Chapter 12 – Drugs, Microbes, Host – The Elements of Chemotherapy*

* Lecture notes are to be used as a study guide only and do not represent the comprehensive information you will need to know for the exams.

_Witch: Fillet of a fenny snake,
In the cauldron boil and bake;
Eye of newt, and toe of frog,
Wool of bat, and tongue of dog,
Adder’s fork, and blindworm’s sting,
Lizard’s leg, and howlet’s wing;
For a charm of pow’rful trouble
Like a hell-broth boil and bubble.
All: Double, double, toil and trouble;
Fire burn, and cauldron bubble._

-Macbeth IV.i.
-W. Shakespeare

**HISTORICAL NOTES**

The subject of this lecture is antimicrobial chemotherapy – the use of chemicals to treat or prevent infection. See 12.1 MAKING CONNECTIONS for a brief history of pharmaceutical development.

Modern antimicrobial pharmacology, that is, the development of drugs to combat or prevent infection from microorganisms, has a long history. Early pharmacology was based on folk remedies consisting of dubious potions with bizarre ingredients (not unlike Shakespeare’s witches’ brew) which occasionally helped, and often harmed whoever took them. While modern chemistry has freed us of using newts’ eyes and frog toes, our brews still depend on much of what we find in nature.

Not until Robert Koch’s germ theory of disease was disease treatment focused on a particular microbe (B._anthracis_ in 1876). Paul Ehrlich, also working in the late 1800s formulated what was to become the theoretical basis of modern chemotherapeutics: the concept of drug specificity – that if a drug was properly selective in its actions, it would zero-in on and destroy a microbial target like a magic bullet and not adversely affect human cells. His drug salvarsan (a chemical derivative of arsenic) was one of the first drugs to be selective for bacteria (T._pallidum_ which causes syphilis).

In 1928, Alexander Fleming noticed an agar plate inoculated with _Staphylococcus aureus_ had become contaminated with mold and there was a clear zone around the mold colony (now called a zone of inhibition). The mold was _Penicillium_ and the chemical it secreted that killed the _S. aureus_ became known as penicillin. The discovery was buried in the journals because sulfa drugs were in vogue as the “cure-all”. Although attempts were being made to isolate and purify the substance, penicillin was not widely used until WWII began. The discovery of penicillin eventually led to the development of a large class of antibiotics called beta-lactams.

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1 Interestingly, there is currently a very active search for naturally occurring chemicals that could be developed for antimicrobial therapy. Prospective sources include Komodo dragon saliva, frog skins, and shark livers. So, it would appear that we aren’t that far removed from the witches’ brew after all.
12.1 Principles of Antimicrobial Therapy

Antimicrobial therapy is the practice of giving chemotherapeutic drugs as a means to control infection. See Table 12.1 for qualities of ideal antimicrobial drugs. Antimicrobial drugs can be derived from natural sources, like the antibiotics, or from synthetic processes in the laboratory.

Considerations when choosing antimicrobial drugs include (Table 12.1):
* Above all, antimicrobial drugs should be selectively toxic, i.e. they should kill or inhibit microbial cells without simultaneously damaging host tissues.

1. **administration**
   How the drug is to be administered (orally, subcutaneous, IV drip, topical, etc.).
2. **absorption & distribution**
   How the drug is absorbed and distributed in the body.
3. **delivery**
   How well the drug is delivered to its site of action, i.e. extracellular or intracellular.
4. **efficacy & selectivity**
   How effective the drug is in killing the infectious agent (or preventing its growth) without harming host cells.
5. **metabolism & excretion**
   The metabolism and excretion of the drug from the body.

The Origins of Antimicrobial Drugs

Antibiotics, natural byproducts of common metabolic biochemistry, are useful to microbes since they will inhibit the growth of other microorganisms in the same habitat; thus the producer has less competition for nutrients and space. Bacteria in the genera *Streptomyces* and *Bacillus*, and molds (fungi) in the genera *Penicillium* and *Cephalosporium* are the greatest source for all of our currently used antibiotics. (Fig. 12.1 and Table 12.2).

Synthetic antimicrobial drugs are compounds manufactured in the laboratory; usually originate as dyes. There is some overlap, since many of the naturally occurring antibiotics are now chemically altered; antibiotics which are altered like this are referred to as semisynthetics.

Antimicrobial – refers to any and all antimicrobial drugs regardless of origin.

See Table 12.3.
Common Drug Strategies

A **chemotherapeutic drug** is any chemical used in the treatment, relief, or prophylaxis of disease. **Prophylaxis** refers specifically to the use of drugs to prevent infection or disease in a person at risk (e.g. if their immune system was compromised). **Synergy** happens when two drugs are more effective than one alone.

Interactions Between Drugs and Microbes

The goal of antimicrobial agents is to prevent microbial processes or their cell structures from functioning. Most importantly, the antimicrobial drugs should be **selectively toxic**.

Mechanisms of Drug Action

Primary Sites of Drug Action (Fig. 12.2; Table 12.4):
1. inhibition of cell wall synthesis
2. inhibition of nucleic acid synthesis or function
3. inhibition of protein synthesis
4. interfere with the function of the cell membrane
5. inhibition of metabolic pathways

Of all these sites, drugs that *inhibit cell wall synthesis* are often the **most specific** since bacteria have cell walls and human cells do not.

Refer back to chapter 9 lecture notes for some drug actions (esp. those on ribosomes).

**THE SPECTRUM OF AN ANTIMICROBIAL DRUG**

- **Narrow-spectrum drugs** – are effective against a limited array of different microbes.
- **Broad-spectrum drugs** – are active against a wider range of different microbes.

See Table 12.5.

**NOTE:** Mechanisms of Antimicrobial Drug Action

Two general classes of drugs:

1. **Microbicidal** – drugs which *kill* microorganisms by inflicting direct damage upon specific cellular targets.
2. **Microbistatic** – drugs which interfere with cell division and thus *inhibit growth* of microbes. These compounds keep the microbes from growing and allow the host’s defenses to destroy and remove the infectious agent.
12.2 Survey of Major Antimicrobial Drug Groups

There are currently about 260 different antimicrobial drugs classified in 20 drug families. Some preparations are available under many trade names (e.g. ampicillin is available under 50 different names). Consult the Physicians’ Desk Reference (PDR) for trade names. The following sections survey those drugs which exemplify their use for the treatment of infections from bacteria (antibacterial antibiotics and synthetics), fungi, protozoans, helminths, and viruses.

Antibacterial Drugs That Act on the Cell Wall

Cell Wall Synthesis Inhibitors

(i) Penicillins (fig. 12.7 and Table 12.4)

(a) source:
Beta-lactam drugs: from *Penicillium chrysogenum* fungi. Natural forms are Penicillin G and V. Semisynthetics vary in spectrum and applications. All penicillins have a beta-lactam ring, a thiazolidine ring, and a variable side chain that dictates its microbicidal activity.

(b) mode of action:
Bactericidal. Blocks repair of the cell wall causing weak points that lead to cell rupture (fig. 12.3). Blocks the peptidases that link the cross-bridges between NAMs; thereby greatly weakening the cell wall peptidoglycan meshwork. Without a cell wall, cell lysis occurs since the bacteria are usually in a hypotonic solution (like human blood) and H₂O flows into the cell causing the cell to swell and burst.

(c) spectrum:
Penicillin G = narrow spectrum. Drug of choice for infections of known sensitive, gram-positive cocci (most streptococci) and some gram-negative bacteria.

Ampicillin & amoxicillin = broad spectrum

Methicillin = broad spectrum, resistant to penicillinase hydrolysis. Used to treat known penicillinase producing *Staphylococci* often encountered in hospitals. Only 1/20th the potency of penicillin G.

(d) problems in therapy:
(1) allergic reactions
(2) bacterial resistance occurs through beta-lactamase enzymes like penicillinase.
   ♦ MRSA² = methicillin resistant *Staphylococcus aureus* – a strain of *S. aureus* that has developed resistance to methicillin and penicillin (and many other antibiotics in different classes).

² MRSA and VRE are the most commonly found multi-drug resistant bacteria in patients in nursing homes and long-term care facilities. PRSP is more common in outpatient settings, physicians clinics, especially in pediatric settings. (Source: CDC.gov)
Vancomycin is the drug of choice for treating MRSA, but for VRSA strains use Linezolid (Zyvox™).

♦ PRSP = penicillin resistant Streptococcus pneumoniae

**Beta-lactamase Inhibitors**

Clavulanic acid (clavulanate) inhibits the bacterial beta-lactamase enzymes (penicillinase and cephalosporinase) and is often administered with a beta-lactam drug.

For example: a prescription might consist of amoxicillin + clavulanate (clavamox = Augmentin™)

This is one way to circumvent the resistance problem. However, clavulanate and other similar drugs aren’t 100% effective against all beta-lactamase producing bacteria.

**(ii) Cephalosporins**

**(a) source:**
Natural and semisynthetic forms from *Cephalosporium* mold. Versatile, broad-spectrum drugs, these are resistant to penicillinase and cause fewer allergic reactions than the penicillins. Chemical structure contains a beta-lactam ring and sites for two ® group attachments (fig. 12.8). Classified as 1st, 2nd, and 3rd generation based on antibacterial activity.

**(b) mode of action:**
Inhibit peptidoglycan synthesis.

**(c) spectrum:**
**Broad spectrum,** especially for gram-negative enteric rods and gram-positive cocci. Also effective against gram-negative cocci and bacilli.

**(d) problems in therapy:**
(1) adverse blood and kidney reactions
(2) allergic reactions
(3) **superinfections**
(4) bacterial resistance through cephalosporinase enzyme

**NOTE:** A bacterium can produce BOTH the enzyme penicillinase (which inactivates penicillin) and the enzyme cephalosporinase (which inactivates cephalosporins). However, the bacterium can also just have one of the enzymes.
(iii) Carbapenems and Monobactams

(a) source:
a naturally derived product of *Streptomyces cattleya*, and chemically synthesized.

(b) mode of action:
Similar to penicillin, but with greater resistance to beta-lactamases.

(c) spectrum:
Broad-spectrum against Gm+ and Gm- bacteria.
Aztreonam is narrow-spectrum for Gm- aerobic bacilli

(d) problems in therapy:
There are now carbapenem-resistant strains of gram negative enteric bacteria, called CRE

MISCELLANEOUS NON-BETA LACTAM CELL WALL INHIBITORS

Vancomycin

(a) source:
*Streptomyces* sp.

(b) mode of action:
Vancomycin interferes with early cell wall synthesis

(c) spectrum:
*Vancomycin* is applied only in life-threatening Staphylococcal infections where resistant strains prevent use of other antibiotics (but, see Linezolid below).

(d) problems in therapy:
(1) neurotoxicity
(2) VRSA and VRE bacteria strains have been confirmed.
* VRSA = vancomycin resistant *Staphylococcus aureus*
* VRE = vancomycin resistant *Enterococcus* species

Bacitracin

(a) source:
Isolated from the bacterium *Bacillus subtilis*.

(b) mode of action:
(i) Bacitracin prevents cell wall synthesis in gram-positive bacteria.

(c) spectrum:
Narrow spectrum - used in ointments with neomycin (Neosporin™) for skin infections.
(d) problems in therapy:
Bacitracin is only useful for topical applications

**Isoniazid (INH)**

(a) source:
Synthetic: isonicotinic acid hydrazide (isoniazid)

(b) mode of action:
Blocks synthesis of the unique cell walls of *Mycobacteria* species. Notable species in this genus include *M. tuberculosis* and *M. leprae*.

(c) spectrum:
Effective against *Mycobacterium* sp. = excellent anti-tuberculosis drug.

(d) problems in therapy:
May cause liver damage (hepatotoxicity).
Drug resistant strains: especially XDR-TB (for Extensively Drug Resistant Tuberculosis), a strain of *M. tuberculosis* with resistance to Isoniazid, Rifampin, and other second-line drugs.

**Rifamycins**

Rifampin inhibits RNA synthesis.
Used with isoniazid as anti-tuberculosis therapy.

Problems
Hepatotoxicity (liver)
Resistance

**Antibiotics That Damage Bacterial Cell Membranes**

**Polymyxin**

(a) source:
Polymyxin: isolated from the bacterium *Bacillus polymyxa*.

(b) mode of action:
Polymyxin has detergent action that disrupts cell membranes of gram-negative bacteria (fig. 12.4).

(c) spectrum:
Narrow spectrum used to treat *Pseudomonas* infections or in skin ointments.

(d) problems in therapy:
Polymyxin can cause nephrotoxic (kidney) and neuromuscular reactions.
Drugs That Act on DNA or RNA

**Fluoroquinolones**

*Ciprofloxacin* for example (“cipro”). Blocks DNA replication by inhibiting DNA gyrase enzymes. Broad-spectrum drugs which were once a last recourse for multi-drug resistant species, but now there are resistant forms.

Drugs That Interfere with Protein Synthesis

**(i) Aminoglycosides**

(a) source: 
*Streptomyces* – filamentous, fungus like bacteria. Chemical form: Amino sugars joined to a hexose carbon ring in glycosidic linkage (fig. 12.9).

(b) mode of action: 
Bactericidal: Inhibit protein synthesis.

(c) spectrum: 
(i) *Streptomycin* = narrow spectrum; for tuberculosis therapy (*Mycobacterium tuberculosis*) and plague (*Yersinia pestis*)
(ii) *Gentamicin* = broad spectrum for gram-negative enteric infections (*Escherichia, Salmonella, Proteus, Pseudomonas*, and *Serratia*)

(d) problems in therapy: 
(1) toxic reactions to 8th cranial nerve (vestibulo-cochlear nerve) 
(2) kidney damage 
(3) intestinal disturbances 
(4) drug resistance

**(ii) Tetracyclines**

(a) source: 
Originally from *Streptomyces*, now all forms semi- or fully synthetic. Tetracyclines have four interlocked six carbon rings (fig. 12.10a).

(b) mode of action: 
Bactericidal: Inhibit protein synthesis.

(c) spectrum: 
*Tetracyclines* = very broad spectrum against numerous types of Gram-positive, Gram-negatives, rickettsias, and mycoplasms. 
One commonly prescribed tetracycline is *doxycycline*.
(d) **problems in therapy:**
Tetracyclines may lead to hepatotoxicity, gastric disturbance, and discoloration of tooth enamel (in children); also superinfection.

(iii) **Chloramphenicol**
(a) **source:**
Synthesized through a chemical process, no longer derived from nature.
(b) **mode of action:**
Block peptide bond formation and protein synthesis. Treatment is limited to typhoid fever, brain abscesses, and rickettsial and chlamydia infections.
(c) **spectrum:**
Broad-spectrum
(d) **problems in therapy:**
Very toxic to humans, long term therapy may lead to aplastic anemia, can be fatal

(iv) **Macrolides**
(a) **source:**
*Streptomyces* sp.
(b) **mode of action:**
Bactericidal: Inhibit protein synthesis.
(c) **spectrum:**
(1) **Erythromycin** (fig. 12.10c) is extended spectrum treatment for penicillin-resistant bacteria. It is the [drug of choice] for *Mycoplasma pneumonia*, legionellosis, *Chlamydia infections*, pertussis, and diphtheria.
(2) **Clindamycin** is used for intestinal infections by anaerobes.
(d) **problems in therapy:**
(1) Clindamycin and Erythromycin can harm the GI tract
(2) Drug resistant species exist for both.

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3 Newer semisynthetic forms of erythromycin include clarithromycin and azithromycin.
Drugs That Block Metabolic Pathways

**Sulfonamides (Sulfa Drugs)**

(a) **source:**
All types have similar basic structure; common form is sulfisoxazole (fig. 12.11)

(b) **mode of action:**
Act as *antimetabolites* (metabolic analogs) by competitive inhibition of bacterial enzymes.

They resemble PABA (p-aminobenzoic acid). PABA is a precursor to a coenzyme needed for amino acid synthesis. Without it, normal cell activity will be disrupted (fig 12.6).

![Metabolic Pathway Diagram](image)

The sulfonamide and trimethoprim bind to the active site of the enzymes necessary for this pathway and block it at two points.

(c) **spectrum:**
   1. Relatively broad spectrum
   2. Some specific uses: urinary tract infections, nocardiosis (*Nocardia asteroides* cause organ lesions), burn, and eye infections.
   3. Often combined with *trimethoprim*.

(d) **problems in therapy:**
   1. Allergic reactions
   2. Formation of crystals in the kidney

**Trimethoprim**

- Medication (often with sulfamethoxazole) for urinary tract, respiratory, and gastrointestinal infections.
- Acts similar to sulfa drugs as an inhibitor in folate synthesis (and therefore nucleic acid synthesis).
- Can cause bone marrow damage.
Newly Developed Classes of Antibiotics

**Oxazolidinones**

(a) **source:**
Synthetic

(b) **mode of action:**
Bactericidal: Inhibit protein synthesis.

(c) **spectrum:**
- **Linezolid** (Zyvox™) – oral or IV drug of choice treatment for known MRSA infections.

(d) **problems is therapy:**
- Anemia, neutropenia (low neutrophil count).

Antifungal Drugs

**Antifungal Drugs** (also see chapter 22 - Table 22.4)

1. **Polyenes:**
   - **Amphotericin B** (fig. 12.12a) – antibiotics that disrupt cell membranes by detergent action. Problems: nephrotoxic.

   Amphotericin B = key drug in systemic fungal infections.

2. **Azoles**
   - Broad spectrum drugs that act to disrupt fungal membrane structure. **Ketoconazole** (Nizoral™), **clotrimazole** (Gyne-Lotrimin™), and **miconazole** (Monistat™) are common forms used orally and topically for cutaneous mycoses, vaginal and oral candidiasis, and some systemic mycoses.

   **Fluconazole** = an excellent, broad-spectrum antifungal used for systemic mycoses.

3. **Grisofulvin**
   - Isolated from **Penicillium griseofulvin** and works against dermatophyte infections such as athlete’s foot.

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4 mycosis = term for fungal infection. mycoses = plural form
Antiparasitic Chemotherapy

Antimalarial Drugs (also see chapter 23 - Table 23.2)

1. Quinines
Chloroquine & primaquine. Used to manage malaria. Can be taken as prophylaxis or after infection. Can cause intestinal symptoms and eye problems.

Resistance of the *Plasmodium* organism can be another problem.

2. Metronidazole
Broad-spectrum antiprotozoal used for amebiasis, giardiasis, and trichomonas infections. Nausea and vomiting are side-effects.

Antihelminth Drugs (also see chapter 23 - Table 23.5)

Mebendazole = all purpose agent in treating intestinal roundworm (ascarias), hookworm, and trichinosis.
Niclosamide = drug of choice for tapeworm infections
Pyrantel = for pinworm (*Enterobius vermicularis*) and hookworm infections. (OTC = Pin-Rid™).

Due to the similarity between helminth and human cellular physiology, all antihelminth drugs tend to have severe side-effects.

Antiviral Chemotherapeutic Agents

Antiviral Drugs (Table 12.6)

The best course of action for combating viruses is prevention via vaccination. Vaccines have been developed for many – but not nearly all – viruses which cause human disease. Most antiviral drugs function intracellularly to block some part of virus multiplication and the main drawbacks are resistance and toxicity. (We will cover vaccines and viruses in more detail in future lectures.)

1. Acyclovir
Synthetic purine nucleoside analog that blocks synthesis of viral DNA and interrupts DNA transcription in herpes virus. Valacyclovir (Valtrex™) has a similar action.

2. Ribavirin
Synthetic guanine analog. Used for severe cases of respiratory syncytial virus (RSV). Contraindicated in pregnant women and partners.
3. HIV & AIDS Treatment

**Azidothymidine (AZT)** – a synthetic *thymine analog*. AZT remains the premier drug of choice for HIV treatment. Specificity for viral reverse-transcriptase enzyme; prevents RNA→DNA transcription so the viral DNA cannot be copied. Thymine analog. Other nucleotide analogs are ddl and ddC; are used in combination with AZT. Combinatorial drug therapy is a must for effective HIV and AIDS treatment; we will cover AIDS therapy in more detail in chapter 25. See also Table 12.7.

4. Influenza Treatment

**Amantadine**, a synthetic tricyclic compound has long been used to treat influenza A. Currently not recommended by the CDC due to high levels of resistant strains. Adverse effects include confusion, hallucinations, and seizures.

**Oseltamivir (Tamiflu™) & Zanamivir (Relenza™)**

Synthetics which block the neuraminidase receptor of influenza A. Can be used as prophylaxis.

5. Interferons: human-based, a glycoprotein, antiviral and anticancer properties. Plays a role in natural immunity. Currently under investigation for extending its use and effectiveness.

12.4 Interactions Between Microbes and Drugs: The Acquisition of Drug Resistance

**How Does Drug Resistance Develop?**

**Resistance factors**

If the concentration of a drug required to inhibit or kill the microorganism is greater than the concentration that can safely be achieved in a patient (without causing severe side-effects), the microorganism is considered to be resistant. According to this definition, *all forms of microorganisms can develop some form of resistance*. Some forms of resistance are more profound than others (i.e. some species are only weakly resistant to certain drugs). See **12.4 MAKING CONNECTIONS- “The Rise of Drug Resistance”**.

In bacteria, the capability of resistance is often determined by only one gene. These resistance genes can be carried on **plasmids (R-factors)** which can be easily exchanged between bacteria of the same species as well as cross-species transfers (fig. 12.13). (NOTE: recall from chapter 9 that bacteria can transfer DNA by conjugation, transduction, and transformation).

**Resistance can develop where it didn’t exist.** If you expose a sufficiently large population of microorganisms to a variety of drugs, there will ALWAYS be some genetically favored individuals that will survive and thrive (fig. 12.15).

**NOTE:** hospitals are a prime environment for these resistant species to develop; **60% of hospital acquired (nosocomial) infections are caused by drug resistant forms of otherwise treatable infectious microbes.**
Specific Mechanisms of Drug Resistance

There are several ways through which a microorganism can develop resistance to any drug. (See fig. 12.14 for examples.)

2. Receptor alteration – drug cannot enter the cell (i.e. decreased permeability).
3. Multidrug resistant (MDR) pumps actively transport drugs out of the cell.
4. Altered binding site.
5. Metabolic circumvention – drug which blocks a step in a biochemical pathway is circumvented by the microbe using an alternative, unblocked pathway.

The All-Time, Top 5 List of Antimicrobial Drug Misuse:
(See Table 12.8)

1. A common misuse of antibacterial agents is to use them for infections that will not respond to them. Primarily, these are viral infections including: measles, chickenpox, mumps, and at least 90% of the upper respiratory tract infections. For these conditions antibacterial therapy is TOTALLY INEFFECTIVE AND WORSE THAN USELESS!

2. “Shotgun” approaches to treatment = the use of broad spectrum agents where narrow-spectrum drugs are better suited. Can lead to superinfection.

3. Treatment of fever of unknown origin. Antibacterial agents are not antipyretics (fever reducers). Fever can be caused by several conditions and its cause should be known prior to any antibacterial therapy.

4. Improper dosage. Either excessive or insufficient dosage use can lead to serious complications. Exceeding recommended doses can lead to toxic side effects and or superinfections. Insufficient dosage can result in continued spread of the infectious agent while allowing drug resistance to develop – this is why you need to take the entire prescription, and not stop taking the drug just because you feel better.

5. The use of antibiotics as food additives for livestock animals. The idea is that by dosing animals such as cattle, pigs, sheep, etc. with antibiotics, they will be less likely to develop infections. However, all this really accomplishes is exposing large populations of microbes to drugs which they will inevitably become resistant to; those drug resistant species can then cross with species endemic to human systems leading to highly resistant pathogenic species.
12.5 Interactions Between Drugs and Hosts

The effect of the drug on the host must be considered. Although the antimicrobial agent is designed to target the microbe, sometimes people can develop side-effects, such as: allergic reactions, damage to tissues, disruption of normal microflora.

Toxicity to Organs

Drugs can damage the following organs:
1. Liver – hepatotoxic, lead to hepatitis and liver failure
2. Kidneys – nephrotoxic, obstruct the flow of urine
3. Gastrointestinal tract (GI), cause diarrhea and/or colitis
4. Cardiovascular system, irregular heartbeats, cardiac arrest
5. Blood – hemotoxic, anemias can form, reduce red and white blood cells, and platelets
6. Nervous system – neurotoxic, cause seizures and damage nerves
7. Respiratory system
8. Skin, skin inflammation
9. Bones and teeth, damage enamel of teeth

Allergic Responses to Drugs

Drugs can produce an allergy if the person is over sensitive to the drug. Allergic responses can manifest as skin rashes, respiratory inflammation, and can be fatal.

Suppression and Alteration of the Microbiota by Antimicrobials

Superinfection (fig 12.17)

There are unique consequences that result from antibiotics causing alterations in the normal microbial flora of the host. All individuals who receive therapeutic doses of these agents undergo alterations in the normal microbial populations of the intestinal, upper respiratory, and genitourinary tracts; some develop superinfections as a result. The more “broad” a course of antibacterial therapy, the greater the chance for destroying the natural flora of the patient’s system; thus the greater the chance for superinfection by a latent pathogen.

Examples: (i) *Candida albicans* is unaffected by cephalosporins (used to treat urinary tract infections) and will bloom to cause common yeast infections.

(ii) *Clostridium difficile* – spore-forming bacillus that can survive antibiotic therapy, outgrow the normal flora of the large intestine and cause antibiotic-associated pseudomembranous colitis.
12.6 Considerations in Selecting an Antimicrobial Drug

In order to select the best antimicrobial agent, it is important to know: 1) the microbe causing the infection, bacteria, virus, fungi, or worms; 2) how sensitive the microbe is to the antimicrobial drug; and 3) current medical status of the patient.

Identifying the Agent

It is critical to collect the patent sample and perform lab tests to determine the infectious agent first, before, treatment begins.

Testing for the Drug Susceptibility of Microorganisms

1. Kirby-Bauer: The bacterium to be tested is spread across the entire surface of an agar plate and antibiotic discs of known concentration of each antibiotic is placed on the surface of the inoculated plate. The zone of inhibition is measured and based on a ratings chart, the most effective antibiotic is used (Fig. 12.18) Not all microbes can be tested using the Kirby-Bauer method.

2. Etest: Another quantitative method to test the effectiveness of an antimicrobial drug to determine the MIC (Fig. 12.19). This test is more versatile in terms of the types of microbes that can be tested.

3. Tube dilution tests: The antimicrobial agent is serially diluted and a uniform concentration of the microbial agent is added to the test tubes. The minimum inhibitory concentration is determined (Figs. 12.20 and 12.21, Table 12.10).

The MIC and the Therapeutic Index

It is critical to select an antimicrobial drug that is selectively toxic to the microbe, but does not harm the human. The therapeutic index is determined to measure the level of toxicity for the patient.

Patient Factors in Choosing an Antimicrobial Drug

1. Patient health history
2. Age of patient: newborn, infant, elderly
3. Pregnant / potential to be pregnant women
4. Other medication being taken by the patient
5. Genetic and/or metabolic abnormalities of the patient
SUMMARY

A. Antibacterial Antibiotics (organized by mode of action)
   1. Cell Wall Synthesis Inhibitors
      (i) Penicillins
          ▪ Penicillin G
          ▪ Ampicillin & amoxicillin
          ▪ Methicillin
      (ii) Cephalosporins
      (iii) Vancomycin
      (iv) Bacitracin
      (v) Isoniazid (INH)

   2. Translation Inhibitors
      (i) Aminoglycosides
          ▪ Streptomycin
          ▪ Gentamicin
      (ii) Tetracyclines
          • Doxycycline
      (iii) Macrolides
          • Erythromycin
          • Clindamycin
      (iv) Oxazolidinones
          • Linezolid

   3. Inhibitors of Metabolic Pathways
      (i) Sulfonamides (Sulfa Drugs)
      (ii) Trimethoprim

   4. Additional Antibacterial Drugs
      (i) Fluoroquinolones
      (ii) Rifamycins
          • Rifampin
      (iii) Polymyxin
      (iv) Beta-lactamase Inhibitors
          • Clavulanic acid (clavulanate)
B. Antifungal Drugs
   1. Polyenes
      Amphotericin B
   2. Azoles
      • Ketoconazole (Nizoral™)
      • Clotrimazole (Gyne-Lotrimin™)
      • Miconazole (Monistat™)
      • Fluconazole
   3. Grisofulvin

C. Antiprotozoal Drugs
   1. Quinines
      • Chloroquine
      • Primaquine
   2. Metronidazole

D. Antihelminth Drugs
   1. Mebendazole
   2. Niclosamide
   3. Pyrantel

E. Antiviral Drugs
   1. Acyclovir
   2. Ribavirin
   3. AZT
   4. Amantadine
   5. Oseltamivir (Tamiflu™)
   6. Zanamivir (Relenza™)