Antibiotics and chemotherapeutics

definition

mechanism of action

type of action

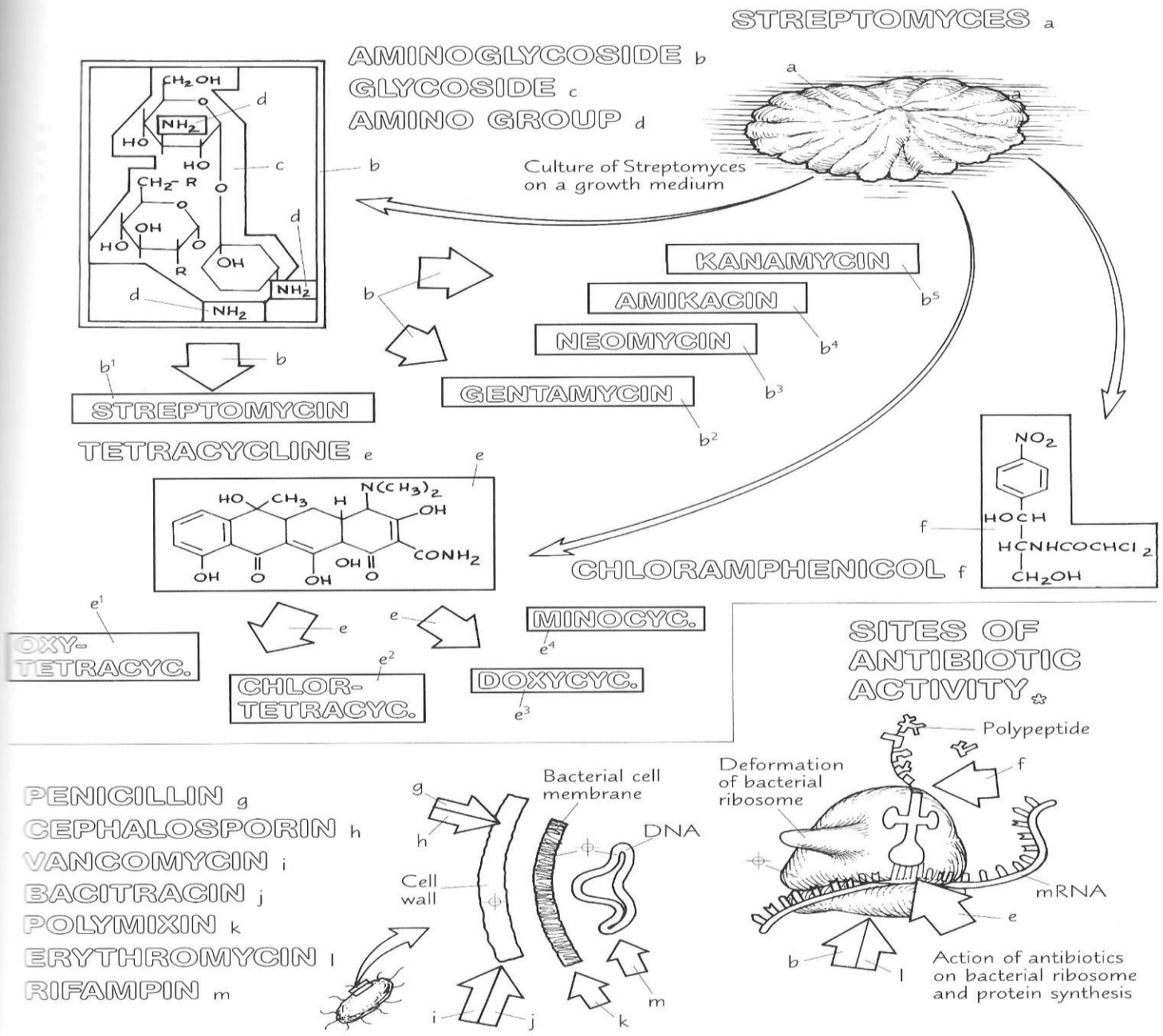
toxicity and undesirable actions

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 chemoterapeutics with antimicrobial activiry that have
  - source in the nature
  - been produced artifitially

ANTIBIOTICS



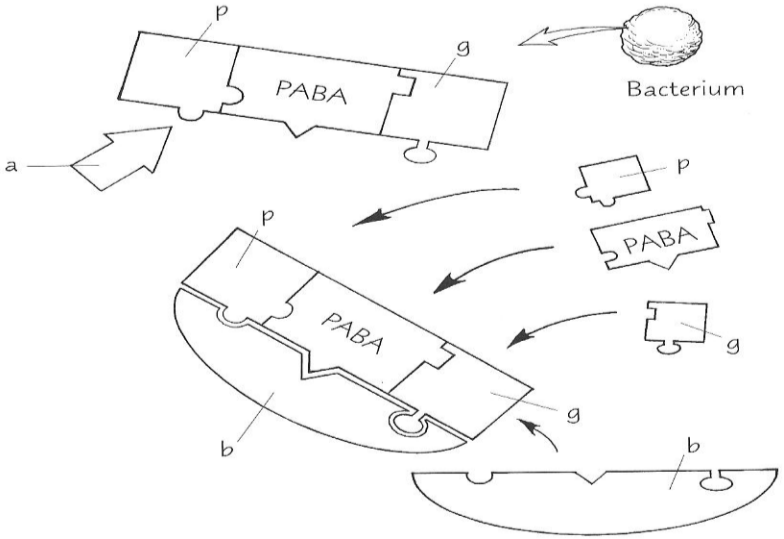
CHEMOTHERAPEUTIC AGENTS

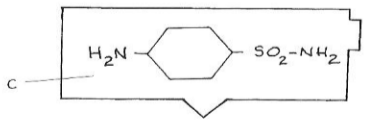
FOLIC ACID a
PTERIDINE p
PABA PABA
GLUTAMIC ACID g

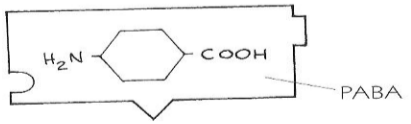
SYNTHESIS OF FOLIC ACID

SYNTHETASE b

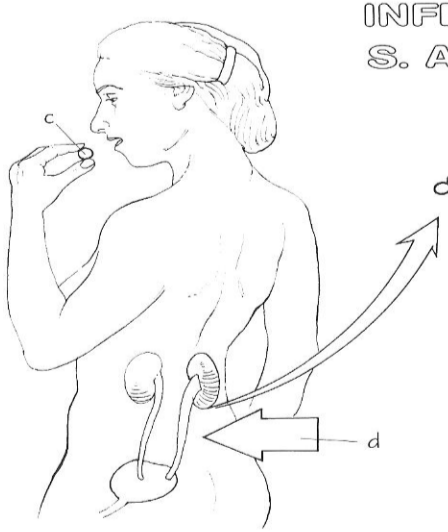
SULFANILAMIDE DERIVATIVE c

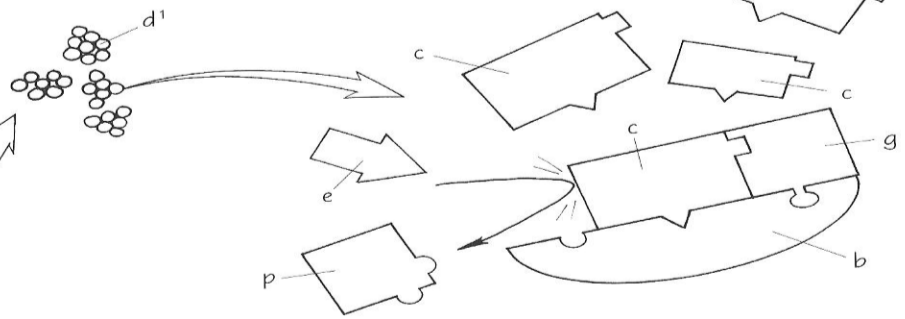






INFECTION d
S. AUREUS d¹





BLOCKED FOLIC ACID SYNTHESIS: COMPETITIVE INHIBITION e

ATB according to their source:

Producers can be:

1.actitnomycetes - aminoglycosides,tetracyclines, macrolides
2.other bacteria (mostly *Bacillus sp*.) - bacitracin, polymyxin

3.microscopic fungi (*penicilium*, *aspergilum*) - penicilíny

ATB can be derived also form plants - fytoncides
- from annimal 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. 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,cyckloserinn
- 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
-nitroimidasoles -

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 -inhibtion of glycid metabolism

chinolons -synthesis of nucleic acids

nitroimidasoles –synthesis of nucleic acids anaerob bacteria

Penicilins -primary bactericidal

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

antistaphylococcal PNC – resistent to betalactamase produce by staphylococci

- meticilin,oxacilin

broad spectrum PNC - G – rods, not nonfermenters, not proteus, not enterococci

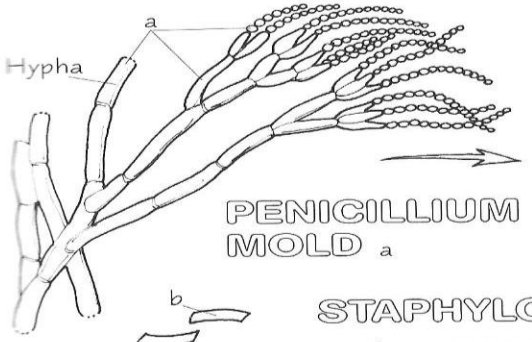
- ampicilin

antipseudomonad PNC – against pseudomonas ,proteus indol +

- carbapenems

acylureidoPNC - G+,G-,pseudomonas

ANTIBIOTICS: PENICILLIN

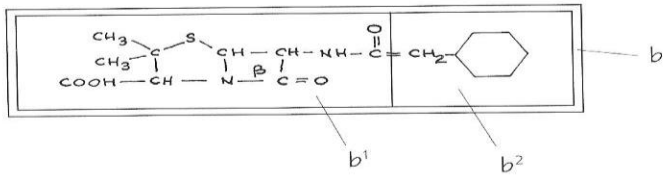


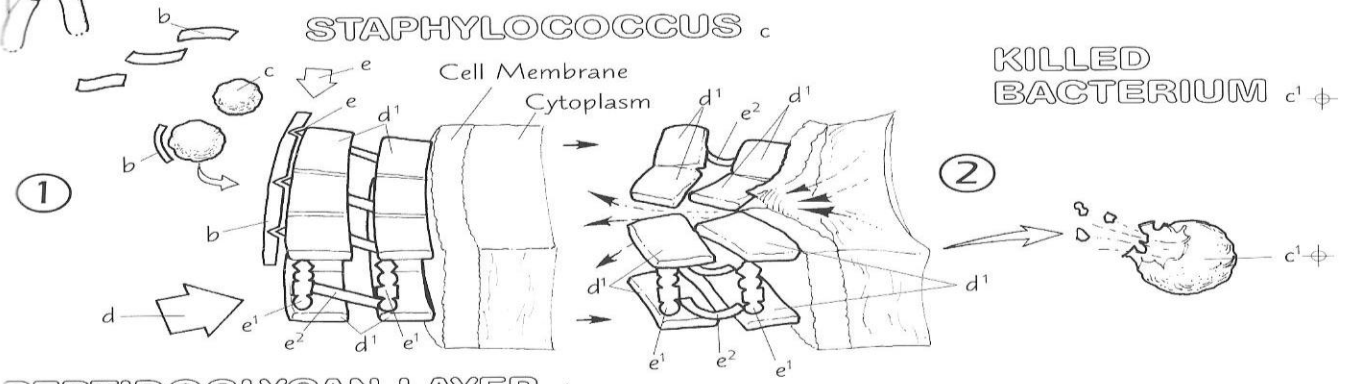
PENICILLIUM MOLD a

PENICILLIN b

BETA LACTUM NUCLEUS b^1

ATTACHED GROUP b^2





PEPTIDOGLYCAN LAYER d

CARBOHYDRATE SHEET d^1

PENICILLIN-BINDING PROTEIN e

AMINO ACID SIDE CHAIN e^1

PEPTIDE CROSS BRIDGE e^2

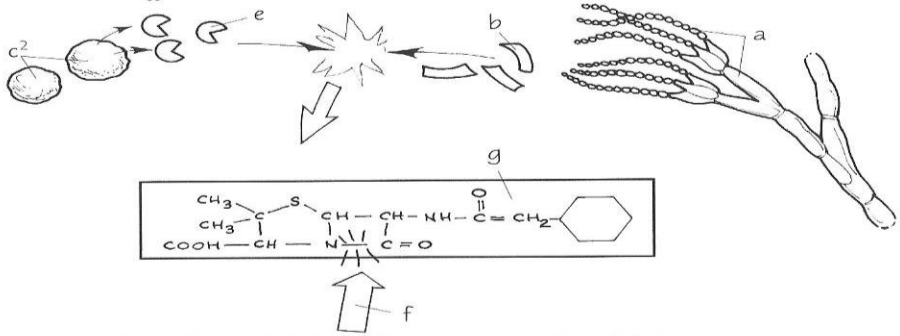
PENICILLIN RESISTANCE

PENICILLIN b

PENICILLIN RESISTANT BACTERIA c^2

PENICILLINASE e

PENICILLOIC ACID g



SITE OF ENZME ACTION f

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,chlamydi

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 (bot
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 recomended 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,eosinofília,edema,conjunctivitis photodermatoses,anaphylactic shock...

-dangerouse 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, diarhoeae, hypovitaminosis K, subsequent disorders of hemostasis

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

Toxic effects

hematotoxic - gancyclovir,chloramphenicol

nefrotoxic - amfotericin B

hepatotoxic - rifampicin, ketokonasol

neurotoxic - nitrofurantoin, gentamycin, izoniazid, streptomycin

Resistence – of bacteria to the effect of ATB ot 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 spectrun of ATB efficiency and without any influence of preliminary therapy with that ATB

-secundary – not senzitivity of the strain belonging to the spectrum of ATB, that arisis after exposition to the that ATB

-mutational – related to previous therapy,
mutation – resistention – multiplication of resistent bacteriae

- transmissible resistence – mediated by plasmids

- more frquent in G-
- transmission of genetic information

Transduction – by bacteriophage to another bacterium

-cross resistence – not sensitivity to several ATB

- bidirectionnal (relative ATB)
- onedirectionnal (Gent.-Amikacin),

Mechanism of resistence

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

Beta laktamase – extracelularly acting ensyms of microbes, that disrupt beha lactam ring so that ATB of these type loss the efficiency.

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

Classification of betalactamases

Cefalosporinase (not inhibited by clavulanic acid)	**Chromosomally mediated ensyms** Ps.aeruginosa, Enterobacter.cloacae
Penicilinase,cefalosporinase Inibited by clavulanic acid	**Mediated by plasmids TEM-typ., Chromosomally mediated ensyms Klebsiela spp.,staphylococcal ensymss**
Metaloensyms	**Ensyms hydrolysing imipenem, Xantomonas maltophylia**
Penicilinase(not inhibited by clavulanic acid)	**Chromosomally mediatedy Ps.cepacia**

2. Mutation at the level of intracellular receptor:

-changes in structures of PBP- resistence to PNC
-metylation of aminoacids on 50 S ribosomes subunits - resistence 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

Mostcommon mechanism of resistence in groups of ATB

Beta lactam ATB — **changes in PBP,**
decreased permeability,
production of ensyms

aminoglycosids,macrolids - **decreased binding to target ribosoms**
decreased permeability of the cell wall
inactivating ensyms

chloramfenicol — **decreased** – binding on ribosomes
- permeability
- acetyltransferase

tetracyclines — **anavaibility 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 agens
- ATB sensitivity testing
- choice of ATB
  (good acceptance, narrow spectrum)
- in chronic disease caused by resistent microbes

Empiric therapy **- choice of ATB acc.to expected spectrum of etiological agens**

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

<u>Intervention therapy</u>- if the ethiological microbe was not identified

- according to algorithm that will identify next therapy if the inicial was not successfull

<u>Broadspectrum therapy</u> – in life threatning infections

-ATB able to cover almost the whole spectrum of possible agenses

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

- **Combination of ATBs**

to increase the efficiency
increase the spectrum of target bacteria
prevention of bacterial resistence

Aditive effect – resulting effect of the combination of 2 ATBs equals the addition of 2 effects

Indiferent effect no change of effect

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

Synergy – resulting effect of 2 used ATBs is higher then if used of individual ATB alone

ATB susceptibility testing

kvalitative test

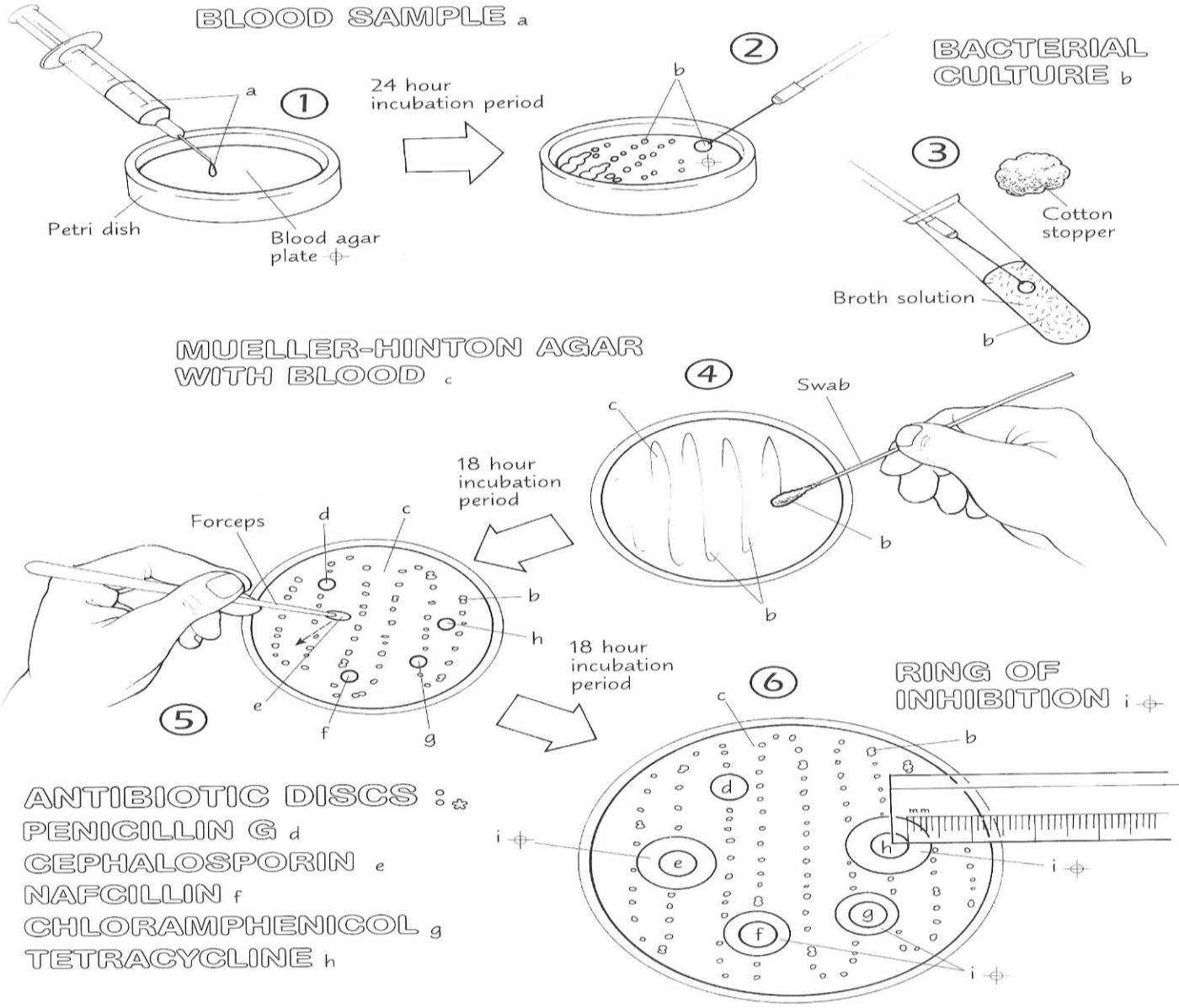
- difuse disc test

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



Minimal inhibition concentration (MIC)

- the lowest concentration of ATB that inhibits the gorwing 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 innoculum, 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 innoculated on solid media.

Aplikation -parenteral
- peroral
-local

Doses -individual
-daily
-overall

Interval of doses
- time between individual doses
- correction in renal inssuficiency
- 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 thract

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