

Antibiotics and chemotherapeutics

definition

mechanism of action

type of action

toxicity and undesirable actions

types of antibiotics, rational therapy

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ANTIBIOTICS (ATB)

- Selectively inhibit or kill microbes in concentrations that are not toxic for macroorganism
- not like disinfections 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

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 - phytoncides

- 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 bakteristatic

- 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. antituberculosics, . 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 penicilines, 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 aminoacids
- 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 -DNK-gyrase
- rifampicin -RNK-polymerase
- nitroimidazoles -

Synthesis of folic acid :

- sulfonamids - synthesis of folic acid
- 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 produce 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

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 : bakteristatic, 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+sulfametoxazol (both bacteriostatic, but in combination the effect is clinically bactericidal)

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 caused by higher reactivity of organism or unfunctional elimination ways

Undesirable effects

Allergy – 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 formes 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

- biological - **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, ketokonazol

neurotoxic - nitrofurantoin, gentamycin, izoniazid,
streptomycin

Resistance – of bacteria to the effect of ATB of 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 – resistance – multiplication of resistant
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 enzymes:

their activity changes the structure of antimicrobial and it causes the loss of efficiency

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

The similar effect is seen in intracellularly acting acetyltransferázy on chloramphenicol.

Classification of betalactamases

Cefalosporinase (not inhibited by clavulanic acid)

Chromosomally mediated enzymes

Ps.aeruginosa,
Enterobacter.cloacae

**Penicilinase,cefalosporinase
Inibited by clavulanic acid**

Mediated by plasmids

TEM-typ.,

Chromosomally mediated enzymes Klebsiela

spp.,staphylococcal enzymes

Metaloenzymes

Enzymes hydrolysing

imipenem, Xantomonas

maltophilia

Penicilinase(not inhibited by clavulanic acid)

Chromosomally mediated

Ps.cepacia

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 erythromycin

3. Inhibition of penetration of ATB through cell wall:

aminoglycosids, tetracyclines

4. Changes in metabolic pathway, in affinity of target enzyme

5. Higher elimination of ATB - efflux

Most common mechanism of resistance in groups of ATB

Beta lactam ATB

**changes in PBP,
decreased permeability,
production of enzymes**

aminoglycosids, macrolids

**- decreased binding to target
ribosomes**

decreased permeability of the cell
wall

inactivating enzymes

chloramfenicol

decreased – binding on ribosomes

- permeability

- acetyltransferase

tetracyclines

unavailability of target ribosomes

active efflux

Chinolons

resistence of DNA -gyrase
decreased permeability
aktive cell efflux

sulfonamides

resistence of syntetase

trimetoprim

rezistene of reduktase
decreased permeability

Etiological therapy - is ideal

- isolation of agents
- 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 agents

- evaluation of clinical state
- knowledge of most common ethiological agents

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 agenses
- combination of several ATB
- used in cases of sepsis, peritonitis,
- imipenem, cefotaxim+piperacilin

- Combination of ATBs

to increase the efficiency

increase the spectrum of target bacteria

prevention of bacterial resistance

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)

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, newborne

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 tract

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