Antibiotic drugs

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Chemotherapy

- coined by Ehrlich
- antibiotics or anticancer drugs?
- antibiotics
  - drugs produced by microorganism, or manufactured by pharmaceutical industries that kill or inhibit the growth of other microorganisms
  - selective toxicity
    - toxic for the pathogens but, innocuous for the host
    - different functional /structural properties

human cell vs. bacterial cell

	Human cell	Bacterial cell
DNA	Nucleus	Chromosome, plasmid
Cell type	Eukariotic cell	Prokariotic cell
Membrane	Lipids, lipopolisacharids, sterols	LPS, no sterols
Osmotic resistance	Low	High
Cell wall	No (only membrane)	peptidoglycan
Mitochondria	+	-
Moving	-	Flagella, pilus

Potential targets of the AB therapy

- Class I reactions
  - reactions, that utilize glucose and other carbon sources to produce ATP
- Class II reactions
  - reactions, that utilize Class I product to synthesise essential molecules (folates, amino acids, nucleotides)
- Class III reactions
  - pathways, that convert small molecules into macromolecules (protein, DNA, peptidoglycan)

Potential targets of the AB therapy

- Class I reactions
  - no inhibition (alternative pathways for energy source)

- Class II reactions
  - folate supply
    - bacterias - „de novo”; humans – obtain from diet
      - sulfonamides – stuctural analog of PABA, inhibition of folate synthesis (bacteristatic effect)
      - trimethoprim, pyrimethamine – inhibition of DHFR (folate utilisation)
  - pyrimidine and purine analogues (chemotherapeutic drugs)

Potential targets of the AB therapy

- Class III reactions
  - peptidoglycan synthesis
    - essential structural component of the cell wall
    - main components:
      - NAMA (N-acetyl muramac acid)
      - NAG (N-acetyl-glucosamine)
    - penicillins (β-lactam antibiotics) prevents the cross-linking
    - cycloserine, vancomycin, bacitracin
  - protein synthesis
    - different ribosomes (50S-30S) from eukariotic cell (60S-40S)
    - structural components
      - mRNA, tRNA,
      - binding sites for tRNA: E, P, A
    - ABs' effects
      - preventing binding of tRNA – tetracyclines
      - promoting misreading of mRNA – aminoglycosides
      - inhibiting transpeptidation – chloramphenicol
      - inhibiting translocation from A to P – erythromycin
  - DNA synthesis
    - inhibiting DNA gyrase – fluoroquinolones (ciprofloxacin)

Resistance to antibiotic drugs

- disturbing/increasing problem in medical wards
- MRSA, Enterococci strains, MACI

- genetic determinants of AB resistance
  - chromosomal mutations
  - plasmid: extrachromosomal genetic element
    - R genes – R plasmids (resistance)

- the transfer of genetic elements
  - transposons
    - small genetic elements
    - carry genetic information between two plasmids within the bacterium
  - conjugation
    - cell to cell contact
  - transduction
    - viral transduction
    - resistant gene is included in the viral genom
  - transformation
    - taking up DNA from the environment

Resistance to antibiotic drugs

- biochemical mechanisms
  - production of enzymes that inactivate the drug
    - β-lactamase – inact. of penicillin
    - acetyltransferases - inact. of chloramphenicol
  - alteration of drug binding sites
    - alteration in 30S or 50S subunit of the ribosome
      - inact. of chloramphenicol, aminoglicosides
  - reduction of drug uptake/accumulation by the bacterium
    - promoting of energy dependent efflux
      - inact. of. tetracyclines
  - alteration of enzyme pathways
    - DHFR isoforms
    - dihydropteroate synthetase

Antibiotics

- Sulfonamides
  - bacteriostatic
  - discovered in 1930
  - prontosil (dye) → sulfanilamide
  - sulfadiazine, sulfadimidine, sulfapyridine, sulfomethoxazole
  - mech. of action:
    - structural analog of PABA (premetabolite of folate) (active folic acid synthesis in bacteriel cell)
    - competition to dihydropteroate synthetase (PABA → folate) – decreased folate synthesis
    - NB! PABA esters (procaine – local anaesthetic) – reduced antimicrobal effect
  - well absorption
  - a.e.:
    - headache, mental depression, skin rash, allergic reactions
  - therapeutical indic.:
    - urinary tract infection
    - conjunctivitis (local appl.→Irgamid®)
    - IBD – sulfasalazine (5-ASA + sulfapyridine)

- Trimethoprim
  - bacteriostatic
  - mech. of action:
    - inhibiting of DHFR
  - high concentrations in lungs, kidneys
    - Pneumocystitis carinii
    - urinary tract infection
  - adverse effects:
    - megaloblastic anaemia
  - combination with sulfomethoxazole (co-triomethoxazole) - Sumetrolim® - bactericid!!!

β-lactam antibiotics

- Penicillin(s)
  - baktericid
  - product of mould (genus *Penicillium*)
  - considerable anti-staphylococci effect
  - 1928 – Alexander Fleming
  - mechanism of action
    - interfere with cell wall synthesis (peptidoglycan)
      - penicillin binding proteins (PBP) –transpeptidation/cross linking
      - penicillins inhibits this process (unstable cell wall, decreased osmotic resistance)
  - structure: 6-amino-penicillinic-acid
    (β-lactame-ring + thiazollidine ring + side chains!)
  - Forms/Classes:
    - Basic penicillines
      - benzyl-penicillin (Penicillin-G)
      - procain penicillin (Retardilln) – i.m.
      - Penicillin V (Maripen) – stabile at gastric pH – p.o.
    - β lactamase resistant penicillines
      - meticillin (MRSA)
      - oxacillin (osteomyelitis)
    - Broad spectrum penicillines
      - ampicillin
      - amoxicillin
    - Broad spectrum penicillins combined with β-lactamase inhibitors
      - amoxicillin + clavulanic acid
      - ampicillin + sulbactam
  - a.e.:
    - allergic reactions – acute anaphylactic reactions!
  - th. indications:
    - Gramm (+) cocci (Staphylococci, Streptococci, Neisseria)

β-lactam antibiotics

- Cephalosporines
  - bactericid
  - structure: 7-amino-cephalosporanic-acid
  - high concentrations in meninx, gall bladder, bons
  - mechanism of action
    - similar to penicillins
  - Forms
    - 1st generation
      - cefazolin, cefalexin
      - spectr.: Staphylococc., Streptococc.,
    - 2nd generation
      - cefuroxim, cefaclor
      - spectr.: + anaerob
    - 3rd generation
      - cefotaxim (Claforan), ceftriaxon (Rocefin)
      - spectr.: Gonococcus
    - 4th generation
      - cefepim
  - a.e.:
    - allergic reactions (10% of penicillin allergy), diarrhea (excretion to gall bladder)
  - th. indications:
    - septicaemia, meningitis, otitis, biliary tract infection, urinary tract infection, sinusitis

Other β-lactam antibiotics

- Carbapenems
  - imipenem, meropenem, ertapenem
  - same mech. of action
  - broad spectrum!
  - resistant to β lactamase

- Monobactams
  - aztreonam
  - Gramm (-) aerobic rods (Pseudomonas, Neisseria, Haemophilus)
  - same action
  - parenteral application

Antibiotics

- Tetracyclines
  - tetracycline, doxycicline, demeclocycline, oxytetracycline
  - very broad antibacterial spectrum
    - Gramm (+) cocci, rods
    - Gramm (-) cocci, rods
    - Mycoplasma, Rickettsia, Chlamydia ssp.
  - bacteriostatic
  - mechanism of action
    - inhibiting protein synthesis
      - preventing binding tRNA to ribosomes 30S
  - widespread resistance
  - adverse effects:
    - photosensitivity
    - erradicating gut flora: pseudomembranosus colitis
    - forming chelate complaxes (Ca^{2+})
      - teeth-bone deformation/hypoplasia
    - vestibular disturbances
  - th.:
    - acne
    - Rickettsia, Chlamydia infections
    - borelliosis
  - other indication:
    - inappropriate secr. of ADH – demeclocycline inhibits ADH action

Antibiotics

- Chloramphenicol
  - bacteriostatic
  - broad antibacterial spectrum
    - Gramm(+) bacterias
    - Gramm(-) bacterias
    - Rickettsias
  - inhibits protein synthesis
    - blocking transpeptidation in ribosome 50S
  - rapidly, completely absorbed
  - a.e.:
    - depression of bone marrow
      - pancytopenia
    - grey baby syndrome
      - Avoid at newborns!
      - vomitting, hypotonia, hyporeflexia, flaccidity, low temperature
  - th. indications:
    - serious, multiresistant infections
      - multiresistant Haemophilus influansae inf.
      - meningitis
      - abscesssus in CNS
    - bacterial conjunctivitis (topically)

Antibiotics

- Aminoglycosides
  - bactericid
  - gentamycin, amikacin, tobramyin, neomycin
  - inhibit protein synthesis
    - promote misreading of mRNA in ribosome 30S
  - broad spectrum
    - resistant: anaerob bacterias (O_2 dependent active transport)
  - parenteral application
  - a.e.:
    - ototoxicity
      - cochlear, vestibular damage (irreversible)
    - nephrotoxicity
  - th. indic.:
    - osteomyelitis (locally – Septopal)
    - skin infections (topically – Gentamycin gel)
    - urinary tract infections
    - Listeria, Pseudomonas aeruginosa

Antibiotics

- Macrolides
  - bacteristatic
  - structure: macrocyclic lactone-ring
  - clarithromycin, azythromycin, spiramycin
  - inhibiting bacterial protein synthesis
    - inhibiting mRNA translocation in ribosome 50S
  - alternative choice at penicillin allergy
  - obligate i.c. microorganisms (Chlamydia, Mycoplasma)
  - oral administration
  - a.e.:
    - GIT disturbances
    - diarrhea – prokinetic effect – motilinR

- Streptogramins
  - bactriostatic
  - quinupristin, dalfopristine combination (3:7)
  - inhibit protein synthesis
    - inhibit protein formation in ribosomal 50S
  - cyclic peptid structure
  - antimicrobal spectrum
    - Gramm(+) bacterias
    - MRSA
    - VR Enterococcus
  - parenteral application (i.v.)

Antibiotics

- Lincosamides
  - bacteriostatic
  - clindamycin
  - inhibit protein synthesis in ribosome 50S
  - antimicrobal spectrum
    - Gramm (+) cocci
    - Bacteroides
  - oral, parenteral application
  - pseudomembranosus colitis – Clostridium difficile (Klion!)

- Fluroquinolones
  - structure: nalidixic acid derivatives
    - 1st generation
      - nalidixic acid – narrow spectrum
      - norfloxacin
    - 2nd generation
      - ciprofloxacin
      - ofloxacin
      - moxifloxacin
  - interfering DNA gyrase (topoisomerase II)
  - broad spectrum
    - Gram (+) bacterias
    - Gram (-) bacterias
    - Enterobacteriaceae
    - Neisseria, Campylobacter
  - th. indications:
    - complicated urinary tract infection
    - infections resistant to penicillins, cephalosporines, amynoglycosides
  - oral application
  - a.e.:
    - QT prolongation (EAD – TdP)
    - convulsions

Microorganism	First choice AB	Second choice AB
Staphylococcus □non β-lactamase prod. □β-lactamase prod. □MRSA □VRSA	 penicillin G (benzyl penicillin) β-lactamase resistant p. (amoxicillin+ clavulanic acid/sulbactam) vancomycin, gentamycin, teicoplanin quinupristin/dalfopristin or linezolid	 cephalosporin cephalosporin or macrolide ciprofloxacin or macrolide -
Enterococcus	benzylpenicillin + gentamycin	vancomycin
Pneumococcus	benzylpenicillin, ampicillin	cephalosporin
Neisseria gonorrheae	amoxicillin + clavulanic acid	cefotaxim
Neisseria meningitidis	amoxicillin + clavulanic acid	cefotaxim, chloramphenicol
Clostridium	benzylpenicillin, amoxycillin	cephalosporine, tetracycline
E. coli, Klebsiella, Enterobacter □urinary infection □septicaemia	 cephalosporine, quinolone aninoglycoside, cefuroxime	 ampicillin, amoxicillin imipenem, quinolone
Shigella	Fluoroquinolones	ampicillin, trimethoprim
Salmonella	Fluoroquinolones, ceftriaxone	amoxicillin, chloramphenicol
Haemophilus influenzae	ampicillin	cefuroxime
Vibrio cholerae	tetracycline	quinolone
Legionella pneumophila	macrolid	-
Pseudomonas aeruginosa	Fluoroquinolones	ampicillin, amoxicillin

Microorganism	First choice AB	Secondary choice AB
Brucella	doxycicline	-
Campylobacter	macrolide, fluoroquinolones	tetracycline, gentamycine
Treponema	benzylpenicillin	macrolide, ceftriaxone
Borellia (Lyme-disease)	tetracycline	-
Rickettsia	tetracycline	fluoroquinolones
Mycoplasma pneumoniae	tetracycline, macrolide	ciprofloxacin
Chlamydia	tetracycline	-
Pneumocystitis carinii (pneumonia in AIDS)	Co-trimoxazole	-

Clinical principles for antibiotic therapy

- exact, adequate indication
  - bacterial infection (viral infection?)
- adequate prescription
  - Consider the AB resistance!
  - sensitivity of the bacteria (broad-spectrum AB)
  - bactericid - bacteriostatic
- adverse effect profile
  - allergic reactions, diarrhea, etc.
- duration of therapy
  - at least 4-5 days long