Lecture 1

Introduction

Antimicrobial Chemotherapy

(MLAB 366)

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A Brief History of Antibiotics

- 1495, mercury to treat syphilis.
- 1630, quinine (chinchona tree) for malarial fever by South American Indians.
- 1910, Paul Ehrlich developed arsenical compound (Salvarsan) for syphilis, term: the chemical knife.
- 1929, Alexander Fleming found penicillin.
- 1940, Ernst Chain and Howard Flory demonstrated the effect of penicillin.
- 1940-1970, search for new antibiotics
- Recent years: modifying old drugs, finding new discipline in combating antibiotics resistance
HISTORICAL PERSPECTIVE

- 100 years ago - 1 in 3 children died of infectious disease before age 5
- Germ theory of disease
- Koch’s postulates
- Robert Ehrlich - microbe specific dyes
- Sir Alexander Fleming discovered penicillin (1929)
- Before antimicrobials, large number of people died from common illnesses
- Now many illnesses easily treated with antimicrobials

Plate of Staphylococcus aureus inhibited by Penicillium notatum

• Fleming: Worked on cultures of Staphylococcus
  • contamination with mold
  • Noticed colonies growing near mold looked odd
  • Found that mold was secreting substance that was killing bacteria
Thanks to work by Alexander Fleming (1881-1955), Howard Florey (1898-1968) and Ernst Chain (1906-1979), penicillin was first produced on a large scale for human use in 1943. At this time, the development of a pill that could reliably kill bacteria was a remarkable development and many lives were saved during World War II because this medication was available.
A Tale by A. Fleming

- He took a sample of the mold from the contaminated plate. He found that it was from the *penicillium* family, later specified as *Penicillium notatum*. Fleming presented his findings in 1929, but they raised little interest. He published a report on penicillin and its potential uses in the *British Journal of Experimental Pathology*.

Sources of Antibacterial Agents

- **Natural** - mainly fungal sources
- **Semi-synthetic** - chemically-altered natural compound
- **Synthetic** - chemically designed in the lab
The original antibiotics were derived from fungal sources. These can be referred to as “natural” antibiotics.

- Organisms develop resistance faster to the natural antimicrobials because they have been pre-exposed to these compounds in nature.
- **Natural antibiotics** are often more toxic than synthetic antibiotics.
- Benzylpenicillin and Gentamicin are natural antibiotics

- **Semi-synthetic drugs** were developed to decrease toxicity and increase effectiveness
- Ampicillin and Amikacin are semi-synthetic antibiotics

  - **Synthetic drugs** have an advantage that the bacteria are not exposed to the compounds until they are released. They are also designed to have even greater effectiveness and less toxicity.
  - Moxifloxacin and Norfloxac in are synthetic antibiotics

- There is an inverse relationship between toxicity and effectiveness as you move from natural to synthetic antibiotics

**Natural Antibiotic Production**

- Many antibiotics are currently produced by large-scale fermentation of fungal or bacterial cultures. The antibiotic producing organism is grown in vats containing thousands of liters of **growth medium** (a mixture of nutrients designed to allow cell growth), and incubated under conditions designed to maximize the production of the antibiotic.

- After the growth process is complete, the antibiotic is separated from the rest of the culture. This typically involves both physical methods (like filtering) and chemical methods (like extraction with organic solvents) to yield a highly purified antibiotic. In many cases,

  - the antibiotic producer is mutated or genetically altered to more efficiently produce the antibiotic.

  - The rapid development of antibiotic resistance has led to a continual need to develop new antibiotics.
**Since then major search for antibiotics, found in 3 major groups of microorganisms:**

1-**Certain molds** (*Penicillium, Cephalosporium*). e.g. penicillin, cephalosporin

2-**Certain strains** of *Bacillus* e.g. bacitracin

3-**Many strains** of *Actinomycetes* (soil bacteria).
   Especially from Genus *Streptomyces*. e.g. streptomycin.

Majority of antibiotics come from these organisms.

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Natural products, including: toxins, antibiotics (*about 70% of all known antibiotics*), antifungals, etc, have historically been isolated and characterized from heterotrophic bacteria (e.g. *Streptomyces*). This was primarily due to the ease with which these organisms can be grown and manipulated in the laboratory.
WHAT ARE ANTIMICROBIALS?

- Drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action
  - Differ in physical, chemical, pharmacological properties
  - Differ in antibacterial spectrum of activity
  - Differ in their mechanism of action

ANTIMICROBIAL CHEMOTHERAPY (DRUGS)

Antimicrobial agent:
Chemical that kills or inhibits the growth of microorganisms

Antimicrobial Chemotherapy:
- Chemicals used to treat microbial infections
- or The use of drugs to treat a disease

Different types of antimicrobial Chemotherapy:
- Antibacterial Chemotherapy
- Antiviral Chemotherapy
- Antifungal Chemotherapy
- Antiparasitic (Antiprotozoan / Antihelminthic) Chemotherapy
ANTIBIOTIC/ANTIMICROBIAL

Antibiotic:
- Chemical produced by a microorganism that kills or inhibits the growth of another microorganism
- Or small molecules usually produced by bacteria or fungi that kill bacteria without harming the person or animal being treated.
- But in this course, both synthetic and naturally produced antibacterial compounds will be called antibiotics.

Antiseptics:
- Antibacterial chemical agents, such as detergents, only suitable for application to the skin

Disinfectants:
- Strong antibacterial chemicals, such as bleach, only suitable for treating inanimate objects.

DIFFERENT TYPES OF ANTIMICROBIAL CHEMOTHERAPY

- Antibacterial Chemotherapy
- Antiviral Chemotherapy
- Antifungal Chemotherapy
- Antiparasitic (Antiprotozoan / Antihelminthic) Chemotherapy
Antibacterials: Relatively easy to develop and find with low toxicity because prokaryotic cells are very different from host cells.

Antihelminthic, antiprotozoan, and antifungal drugs: More difficult to develop because eukaryotic cells resemble human cells.

Antivirals: Most difficult to develop because virus reproduces using host cell enzymes and machinery.

SPECTRUM OF ACTION (OR ACTIVITY)

Spectrum of action: Antimicrobial medications vary with respect to the range of microorganisms they kill or inhibit.

1-Broad spectrum antimicrobial: an antimicrobial agent that is effective against a wide range of microorganisms, often against gram positive and gram negative organisms.

2-Narrow spectrum antimicrobial: an anti microbial agent that effective against a limited number of organisms. e.x (gram +ve or gram –ve) bacteria.

3- Limited spectrum: If effective against a single organism or disease, they are referred to as limited spectrum.
LABORATORY TERMS

• **Susceptible:**
The organism is killed or inhibited by given levels of antibiotics

• **Resistant:**
The organism not killed or inhibited by given level of antibiotics

• **Minimal Inhibitory Concentration (MIC):**
Minimum concentration of antibiotics needed to inhibit visual growth of the organism: the lower the better
**PRINCIPLES OF ANTIBIOTICS**

- **Selective toxicity:** Ability of the antibiotic to inhibit the growth or kill the pathogen without harming the host cell.

- **Cidal:**
  Antimicrobials that kill a microbe (penicillin)
  - **cidal (killing) effect**
  - *(Bactericidal: Kill microorganisms)*

- **Static:**
  Antimicrobial that only inhibit the growth (sulphonamides)
  - **static (inhibitory) effect** on a range of microbes *(Bacteriostatic: inhibit growth of microorganisms)*

**FACTORS AFFECTING CHOICE OF THE ANTIBIOTIC:**

1. Possible infecting organism: Spectrum of activity.

2. Type of infection: Site (meningitis, osteomyelitis, endocarditis).


4. Host factors: Age, other medications, Renal and liver status, pregnancy, if the organism intracellular or extracellular.
INDICATION FOR ANTIMICROBIALS THERAPY:

- **Empirical:**
  based on:
  - Site and type of infection
  - Likely causative agent
  - The common antimicrobial susceptibility pattern.

- **Directed therapy:**
  - Based on culture and sensitivity

A CLINICALLY-USEFUL ANTIBIOTIC SHOULD HAVE AS MANY OF THESE CHARACTERISTICS AS POSSIBLE:

1- It should have a wide spectrum of activity with the ability to destroy or inhibit many different species of pathogenic organisms.

2- It should be nontoxic to the host and without undesirable side effects.

3- It should be non allergenic to the host.

4- It should not eliminate the normal flora of the host (when normal flora killed, other pathogens may be able to grow to high numbers).
5- It should be able to reach the part of the human body where the infection is occurring.

6- It should be inexpensive and easy to produce.

7- It should be chemically-stable (have a long shelf-life).

- **Administration of antibiotic:**
  
  I. Oral
  
  II. Systemic: IV, IM
  
  III. Topical

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**COMMON GROUPS OF ANTIMICROBIAL AGENTS:**

**Beta-lactams:**

- Penicillins
  
  • Penicillin G
  
  • Ampicillin/amoxicillin
  
  • Co-amoxiclav
  
  • Flucloxacillin/cloxacillin: Resistant to staphylococcal B-lactamases

- **Cephalosporins:**
  
  • First generation: cephadine
  
  • Second generation: cefuroxime
  
  • Third generation: ceftazidime
  
  • Fourth generation
○ **Carbapenems:**
  - imipenem, meropenem: very broad spectrum (Gram-positive, Gram-negative and anaerobes)

○ **Aminoglycosides:**
  - Gentamicin, amikacin

○ **Glycopeptides:**
  - Vancomycin, teicoplanin

○ **Macrolides:**
  - Erythromycin, clarithromycin

○ **Quinolones:**
  - Ciprofloxacin

○ **Miscellaneous:**
  - Metronidazole
  - Fusidic acid
  - Trimethoprim & sulphamethoxazole
  - Chloramphenicol
  - Tetracycline