Chemotherapeutic Agents

- Antibiotics
- Antifungals
- Antivirals
- Antiprotozoal
- Antihelmintics
- Anticancer drugs
Antibiotics

General Aspects:

• Principle:
  inhibit growth of bacteria without harming the host
  – Drug must penetrate body tissue to reach bacteria (exception: GI infection)
    (unique targets: cell wall, protein synthesis, metabolic pathways…)
  – Bacteria targeted must be within the spectrum of the AB
  – Drug can be bactericidal or bacteriostatic
  – Different agents can be combined for synergistic effect
    (Note: not all combinations are useful, e.g. cell wall synthesis inhibitors loose effectiveness when combined with bacteriostatic drugs)
  – Identification of the invasive microorganism necessary for optimal treatment

• General side effect:
  Alteration in normal body flora
  – GI tract harbors symbiotic bacteria which are killed by AB => resistant bacteria repopulate the niche = secondary or superinfection
    (most common: overgrowth of Clostridium difficile)
Antibiotics

- **Resistance:**
  
  *loss of efficacy of a given AB against a particular strain*
  
  - Frequently: *Staphylococcus aureus*, *pseudomonas aeruginosa*, *mycobacterium tuberculosis*

- **Acquisition:**
  
  - Spontaneous mutation
  - Adaption: drug metabolism (β-lactamase); alternative metabolic pathways
  - Gene transfer: plasmids (via conjugation and transduction); transposons

- **Manifestation:**
  
  - Microbes may increase manufacture of drug-metabolizing enzymes (penicillins)
  - Microbes may cease active uptake of certain drugs (tetracyclines)
  - Changes in receptors which decrease antibiotic binding and action
  - Microbes may synthesize compounds that antagonize drug actions

- Antibiotic use promotes the emergence of drug-resistant microbes (especially the use of broad-spectrum antibiotics)

**!!! The more ABs are used, the greater the chance of resistance !!!**
Antibiotics

• Resistance avoided/delayed by:
  – Using AB only when absolutely needed and indicated:
    AB often abused for viral infections (diarrhea, flu-symptoms, etc.)
  – Starting with narrow-spectrum drugs
  – Limiting use of newer drugs
  – (Minimizing giving antibiotics to livestock)
  – Identifying the infecting organism
  – Defining the drug sensitivity of the infecting organism
  – Considering all host factors:
    site of infection, inability of drug of choice to penetrate the site of infection, etc.
  – Using AB combinations only when indicated:
    Severe or mixed infections, prevention of resistance (tuberculosis)

Worldwide more than 500 metric tons antibiotics are used annually !!!
Antibiotics

Classification:

• **Cell wall synthesis inhibitors**
  – Beta-lactams (penicillins, cephalosporins, aztreonam, imipenem)
  – Poly-peptides (bacitracin, vancomycin)

• **Protein synthesis inhibitors**
  – Aminoglycosides
  – Tetracyclins
  – Macrolides
  – Chloramphenicol
  – Clindamycin

• **Folate antagonists**
  – Sulfonamides
  – Trimethoprim

• **Quinolones**
Antibiotics - Cell wall synthesis inhibitors

Bacterial cell wall:

Three types:

- **Gram-negative** (e.g. E.coli, Salmonella)
  - Few peptidoglycan layers
    (Lipopolysaccharide)
- **Gram-positive** (e.g. Staphylococci, Listeria)
  - Many peptidoglycan layers
    (Lipoteichoic acid)
  - Stains w/ crystal-violet/iodine
- **Acid-fast positive** (Mycobacteria)
  - Cell wall contains waxy substance
    (Mycolic acid)
  - Stain w/ acid fast test (heating required)
Antibiotics - Cell wall synthesis inhibitors

**Beta-lactam antibiotics:**

1928 - Alexander Fleming observes the antibacterial effects of Penicillin

1940 - Florey and Chain extract Penicillin

**Classification:**

- Penicillins
  - Narrow spectrum – penicillinase sensitive
  - Narrow spectrum – penicillinase resistant
  - Broad spectrum penicillins
  - Extended-spectrum penicillins

- Cephalosporines
- Carbapenems
- Monobactams
- Vancomycin, Bacitracin
Antibiotics - Cell wall synthesis inhibitors

Penicillins
Inhibit transpeptidase required for cross-linking peptidoglycan chains
Also inactivate an inhibitor of an autolytic bacterial enzyme => lysis

Narrow spectrum – penicillinase (= β-lactamase) sensitive

• Benzylpenicillin
  – Naturally occurring
  – Poor oral availability (sensitive to stomach acid)
    => given by injection
  – Active against gram-positive bacteria

• Phenoxyacetylpenicillin
  – Better oral availability (acid resistant)
Antibiotics - Cell wall synthesis inhibitors

Narrow spectrum – penicillinase (= β-lactamase) resistant

- Methicillin
  - Semisynthetic
  - Poor oral availability (only parenteral)
  - Active against gram-pos bacteria
  - Mostly used for *Staphylococcus aureus*

- Oxacillin
  - Good oral availability

- Cloxacillin

- Dicloxacillin
Antibiotics - Cell wall synthesis inhibitors

Broad spectrum – penicillinase (= β-lactamase) **sensitive**
(= Aminopenicillins)

- **Ampicillin**
  - Semisynthetic
  - Good oral availability
  - Active against gram-pos and gram-neg bacteria
  - Active against enterobacteria

- **Amoxicillin**
  - Excellent oral availability
Antibiotics - Cell wall synthesis inhibitors

Extended spectrum – penicillinase (= β-lactamase) sensitive
(= Carboxypenicillins)

• Carbenicillin
  – Semisynthetic
  – Poor oral availability
  – Active against gram-pos and gram-neg bacteria
  – Active against Pseudomonas aeruginosa, Klebsiella

• Ticarcillin
• Mezlocillin
• Pipercillin
Antibiotics - Cell wall synthesis inhibitors

Cephalosporines

Derived from *Cephalosporium sp.* (same antibiotic mechanism as penicillins)

Cross-allergies with penicillins are common

Some CSs antagonize Vitamin K => bleeding

Some CSs block alcohol oxidation => disulfiram effect

Classified into generations:

- 1-4
- Increasing activity against gram-negative bacterial and anaerobes
- Increasing resistance to destruction by beta-lactamases
- Increasing ability to reach cerebrospinal fluid
Antibiotics - Cell wall synthesis inhibitors

First generation – β-lactamase sensitive
• Cefazolin
  – Naturally occurring
  – Active against gram-positive bacteria
• Cephalexin

Second generation – β-lactamase sensitive
• Cefaclor
  – Some activity against gram-neg bacteria
• Cefamandole
• Cefoxitin
Antibiotics - Cell wall synthesis inhibitors

Third generation – mostly \( \beta \)-lactamase resistant
- **Cefotaxime**
  - Active against gram-negative bacteria
  - Active against *Pseudomonas aeruginosa*
  - Active against enterobacteria, gonococcus
  - Penetrates the CNS => used for meningitis
- **Ceftriaxone**

Fourth generation – mostly \( \beta \)-lactamase resistant
- **Cefepime**
  - Broadest antimicrobial spectrum of any drug
  - Used for MDR bacteria and mixed infections
- **Cefpirome**
Antibiotics - Cell wall synthesis inhibitors

Beta-lactamase inhibitors

• Clavulanic acid
  – Irreversible inhibitor of β-lactamase
  – Good oral absorption
  – Combined with amoxicillin or ticarcillin

• Sulbactam
Antibiotics - Cell wall synthesis inhibitors

**Vancomycin**
- Only effective against gram-positive bacteria
- Poor oral absorption => used for GI infections
- Used to be the “Magic bullet” for methicillin-resistant staphylococci, but now staph are becoming V-resistant.
- Dose-related ototoxicity: Tinnitus, high-tone deafness; can progress to total deafness

**Bacitracin**
- Mixture of polypeptides
- Serious nephrotoxicity => only topical use
Antibiotics - Protein synthesis inhibitors

Protein synthesis inhibitors:
Inhibit either the 30s or 50s ribosomal subunit (bacterial ribosomal subunits differ from mammalian ones => drugs are selective for bacterial protein synthesis)
Class based on chemical structure of the compounds
Drugs need to enter bacteria => entry inhibition is a point of drug resistance

• Classification:
  – Aminoglycosides (bactericidal)
  – Tetracyclins
  – Macrolides
  – Chloramphenicol
  – Clindamycin
Antibiotics - Protein synthesis inhibitors

**Aminoglycosides**

- Broad spectrum antibiotics (bactericidal)
- Penetration into cell requires an oxygen-dependent transport => anaerobes are resistant
  (Chloramphenicol blocks this transport => inhibits AG uptake into bacteria; Penicillins weaken the cell wall => promote AG uptake)
- Poor oral absorption (very polar) => parenteral administration
- Narrow therapeutic range - severe side effects:
  Ototoxicity: destruction of outer hair cells in organ of Corti
  Nephrotoxicity: killing of proximal tubular cells
  Neuromuscular toxicity: blockage of presynaptic ACh release => respiratory suppression
- Elimination almost completely by glomerular filtration
  (impaired kidney function => concentration of AG increases => toxicity)
Antibiotics - Protein synthesis inhibitors

Aminoglycosides

- Gentamicin
- Tobramycin
- Streptomycin
- Neomycin
- Kanamycin
- Amikacin
Antibiotics - Protein synthesis inhibitors

**Tetracyclines**

Penetration into cell requires an energy-dependent transport not present in mammals

Oral absorption impaired by food (insoluble chelates with Ca, Mg => caution w/ antacids)

Side effects:

- Incorporation into teeth and bone => staining of teeth; retardation of bone growth
  - (not used in children and during pregnancy)
- Photosensitivity

Broad spectrum antibiotics (bacteriostatic)

Also useful for treating rickettsial diseases (Rocky mountain spotted fever), Spirochetes (Lyme disease), Mycoplasma (pneumonia)
Antibiotics - Protein synthesis inhibitors

Tetracyclines

- **Tetracycline**
  - From *Streptomyces sp.*

- **Oxytetracycline**
- **Minocycline**
- **Doxycycline**
  - Used to treat rosacea and prevent rhinophyma
  - No food interaction
Antibiotics - Protein synthesis inhibitors

**Macrolides**

Narrow spectrum antibiotics similar to penicillin (bacteriostatic or bactericidal)

=> good alternative for patients w/ penicillin allergy

Few side effects (GI disturbances), similar food interaction as tetracyclines

Also used for treating Mycoplasma (pneumonia) and Legionella (Legionnaire’s disease)

- **Erythromycin**
  - From *Streptomyces erythreus*

- **Azithromycin**
  - Very long half-life (>24 h)
  - Convient use (Z-Pak®, Zithromax®) - 6 pill regimen

- **Clarithromycin**
  - Used for H. pylori infection
Antibiotics - Protein synthesis inhibitors

**Chloramphenicol**

Very broad spectrum (almost all bacteria except *Pseudomonas aeruginosa*)

Very severe side effects

- Bone marrow depression => fatal aplastic anemia

Reserved for life-threatening, otherwise treatment-resistant infections

![Chloramphenicol molecule](image)

**Clindamycin**

Medium broad spectrum (gram-positive organisms, anaerobes)

Used for treatment of penicillin-resistant cocci

Side effects: Colitis (triggered by toxin from clindamycin-resistant *Clostridium difficile*)

combined w/ vancomycin to kill *C. difficile*
Antibiotics - Folate Antagonists

**Folate antagonists**

Bacteria cannot absorb folic acid => synthesis from p-aminobenzoic acid (PABA) required (Folic acid is a vitamin for humans => synthesis pathway is restricted to bacteria => selective drug target)

Folate antagonists block folate synthesis => inhibition of nucleotide synthesis => bacteriostatic effect

(pus provides alternative source for nucleotides => drugs are inactive in the presence of pus or necrotic tissue)
Antibiotics - Folate Antagonists

Sulfonamides

Structural analogues of PABA => compete with PABA for Dihydropteroate-synthase
Used for infected burns, STDs, toxoplasmosis…

Note:
Many local anesthetics are PABA-esters => they antagonize folate antagonists

- Sulfadiazine
- Sulfadimidine
- Sulfamethoxazole
Trimethoprim

- Resembles pteridine moiety of folates => compete with folates for Dihydrofolate-reductase
- Use similar to sulfonamides
- Combined with Sulfomethoxazole (synergistic effect) = Co-trimoxazole (Bactrim®)
- Used for urinary tract infections

Trimethoprim (dihydrofolate reductase inhibitor)
Antibiotics - Quinolones

Quinolones

Synthetic inhibitors of DNA-Gyrase (= Topoisomerase II), a bacterial enzyme that winds and unwinds DNA (required for supercoiling the bacterial genome) => inhibition of DNA synthesis and transcription

Very broad spectrum, bactericidal - well tolerated

Al and Mg interfere with absorption (antacids!)

Mostly fluorinated = Fluoroquinolones (except nalidixic acid = first quinolone)
Antibiotics - Quinolones

Quinolones

- Nalidixic acid
  - Oldest quinolone
  - Only used for urinary tract infections
  - Improvement through structure-activity relationship:
    - Adding fluorine at position 6 will significantly increase activity
    - Substitution of piperazinyl-ring at position-7 will give the drug antipseudomonal activity

- Ciprofloxacin
  - Most commonly used quinolone (Cipro®)
  - Very broad spectrum => used for emergencies
    (B. anthracis attacks in 2001)

- Levofloxacin
- Ofloxacin
- Norfloxacin
- Travofloxacin ...