1 Chapter 20
   • Antimicrobial Drugs

2

3 The History of Chemotherapy
   • 20-1 Identify the contributions of Paul Ehrlich and Alexander Fleming to chemotherapy.
   • 20-2 Name the microbes that produce most antibiotics.

4 Antimicrobial Drugs
   • Chemotherapy: the use of drugs to treat a disease
   • Antimicrobial drugs: interfere with the growth of microbes within a host
   • Antibiotic: a substance produced by a microbe that, in small amounts, inhibits another microbe
   • Selective toxicity: killing harmful microbes without damaging the host

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6 Antimicrobial Drugs
   • 1928: Fleming discovered penicillin, produced by Penicillium
   • 1940: Howard Florey and Ernst Chain performed first clinical trials of penicillin

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   • Who coined the term magic bullet? 20-1
   • More than half our antibiotics are produced by a certain genus of bacteria. What is it? 20-2

10 The Spectrum of Antimicrobial Activity
   • 20-3 Describe the problems of chemotherapy for viral, fungal, protozoan, and helminthic infections.
   • 20-4 Define the following terms: spectrum of activity, broad-spectrum antibiotic, superinfection.

11 The Spectrum of Antimicrobial Activity
   • Broad spectrum
   • Narrow spectrum
   • Superinfection

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• Identify at least one reason why it is so difficult to target a pathogenic virus without damaging the host’s cells. 20-3
• Why are antibiotics with a very broad spectrum of activity not as useful as one might first think? 20-4

14 The Action of Antimicrobial Drugs
• Identify five modes of action of antimicrobial drugs.

15 The Action of Antimicrobial Drugs

• Bactericidal
  • Kill microbes directly
• Bacteriostatic
  • Prevent microbes from growing

26 Commonly Used Antimicrobial Drugs

• Explain why the drugs described in this section are specific for bacteria.
• List the advantages of each of the following over penicillin: semisynthetic penicillins, cephalosporins, and vancomycin.
• Explain why isoniazid (INH) and ethambutol are antimycobacterial agents.

27 Commonly Used Antimicrobial Drugs

• Describe how each of the following inhibits protein synthesis: aminoglycosides, tetracyclines, chloramphenicol, macrolides.
• Compare the mode of action of polymyxin B, bacitracin, and neomycin.
• Describe how rifamycins and quinolones kill bacteria.
28 Inhibitors of Cell Wall Synthesis
- Penicillin
  - Natural penicillins
  - Semisynthetic penicillins
  - Extended-spectrum penicillins

33 β-Lactam Antibiotics
- Penicillin
  - Penicillinase-resistant penicillins
  - Penicillins + β-lactamase inhibitors
- Carbapenems
  - Substitute a C for an S, add a double bond
- Monobactam
  - Single ring

34 Inhibitors of Cell Wall Synthesis
- Cephalosporins
  - First-generation: narrow spectrum; act against gram-positive bacteria
  - Second-generation: extended spectrum includes gram-negative bacteria
  - Third-generation: includes pseudomonads; injected
  - Fourth-generation: oral

36 Inhibitors of Cell Wall Synthesis
- Polypeptide antibiotics
  - Bacitracin
    - Topical application
    - Against gram-positives
  - Vancomycin
    - Glycopeptide
    - Important “last line” against antibiotic-resistant S. aureus

37 Inhibitors of Cell Wall Synthesis
- Antimycobacterial antibiotics
- Isoniazid (INH)
  - Inhibits mycolic acid synthesis
- Ethambutol
  - Inhibits incorporation of mycolic acid

38
- One of the most successful groups of antibiotics targets the synthesis of bacterial cell walls; why does the antibiotic not affect the mammalian cell? 20-6
- What phenomenon prompted the development of the first semisynthetic antibiotics, such as methicillin? 20-7
- In what genus of bacteria do we find mycolic acids in the cell wall? 20-8

39 Inhibitors of Protein Synthesis
- Chloramphenicol
  - Broad spectrum
    - Binds 50S subunit; inhibits peptide bond formation

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41 Inhibitors of Protein Synthesis
- Aminoglycosides
  - Streptomycin, neomycin, gentamicin
    - Broad spectrum
      - Change shape of 30S subunit

42 Inhibitors of Protein Synthesis
- Tetracyclines
  - Broad spectrum
    - Interfere with tRNA attachment

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44 Inhibitors of Protein Synthesis
- Glycylcyclines
  - MRSA and Acinetobacter baumanii
    - Bind 30S subunit; inhibit translation

45 Inhibitors of Protein Synthesis
- Macrolides
  - Gram-positives
    - Bind 50S; prevent translocation

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47 Inhibitors of Protein Synthesis
- Streptogramins
• Gram-positives
  • Bind 50S subunit; inhibit translation

48 [Inhibitors of Protein Synthesis]
• Oxazolidinones
  • Linezolid
  • MRSA
  • Bind 50S subunit; prevent formation of 70S ribosome

49 [Inhibitors of Protein Synthesis]
• Pleuromutilins
  • From the mushroom Pleurotis mutilus
  • MRSA
  • Bind 50S; prevent translocation

50 [Injury to the Plasma Membrane]
• Lipopeptides
  • Structural changes in the membrane, followed by arrest of the synthesis of DNA, RNA, and protein
  • MRSA
• Polymyxin B
  • Topical
  • Combined with bacitracin and neomycin in over-the-counter preparation

51 [ ]
• Why does erythromycin, a macrolide antibiotic, have a spectrum of activity limited largely to gram-positive bacteria even though its mode of action is similar to that of the broad-spectrum tetracyclines? 20-9
• Of the three drugs often found in over-the-counter antiseptic creams—polymyxin B, bacitracin, and neomycin—which has a mode of action most similar to that of penicillin? 20-10

52 [Inhibitors of Nucleic Acid Synthesis]
• Rifamycin
  • Inhibits RNA synthesis
  • Antituberculosis
• Quinolones and fluoroquinolones
  • Nalidixic acid: urinary infections
  • Ciprofloxacin
  • Inhibit DNA gyrase
  • Urinary tract infections

53 [Competitive Inhibitors]
• Sulfonamides (sulfa drugs)
  • Inhibit folic acid synthesis
  • Broad spectrum

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• What group of antibiotics interferes with the DNA-replicating enzyme DNA gyrase? 20-11
• Both humans and bacteria need the essential nutrient para-aminobenzoic acid; why, then, are only bacteria affected by sulfa drugs? 20-12

57 Commonly Used Antimicrobial Drugs
• 20-13 Explain the modes of action of currently used antifungal drugs.
• 20-14 Explain the modes of action of currently used antiviral drugs.
• 20-15 Explain the modes of action of currently used antiprotozoan and antihelminthic drugs.

58 Antifungal Drugs: Inhibition of Ergosterol Synthesis
• Polyenes
  • Amphotericin B

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60 Antifungal Drugs: Inhibition of Ergosterol Synthesis
• Azoles
  • Miconazole
  • Triazole
• Allylamines
  • Forazole-resistant infections

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62 Antifungal Drugs: Inhibiting Cell Wall Synthesis
• Echinocandins
  • Inhibit synthesis of β-glucan
  • Cancidas is used against Candida and Pneumocystis

63 Inhibition of Nucleic Acids
• Flucytosine
  • Cytosine analog interferes with RNA synthesis
• Pentamidine isethionate
  • Anti-Pneumocystis; may bind DNA

64 Other Antifungal Drugs
• Griseofulvin
• Inhibits microtubule formation
• Superficial dermatophytes
• Tolnaftate
  • Action unknown

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• What sterol in the cell membrane of fungi is the most common target for antifungal action? 20-13

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68 [Antiviral Drugs: Enzyme Inhibitors]
• Protease inhibitors
  • Indinavir: HIV
• Integrase inhibitors
  • HIV

69 [Antiviral Drugs: Entry Inhibitors]
• Entry inhibitors
  • Amantadine: influenza
• Fusion inhibitors
  • Zanamivir: influenza
  • Block CCR5: HIV

70 [Antiviral Drugs: Interferons]
• Prevent spread of viruses to new cells
  • Alpha interferon: Viral hepatitis
• Imiquimod
  • Promotes interferon production

71 [Antiprotozoan Drugs]
• Chloroquine
  • Inhibits DNA synthesis
    • Malaria
• Artemisinin
  • Kills Plasmodium sporozoites
• Metronidazole
  • Interferes with anaerobic metabolism
    • Trichomonas and Giardia

72 [Antihelminthic Drugs]
• Niclosamide
  • Prevents ATP generation
- Tapeworms
  - Praziquantel
    - Alters membrane permeability
  - Flatworms
- Mebendazole and albendazole
  - Interfere with nutrient absorption
    - Intestinal roundworms
- Ivermectin
  - Paralysis of helminths
  - Intestinal roundworms

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- One of the most widely used antivirals, acyclovir, inhibits the synthesis of DNA. Humans also synthesize DNA, so why is the drug still useful in treating viral infections? 20-14
- What was the first drug available for use against parasitic infections? 20-15

74 **Tests to Guide Chemotherapy**
- 20-16 Describe two tests for microbial susceptibility to chemotherapeutic agents.

75 **Tests to Guide Chemotherapy**

- MIC: minimal inhibitory concentration
- MBC: minimal bactericidal concentration
- Antibiogram

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- In the disk-diffusion (Kirby-Bauer) test, the zone of inhibition indicating sensitivity around the disk varies with the antibiotic. Why? 20-16

80 **Resistance to Antimicrobial Drugs**
- 20-17 Describe the mechanisms of drug resistance.

81

82 **Antibiotic Resistance**
- A variety of mutations can lead to antibiotic resistance
- Resistance genes are often on plasmids or transposons that can be transferred between bacteria
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 to complete the prescribed regimen
  - Using someone else’s leftover prescription

What is the most common mechanism that a bacterium uses to resist the effects of penicillin? 20-17

Effects of Combinations of Drugs
- Compare and contrast synergism and antagonism.

Effects of Combinations of Drugs
- Synergism occurs when the effect of two drugs together is greater than the effect of either alone
- Antagonism occurs when the effect of two drugs together is less than the effect of either alone

Antibiotic Safety
- Therapeutic index: risk versus benefit

- Tetracycline sometimes interferes with the activity of penicillin. How? 20-18

Future of Chemotherapeutic Agents
- Identify three areas of research on new chemotherapeutic agents.

Future of Chemotherapeutic Agents
- Antimicrobial peptides
  - Broad-spectrum antibiotics
    - Nisin (lactic acid bacteria)
    - Defensins (human)
• Magainin (frogs)
• Squalamine (sharks)
• Phage therapy

• What are defensins? 20-19