from animal tissues – ecmolins
ATB according to the aim group:

1. antibacterial, antibiotics in proper sense  
   -mostly used common

2. antimycotics  
   -against molds and yeast

3. antiprotozoal  
   -against eucaryotic worms, protozoa

4. antiviral  
   -certain antiviral chemotherapeutics
**Bakteriostasis**
- situation when ATB inhibit multiplication, division of bacterial cell
- bacteria are not killed

Natural dieing of living form of bacteria is not influenced

**Baktericidia**
- killing of bacterial cells by ATB
- specific impact is during the first 4 hours of ATB therapy
- if during this period 99% of bacterial populations is killed the bactericidia is clinically relevant
ATB according to the type of action

1. Primary bakteriostatic
   - chloramphenikol
   - tetracyclins
   - macrolides
   - sulphonamides
   - nitrofurans...

2. Primary baktericidal
   - penicilins
   - cephalosporins
   - streptomycine
   - polymyxin,...

Penicilins and cephalosporins are acting only on dividing bacteria.
Aminoglykosides kill also resting, not dividing cells.
ATB according to the spectrum of action:

1. Narrow spectrum of ATBs and chemotherapeutics
   - allow the targeted therapy of usually 1 bacterial group, species
     Mycobacterium sp, G+, or only staphylococci:
     napr. antituberculotics, antistaphylococcal atbs

2. Broad spectrum ATBs and chemotherapeutics – active on several species (G+ and G-)
   - aminoglycosides
   - ampicilin
   - chloramphenicol
   - tetracyclins
   - sulphonamides
Mechanism of action at the level of:

1. Synthesis of cell wall
2. Disruption of protoplasmatic membrane
3. Inhibition of proteosynthesis
4. Interference of nucleic acid metabolism
Mechanism of action:

1. **Inhibition of synthesis of peptidoglycans of cell wall**

Synthesis is going on in 4 phases:

I. synthesis of monomers, II. condensation, III synthesis of phospholipids in cell wall, IV incorporation of peptidoglycan in the preexisting cell wall structure

- I to III: bacitracin, vancomycin, cycloserin
- IV penicillines, cephalosporines

**beta-lactam ATBs** – those that have heterocyclic beta lactam ring – PNC, cephalosporins – inhibit synthesis of peptidoglycans

vancomycin, teicoplanin – inhibition of condensation of monomers

acyl-D-alanyl-D-Ala

bacitracin - inhibition of phospholipids synthesis
Mechanism of action

2. Disruption of protoplasmatic membrane
   - polymyxin ATBs,
   - some of polyen antimycotics

Polymyxins bind lipid and protein molecules and unables bariere function of plasmatic membrane

- polymyxins - phospholipids of cytoplasmatic membrane
- amphotericin B – synthesis of ergosterol
- asoles - synthesis of ergosterol
Mechanism of ATBs action:

3. **Inhibition of proteosynthesis**
   - tetracyclins, macrolides, aminoglycosides, ...
   - inhibition of the binding of aminoacyl-tRNA on receptors of ribosomes
   - lack of amino acids
   - inhibition of polysomes formation from free ribosomes and mRNA

- chloramphenicol
- tetracyclins
- macrolides
- clindamycin
- aminoglycosides
Mechanism of ATBs action

4. Inhibition of nucleic acid metabolism

Nucleic acids:
- chinolons
- Rifampicin
- Nitroimidazoles
- DNK-gyrase
- RNK-polymerase
- Synthesis of folic acid:
- Sulfonamids
- Trimetoprim
- Reductase of dihydrofolic acid
Groups of antibacterial ATBs

penicilins - synthesis of peptidoglycan of cell wall
cefalosporins -
carbapenems -
monobactams -
inhibition of beta-lactamase
aminoglycosids -
tetracyclins - synthesis of microbial proteins
chloramphenicol -
macrolids -
polypeptids - synthesis of cell wall structures
lincosamids - proteosynthesis
glykopeptids - synthesis of mucopeptids of cell wall
Antibacterial chemotherapeutics

sulphonamids - synthesis of folic acid
sulphonamids
-diaminopyrimidins

nitrofurans - inhibition of glycid metabolism
chinolons - synthesis of nucleic acids

nitroimidazoles - synthesis of nucleic acids anaerob bacteria
Penicilins - primary bactericidal

G PNC - G+ - streptococci, pneumococci, corynebacteria, listeriae, staphylococci not producing beta lactamase

Antistaphylococcal PNC – resistant to betalactamase produced by staphylococci
- meticilin, oxacilin

Broad spectrum PNC - G – rods, not nonfermenters, not proteus, not enterococci
- ampicilin

Antipseudomonad PNC – against pseudomonas, proteus indol +
- carbapenems

AcylureidoPNC - G+, G-, pseudomonas
ANTIBIOTICS: PENICILLIN

PENICILLIN
BETA LACTUM NUCLEUS ATTACHED GROUP

PENICILLIUM MOLD

STAPHYLOCOCCUS KILLED BACTERIUM

PEPTIDOGLYCAN LAYER CARBOHYDRATE SHEET PENICILLIN-BINDING PROTEIN AMINO ACID SIDE CHAIN PEPTIDE CROSS BRIDGE

PENICILLIN RESISTANCE

PENICILLIN PENICILLIN RESISTANT BACTERIA PENICILLINASE PENICILLOIC ACID

SITE OF ENZMME ACTION
Cephalosporins
- semisynthetic
- bactericidal
- high concentration in urine and CSF

1st generation - G +
   G - enterobacteriae, urinary tract infection

2nd generation - G - rods
   G - cocci

3rd generation - G-

4th generation - enterococci, staphylococci, pseudomonas
**Other betalactams**

monobactams: bactericidal

G - enterobacteriaceae, serratia, pseudomonas

karbapenems: baktericidal

G+  G-

very broad spectrum

**Chloramphenicol**: bacteriostatic

G+  G-

**Tetracyclines**: bakteriostatic, in higher concentration

bactericidal  G+  G-

treponema, leptospira, mycoplasma, chlamydia
Macrolides: bacteriostatic, mid broad spectrum, G +

Aminoglycosides: baktericidal broad spectrum, G + G-

Polypeptids: baktericidal G - rods (exc. proteus)

Linkomycin, clindamicin - G+ cocci Vancomycin G+ (staphylococci, enterococci)
Antituberculotics: bakteriostatic
  toxic
  only for TBC
  rifampicin
  INH, ETM, PYR, PAS
Chemotherapeutics

sulfonamids: bacteriostatic
\[ G + G^- \]
*chlamydia, mycoplasma, nocardia, toxoplasma*

cotrimoxazol: combination of trimetoprim+sulfametoxasol (both bacteriostatic, but in combination the effect is clinically baktericidal)
\[ G + G^- \]
chinolons

baktericidal

1.gen. nalidixin acid  G-, uroinfections

2.gen. Fluorochinolons, G +, G-

3.gen. Di.-Tri.-fluorated chinolons
Undesirable effect

arising when normal general doses and recommended concentrations of ATBs are applied

Toxic effect

arising when high doses and elevated plasmatic concentration are reached, or are cause by higher reactivity of organisation or unfunctional elimination ways
Undesirable effects

Alergy – usually after sensibilisation caused by very small dose and given in not natural way
- frequent in PNC
- look for them in history
- polymorphic exanthema, eosinofilia, edema, conjunctivitis
  photodermatoses, anaphylactic shock...
- dangerous forms in parenteral application of ATB
- can arise as early or late, whenever during therapy or after it ended
- reaction could be caused by other molecules (adjuvants, conservations)
Undesirable effects

- are connected with the influence of natural bacterial flora of skin or mucous membranes
- frequent in broadspectrum ATBs (ampicilin, tetracyklín)

- clinically like dyspepsia, diarrhoeae, hypovitaminosis K, subsequent disorders of hemostasis

- overgrowth of candida or resistant bacteria staphylococci, pseudomonas
  these complications are problem for therapy pseudomembran colitis
Toxic effects

hematotoxic - gancyclovir, chloramphenicol

nefrotoxic - amfotericin B

hepatotoxic - rifampicin, ketokonolasol

neurotoxic - nitrofurantoin, gentamycin, izoniazid, streptomycin
Resistence – of bacteria to the effect of ATB or chemotherapeutics

- natural – microbes are out of spectrum of ATB (bacteria without cell wall to PNC)

- primary – not sensitivity of a part of bacterial population, that is normally in spectrum of ATB efficiency and without any influence of preliminary therapy with that ATB

- secondary – not sensitivity of the strain belonging to the spectrum of ATB, that arises after exposition to the that ATB

- mutational – related to previous therapy, mutation – resistention – multiplication of resistent bacteriae
- Transmissible resistance – mediated by plasmids
  - More frequent in G-
  - Transmission of genetic information

Transduction – by bacteriophage to another bacterium

-Cross resistance – not sensitivity to several ATB
  - Bidirectionnal (relative ATB)
  - Onedirectionnal (Gent.-Amikacin),
Mechanism of resistance

1. Production of enzymcs: their activity changes the structure of antimicrobial and it causes the loss of efficiency

**Beta laktamase** – extracellularly acting enzymcs of microbes, that disrupt beta lactam ring so that ATB of these type loss the efficiency.

The similar effect is seen in intracellularly acting *acetyltransferázy* on chloramphenicol.
<table>
<thead>
<tr>
<th>Classification of betalactamases</th>
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<tr>
<td><strong>Cefalosporinase (not inhibited by clavulanic acid)</strong></td>
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<tr>
<td>Chromosomally mediated ensyms</td>
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<tr>
<td>Ps. aeruginosa, Enterobacter cloacae</td>
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<td><strong>Penicillinase, cefalosporinase</strong></td>
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<td>Mediated by plasmids</td>
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<td>TEM-typ., Chromosomally mediated ensyms Klebsiela</td>
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<td>Staphylococcal ensyms</td>
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<tr>
<td>Ensysms hydrolysing imipenem, Xantomonas maltophilia</td>
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<td>Chromosomally mediated Ps. cepacia</td>
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2. **Mutation at the level of intracellular receptor:**

- changes in structures of PBP - resistance to PNC
- methylation of aminoacids on 50 S ribosomes subunits - resistance to erytromycin

3. **Inhibition of penetration of ATB through cell wall:**

aminoglycosids, tetracyclines

4. **Changes in metabolic pathway, in affinity of target ensym**

5. **Higher elimination of ATB - efflux**
<table>
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<th>ATB Group</th>
<th>Mechanisms</th>
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<tr>
<td>beta lactam ATB</td>
<td>changes in PBP, decreased permeability, production of enzymes</td>
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<tr>
<td>aminoglycosids, macrolids</td>
<td>decreased binding to target ribosomes, decreased permeability of the cell wall, inactivating enzymes</td>
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<tr>
<td>chloramphenicol</td>
<td>decreased binding on ribosomes, permeability, acetyltransferase</td>
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<td>tetracyclines</td>
<td>unavailability of target ribosomes, active efflux</td>
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<td>Drug</td>
<td>Resistance of DNA-gyrase</td>
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Etiological therapy - is ideal
- isolation of agens
- ATB sensitivity testing
- choice of ATB
  (good acceptance, narrow spectrum)
- in chronic disease caused by resistant microbes

Empiric therapy - choice of ATB acc. to expected spectrum of etiological agens
- evaluation of clinical state
- knowledge of most common ethiological agens
**Intervention therapy** - if the ethiological microbe was not identified

- according to algorithm that will identify next therapy if the initial was not successful

**Broadspectrum therapy** – in life threatening infections

- ATB able to cover almost the whole spectrum of possible agencies
- combination of several ATB
- used in cases of sepses, peritonitis,
- imipenem, cefotaxim+piperacillin
• **Combination of ATBs**
  
to increase the efficiency
  increase the spectrum of target bacteria
  prevention of bacterial resistence

**Additive effect** – resulting effect of the combination of 2 ATBs equals the addition of 2 effects

**Indifferent effect** no change of effect

**Antagonistic effect** – resulting effect of 2 used ATB is less efficient than use of individual ATB alone

**Synergy** – resulting effect of 2 used ATBs is higher than if used of individual ATB alone
ATB susceptibility testing

kvalitative test
- diffuse disc test

kvantitative
- MIC – minimal inhibition concentration
- MBC – minimal bactericidal concentration
- E test – combination of DDT and MBC

On liquid cultivation media (MIC) or solid media (DDT, E test, MBC)
ANTIBIOTIC SUSCEPTIBILITY TEST

BLOOD SAMPLE

1. Petri dish
2. Blood agar plate
3. 24 hour incubation period

BACTERIAL CULTURE

1. Cotton stopper
2. Broth solution

MUELLER-HINTON AGAR WITH BLOOD

1. Swing plate
2. Forceps
3. 18 hour incubation period

ANTIBIOTIC DISCS:

1. PENICILLIN G
2. CEPHALOSPORIN
3. NAPGCILLIN
4. CHLORAMPHENICOL
5. TETRACYCLINE
Minimal inhibition concentration (MIC)
- the lowest concentration of ATB that inhibits the growing and multiplication of bacterium in test medium in vitro.

-in testing MIC the standardisation of conditions is crucial, results can be influenced by the size of inoculum, quality of test medium, temperature....

Minimal baktericidal concentration (MBC)
-lowest concentration of ATB that kills in vitro exposed bacterial population during 24 hours incubation in liquid media and then inoculated on solid media.
Aplikation - parenteral
- peroral
- local

Doses - individual
- daily
- overall

Interval of doses
- time between individual doses
- correction in renal insufficiency
- depends on capacity of the elimination of ATB from the body

Age – old, young, newborn
Disease – some ATBs do not enter the target place, or do not be active in some places
Period of therapy – individual (nen complicated gonorrhoeae)

-7-10 days – common infection of respiratory thract

- longlasting - absces, granulomas, osteomyelitis tuberculosis, sepsa, endokarditis, borreliosis, chlamydiosis

- immunodeficient