Chemotherapeutic Agents / Antibiotics, chapter 38-43

• Antibacterial compounds (procaryotes) - Antimycobacterials
  chapt. 41
• Antiparasitic agents (eucarytotes)
• Antifungal compounds (eucarytotes)
• Antiviral compounds
• Anticancer compounds

\[ G^+ \quad G^- \quad \text{Mycobacteria} \]
Pathogenic mycobacteria:
*M. tuberculosis* (tuberculosis)
*M. Lepra* (Leprosy)
*M. Avium* (Opportunistic infection in AIDS patients)
*M. bovis* (mainly cattle infect, infected milk USA)

**TUBERCULOSIS** (TB)

High lipid / wax content in cell wall (mycolic acid)
Slow growing organisms
Aerobe bacteria
Resistant to chemicals and drying
Easily killed by heat

Until ca. 1950; 50 % of all infected died
Infection by inhalation of the bacteria
Pulmonary TB most common
May also attack other organs including CNS

30 million people will die from TB the next 10 years
8 million new cases each year
c. 1/3 of the world population are infected (incl. dormant infections)
c. 95% of the cases in developing countries
no new drugs on the marked for the last 25 - 30 years

WHO (1993): TB a "global emergency"
First effective drug: Streptomycin 1946

Inhibits protein synthesis  
Toxic!

Treatment
• Long time $\geq 6$ mnds
• Combination of drugs  

$$\text{DOT: Directly observed therapy}$$

Different stages of bacterial growth
First-line drugs

**Isoniazid**

Isoniazid®

![Chemical structure of Isoniazid](image)

Isoniazide Antituberculosis drug

NADH co-enzyme in enzyme involved in cell wall component synth

**Long Chain ACP-Enoyl Fatty Acid Reductase (inhA)**

![Diagram of mycolic acid metabolism](image)

- **α-mycolates**
- **ketomycolates**
- **methoxymycolates**

Active acyl radical formed *in vivo*

Inactive der. of co-enz

APC: Acyl carrier protein

1,4 hydride add.
First-line drugs

**Pyrazinamide**

Mechanism not known

**Ethambutol**

Mechanism not fully known
- Synth of cell wall comp.: Inhib. arabinocyl transferase?
- Arabinose, Arabinomannan and Lipoarabinomannan

**Rifampicin**

Mechanism not known
- Broad spectrum antibiotic
- From *Streptomyces* sp
- Inhib bacterial RNA polymerase
- Inhibit. RNA-synth.
- Synth. arabinocyl transferase
- Induce CYP2C; increased metabol. of certain anti AIDS drugs
Second-line drugs

**Ethionamide**

Mech. ≈ Isoniazide

**p-Aminosalicylic acid**

PABA antimetabolite

**Cycloserine**

Isolated *Spreptomyces sp*

Inhib. alanine racemase and alanine ligase;
Inhib. peptidoglycan synth

**Kanamycin**

(aminoglycoside antibiotics)

R=OH: Kanamycin A
R=NH₂: Kanamycin B
Others

**Quinolones**

![Quinolones structure](image)

**Oxazolidinones**

![Oxazolidinones structure](image)

Treatment of MAC infections

*Clarithromycin*

*(Macrolide)*

![Clarithromycin structure](image)

Other macrolides
Ethambutol
Quinolones
Rifabutin (Rifamycin)
Chemotherapeutic Agents / Antibiotics, chapter 38-43

- Antibacterial compounds (procaryotes)
- Antiparasitic agents (eucaryotes) - Chapt 39
- Antifungal compounds (eucaryotes)
- Antiviral compounds
- Anticancer compounds

Protozoa
Helmints
Insects (Scabies lice etc.)

(Fungi chapt. 40)
Protozoa

Eucaryotes, unicellular (may exist in colonies)
Protozoa and algae (protocista)
Complex replication (sexual and asexual)
Patogenic P. most common tropical area
3. world diseases
Many diseases can be prevented by clean drinking water
Certain protozal diseases spread by insects

Ex. pathogenic protozoa

- *Trichomonas vaginalis*: Genital infections
- *Giardia lamblia*: Diarea
- *Toxoplasma gondii*: Toxoplasmosis
- *Trypanozomas sp*: Sleeping sickness
- *Entamoeba histolytica*: Dysentery
- *Plasmodium sp*: Malaria
- *Pneumocystis carinii*: Opportunistic, AIDS
Treatment of diseases caused by amebia, giardia, trichomonas

**Metronidazol**
Flagyl®, Metronidazol®

Also effective against anaerobic bacteria
Probably pro-drug - reductive activation (mech. not fully understood)

Related comp.
treatment of
African sleeping sickness

Formation of toxic reactive oxygen species
Anti - Malaria drugs

Plasmodium sp.
Vektor: Anopheles moskito.
Complex life cyclus.

Mal aria = bad air

40% of world population at risk
300 mil acute illnesess pr year
ca 1 mill deaths pr year
Malaria kills a child every 30 sec.
90% in incidents sub-sahara Africa

Figure 9-1 - Stages of the parasite that causes malaria after injection into its victim. See discussion in the text. * indicates site of antimalarial drug action in humans.
**Historic drugs**

- Azodyes and salvarsan (1. synthetic effective drug)
- Quinine from Cinchona (Kinabark)

![Chemical structures of Azodyes and Salvarsan](image)

**Screening of dyes as antibacterials**

1932: *Prontocil* active against Streptococces infection
   no activity on bacterial cultures

1935: Prontocil metabolized (azoreductase) to *Sulfanilamid* in vivo
   (rel. toxic)

Modern sulfa drugs

**Cinchona pubescens (Kinatre) from South America**
Mechanism

Quinolines

(DNA Intercalation)

Ferrisoproporphyrin IX: Binds to FPIX (metabolite from hemoglobin); tox. form of FPIX, proteinbound FPIX less tox.

Weak base Hypothesis: Increase pH in parasite

More active, less tox (comp Quinine)

Resistance!

Quinine

Kinin®

Klorokin

Klorokinfosfat®

Hydroksyklorokin

Plaquenil®

Meflokin

Lariam®

Meflokin resistant

P. palsyfarum

Pamakin, 1926
**Biguanides**

*Proguanil (= Chloroguanide)*

*Paludrine®*

*Malarone® + atovakvon*

Pro-drug

Inhib. protozoan folate reduktase

(c.f. Trimetoprim)

Essensielle prosesser hos bakterier og dyr

Inkl tymidinsyntese

**Other biguanides**

Klorhexidine
Others

Atovakvon
Malarone® + proguanil.
Also other parasites (P. carinii)
Ubiquinone antimetabolite?

Artemisin
from Artemisia annua
Chinese trad. med.

Artemeter
Semisynth. analog
Improved solubil.

Mech. involves radicals
No cross resist.
Synth. analogs, active field

Artemeter og Lumeefandrin
Riamet®
Drugs for Helminth infections

Eukaryotes – Invertebrates.
Tropical diseases!
Animal parasites; ex *Trichinella spiralis* (trikiner).

Benzimidazoles
Many active analogs known
Binds to tubulin - prevents formation of microtubules
inhib. mitosis (c.f. certain anticancer drugs)
May also inhib. fumarate reductase

Mebendazol
Vermox®
Drugs against Ectoparasites (insects)

Lice, scabies etc

**Pyretrines**
Insecticides from *Crysantemum* sp

![Pyretrine structure](image)

**Permetrin**
Synth. analog, more stable Mixt. of 4 stereoisomers

**Chlorinated pesticides:**
Lindane
Block GABA CNS neurotransmitter
(Also neurotox. effects on humans)

![Lindane structure](image)
Irreversible Inhibitors
Acetylcholine esterase

Gen structur mustard gasses

L: Leaving group
R1: alkoxsy
R2: alkyl, alkoxsy, amino

Not drugs, nerve gasses, *insecticides* etc.

Malation
Prioderm® lice

Only insects
Malation
not tox.
Maloxon
Act as mustard gasses
Chemotherapeutic Agents / Antibiotics, chapter 38-43

• Antibacterial compounds (procaryotes)
• Antiparasitic agents (eucaryotes) -
• Antifungal compounds (eucaryotes) - Chapt 40
• Antiviral compounds
• Anticancer compounds

Fungicides / Fungistatika / Antimykotika
Chemotherapeutics / Antibiotics
**Synthetic Antifungals**

**Azoles**

| Azol / Pyrrol | 1,2-Diazol | 1,3-Diazol / Imidazol | 1,2,4-Triazol |

**Component of fungus cell walls**

1. Squalen epoxidase
2. Squalen epoxidase-syklase
3. Lanosterol 14a-demetylase
4. Antimycotic allylic amines
5. Antimycotic azoles
Lanosterol

14a-demethylase heme (CYP450 fungi)

Antimyc. azole
**Klotrimazol:**
Canesten®, Klotrimazol® utvortes
Canesten®, vaginal behandling

**Ekonazol:**
Pevaryl®, utvortes
Pevaryl®, vaginal behandling

**Miconazol:**
Daktar®, utvortes
Daktar®, vaginal behandling

**SAR:**
- Weakly basic azole ring, imidazol / 1,2,4-triazol (less tox. humans), pKa 6.5-6.8
- 2 or 3 other aromatic rings
- Cl (or F) on at least one aromatic ring
  (F i flukonazol)
- Lipophilic structures (as lanosterol)
**Allylic amines**

**Terbinafin**

**Lamicil®**

Prevents formation of cell wall comp.
Accumulation of toxic squalene
Antimycotic Antibiotics

Polyenes

Broad spectrum. Some effect on certain protozoa.

Isolated, *Streptomyces* sp.

Binds to sterols in fungal cell membrane; cell leaks K⁺, small org. molecules

SAR:

- Macrolaktone [26 or 38-ring, Larger than macrolides (erytromycin etc)]
- Polyene (Macrolides not polyenes)
- Several OH-groups
- Amino sugar, mykosamin
- Bad water sol.
**Nystatin A**

Toxic, bad oral avail;
Local treatment, mouth, GI tract

**Amphotericin B**

Systemic infect (infusion)
Somewhat less tox.

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Amfoterici struktur

Hemiacetal
Peptides

Caspofungin

Serious systemic infect.

Semisynth. from prod. of fermentation (Glarea lozoyensis)

Inhib. synth of β-1,3-D-glucan; cell wall comp. certain fungi

Few good inhib. of fungi cell wall comp. compared to antibacterials