Slide 1

Drugs, Microbe-Host interactions –
The Elements of Chemotherapy

Slide 2

• This presentation relates to the use of antibiotics for control of microorganisms as outlined in chapter eleven of your text. Please read and understand this chapter.

Slide 3

Objectives
• Explore the advantages and disadvantages of using antibiotics to control microbes in the body.
• Identify some of the important antibiotics used to treat disease and indicate how these drugs achieve the antimicrobial activity.
• Discuss the problem of antibiotic resistance with reference to its origins and the implications.

Slide 4

Origins of antimicrobial drugs
Antibiotics are common metabolic products of aerobic spore-forming bacteria & fungi.
- By inhibiting the other microbes in the same habitat, antibiotic producers have less competition for nutrients & space.
- Bacteria in genera Streptomyces & Bacillus
- Molds in genera Penicillium & Cephalosporium
Selectively toxic

• Drugs should kill or inhibit microbial cells without simultaneously damaging host tissues.

As the characteristics of the infectious agent become more similar to the vertebrate host cell, complete selective toxicity becomes more difficult to achieve & more side effects are seen.

First attempts

• Robert Erlich wanted to develop a chemical compound that was a “magic bullet” which would selectively kill bacterial pathogens.
  – Developed an arsenic compound dioxy-diamino-arsenobenzol-dihydro-chloride, called arsphenamine (America) or Salvarsan (German) also called 606 against syphilis.
Gerhard Domagk developed prontosil. The active substance in this was later found to be Sulfanilamide.
– Usage in world war II save many lives.
Alexander Fleming discovered Penicillin in 1928.
• In 1939 researchers found his report and were able to isolate the active ingredient.

Targets of antimicrobial drugs

• Inhibition of cell wall synthesis
• Inhibition of nucleic acid synthesis, structure or function
• Inhibition of protein synthesis
• Disruption of cell membrane structure or function

1. Drugs that affect the bacterial cell wall
• Most bacterial cell walls contain a rigid gridle of peptidoglycan.
  • Penicillin and cephalosporin block synthesis of peptidoglycan, causing the cell wall to lyse.
  • Penicillins do not penetrate the outer membrane and are less effective against gram-negative bacteria.
  • Broad spectrum penicillins and cephalosporins can cross the cell walls of gram-negative bacteria.
2. Drugs that inhibit nucleic acid synthesis

- May block synthesis of nucleotides, inhibit replication, or stop transcription.
- Sulfonamides and trimethoprim block enzymes required for DNA & RNA synthesis.
- Competitive inhibition – drug competes with normal substrate for enzyme’s active site.
- Synergistic effect – an additive effect, achieved by multiple drugs working together, requiring a lower dose of each.

3. Drugs that block protein synthesis

- Ribosomes of eucaryotes differ in size and structure from procaryotes, so antimicrobics usually have a selective action against procaryotes. But they can also damage the eucaryotic mitochondria.
- Aminoglycosides (streptomycin, gentamicin) insert on sites on the 30S subunit and cause misreading of mRNA.
- Tetracyclines block attachment of tRNA on the acceptor site and stop further synthesis.

4. Drugs that disrupt cell membrane function

- A cell with a damaged membrane dies from disruption in metabolism or lysis.
- These drugs have specificity for a particular microbial group, based on differences in types of lipids in their cell membranes.
- Polymyxins interact with phospholipids and cause leakage, particularly in gram-negative bacteria.
- Amphotericin B and nystatin form complexes with sterols on fungal membranes which causes leakage.
Survey of major antimicrobial drug groups

• Antibacterial drugs
  – About 260 different antimicrobial drugs are classified in 20 drug families.
     Antibiotics
     Synthetic drugs
     Antifungal drugs
     Antiparasitic drugs
     Antiviral drugs

Antibacterial antibiotics

• Penicillins
   Cephalosporins
   Other beta-lactam antibiotics
   Aminoglycosides
   Tetracycline antibiotics
   Chloramphenicol
   Other Streptomyces antibiotics
   The Bacillus antibiotics
   New classes

Penicillins

• Large diverse group of compounds
   Could be synthesized in the laboratory
   More economical to obtain natural penicillin through microbial fermentation and modify it to semi-synthetic forms
   Penicillium chrysogenum – major source
   All consist of 3 parts
     Thiazolidine ring
     Beta-lactam ring
     Variable side chain dictates microbial activity

Penicillins

• Penicillins G and V most important natural forms
   Penicillin is the drug of choice for gram-positive cocci (streptococci) and some gram-negative bacteria (meningococci and syphiilis spirochate)
   Semisynthetic penicillins – ampicillin, carbenicillin & amoxicillin have broader spectra – gram negative enterics rods
   Penicillinase-resistant – methicillin, natocillin, cloxacillin
   Primary problems – allergies and resistant strains of bacteria
Cephalosporins

• Account for majority of all antibiotics administered
• Isolated from Cephalosporium acremonium mold
• Beta-lactam ring that can be altered
• Relatively broad-spectrum, resistant to most penicillinases, & cause fewer allergic reactions
• Some are given orally, many must be administered parenterally

First generation – cephalothin, cefazolin – most effective against gram-positive cocci
Second generation – cefaclor, ceforanid – more effective against gram-negative bacteria
Third generation – cephalaxin, cefotaxime – broad-spectrum activity against enteric bacteria with beta-lactamases
Ceftriaxone – new semisynthetic broad-spectrum drug for treating wide variety of infections

Aminoglycosides

• Products of various species of soil actinomycetes in genera Streptomyces & Micromonospora
• Broad-spectrum, inhibit protein synthesis, especially useful against aerobic gram-negative rods & certain gram-positive bacteria
  • Streptomycin – bubonic plague, tularemia, TB
  • Gentamicin – less toxic, used against gram-negative rods
  • Newer – Tobramycin & amikacin gram-negative bacteria

Gentamicin toxicity

• The most common single known cause of bilateral vestibulopathy. This occurs when the balance portions of both inner ears are damaged.
• The symptoms typically include imbalance and visual symptoms. The imbalance is worse in the dark, or in situations where footing is uncertain.
• The visual symptoms, only occur when the head is moving. Quick movements of the head are associated with transient visual blurring. This can cause difficulties with seeing signs while driving, or recognizing people’s faces while walking.
Tetracycline antibiotics

- Broad-spectrum, block protein synthesis
- Doxycycline & minocycline – oral drugs taken for STDs, Rocky Mountain spotted fever, Lyme disease, typhus, acne & protozoa
- Can stain teeth

Chloramphenicol

- Isolated from Streptomyces venezuelae
- Potent broad-spectrum drug with unique nitrobenzene structure
- Blocks peptide bond formation
- No longer derived from natural source
- Very toxic, restricted uses, can cause irreversible damage to bone marrow
- Typhoid fever, brain abscesses, rickettsial & chlamydial infections
Other *Streptomyces* antibiotics

- **Erythromycin** – macrolide, large lactone ring with sugars
  - Broad-spectrum, fairly low toxicity
  - Attachment to ribosome
  - Taken orally for *Mycoplasma pneumonia*, *legionellosis*, *Chlamydia, pertussis, diphtheria* and as a prophylactic prior to intestinal surgery
  - For penicillin-resistant – *gonococci, syphilis, acne*
- **Newer semi-synthetic macrolides** – clarithromycin, azithromycin

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Other *Streptomyces* antibiotics

- **Clindamycin** – broad-spectrum, serious abdominal anaerobic infections. (can cause pseudomembranous colitis)
- **Vancomycin** – narrow-spectrum, effective against penicillin & methicillin resistant staphylococcal infections; very toxic, hard to administer
- **Rifampin** – limited spectrum, cannot pause through many cell membranes, used to treat gram-positive bacteria, TB, leprosy

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The *Bacillus* antibiotics

- **Bacitracin** – narrow-spectrum peptide produce by *Bacillus subtilis*, major ingredient of neosporin ointment
- **Polymyxin** – narrow-spectrum peptide with fatty acid component, detergent activity; limited by toxicity to kidney; drug resistant *Pseudomonas aeruginosa* & UTI

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Synthetic antibacterial drugs

- **Sulfonamides**, sulfa drugs – first antimicrobial drugs
  - **Sulfisoxazole** – shigellosis, UTI, protozoan infections
  - **Silver sulfadiazine** – burns, eye infections
  - **Trimethoprim** – given in combination with sulfathiazole – UTI, PCP
Miscellaneous antibacterial drugs
- Isoniazid - used with rifampicin to treat TB
- Oxazolidinones - new class of antibacterial drugs
  inhibit initiation of protein synthesis
  - Linezolid - MRSA, VRE
- Fluoroquinolones - broad-spectrum, potent
  - norfloxacin, ciprofloxacin - UTI, STD, GI, osteomyelitis, respiratory & soft tissue infections
  - sparofloxacin, levofloxacin - pneumonia, bronchitis, sinusitis
- Fluoroquinolones - UTI, STD, GI, osteomyelitis, respiratory & soft tissue infections
  - norfloxacin, ciprofloxacin
  - sparofloxacin, levofloxacin

Antifungal drugs
- Macrolide polyene
  - Amphotericin B - mimic lipids, most versatile & effective, topical & systemic treatments
  - Nystatin - topical treatment
- Griseofulvin - stubborn cases of dermatophyte infections, nephrotoxic
- Synthetic azoles - broad-spectrum;
  - ketoconazole, clotrimazole, miconazole
- Flucytosine - analog of cytosine; cutaneous mycoses or in combination with amphotericin B for systemic mycoses

Antiparasitic drugs
- Antimalarial drugs - quinine, chloroquine, primaquine, mefloquine
- Antiprotozoan drugs - Metronidazole (Flagyl), quinacrine, sulfonamides, tetracyclines
- Anthelminthic drugs (worms) - immobilize, disintegrate, or inhibit metabolism
  - mebendazole, thiabendazole - broad-spectrum - inhibit function of microtubules, interferes with glucose utilization & disables them
  - pyrantel, piperazine - paralyze muscles
  - niclosamide - destroys scolex

Antiviral drugs
- Block penetration into host cell
- Block transcription or translation
  - Nucleotide analogs
    - Acyclovir - herpesviruses
  - Ribavarin - a guanine analog - RSV, hemorrhagic fevers
  - AZT - thymine analog - HIV
- Prevent maturation of viral particles
  - Protease inhibitors - HIV
- Interferon - HCV
Mechanisms drug resistance

- Drug inactivation – penicillinases
- Decreased permeability to drug or increased elimination of drug from cell
- Change in metabolic patterns
- Change in drug receptors

Selection for drug resistance

Side effects of drugs

1. Toxicity to organs
2. Allergic responses
3. Suppression and alteration of microflora
Considerations in selecting an antimicrobial drug

1. nature of microbe causing infection
2. degree of microbe’s sensitivity to various drugs
3. overall medical condition of patient

- Minimum inhibitory concentration (MIC) - smallest concentration of drug that visibly inhibits growth
- Therapeutic index – the ratio of the dose of the drug that is toxic to humans as compared to its minimum effective dose
- LD 50 - what dose will kill 50% of a population.