Lecture 25 - Chapter 12

Drugs, Microbes, Host – The Elements of Chemotherapy

Therapies to combat causal agents of disease

Supportive Therapies

Preventive Therapies

Supportive Therapies:

- Reduction in Stress
- Improvement in Diet
- Exercise
- Good Hygiene

Preventive Therapies:

(fending off, interception/prevention of causal agents)
including antimicrobial chemotherapy

- Prevent transmission of causal agents
  - Disinfection (inanimate objects)
  - Eradication of reservoirs
  - Elimination of vectors
  - Antisepsis
- Prevent infection
  - Restriction & localization by enforcing physical, chemical and biological barriers

Antimicrobial Chemotherapy

- **Goal** of antimicrobial chemotherapy: administer a drug to an infected person, which destroys the infective agent without harming the host's cells
- Chemotherapeutic agents are described with regard to their origin, range of effectiveness, and whether they are naturally produced or chemically synthesized

TABLE 12.1 Characteristics of the Ideal Antimicrobial Drug

- Selectively toxic to the microbe but nontoxic to host cells
- Microbicidal rather than microbiostatic
- Relatively soluble; functions even when highly diluted in body fluids
- Remains potent long enough to act and is not broken down or excreted prematurely
- Doesn't lead to the development of antimicrobial resistance
- Complements or assists the activities of the host's defenses
- Remains active in tissues and body fluids
- Readily delivered to the site of infection
- Reasonably priced
- Does not disrupt the host's health by causing allergies or predisposing the host to other infections

TABLE 12.2 Terminology of Chemotherapy

Chemotherapeutic Drug	Any chemical used in the treatment, relief, or prophylaxis of a disease
Prophylaxis	Use of a drug to prevent imminent infection of a person at risk
Antimicrobial Chemotherapy	The use of chemotherapeutic drugs to control infection
Antimicrobials	All-inclusive term for any antimicrobial drug, regardless of its origin
Antibiotics	Substances produced by the natural metabolic processes of some microorganisms that can inhibit or destroy other microorganisms
Semisynthetic Drugs	Drugs that are chemically modified in the laboratory after being isolated from natural sources
Synthetic Drugs	The use of chemical reactions to synthesize antimicrobial compounds in the laboratory
Narrow Spectrum (Limited Spectrum)	Antimicrobials effective against a limited array of microbial types—for example, a drug effective mainly on gram-positive bacteria
Broad Spectrum (Extended Spectrum)	Antimicrobials effective against a wide variety of microbial types—for example, a drug effective against both gram-positive and gram-negative bacteria

Origins of Antimicrobial Drugs

- **Antibioitics** are secondary metabolic products of aerobic bacteria and fungi
  - Bacteria: *Streptomyces* and *Bacillus*
  - Molds: *Penicillium* and *Cephalosporium*
- Chemists have created new generations of drugs by altering the structure of naturally occurring antibiotics (semi-synthetic drugs)
- Researchers continue to search for new antimicrobial compounds also in organisms other than bacteria and fungi (bioprospecting)

Interactions between Drug & Microbe

- **Goal** of antimicrobial and antiviral drugs:
  - Disrupt cellular processes or structures of bacteria, fungi, and protozoa
  - Inhibit virus replication
- Most antimicrobial and antiviral drugs
  - interfere with the function of enzymes required to synthesize or assemble macromolecules or
  - destroy structures already formed in the cell
- Antimicrobial drugs should be **selectively toxic** in that they destroy or inhibit microbial cells without damaging host tissues.

Major Mechanisms of Drug Action

- Inhibition of synthesis and interference with structure and function of **nucleic acids**
- Inhibition of synthesis and interference with structure and function of **proteins**
- Inhibition of **cell wall** synthesis
- Interference with **cell membrane structure or function**
- Inhibition of specific **metabolic pathways** such as folic acid synthesis

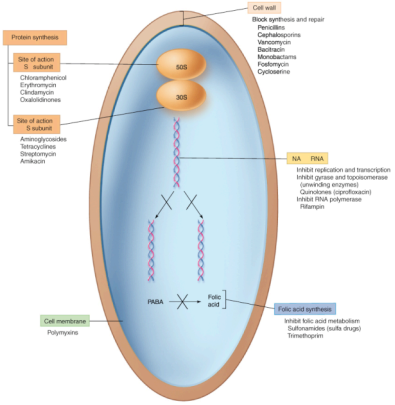


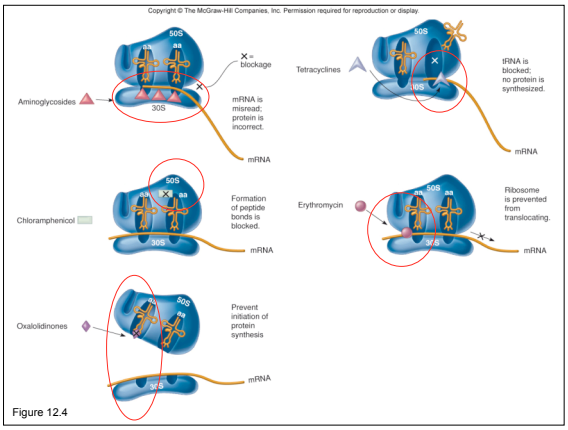
Figure 12.1

Antimicrobial Drugs that affect Nucleic Acid Synthesis

- Block synthesis of nucleotides
- Inhibit replication (DNA synthesis)
- Inhibit (prevent or stop) transcription (RNA synthesis)

Antimicrobial Drugs that block Protein Synthesis

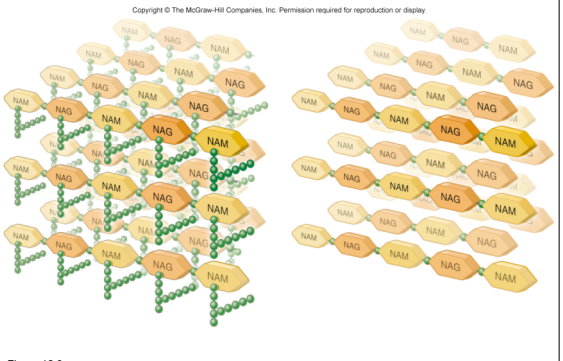
- Inhibit translation by reacting with the ribosome-mRNA complex
- selective effect is possible because: bacterial ribosomes are different from eukaryotic ribosomes

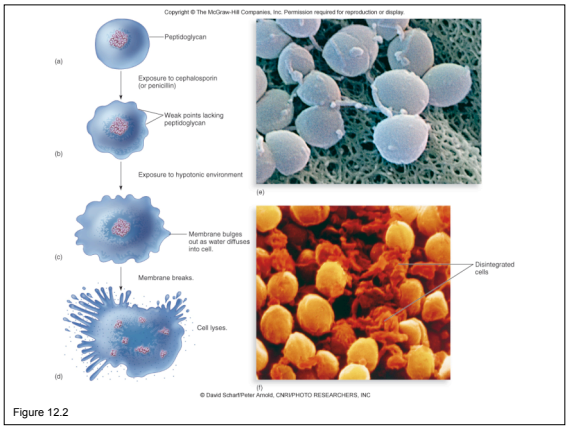


Antimicrobial Drugs that Affect the Bacterial Cell Wall

- Active cells with a cell wall must constantly synthesize new NAM-NAG units, transport them across the plasma membrane to the proper place and incorporate them into the existing peptidoglycan layer in the cell envelope
- Penicillins and cephalosporins react with one or more of the enzymes required to complete this process (PBPs)

===> Bactericidal antibiotics



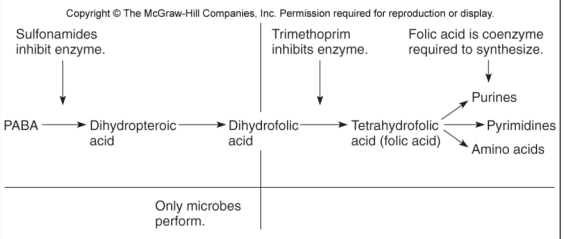


Antimicrobial Drugs that Disrupt Cell Membrane Function

- Damaged cell membranes invariably result in death from elimination of gradients or lysis
- Specificity is possible because particular microbial groups have differences in the types of lipids in their cell membranes

Antimicrobial Drugs that Inhibit Folic Acid Synthesis

- Sulfonamides and trimethoprim- act via **competitive inhibition**
- Supplied to cells in high concentrations to make sure enzyme is constantly occupied with the **metabolic analog inhibitor** rather than the true substrate



PABA: para-aminobenzoic acid

Figure 12.5

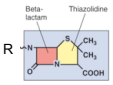
Major Antimicrobial Drug Groups

- About 260 different antimicrobial drugs
- Classified in 20 drug families
- Largest number of antimicrobial drugs are **used to combat bacterial infections**

TABLE 12.3 Selected Survey of Chemotherapeutic Agents in Infectious Diseases

Infectious Agent	Typical Infection	Drugs of Choice*
Bacteria		
Gram-positive cocci		
Staphylococcus aureus	Abscess, skin infections, toxic shock	Penicillins, vancomycin, cephalosporin
Streptococcus pyogenes	Strep throat, erysipelas, rheumatic fever	Penicillin, cephalosporin, erythromycin
Gram-positive rods		
Bacillus	Anthrax	Ciprofloxacin, doxycycline
Acid-fast rods		
Mycobacterium tuberculosis	Tuberculosis	Isoniazid, rifampin, pyrazinamide,† ethambutol streptomycin
Gram-negative cocci		
Neisseria gonorrhoeae	Gonorrhea	Ceftriaxone, ciprofloxacin
Neisseria meningitidis	Meningitis	Penicillin G, cefotaxime
Gram-negative rods		
Escherichia coli	Sepsis, diarrhea, urinary tract infection	Cephalosporin
Haemophilus influenzae	Meningitis	Cefotaxime, ceftriaxone
Pseudomonas	Opportunistic lung and burn infections	Ticarcillin, aminoglycoside
Vibrio cholerae	Cholera	Tetracyclines, sulfamethoxazole-trimethoprim
Spirochetes		
Borrelia	Lyme disease	Doxycycline, amoxicillin
Treponema pallidum	Syphilis	Penicillin, tetracyclines
Rickettsia	Rocky Mountain spotted fever	Doxycycline
Chlamydia	Urethritis, vaginitis	Azithromycin, doxycycline
Fungi		
Systemic mycoses		
Aspergillus	Aspergillosis	Amphotericin B, azoles, flucytosine
Candida albicans	Candidiasis	Itraconazole, fluconazole
Cryptococcus neoformans	Cryptococcosis	Amphotericin B, fluconazole
Pneumocystis carinii jirovci	Pneumonia (PCP)	Sulfamethoxazole-trimethoprim
Protozoa		
Giardia lamblia	Giardiasis	Quinacrine, metronidazole
Plasmodium	Malaria	Chloroquine, mefloquine
Toxoplasma gondii	Toxoplasmosis	Pyrimethamine, sulfadiazine
Trichomonas vaginalis	Trichomoniasis	Metronidazole
Helminths		
Cestodes	Tapeworm	Niclosamide, praziquantel
Various roundworm infections		Albendazole
Viruses		
Herpesvirus	Genital herpes, oral herpes, shingles	Acyclovir, valacyclovir
HIV	AIDS	(AZT, protease inhibitors), ddI, ddC, d4T
Orthomyxovirus	Type A influenza	Amantadine, rimantidine

Antibacterial Drugs Targeting the Cell Wall



- Penicillin group
  - Most end in the suffix *–cillin*
  - Can obtain natural penicillin through microbial fermentation
  - All consist of three parts: a thiazolidine ring, a beta-lactam ring, and a variable side chain

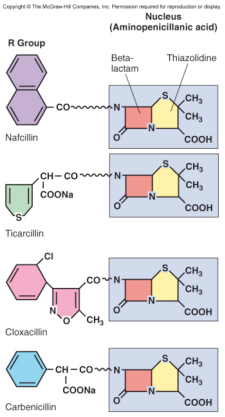


Figure 12.6

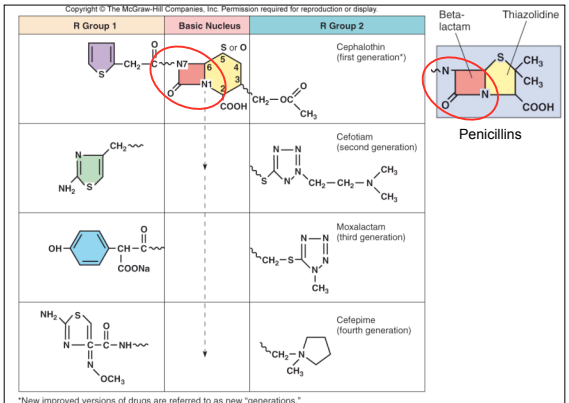
Subgroups and Uses of Penicillins

TABLE 12.4 Characteristics of Selected Penicillin Drugs

Name	Spectrum of Action	Uses, Advantages	Disadvantages
Penicillin G	Narrow	Best drug of choice when bacteria are sensitive; low cost; low toxicity	Can be hydrolyzed by penicillinase; allergies occur; requires injection
Penicillin V	Narrow	Good absorption from intestine; otherwise, similar to penicillin G	Hydrolysis by penicillinase; allergies
Oxacillin, dicloxacillin	Narrow	Not susceptible to penicillinase; good absorption	Allergies; expensive
Methicillin, nafcillin	Narrow	Not usually susceptible to penicillinase	Poor absorption; allergies; growing resistance
Ampicillin	Broad	Works on gram-negative bacilli	Can be hydrolyzed by penicillinase; allergies; only fair absorption
Amoxicillin	Broad	Gram-negative infections; good absorption	Hydrolysis by penicillinase; allergies
Carbenicillin	Broad	Same as ampicillin	Poor absorption; used only parenterally
Azlocillin, mezlocillin ticarcillin	Very broad	Effective against *Pseudomonas* species; low toxicity compared with aminoglycosides	Allergies, susceptible to many beta-lactamases

The Cephalosporin Group of Drugs

- Newer than penicillins
- Currently account for the majority of all antibiotics administered



*New improved versions of drugs are referred to as new "generations."

Figure 12.7

Subgroups and Uses of Cephalosporins

- **Broad-spectrum**
- **Resistant** to most penicillinases (PBPs)
- Cause **fewer allergic reactions** than penicillins
- Four generations of cephalosporins exist based on their antibacterial activity

Other Beta-Lactam Antibiotics

- Imipenem

  (activity against *Pseudomonas aeruginosa* and the *Enterococcus* species. It is not active against methicillin-resistant *Staphylococcus aureus*, MRSA)
- Aztreonam

  (strong activity against susceptible Gram-negative bacteria, including *Pseudomonas aeruginosa*. It has no useful activity against Gram-positive bacteria or anaerobic bacteria)

Other Drugs Targeting the Cell Wall

- Bacitracin - interferes with bactoprenol, which exports "pre-fabricated" NAM-NAG units across the bacterial plasma membrane
- Isoniazid - It is activated by KatG to form isonicotinic acyl radical; react with a NADH to form isonicotinic acyl-NADH complex. This complex will inhibit the synthesis of mycolic acid in the mycobacterial cell wall.
- Vancomycin - for the treatment of serious, life-threatening infections by Gram-positive bacteria which are unresponsive to other less toxic antibiotics.
- Fosfomycin trimethamine - treatment of urinary tract infections, where it is usually administered as a single dose

Antibacterial Drugs Targeting Protein Synthesis

- **Aminoglycoside** Drugs
  - Products of various species of soil actinomycetes in the genera *Streptomyces* and *Micromonospora*
  - Relatively broad spectrum because they **inhibit protein synthesis**
  - Most used to combat aerobic Gram-negative rods and certain gram-positive bacteria:
    - **Streptomycin**: Bubonic plague and tularemia and good antituberculosis agent
    - **Gentamicin**: Less toxic and used for gram-negative rods

Tetracycline Antibiotics

- Bind to ribosomes and block protein synthesis
- **Broad-spectrum**
- Used to combat aerobic and anerobic Gram-positive and Gram-negative rods and cocci
  - **Mycoplasmas, rickettsias, and spirochetes**
  - STDs, Rocky Mountain spotted fever, Lyme disease, typhus, *Mycoplasma* pneumonia, cholera, leptospirosis, acne (Doxycycline and minocycline)
  - some protozoa

Chloramphenicol

- Unique nitrobenzene structure
- Entirely chemosynthetic
- Blocks peptide bond formation and protein synthesis ==> Broad-spectrum
- **Very toxic to human cells** so its uses are restricted

Erythromycin and **Clindamycin**

- **Erythromycin**
  - Large lactone rinig with sugars attached
  - Relatively broad-spectrum
  - Fairly **low toxicity**
  - Blocks protein synthesis by attaching to the ribosome
  - ***Mycoplasma* pneumonia, legionellosis, *Chlamydia* infections, pertussis, diphtheria**
- **Clindamycin** (derived from lincomycin)
  - Broad-spectrum
  - Causes adverse reactions in the GI tract, so applications are limited. Often used against **oral cavity infections**.

Synercid and Oxazolidones

- Synercid
  - Combined antibiotic from the streptogramin group
  - Effective against *Staphylococcus* and *Enterococcus* species and against resistant strains of *Streptococcus*
  - Binds to sites on the 50S ribosome, inhibiting translation
- **Oxazolidones**
  - Inhibit the initiation of protein synthesis
  - Not found in nature ==> Hope that drug resistance among bacteria will be slow to develop
  - Used to treat infections caused by two of the most difficult clinical pathogens: **methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE)**

Antibacterial Drugs Targeting Folic Acid Synthesis

- **Sulfonamides, Trimethoprim, and Sulfones**
  - Sulfonamides ("Sulfa drugs")
    - First modern synthetic antimicrobial drug
    - Used to combat **shigellosis, acute UTIs, certain protozoan infections**
  - Trimethoprim
    - Inhibits the enzymatic step immediately following the step inhibited by sulfonamides in the synthesis of folic acid
    - Often given in combination with sulfamethoxazole
    - One of the primary treatments for pneumonia caused in AIDS patients by ***Pneumocystis carinii*** (and *P. jiroveci*), called PCP
  - Sulfones
    - Chemically related to sulfonamides
    - Lack their broad-spectrum effects
    - Key drugs in treating **leprosy** (Hansen's disease)

Antibacterial Drugs Targeting **DNA or RNA synthesis**

- **Fluoroquinolones**
- **High potency and broad spectrum**
- Inhibit a wide variety of Gram-positive and Gram-negative bacteria even at low concentrations of bacteria

Norfloxacin and **Cipro**floxacin

- **UTIs, STDs, gastrointestinal infections**, osteomyelitis, respiratory infections (**anthrax**!), soft tissue infections

Sparfloxacin and Levofloxacin

- Pneumonia, bronchitis sinusitis

Rifampi(ci)n

- Product of the genus *Streptomyces*
- Limited in spectrum
- Mainly for infections by several Gram-positive rods and cocci (a few Gram-negative bacteria)
- In particular, used **against mycobacterial infections** such as tuberculosis and leprosy
- Usually given **in combination with other drugs**

Antibacterial Drugs Targeting Cell Membranes

- **Polymyxins**: narrow-spectrum peptide antibiotics
  - From *Bacillus polymyxa*
  - Limited by their **toxicity to the kidney**
  - Some can be used to treat **drug-resistant *Pseudomonas aeruginosa***
- **Daptomycin**
  - Lipopeptide made by *Streptomyces*
  - Most active **against Gram-positive bacteria**

Agents to Treat Fungal Infections

- Fungal cells are eukaryotic, so present special problems
  - Majority of chemotherapeutic **drugs are designed to act on bacteria** and **are ineffective for fungal infections**
  - Similarities between fungal and human cells-**toxicity to humans**
- Four main groups
  - Macrolide polyene antibiotics, Griseofulvin, Synthetic azoles, Flucystosine

Antiparasitic Chemotherapy

- **Antimalarial Drugs**: Quinine and its derivatives
  - Quinine: extracted from the bark of the cinchona tree
  - Replaced by synthesized quinolines (chloroquine and primaquine), which have less toxicity to humans
- Chemotherapy for Other Protozoan Infections
  - Metronidazole (Flagyl) - **Amoebicide**
    - treating intestinal infections by *Entamoeba histolytica*
    - Orally applied also suited to combat infections by *Giardia lamblia* and *Trichomonas vaginalis*
  - Quinicrine, sulfonamides, tetracyclines

Antihelminthic Drug Therapy

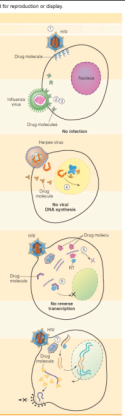
- Flukes, tapeworms, and roundworms have greater similarities to human physiology
  - Using drugs to block their reproduction is usually not successful in eradicating adult worms
  - Most effective drugs immobilize, disintegrate, or inhibit the metabolism of all stages of the life cycle

Antiviral Chemotherapeutic Agents

- Selective toxicity is almost impossible to achieve because then same metabolic system is responsible for the well-being of both virus & host
- Several antiviral drugs have been developed that target specific points in the infectious cycle of viruses
- Three major modes of action:
  - Prevent attachment & penetration of the virus into the host cell
  - Blocking the transcription & translation of viral macromolecules
  - Preventing the maturation of viral particles

TABLE 12.3 Actions of Antiviral Drugs

Mode of Action	Examples	Effects of Drug
Inhibition of Virus Entry: Receptor/Fusion/ Uncoating Inhibitors	Enfuvirtide (Fuzeon)	Blocks **HIV** infection by preventing the binding of viral GP-41 receptors to cell receptor ①, thereby preventing fusion of virus with cell
	Amantidine and its relatives, zanamivir (Relenza), oseltamivir (Tamiflu)	Block entry of **influenza virus** by interfering with fusion of virus with cell membrane (also release); stop the action of influenza neuraminidase, required for entry of virus into cell (also assembly) ①, ⑤
Inhibition of Nucleic Acid Synthesis	Acyclovir (Zovirax), other "cyclovirs," vidarabine	Purine analogs that terminate DNA replication in **herpesviruses** ④
	Ribavirin	Purine analog, used for **respiratory syncytial virus (RSV)** and some **hemorrhagic fever viruses**
	Zidovudine (AZT), abacavir, lamivudine (3TC), didanosine (ddI), zalcitabine (ddC), and stavudine (d4T)	Nucleotide analog reverse transcriptase (RT) inhibitors; stop the action of RT in **HIV**, blocking viral DNA production ③
	Nevirapine, efavirenz, delavirdine	Nonnucleotide analog reverse transcriptase inhibitors; attach to **HIV** RT binding site, stopping its action ③
Inhibition of Viral Assembly/Release	Indinavir, saquinavir, nelfinavir, ritonavir	Protease inhibitors; insert into **HIV** protease, stopping its action and resulting in inactive noninfectious viruses ⑦



Interferon (IFN): An Alternative to Artificial Drugs

- Glycoprotein produced by fibroblasts and leukocytes in response to various immune stimuli
- Produced also using recombinant DNA technologies
- Known therapeutic benefits:
  - Reducing the time of healing and some of the complications in certain infections
  - Preventing or reducing some symptoms of cold and HPV
  - Slowing the progress of certain cancers
  - Treating hairy-cell leukemia (a rare cancer), hepatitis C, genital warts, and Kaposi's sarcoma in AIDS patients
- Often results in serious side effects

Interactions Between Microbes and Drugs: The Acquisition of Drug Resistance

- **Drug resistance**: an adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory
- Can be intrinsic or acquired
- Microbes become newly resistant to a drug after
  - Spontaneous mutations in critical chromosomal genes
  - Acquisition of new genes or sets of genes via transfer from another species (i.e., via plasmids) called **resistance factors**

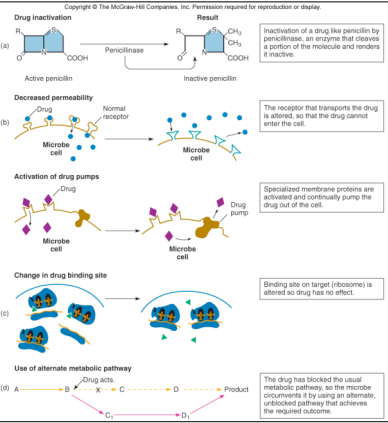


Figure 12.13

New Approaches to Antimicrobial Therapy

- Often researchers try to find new targets in the bacterial cell and custom-design drugs that aim for processes such as:
  - iron-scavenging capabilities of bacteria
  - genetic control mechanisms in bacteria referred to as riboswitches
- **Probiotics** and **prebiotics**, **Lantibiotics**

Problems with Chemotherapy:

Toxicity to Organs

- Liver, kidneys, gastrointestinal tract, cardiovascular system and blood-forming tissue, nervous system, respiratory tract, skin, bones, and teeth, etc.

Allergic Responses to Drugs

- **Allergy**: heightened sensitivity
- The drug acts as an antigen and stimulates an allergic response
- Reactions such as skin rash, respiratory inflammation, and rarely anaphylaxis

Superinfection

- When certain beneficial species (natural flora) are destroyed, microbes that were once kept in check can begin to overgrow and cause disease, called then a **superinfection**
  - Using a broad-spectrum cephalosporin for UTI destroys lactobacilli in the vagina; without the lactobacilli, *Candida albicans* can proliferate and cause a yeast infection
  - Oral therapy with tetracyclines, clindamycin, and broad-spectrum penicillins and cephalosporins is associated with antibiotic-associated colitis

Selecting an Antimicrobial Drug

- Three factors must be known
  - The nature of the microorganism causing the infection
  - The degree of the microorganism's susceptibility to various drugs
  - The overall medical condition of the patient
- Identifying the Agent
  - Direct examination of body fluids, sputum, or stool is a rapid initial method
  - The choice of drug will be based on experience with drugs that are known to be effective against the microbe: the "informed best guess"
- Testing for the Drug Susceptibility of Microorganisms

The MIC and Therapeutic Index

- **MIC**- **minimum inhibitory concentration**: the smallest concentration (highest dilution) of drug that visibly inhibits bacterial growth
- Once therapy has begun, it is important to observe the patient's clinical response