Antibiotics III.

Cephamycins

- Cephamycin A-C, 1971, Str. lipmanii
- 7α-Methoxy group:
  - Somewhat diminished antibacterial activity
  - Resistant to a wide range of β-lactamase enzymes
- 3-CH₂-carbamoyl group:
  - Metabolically more stable than the acetyloxy deriv.

Cephamycins

Oxacephems

- Moxilactam (Laromoxyc™)
- Piromoxif

Monocyclic β-lactams, monobactams

- Nocardicin A-F, 1976, Nocardia uniformis sp. (Fujisawa)
- Sulfaçezin, 1981, Pseudomonas acidophila (Takeda)

Monocyclic β-lactams
Carbapenem antibiotics

- About 40 carbapenems were isolated 1977-1980 by Beecham from Str. olivaceus and by Merck from Str. cattleya. They differ in their 6- and 2-side chains.

Thienamycin, R = H
N-Formimido-thienamycin, Imipenem, R = CH=NH

- Thienamycin: Very broad spectrum and ß-lactamase stable antibiotics, but chemically it is not stable enough.
- Stable N-formimido derivative → Imipenem

Imipenem, Tienam

- Problems arising from renal dehydropeptidase-II (DHP-II) enzyme found in mammals.
- In combination with the specific enzyme inhibitor cilastatin

Imipenem + Cilastatin = Tienam

DHP-II resistant 1ß-methyl carbapenems

- 1ß-Methyl substitution:
  - Antibiotic spectrum and level of activity is not influenced;
  - Provides stability against DHP-II.

Problems arising from renal dehydropeptidase-II (DHP-II) enzyme found in mammals. In combination with the specific enzyme inhibitor cilastatin.

Imipenem + Cilastatin = Tienam

DHP-II resistant 1ß-methyl carbapenems

- Active against a wide range of Gram-negative and Gram-positive bacteria, incl. anaerobes.
- Recommended: meningitis, septicemia, renal and urogenital infections etc.
- Expensive because of subtle and long total synthesis.

Penems

- Totally synthetic derivatives
- Very good but not used because it is too expensive.

Mode of action of ß-lactam antibiotics

The first part of the synthesis of the bacterial cell wall.
The final steps of the synthesis of the cell wall:

Biosynthesis

- Biosynthesis
  - Penicillin G, etc.
  - Isopenicillin N
  - Penicillin N
  - Cephalosporin

Aminoglycoside (aminocyclitol) antibiotics

- History of aminoglycosides starts with streptomycin, Waksman and Schatz (~1943)
- 10-15 are used in human therapy.
  
Dr. Selman Waksman
1888-1973

Aminoglycosides comprise two or more aminosugars (usually aminohexoses) and an aminocyclitol moiety linked by glycosidic –O- bonds.
On carbohydrates...

Aminoglycosides

Classification:
- Oligosaccharides
  - 4-O-monoglycosides
  - 4,5-O-diglycosides
- Pseudo-oligosaccharides (glycoside links only between sugar and cyclitol)
  - 1-O-, 3-O- or 5-O-monoglycosides
  - 4- and 4,6-O-diglycosides
- Other

Aminoglycoside antibiotics

Generally:
- Broad spectrum antibiotics: mainly Gram-positive, many Gram-negative strains, Mycobacteria. Not active against anaerobe sp.
- Adverse effects: some possess ototoxicity (irreversible), nephrotoxicity (reversible) → few drugs are never used internally.
- Chemically strongly basic (several –NH₂ groups), ionic and hydrophilic compounds.
- Do not absorb from the gut when administered orally → used intravenously and intramuscularly, locally (skin, eye etc. infections), used orally to treat gastrointestinal infections.
- Synergism with ß-lactam antibiotics
- Mode of action → inhibition of protein synthesis

Streptomycin

Synergism with ß-lactam antibiotics
Mode of action → inhibition of protein synthesis
Components

- Waksman and Schatz, 1943, *Str. griseus*
- Dihydrostreptomycin, same bioactivity but less toxic (??).
- Broad spectrum antibiotic, but used only against *M. tuberculosis* (brucellosis, tularemia).
- The cheapest first line antibiotics against TB;
- Adverse effects: vertigo, ototoxicity (esp. dihydrostreptomy-cin), nefrotoxicity.
- Agricultural use.

Streptomycin sulfate

- Waksman and Schatz, 1943, *Str. griseus*
- Streptomycin sulfate
- Streptomycin injection

Streptomycin

- Agricultural use
- Fireblight of apple, *Erwinia amylovora*

Neomycin

- Waksman and Lechavalier, 1949, *Str. fradiae*. Mixture of isomers A (~1%), B (>90%) and C (<10%).
- More toxic than streptomycin, used only for gastrointestinal (abdominal surgery), dermatological and eye infections.
- Often used in combinations.
- Veterinary use (udder infections of bovine)

Neomycin sulfate

- Neomycin sulfate (Eu. Ph. 5.)
- Banone® ointment and powder (with bacitracin)
- Desapar® ointment
- Flucon® ointment (antibact. component)
- Pimafuc® ointment and solution (with natamycin)
**Paramomycin**

- Differs only at C-6' from neomycin

**Components**

- Kanamycin: Umezawa et al., 1957, *Str. kanamycetus*
- It was active against many already resistant bacteria, however, sensitive strains develop resistance very quickly.
- Used against Gram-negative infections, TB
- Today rarely used.
- Serves as starting material for a few semisynthetic derivatives.

**Kanamycin**

- Kanamycin A: $R^1 = -\text{NH}_2$, $R^2 = -\text{OH}$
- Kanamycin B: $R^1 = -\text{NH}_2$, $R^2 = -\text{NH}_2$
- Kanamycin C: $R^1 = -\text{OH}$, $R^2 = -\text{NH}_2$

**Kanamycin and analogs**

- Belong to the pseudooligosaccharide type of aminoglycosides

**Components**

- Kanosamine
- 3-Amino-3-deoxy-D-glucosamine

**Tobramycin**

- 2-deoxy-streptamine
- Tobramycin (3-deoxy-kanamycin B)
Stark et al., 1967, Streptomyces tenebrarius.
Deoxy derivative of kanamycin, more resistant to phosphotransferase enzymes causing inactivation.
Active against Staphylococci, many Gram-negative strains, especially Pseudomonas aeruginosa sp. are sensitive to it.
Often used in combinations.

Gentamicin

Two-fold deoxy derivative

Gentamicin sulfate

Weinstein et al., 1963, Micromonospora purpurea, the mixture is used.
Less sensitive to inactivating enzymes (no 3' and 4' OH groups).
Broad spectrum antibiotic, especially against Pseudomonas sp.
Its use is preserved for nosocomial infections.
Used as preventive in surgical operations (sponge, chain)

Netilmicin

Semisynthetic derivative of sisomicin, which is a dehydro analogue of gentamicin C14

Netilmicin sulfate
Amikacin

Amikacin sulfate
- *Amikacin* sulfate (Eu. Ph. 5.)
- Amikin® injection, Likacin® injection

Somewhat less active than kanamicin or gentamicin, but active against resistant strains, it resists to most bacterial inactivating enzymes.

Spectinomycin

- Lewis and Clapp, 1961, Str. spectabilis
- Aqueous solution is unstable.
- Broad spectrum antibiotic, used only against penicillin resistant gonorrhea.

Mode of action of aminoglycosides

Resistance

Bacteria have three mechanisms to overcome the antibiotic:
- Modification of the substrate
- Modification of the target site
- Change of permeability of membranes
Lincosaminides

- Mason et al., 1963, *Streptomyces lincolnensis*
- Active mainly against Gram-positive, anaerob strains.
- In aqueous solution slowly hydrolyses, in acidic media within minutes.
- Lincocin® (Upjohn) – today only its chlorine derivative clindamycin is used.

Lincomycin

- Chloro derivative of lincomycin (Birkenmayer, 1967)
- More stable than the parent lincomycin, however, not very stable in acidic or basic media.
- Reserved drug for serious upper respiratory, skin (acne) and soft tissue Gram-positive and anaerob infections.
- 2-phosphate (better solubility) or palmitate (tasteless) esters are also used.