CONTROLLING MICROBIAL GROWTH IN THE BODY

Chapter 10

CCV

Microbiology

1

The History of Antimicrobial Agents

- Drugs
  - Chemicals that affect physiology in any manner
- Chemotherapeutic agents
  - Drugs that act against diseases
- Antimicrobial agents
  - Drugs that treat infections

2

The History of Antimicrobial Agents

- Paul Ehrlich
  - "Magic bullets"
    - Arsenic compounds that killed microbes
- Alexander Fleming
  - Penicillin released from *Penicillium*
- Gerhard Domagk
  - Discovered sulfanilamide
- Selman Waksman
  - Antibiotics
    - Antimicrobial agents produced naturally by organisms

3

Figure 10.1 Antibiotic effect of the mold *Penicillium chrysogenum*.

4

The History of Antimicrobial Agents

- Semisynthetics
  - Chemically altered antibiotics that are more effective, longer lasting, or easier to administer than naturally occurring ones
- Synthetics
  - Antimicrobials that are completely synthesized in a lab

5

TABLE 10.1 Sources of Some Common Antibiotics and Semisynthetics

Microorganism	Antimicrobial
Fungi	
Penicillium chrysogenum	Penicillin
Penicillium griseofulvum	Griseofulvin
Acremonium[a] *spp.*[b]	Cephalothin
Bacteria	
Amycolatopsis orientalis	Vancomycin
Amycolatopsis rifamycinica	Rifampin
Bacillus licheniformis	Bacitracin
Bacillus polymyxa	Polymyxin
Micromonospora purpurea	Gentamicin
Pseudomonas fluorescens	Mupirocin
Saccharopolyspora erythraea	Erythromycin
Streptomyces griseus	Streptomycin
Streptomyces fradiae	Neomycin
Streptomyces aureofaciens	Tetracycline
Streptomyces venezuelae	Chloramphenicol
Streptomyces nodosus	Amphotericin B
Streptomyces avermitilis	Ivermectin

[a]This genus was formerly called *cephalosporium*.
[b]spp. is the abbreviation for multiple species of a genus.

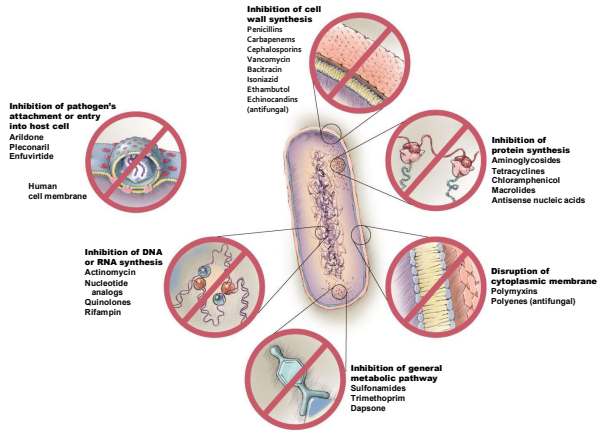
6

Mechanisms of Antimicrobial Action

- Successful chemotherapy requires selective toxicity
- Antibacterial drugs constitute largest number and diversity of antimicrobial agents
- Fewer drugs to treat eukaryotic infections
- Antiviral drugs limited

7

Figure 10.2 Mechanisms of action of microbial drugs.



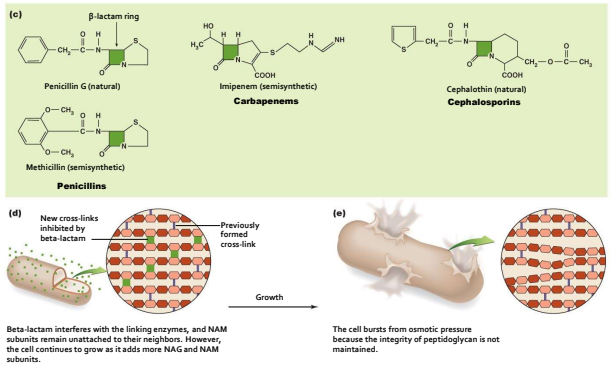
8

Mechanisms of Antimicrobial Action

- **Inhibition of Cell Wall Synthesis**
  - Inhibition of synthesis of bacterial walls
    - Most common agents prevent cross-linkage of NAM subunits
    - Beta-lactams are most prominent in this group
      - Functional groups are beta-lactam rings
      - Beta-lactams bind to enzymes that cross-link NAM subunits
    - Bacteria have weakened cell walls and eventually lyse

9

Figure 10.3c-e Bacterial cell wall synthesis and the inhibitory effects of beta-lactams on it.



10

Mechanisms of Antimicrobial Action

- **Inhibition of Cell Wall Synthesis**
  - Inhibition of synthesis of bacterial walls
    - Semisynthetic derivatives of beta-lactams
      - More stable in acidic environments
      - More readily absorbed
      - Less susceptible to deactivation
      - More active against more types of bacteria

11

Mechanisms of Antimicrobial Action

- **Inhibition of Cell Wall Synthesis**
  - Inhibition of synthesis of bacterial walls
    - Vancomycin and cycloserine
      - Interfere with particular bridges that link NAM subunits in many Gram-positive bacteria
    - Bacitracin
      - Blocks transport of NAG and NAM from cytoplasm
    - Isoniazid and ethambutol
      - Disrupt mycolic acid formation in mycobacterial species

12

Mechanisms of Antimicrobial Action

- **Inhibition of Cell Wall Synthesis**
  - Inhibition of synthesis of bacterial walls
    - Prevent bacteria from increasing amount of peptidoglycan
    - Have no effect on existing peptidoglycan layer
    - Effective only for growing cells

13

Mechanisms of Antimicrobial Action

- **Inhibition of Cell Wall Synthesis**
  - Inhibition of synthesis of fungal walls
    - Fungal cells are composed of various polysaccharides not found in mammalian cells
    - Echinocandins inhibit the enzyme that synthesizes glucan

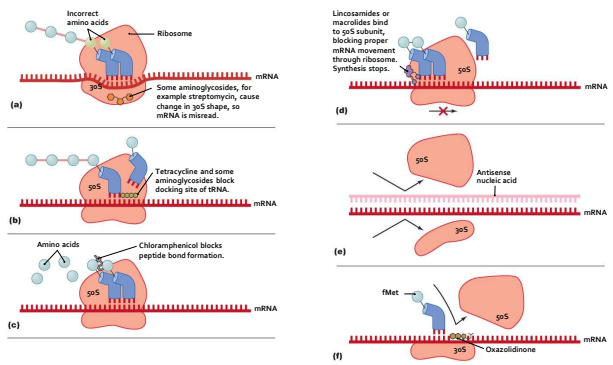
14

Mechanisms of Antimicrobial Action

- **Inhibition of Protein Synthesis**
  - Prokaryotic ribosomes are 70S (30S and 50S)
  - Eukaryotic ribosomes are 80S (40S and 60S)
  - Drugs can selectively target translation
  - Mitochondria of animals and humans contain 70S ribosomes
    - Can be harmful

15

Figure 10.4 The mechanisms by which antimicrobials target prokaryotic ribosomes to inhibit protein synthesis.



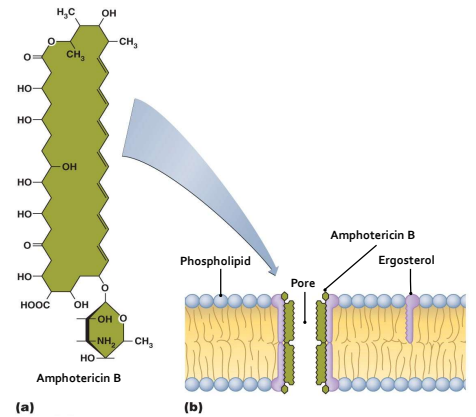
16

Mechanisms of Antimicrobial Action

- **Disruption of Cytoplasmic Membranes**
  - Some drugs form channel through cytoplasmic membrane and damage its integrity
  - Amphotericin B attaches to ergosterol in fungal membranes
    - Humans somewhat susceptible because cholesterol is similar to ergosterol
    - Bacteria lack sterols; not susceptible

17

Figure 10.5 Disruption of the cytoplasmic membrane by the antifungal amphotericin B.



18

Mechanisms of Antimicrobial Action

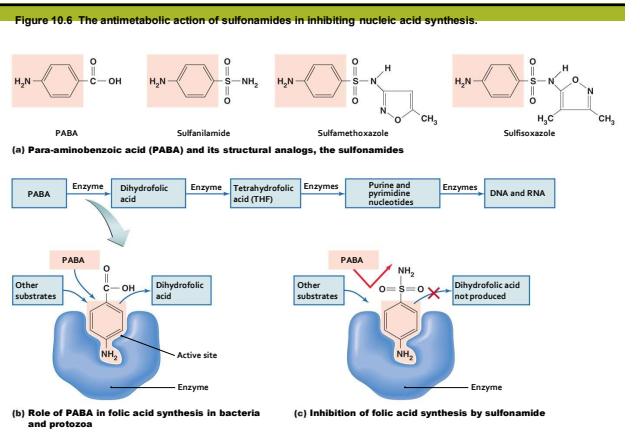
- **Disruption of Cytoplasmic Membranes**
  - Azoles and allylamines inhibit ergosterol synthesis
  - Polymyxin disrupts cytoplasmic membranes of Gram-negative bacteria
    - Toxic to human kidneys
  - Pyrazinamide only disrupts transport across the cytoplasmic membrane of *Mycobacterium tuberculosis*
  - Some antiparasitic drugs act against cytoplasmic membranes

19

Mechanisms of Antimicrobial Action

- **Inhibition of Metabolic Pathways**
  - Antimetabolic agents can be effective when pathogen and host metabolic processes differ
  - Atovaquone interferes with electron transport in protozoa and fungi
  - Heavy metals inactivate enzymes
  - Agents that disrupt tubulin polymerization and glucose uptake by many protozoa and parasitic worms
  - Drugs block activation of viruses
  - Metabolic antagonists

20



21

Mechanisms of Antimicrobial Action

- **Inhibition of Metabolic Pathways**
  - Antiviral agents can target unique aspects of viral metabolism
    - Amantadine, rimantadine, and weak organic bases prevent viral uncoating
  - Protease inhibitors interfere with an enzyme that HIV needs in its replication cycle

22

Mechanisms of Antimicrobial Action

- **Inhibition of Nucleic Acid Synthesis**
  - Several drugs block DNA replication or RNA transcription
  - Drugs often affect both eukaryotic and prokaryotic cells
  - Not normally used to treat infections
  - Used primarily in research and perhaps to slow cancer cell replication

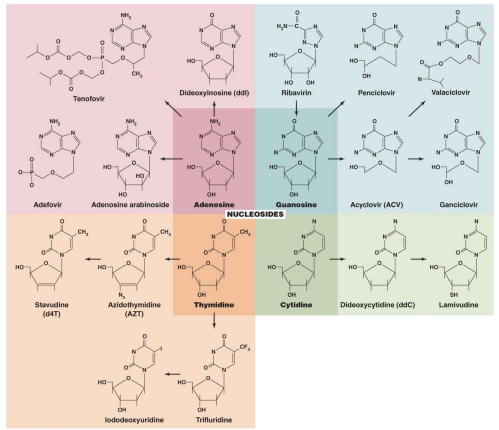
23

Mechanisms of Antimicrobial Action

- **Inhibition of Nucleic Acid Synthesis**
  - Nucleotide or nucleoside analogs
    - Interfere with function of nucleic acids
    - Distort shapes of nucleic acid molecules and prevent further replication, transcription, or translation
    - Most often used against viruses
    - Effective against rapidly dividing cancer cells

24

Figure 10.7 Nucleosides and some of their antimicrobial analogs.



25

Mechanisms of Antimicrobial Action

- **Inhibition of Nucleic Acid Synthesis**
  - Quinolones and fluoroquinolones
    - Act against prokaryotic DNA gyrase
  - Inhibitors of RNA polymerase
  - Reverse transcriptase inhibitors
    - Act against an enzyme HIV uses in its replication cycle
    - Do not harm people because humans lack reverse transcriptase

26

Mechanisms of Antimicrobial Action

- **Prevention of Virus Attachment and Entry**
  - Attachment antagonists block viral attachment or receptor proteins
  - New area of antimicrobial drug development

27

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Ideal Antimicrobial Agent**
  - Readily available
  - Inexpensive
  - Chemically stable
  - Easily administered
  - Nontoxic and nonallergenic
  - Selectively toxic against wide range of pathogens

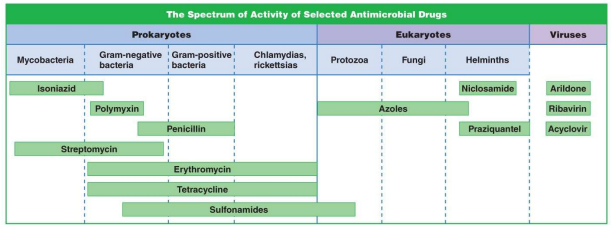
28

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Spectrum of Action**
  - Number of different pathogens a drug acts against
    - Narrow-spectrum: effective against few organisms
    - Broad-spectrum: effective against many organisms
      - May allow for secondary or superinfections to develop
      - Killing of normal flora reduces microbial antagonism

29

Figure 10.8 Spectrum of action for selected antimicrobial agents.



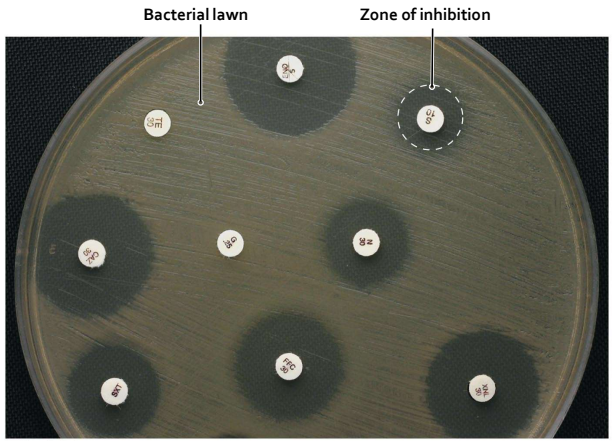
30

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Effectiveness**
  - Efficacy of antimicrobials assessed by a variety of tests
    - Diffusion susceptibility test
    - Minimum inhibitory concentration test
    - Minimum bactericidal concentration test

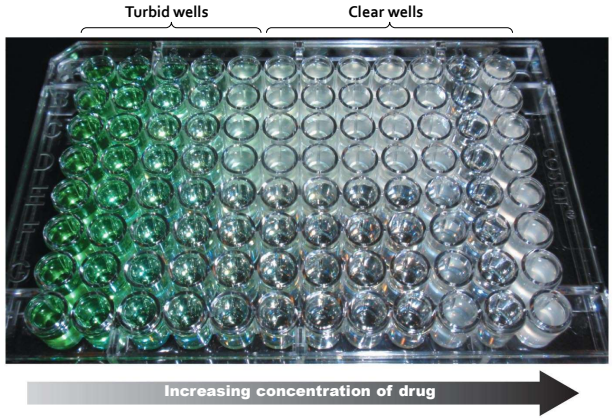
31

Figure 10.9 Zones of inhibition in a diffusion susceptibility (Kirby-Bauer) test.



32

Figure 10.10 Minimum inhibitory concentration (MIC) test in test tubes.

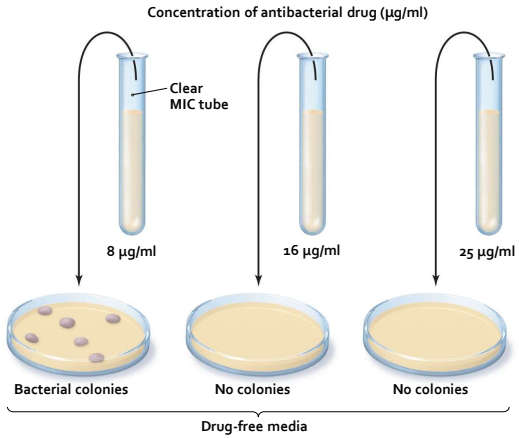


33

Figure 10.11 An Etest, which combines aspects of Kirby-Bauer and MIC tests.

34

Figure 10.12 A minimum bactericidal concentration (MBC) test.



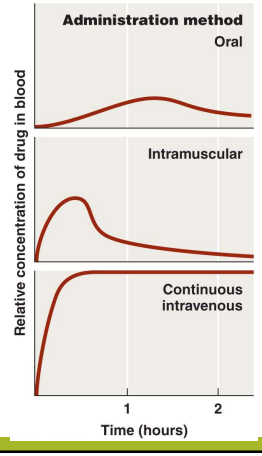
35

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Routes of Administration**
  - Topical application of drug for external infections
  - Oral route requires no needles and is self-administered
  - Intramuscular administration delivers drug via needle into muscle
  - Intravenous administration delivers drug directly to bloodstream
  - Must know how antimicrobial agent will be distributed to infected tissues

36

Figure 10.13 The effect of route of administration on blood levels of a chemotherapeutic agent.



37

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Safety and Side Effects**
  - Toxicity
    - Cause of many adverse reactions is poorly understood
    - Drugs may be toxic to kidneys, liver, or nerves
    - Consideration needed when prescribing drugs to pregnant women
    - Therapeutic index is the ratio of the dose of a drug that can be tolerated to the drug's effective dose
      - Use drug within its therapeutic range

38

Figure 10.14 Some side effects resulting from toxicity of antimicrobial agents.

39

Clinical Considerations in Prescribing Antimicrobial Drugs

- **Safety and Side Effects**
  - Allergies
    - Allergic reactions are rare but may be life threatening
    - Anaphylactic shock
  - Disruption of normal microbiota
    - May result in secondary infections
    - Overgrowth of normal flora, causing superinfections
    - Of greatest concern for hospitalized patients

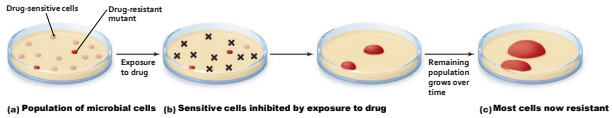
40

Resistance to Antimicrobial Drugs

- **The Development of Resistance in Populations**
  - Some pathogens are naturally resistant
  - Bacteria acquire resistance in two ways
    - New mutations of chromosomal genes
    - Acquisition of R plasmids via transformation, transduction, and conjugation.

41

Figure 10.15 The development of a resistant strain of bacteria.



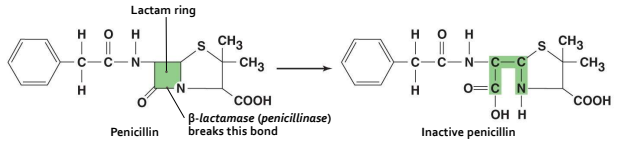
42

Resistance to Antimicrobial Drugs

- **Mechanisms of Resistance**
  - At least seven mechanisms of microbial resistance exist
    - Produce enzyme that destroys or deactivates drug
    - Slow or prevent entry of drug into the cell
    - Alter target of drug so it binds less effectively
    - Alter their own metabolic chemistry
    - Pump antimicrobial drug out of the cell before it can act
    - Bacteria in biofilms can resist antimicrobials
    - *Mycobacterium tuberculosis* produces MfpA protein
      - Binds DNA gyrase, preventing the binding of fluoroquinolone drugs

43

Figure 10.16 How β-lactamase (penicillinase) renders penicillin inactive.



44

Resistance to Antimicrobial Drugs

- **Multiple Resistance and Cross Resistance**
  - Pathogen can acquire resistance to more than one drug
  - Common when R plasmids exchanged
  - Develop in hospitals and nursing homes
    - Constant use of drugs eliminates sensitive cells
  - Multi-drug-resistant pathogens are resistant to at least three antimicrobial agents
  - Cross resistance to similar drugs may develop

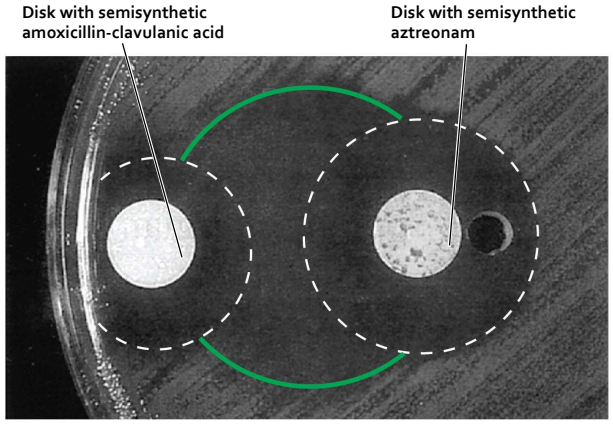
45

Resistance to Antimicrobial Drugs

- **Retarding Resistance**
  - Maintain high concentration of drug in patient for sufficient time
    - Inhibit the pathogen so immune system can eliminate
  - Use antimicrobial agents in combination
    - Synergism versus antagonism

46

Figure 10.17 An example of synergism between two antimicrobial agents.



47

Resistance to Antimicrobial Drugs

- **Retarding Resistance**
  - Use antimicrobials only when necessary
  - Develop new variations of existing drugs
    - Second-generation drugs
    - Third-generation drugs
  - Search for new antibiotics, semisynthetics, and synthetics

48