**Lecture 28: Antimicrobial Drugs - Mechanisms of action, antibacterial drugs, antiviral and antifungal drugs**

**Antimicrobial drugs** are chemotherapeutic agents used to selectively interfere with the growth of microorganisms.

- The "ideal" antimicrobial drug kills the pathogenic microorganism without harming the host.
- Many antimicrobial drugs are **antibiotics**, natural compounds produced by microorganisms; others are synthetic compounds.
- Antimicrobial drugs were sought from the time when the microbial basis of infectious diseases was known.
  - Paul Erlich coined the term, and was responsible for development of heavy metal salts for treatment of syphilis.
  - The first synthetic compounds used as antimicrobial drugs were the sulfanilamides, or "sufla drugs", which are still used today.
- In 1928, Alexander Fleming revealed that the fungus *Penicillium notatum* was able to inhibit growth of surrounding colonies of *Staphylococcus aureus* (Tortora et al., Figure 20.1).
  - The compound responsible for this effect was eventually isolated as penicillin.
  - Penicillin was the first antibiotic.
  - Since that time, a variety of antibiotics, produced by a variety of genera of fungi and bacteria, have been discovered (Tortora et al., Table 20.1).
  - The majority of antibiotics in clinical use are produced by species of *Streptomyces*, which is a filamentous bacterium.
- Finding an effective antimicrobial drug for a particular infection often depends on the identity of the pathogen.
  - Since there are so many differences between the biology of eucaryotes and procaryotes, there are a variety of drugs that are useful against bacterial infections.
  - Infections caused by fungi and protozoa are more difficult to treat, since the cellular physiology of the pathogen is so close to that of the host.
  - Infections caused by viruses are especially difficult, since the cellular physiology of the pathogen IS that of the host!
- Antimicrobial drugs are characterized by a spectrum of activity.
  - **Narrow spectrum** antimicrobial drugs are effective against a limited number of microorganisms.
  - **Broad spectrum** antimicrobial drugs target a wider range of pathogens.
  - Although broad spectrum drugs have an advantage in that the pathogen need not be identified before treatment, they cause problems by destroying the native flora and selecting for antibiotic-resistant opportunists.

Antimicrobial drugs directed against bacterial infections target a variety of features unique to procaryotic cells (Tortora et al., Figure 20.2).

- Antibacterial drugs may be **bactericidal** (killing the bacteria) or **bacteriostatic** (inhibiting growth of the bacteria); in both cases, "clearing" of the pathogen is largely left to the host immune system.
- Several antibacterial drugs target the peptidoglycan cell wall of bacteria, a macromolecular feature not found in the host.
  - The **penicillins** and **cephalosporins** (Tortora et al. Figure 20.7) are known as β-lactam antibiotics because of a common chemical structure.
  - A variety of **semisynthetic** β-lactams have been developed to improve spectrum of activity and try to control resistance due to β-lactamases.
  - The **carbapenems** are a recently released class of synthetic β-lactam antibiotics.
- **Bacitracin** is a polypeptide that interferes with cell wall synthesis; its use is limited to topical application.
Vancomycin, a glycopeptide antibiotic, is useful for systemic treatment of Staphylococcus aureus infections resistant to β-lactams.
- Resistance to vancomycin is fairly common among Enterococcus faecium isolates, the so-called VRE.
- There is much concern that vancomycin resistance might spread to S. aureus.

Isoniazid and ethambutol are used to treat Mycobacterium tuberculosis infections; they interfere with different stages in the incorporation of mycolic acids into the mycobacterial cell wall.

Some of the most effective antibiotics are targeted to the prokaryotic ribosome.
- The aminoglycosides were one of the first antibiotics to show significant activity against Gram-negative bacteria.
  - Streptomycin was the first aminoglycoside discovered; it is relatively toxic and is currently used only in treatment of tuberculosis.
  - Other aminoglycosides include gentamicin and tobramycin.
- The tetracyclines (Tortora et al. Figure 20.11) have been widely used for their broad spectrum and tissue availability.
  - Examples of natural and semisynthetic tetracyclines include oxytetracycline, chlortetracycline, doxycycline, and minocycline.
  - Unfortunately, resistance to tetracyclines is relatively common, perhaps reflecting their widespread use as agents to promote growth of livestock.
- Chloramphenicol (Tortora et al. Figure 20.12) is an effective protein synthesis inhibitor, use of which is limited by its potential for bone marrow suppression.
- The macrolides, of which erythromycin (Tortora et al. Figure 20.13) is an example, are the drug of choice for treatment of infections caused by wall-less bacteria (e.g., Mycoplasma, Legionella).

Features unique to prokaryotic nucleic acid synthesis provide targets for action of some antibiotics.
- The rifamycins interfere with prokaryotic RNA synthesis; the best known, rifampin, is used against tuberculosis and as a prophylactic drug to protect contacts of meningitis cases.
- The quinolones and fluoroquinolones are synthetic drugs that interfere with prokaryotic DNA replication.
  - Nalidixic acid was the first quinolone developed.
  - Norfloxacin and ciprofloxacin are widely used fluoroquinolones.
- The sulfonamides and trimethoprim serve to inhibit enzymes essential to folic acid metabolism in bacteria (Tortora et al. Figure 20.14).
  - The sulfonamides, or “sulfa drugs”, were some of the first drugs used to treat infection.
  - Sulfamethoxazole and trimethoprim, in synergistic combination as TMP-SMZ, are widely used for treatment of urinary tract infection.

The need for antifungal drugs is increasing, but toxicity of systemic drugs remains a problem.
- Amphotericin B (Tortora et al. Figure 20.15) is a polyene antimicrobial used to treat systemic fungal infections.
  - The polyenes combine with sterols found in fungal cell membranes, increasing membrane permeability.
  - Amphotericin B is relatively toxic and requires careful monitoring.
- The imidazoles and triazoles interfere with fungal sterol synthesis.
  - Clotrimazole and miconazole (Tortora et al. Figure 20.16) are sold without prescription for treatment of cutaneous mycoses such as athlete’s foot and candidal vulvovaginitis.
  - Ketoconazole, fluconazole, and itraconazole may be prescribed for systemic fungal infections.
- Griseofulvin is used to treat dermatophytic fungal infections.
The number of *antiviral* drugs remains limited, and those that are available show very narrow spectra.

- Several important antiviral drugs are *nucleoside analogues* (see Tortora et al. Figure 8.19 on p. 229)
  - *Acylovir* and its derivatives *ganciclovir* and *famiciclovir* are used to limit the severity of reactivation in Herpesvirus infections
  - Numerous nucleoside analogues have been developed to treat HIV infection; *zidovudine (AZT)* was the first of these
- Treatment of HIV infection has been enhanced by *protease inhibitors* such as *indinavir* and *saquinavir*; today, the standard for *highly effective anti-retroviral therapy (HAART)* is a combination of a protease inhibitor with one or more nucleoside analogues
- There is considerable interest in the use of cytokines to limit viral infection; *α-interferon* is useful against hepatitis C infection in some individuals

Because much of the world’s population is debilitated by protozoal and helminthic infections, development of *antiprotozoan* and *antihelminthic* drugs is urgently needed.

- *Quinine*, and synthetic derivatives such as *chloroquine*, remain the first line of attack against malaria
- *Metronidazole* is one of the most widely used antiprotozoan drugs