Ch 20

Antimicrobial Drugs
SLOs

Describe the history of chemotherapy.

Name the microbes that produce the most antibiotics.

Describe problems of chemotherapy for viral, fungal, protozoan, and helminthic infections.

Define: *Therapeutic index, antibiotic, activity spectrum, bacteriostatic, -cidal*

Identify five modes of action of antimicrobial drugs.

Describe the mechanism of action of penicillin and the mechanism of resistance to penicillin.

Compare penicillin, cephalosporin, and vancomycin

Briefly explain the modes of action of some antifungal drugs.

Explain the modes of action of some antiviral drugs.

Explain the modes of action of some antiprotozoan and antihelminthic drugs.

Describe the Kirby Bauer test.

Describe mechanisms of drug resistance.
Antimicrobial Drugs

- Chemotherapy: The use of drugs to treat a disease.
- Antimicrobial drugs: Interfere with the growth of microbes within a host.
- **Antibiotic**: Of biological origin. Produced by a microbe, inhibits other microbes.
- **Chemotherapeutic agent**: synthetic chemicals
- Today distinction blurred → many newer "antibiotics" are biological products that are
  - chemically modified or
  - chemically synthesized
Paul Ehrlich and Sahachiro Hata developed Salvarsan (Arsphenamine) against syphilis in 1910: The concept of chemotherapy to treat microbial diseases was born.

Sulfa drugs (sulfanilamide) discovered in 1932 → against Gram+ bacteria
1928: **Fleming** discovered penicillin

1940: Howard **Florey** and Ernst **Chain** performed first clinical trials of penicillin.
Features of Antimicrobial Drugs

- **Selective toxicity:** Drug kills pathogens without damaging the host.
- **Therapeutic index:** ratio between toxic dose and therapeutic dose – or ratio of LD$_{50}$ to ED$_{50}$
  High therapeutic index $\Rightarrow$ less toxic
- **Antimicrobial action** – Bacteriostatic vs. bactericidal
- **Activity Spectrum** – Broad-spectrum vs. narrow-spectrum
- **Tissue distribution, metabolism, and excretion** – BBB; Unstable in acid; half-life duration
The Action of Antimicrobial Drugs

1. Inhibition of cell wall synthesis: penicillins, cephalosporins, bacitracin, vancomycin

2. Inhibition of protein synthesis: chloramphenicol, erythromycin, tetracyclines, streptomycin

3. Inhibition of nucleic acid replication and transcription: quinolones, rifampin

4. Injury to plasma membrane: polymyxin B

5. Inhibition of synthesis of essential metabolites: sulfanilamide, trimethoprim
Inhibition of Protein Synthesis by Antibiotics

(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome.

(b) Diagram indicating the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities.

- Chloramphenicol: Binds to 50S portion and inhibits formation of peptide bond.
- Streptomycin: Changes shape of 30S portion, causing code on mRNA to be read incorrectly.
- Tetracyclines: Interfere with attachment of tRNA to mRNA–ribosome complex.

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Antibacterial Antibiotics
Inhibitors of Cell Wall Synthesis: Penicillin

Natural and semisynthetic penicilins contain β-lactam ring.

Natural penicillins produced by *Penicillium* are effective against Gram + cocci and spirochetes.

Semisynthetic penicillins: made in laboratory by adding different side chains onto β-lactam ring ⇒ penicillinase resistant and broader spectrum of activity.

### Natural Penicillin

- **Penicillin G** (requires injection)
  
- **Penicillin V** (can be taken orally)
Retention of Penicillin G

- Penicillin G (injected intramuscularly)
- Penicillin G (oral)
- Procaine penicillin
- Benzathine penicillin

Time (hr) | Concentration in blood
--- | ---
0 | (peaking) 2 | 4 | 6 | 8 | 12 | 18 | 24 | 30

Figure 20.7
Penicillin \textit{cont.}

Penicillinase (\textit{\(\beta\)-lactamase}): bacterial enzyme that destroys natural penicillins

\textbf{Penicillinase resistant penicillins}: methicillin replaced by oxacilin and nafcilin due to MRSA

\textbf{Extended-spectrum penicillins}: Ampicilin, amoxicilin; new: carboxypenicilins and ureidopenicillins (also good against \textit{P. aeruginosa})

\begin{itemize}
  \item \textit{\(\beta\)-lactam ring}
  \item Penicillin
  \item Penicilloic acid
  \item Fig 20.8
\end{itemize}
Cephalosporins

Fungi of genus *Cephalosporium* ⇒ 4 Generations of cephalosporins

1. First-generation: Narrow spectrum, gram-positive
2. Second-generation: Extended spectrum includes gram-negative
3. Third-generation: Includes pseudomonads; mostly injected, some oral.
4. Fourth-generation: Most extended spectrum
Cephalosporins cont.

Structure and mode of action resembles penicilins

1. More stable to bacterial β-lactamases than penicilins

2. Broader spectrum ⇒ used against penicillin-resistant strains
Vancomycin

- Glycopeptide from *Streptomyces*
- Inhibition of cell wall synthesis
- Used to kill **MRSA**
- Emerging Vancomycin resistance: **VRE** and **VRSA**
Antifungal Drugs

- **Polyenes**, such as *nystatin* and *amphotericin B*, for systemic fungal infections. Inhibition of ergosterol synthesis $\Rightarrow$ fungicidal. Nephrotoxic

- **Griseofulvin** from *Penicillium*. Systemic/oral. Binds to tubulin $\Rightarrow$
For *Tineae*
Nucleoside analogs inhibit DNA synthesis

**Acyclovir** and newer derivatives: Selective inhibition of herpes virus replication. Acyclovir conversion to nucleotide analog only in virus infected cells ⇒ very little harm to uninfected cells!

*Fig 20.16*

(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.
Mechanism of Action of Acyclovir

(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.

(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) into a false nucleotide—which blocks DNA synthesis by DNA polymerase.
Antiviral Drugs for Treating HIV/AIDS: HAART

1. NRTIs and NNRTIs
2. Protease Inhibitors
3. Fusion Inhibitors
4. Integrase Inhibitors

HIV protease cleaves viral polypeptide into functional proteins

Protease inhibition $\Rightarrow$ HIV cannot mature and noninfectious viruses are produced.
Examples of *Antiprotozoan*:

- Chloroquine: Malaria
- Quinacrine: Giardia
- **Metronidazole** (Flagyl): Vaginitis, anaerobic bacteria

Examples of *Antihelminthic*:

- Niclosamide and praziquantel: Tapeworm
- Mebendazole: broadspectrum antihelmintic
- Ivermectin: nematodes, mites, lice . . .
Antibiotic Assays to Guide Chemotherapy

**Agar Disk Diffusion Method** determines susceptibility of an organism to a series of antibiotics: **Kirby-Bauer test**

More sophisticated methods available for clinical labs
Drug Resistance

Penicillin G resistance of *S. aureus* from 3% to > 90%

Multidrug-resistant *S. aureus* = **MRSA** or “super-bug”

Vancomycin-resistance $\rightarrow$

Multi drug resistant TB = **MDR-TB**

*Evolution of drug resistance:*
- Vertical evolution due to spontaneous mutation
- Horizontal evolution due to gene transfer
Antibiotic Resistance

- A variety of mutations can lead to antibiotic resistance

- Mechanisms of antibiotic resistance
  1. Enzymatic destruction of drug
  2. Prevention of penetration of drug
  3. Alteration of drug's target site
  4. Rapid ejection of the drug

- Resistance genes are often on plasmids or transposons that can be transferred between bacteria.
Resistance to Antibiotics

1. Blocking entry
2. Inactivating enzymes
3. Alteration of target molecule
4. Efflux of antibiotic
Antibiotic Resistance

- Misuse of antibiotics selects for resistance mutants. Misuse includes
  - Using outdated or weakened antibiotics
  - Using antibiotics for the common cold and other inappropriate conditions
  - Using antibiotics in animal feed
  - Failing complete the prescribed regimen
  - Using someone else's leftover prescription

Read Clinical Focus: Antibiotics in Animal Feed Linked to Human Disease (p. 577)