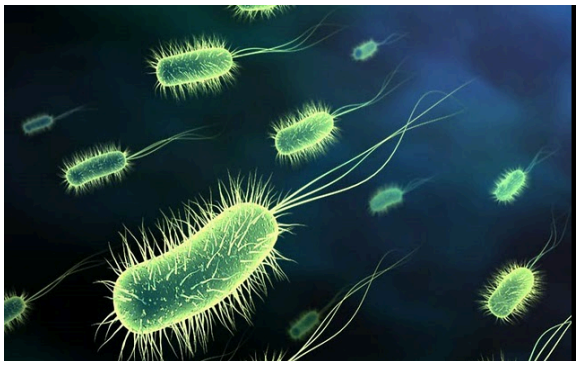
Module 16 – Antibiotics

16.1 – Bacteria

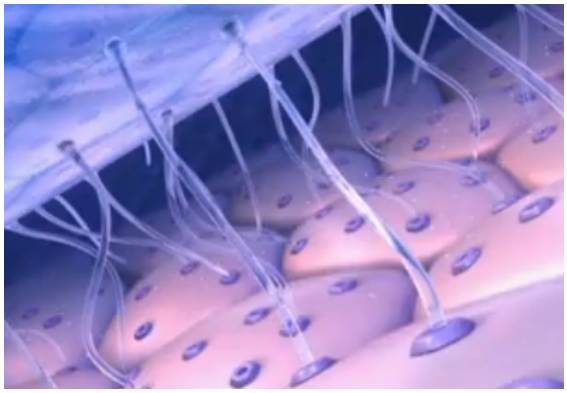


- Bacteria are single celled organisms that can be shaped as rods, spheres, or spirals.
- Bacteria occupy almost every habitat on Earth, including humans!
- Most bacteria are rendered harmless by our immune system and some even play beneficial roles.
- However, some bacteria are pathogenic and cause diseases such as cholera, syphilis and tuberculosis.
- Before the discovery of antibiotics, bacterial infection was a major cause of morbidity and death.

<u>Bacterial Pathogenicity</u>

- Bacteria have a number of virulence factors that they use to cause infection.
- Virulence factors include:
    - Fimbriae and pilli
    - Flagella
    - Secretion of toxins and enzymes
    - Invasion

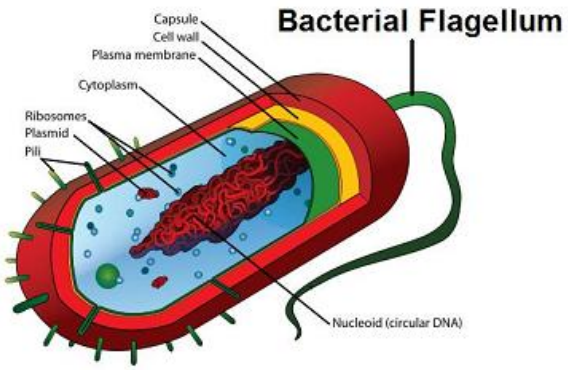
<u>Fimbriae and Pilli</u>



- Fimbriae and pilli are hair like structures that project from the surface of bacterial cells.
- They allow bacteria to attach to certain sites in our body so they are not washed away.
- For example, the bacteria *E. coli* are known to cause bladder infections.
- *E. coli* produce fimbriae that attach to the urogenital tract.

Flagella

- Bacteria typically live in aqueous environments and need to move to sites where they can survive.
- The flagellum that bacteria possess allows them to "swim" through the watery environment of our body to the site where they may survive.

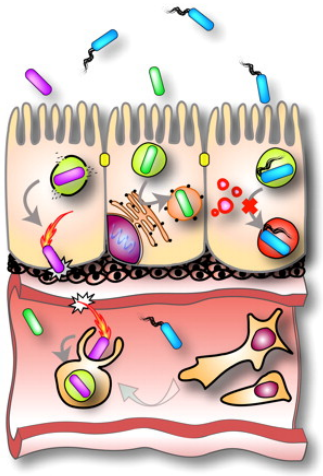


Toxins and Enzymes

- Some bacteria secrete toxins and/or enzymes.
- Secreted toxins can have a wide array of effects including nausea, vomiting, diarrhea, cramps, pain, fever, or even paralysis.
- In some cases, bacterial toxins produced outside of our body can mediate toxic reactions if they gain entry to our body. A good example is what occurs in some cases of poisoning.
- In addition to toxins, bacteria also release enzymes. Some of these enzymes can degrade tissue or breakdown antibodies, our defense against infection.

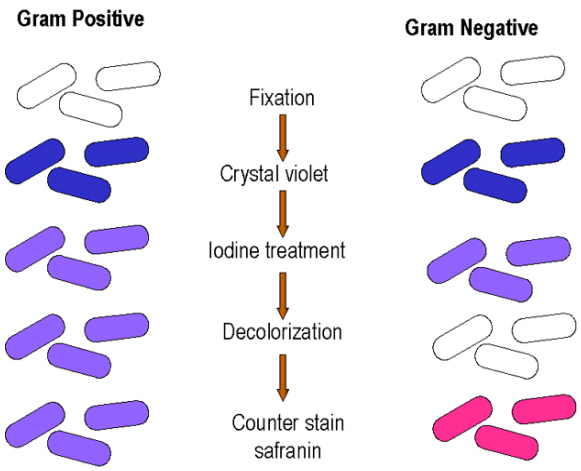
Invasion

- Some bacteria can actually invade (enter) our cells.
- For example, the bacteria that cause Salmonella invade cells of the intestine and cause severe diarrhea.
- Bacteria that cause tuberculosis usually enter our body in the lungs and can "hide" inside cells making it impossible for our immune system to act on them.

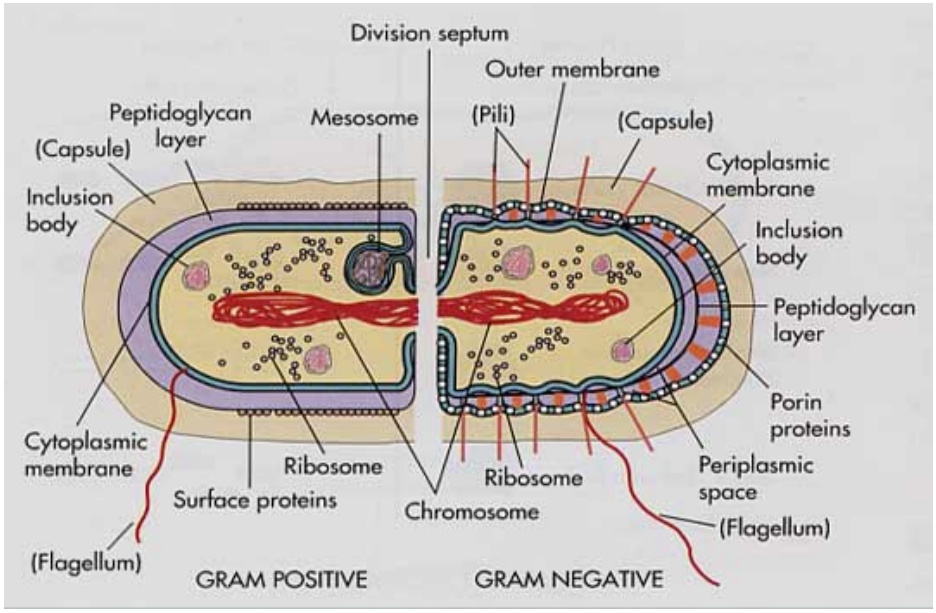


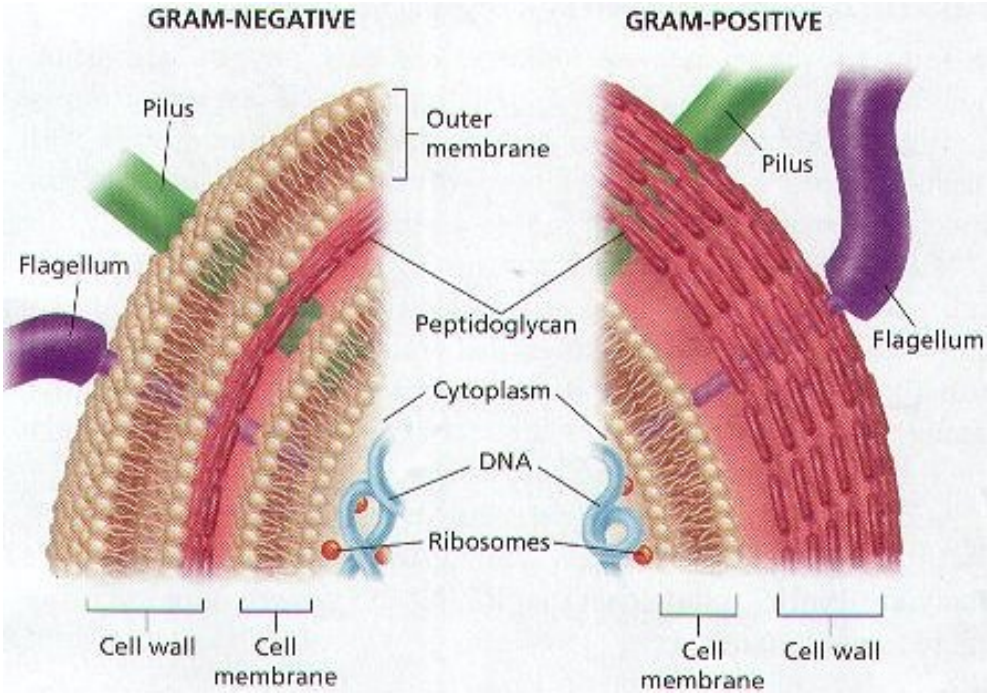
Gram Staining of Bacteria

- Gram staining is a technique that is used to classify bacteria as either gram positive or gram negative.
- Why is this classification important? The gram stain tells us about the cell wall structure of bacteria, in particular the amount of peptidoglycan. This can be important in the determination of which antibiotic we use.
- Gram positive cells have a thick peptidoglycan wall that stains purple during gram staining.
- Gram negative cells have a thin peptidoglycan layer and stain pink during gram staining.



Gram Positive vs. Gram Negative Bacteria



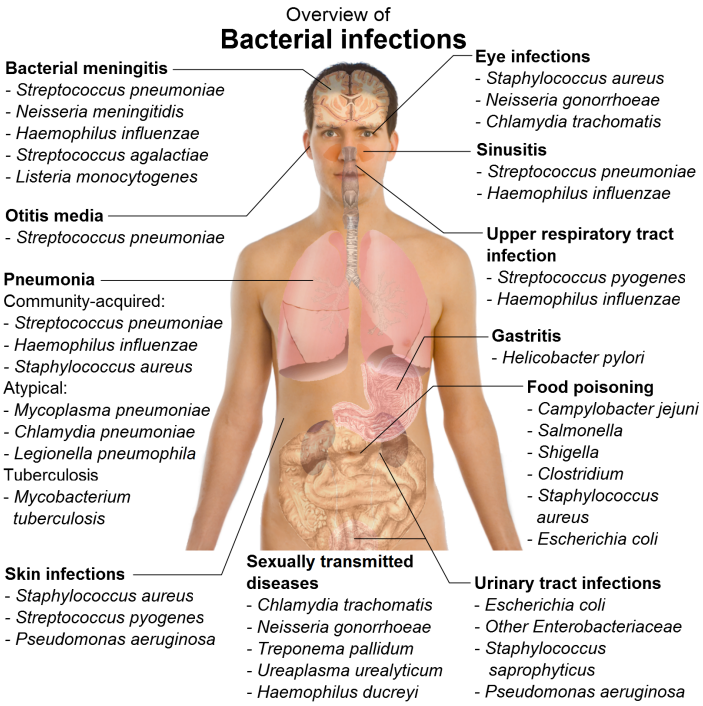


- Notice the thin peptidoglycan layer (i.e. cell wall) in the gram negative bacteria compared to the thick peptidoglycan layer in the gram positive bacteria. Also notice how the gram negative bacteria has an outer membrane, whereas that gram negative bacteria doesn't

Gram Positive	Gram Negative
Thick peptidoglycan layer (cell wall)	Thin peptidoglycan layer (cell wall)
Techoic acids – provide rigidity to the cell wall. The major surface antigen in gram positive bacteria.	Do not have techoic acids.
Do not have LPSs	Lipopolysaccharides (LPSs) – Are a structural component of the outer membrane and the major surface antigen in gram negative bacteria.
Do not have an outer membrane.	Outer membrane – protects gram negative bacteria from bile salts and detergents.
Do not have porins (a few exceptions).	Porins – on the outer membrane. Allow certain sugars, ions and amino acids to enter the bacteria.

Signs of Infection

- The typical signs of infections include fever, overall malaise, local redness, and swelling.
- Other signs of infection include increased respiratory rate and tachycardia.
- In some cases patients may not have a fever despite having an infection. For example, newborn babies may have an immature hypothalamus or the elderly may have decreased hypothalamic function. The hypothalamus is important in regulating body temperature.
- There may be other signs of infection depending on the location of the infection. For example, patients with a urinary tract infection feel the frequent need to urinate.

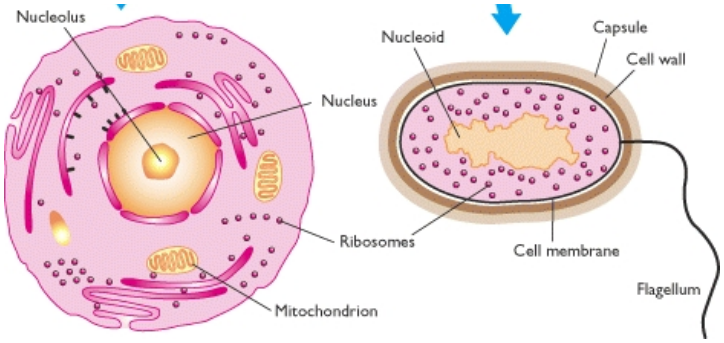


**Note – You do not have to memorize the names of the bacteria shown in this picture

Selective Toxicity

- The treatment of a bacterial infection is critically dependent on the ability to produce selective toxicity.
- Selective toxicity means the therapy is able to destroy the bacteria without harming the host (i.e. human cells).
- Selective toxicity is produced by targeting differences between the cellular chemistry of bacteria and humans.
- Antibiotic therapy produces selective toxicity by:

    - Disrupting the bacterial cell wall (human cells do not have a cell wall).
    - Targeting enzymes that are unique to bacteria.
    - Disrupting bacterial protein synthesis (bacterial and human ribosomes are different).



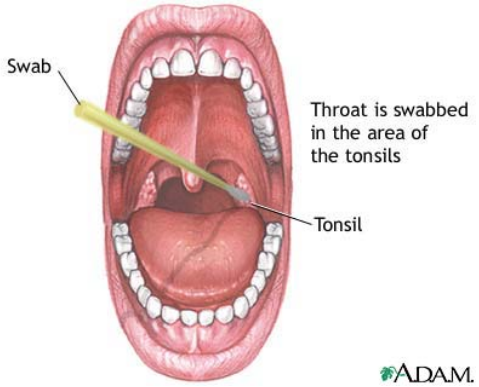
16.2 – Selection of the Proper Antibiotic

Several questions must be considered when selecting an antibiotic including:

1. Has the infectious bacteria been identified?
2. Bacterial sensitivity to the antibiotic?
3. Can the antibiotic access the site of infection?
4. Is the patient able to battle the infection?

1. Identification of the Bacteria

- Ideally, bacteria are identified prior to selection of the treatment.
- The gram stain is a rapid test that provides information on the structural features of the bacteria.
- In general, culturing the bacteria to properly identify it will provide the best basis for selection of the therapy.
- In some cases, cultures are not possible or reliable for identifying the bacteria. For example, cultures are rarely taken from children who have an ear infection because they are difficult to obtain. In addition, samples from patients with lower respiratory infections may contain several species of bacteria.



2. Bacterial Sensitivity to the Antibiotic

- Antibiotics can be **bacteriostatic** or **bactericidal**.

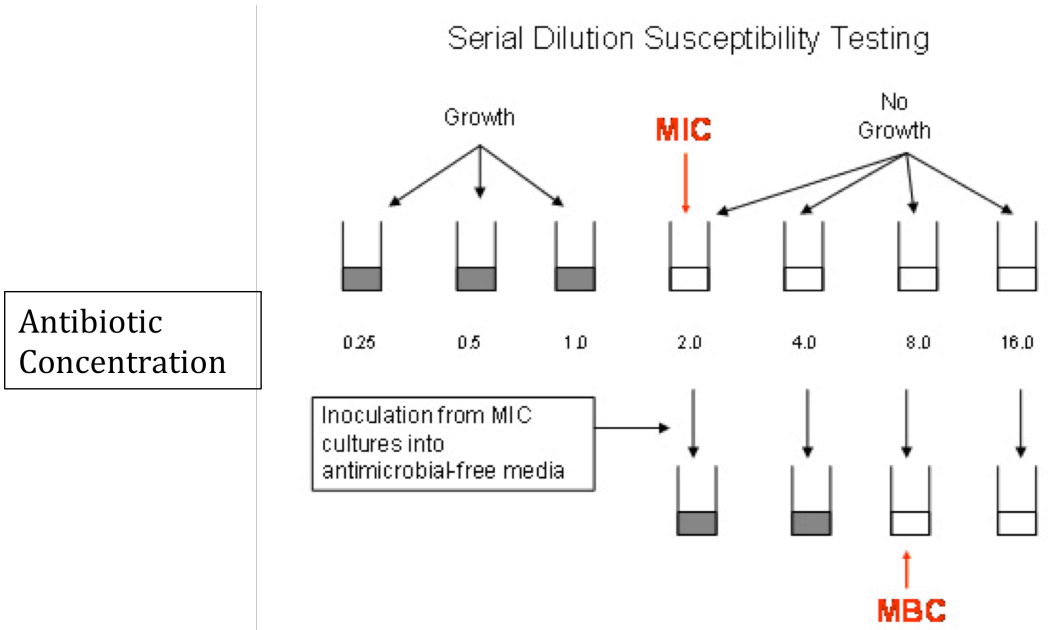
  Bacteriostatic

  - Stops the *growth and replication* of bacteria and in doing so, stops the spread of infection.
  - The body's immune system can then attack and remove the bacteria.

  Bactericidal

  - Drugs *kill* the bacteria.

- Microbiologists can culture bacteria and determine the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of antibiotic drugs.

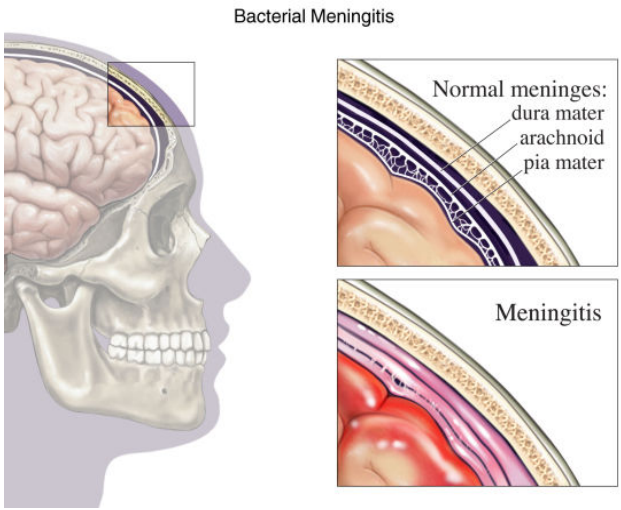


3. Penetration to the Site of Action

- Some infections are difficult for antibiotics to penetrate. These infections require careful selection of antibiotics that are able to penetrate to the site of action.
    - Meningitis
    - Urinary Tract Infections
    - Osteomyelitis
    - Abscesses
    - Otitis Media

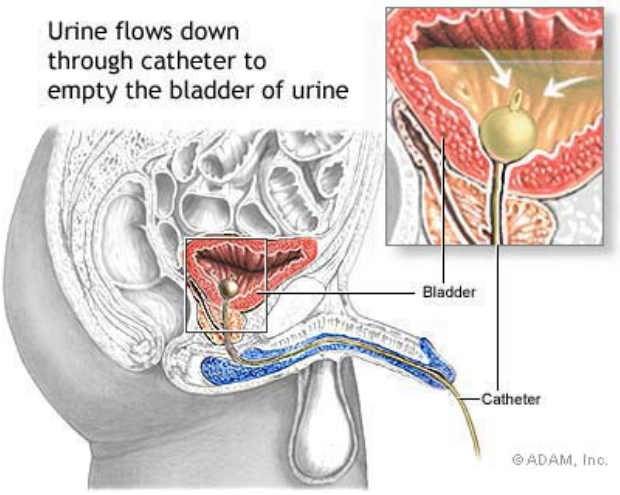
Meningitis

- Is an infection of the meninges, which are the membranes that cover the brain and spinal cord.
- Bacterial meningitis is rare but is much more serious than viral meningitis (i.e. life threatening).
- Many antibiotics are unable to penetrate the meninges.
- Therefore, effective treatment requires an antibiotic that penetrates the meninges and effectively eradicates the bacteria.



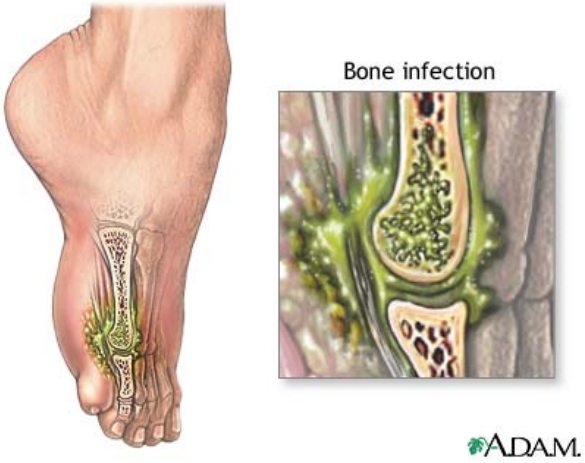
Urinary Tract Infections (UTIs)

- Urinary tract infections occur when bacteria enter any part of the urinary system.
- The most common type is an infection of the bladder, which may be caused during catheterization.
- Effective treatment of UTIs requires an antibiotic that enters the urinary system.



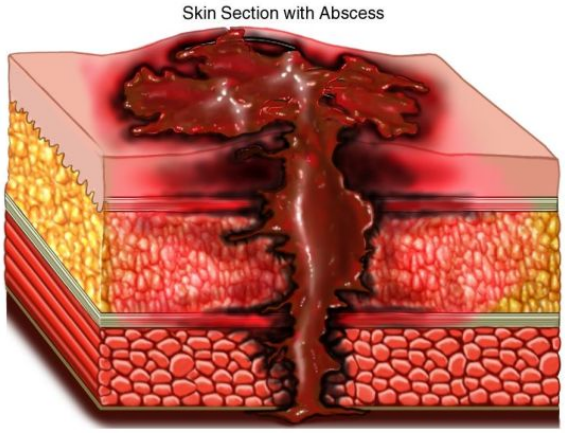
Osteomyelitis

- Osteomyelitis is an infection of the bone.
- Very few antibiotics are able to enter the bone, making treatment options limited.
- Treatment of osteomyelitis usually requires antibiotics for 4 – 6 weeks.



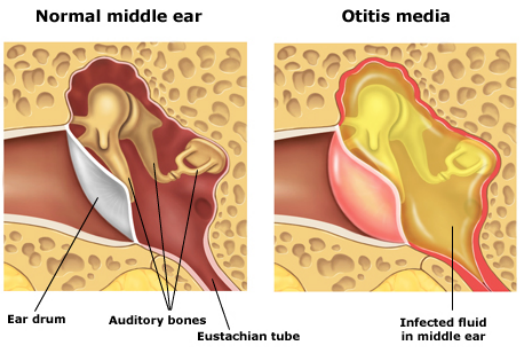
Abscesses

- Skin abscesses occur when pus or other infected material collect under the skin.
- Abscesses are difficult to treat with antibiotics because they are poorly perfused with blood.



Otitis Media

- Otitis media is an infection of the middle ear and more commonly referred to as an ear infection.
- Anybody can get an ear infection, but they are much more common in children.
- Many antibiotics do not penetrate the inner ear and are therefore not effective in the treatment of otitis media.



4. Ability of the Patient to Battle Infection

- The immunological state of the patient can be a critical determinant in the selection of an antibiotic.
- Bactericidal antibiotics kill bacteria and can therefore be used effectively in patients with compromised immune function.
- Bacteriostatic antibiotics only decrease the ability of bacteria to multiply, and therefore require the actions of the immune system to kill the bacteria.
- Patients with compromised immune function may not respond to bacteriostatic antibiotics. Some examples of these patients include those having:

    - AIDS
    - Organ transplantation
    - Cancer chemotherapy

and also elderly patients

16.3 – Potential Complications of Antibiotic Therapy

- Antibiotics have a number of common complications which include:

    - Resistance
    - Allergy
    - Serum sickness
    - Superinfection
    - Destruction of normal bacterial flora
    - Bone marrow toxicity

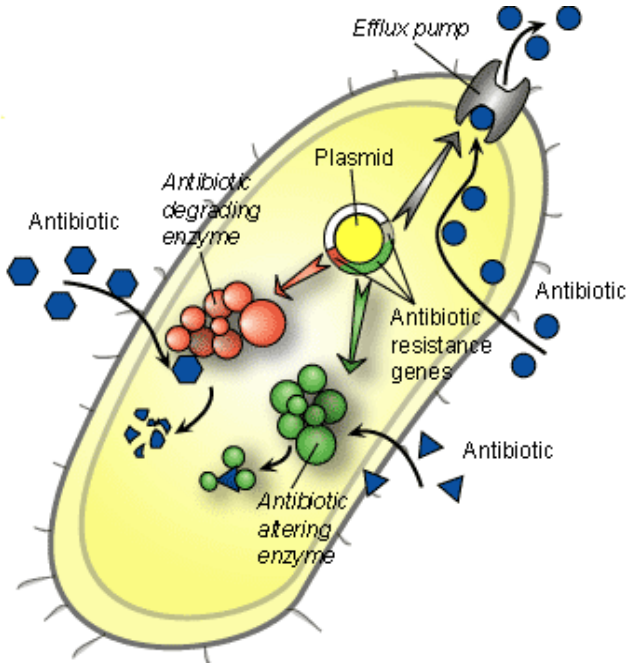
Resistance

- Antibiotic resistance refers to bacteria that did respond to an antibiotic and have lost sensitivity over time.
- Antibiotic resistance is an enormous concern in medicine as over 70% of bacteria associated with hospital infections show some resistance to at least one antibiotic that was once effective in treating them
- Antibiotic resistance can be acquired by one of three major mechanisms:

    1. Reduction of the drug at the site of the target.
    2. Increased drug inactivation.
    3. Alteration of the bacterial target.

1. Reduction of the drug at the site of the target.

- Over time, some bacteria will decrease the uptake of some antibiotics.
- Similarly, some bacteria increase the expression of efflux pumps and therefore bacteria more effectively extrude antibiotics.
- The combination of decreased uptake and increased efflux results in decreased drug that is able to access its bacterial target.

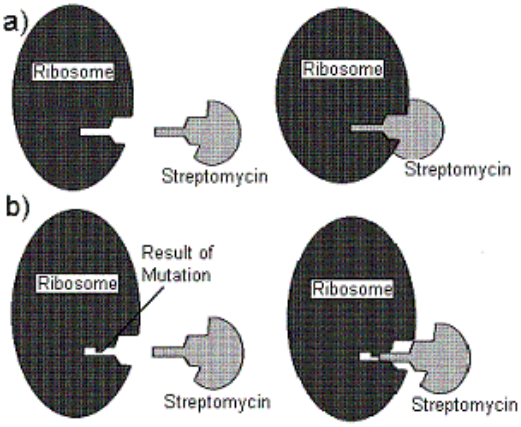


2. Increased drug inactivation.

- Some bacteria have evolved to produce increased amounts of enzymes that inactivate antibiotics.
- For example, some bacteria produce an enzyme called beta lactamase, which degrades all antibiotics that have a beta lactam ring in their structure (i.e. penicillins and cephalosporins).

3. Alteration of the bacterial target.

- Like most drugs, antibiotics act on targets to produce their effect.
- Over time, bacteria may evolve mutations in the target that make the antibiotic ineffective.
- In the example, a mutation in bacterial ribosomes renders some antibiotics ineffective, as the antibiotics are not able to bind to the target.



Preventing Resistance

- Strategies to prevent resistance include:

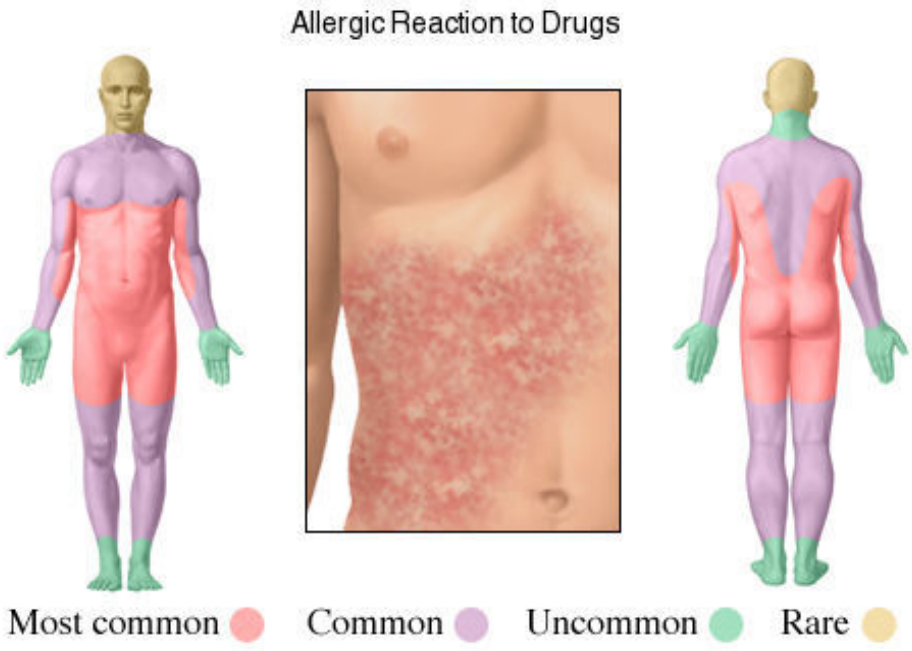
1. Prevent infection – Vaccinate where appropriate, get catheters out if possible.
2. Diagnose and treat infection effectively – Many patients who have the common cold (a virus) expect their doctor to give antibiotics, despite the fact that they are not effective against viruses!
3. Use antibiotics wisely – Only use antibiotics when necessary.
4. Prevent transmission – Isolate the pathogen and prevent its spread. This can be as simple as washing your hands. As a rule you should wash your hands before and after you touch any patient.

Allergy

- Allergy is a significant concern for some patients.
- The most common antibiotic allergy is penicillin.
- Signs of allergy include:

    - Urticaria (hives)
    - Anxiety
    - Swelling of hands, feet, throat
    - Difficulty breathing
    - Hypotension

- Most fatal antibiotic allergic reactions occur within 20 minutes of dosing.
- Most allergic reactions experienced by patients are not true immune mediated allergies. These patients experience symptoms such as vomiting, diarrhea and non-specific rash.
- If your patient is having an allergic reaction you should stop the antibiotic immediately and monitor vital signs. Patients may require treatment with diphenhydramine (an antihistamine) and an epipen (epinephrine, a vasoconstrictor).



Serum Sickness

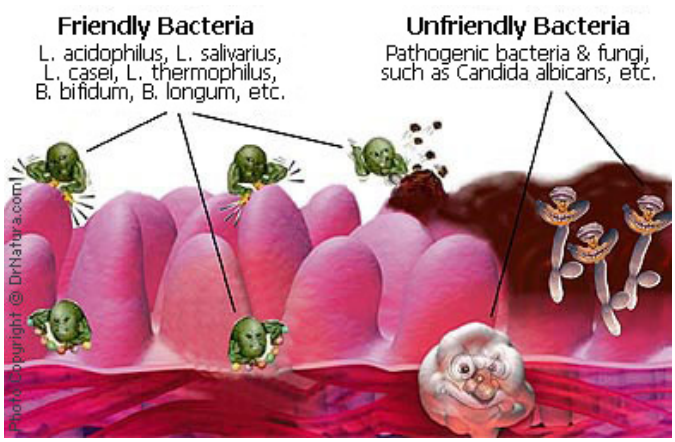
- Serum sickness is similar to an allergy but it typically develops 7-21 days after antibiotic exposure.
- During serum sickness, the body's immune system improperly identifies a drug or drug-protein complex as harmful.
- The body then produces an immune reaction, which produces inflammation and other symptoms such as fever, hives, rash, joint pain, itching, angioedema and enlarged lymph nodes.
- Treatment of serum sickness includes antihistamine (for itching), analgesics (for pain), and corticosteroids (for inflammation).

Superinfection

- Superinfection is an example of a special type of resistance.
- Superinfection is a new type of infection that develops during the course of antibiotic therapy.
- Broad spectrum antibiotics kill both pathogenic bacteria and normal bacterial flora.
- Destruction of normal bacterial flora can allow new bacteria to flourish.
- Since superinfections are caused by drug-resistant bacteria, they are difficult to treat.

Destruction of Normal Bacterial Flora

- In addition to superinfection, destruction of normal bacterial flora can have the following consequences:
    - Intestinal bacteria synthesize vitamin K. Patients taking the anticoagulant warfarin require vitamin K and are at increased risk of bleeding side effects when vitamin K is low.

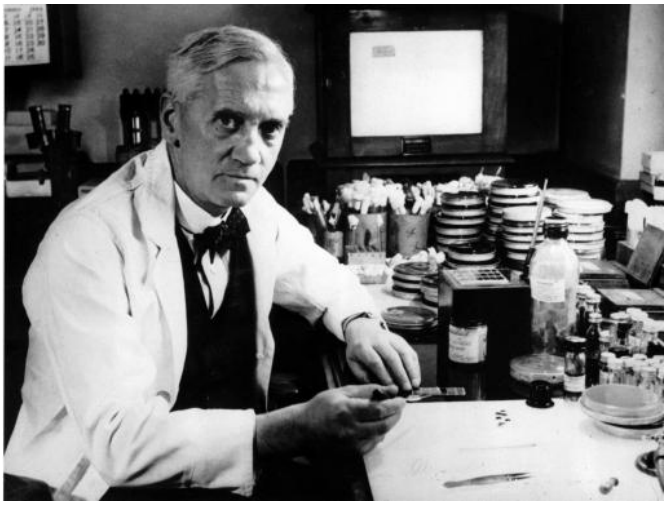


    - Intestinal bacteria metabolize some drugs and contribute to the first pass effect. *(Remember Module 4?)* Destruction of normal intestinal flora can lead to increased blood drug levels and therefore toxicity.
    - Intestinal bacteria are involved in enterohepatic recycling of drugs. *(Remember Module 5?)* Destruction of intestinal bacteria can decrease enterohepatic recycling and have devastating consequences to drug therapy (i.e. contraceptive failure with oral contraceptive drugs).

Bone Marrow Toxicity

- Bone marrow toxicity is a very rare but serious complication of antibiotic therapy.
- Symptoms of bone marrow toxicity include aplastic anemia, thrombocytopenia, agranulocytosis and leukopenia.
- Patients should be educated to look out for symptoms such as sore throat, bruising, and fatigue as they are signs of bone marrow toxicity.

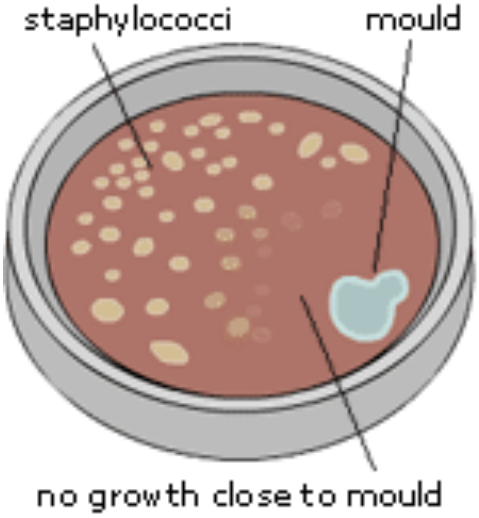
16.4 Penicillins



- Penicillin was discovered in 1928 by Scottish physician Sir Alexander Fleming.
- Fleming became interested in drugs to treat bacteria after serving in World War I where he witnessed many friends die due to bacterial infection of wounds.
- His discovery of penicillin is probably one of the most influential discoveries in medicine and has since saved many lives.
- Fleming won the Nobel prize in medicine/physiology in 1945.

Discovery of Penicillin

- Fleming was doing work on bacteria called staphylococci in his lab.
- He went on vacation for a month and when he returned, his plates were contaminated with mould.
- Fleming noticed that the mould killed the staphylococci in close proximity.
- The discovery of penicillin was a serendipitous observation!



Penicillin and the Bacterial Cell Wall

- The bacterial cell wall is composed of a peptidoglycan layer.
- Transpeptidases are enzymes that function to form cross bridges between the peptidoglycan strands, therefore making the cell wall strong.
- Autolysins are bacterial enzymes that degrade the peptidoglycan cell wall.
- Together transpeptidases and autolysins are called penicillin binding proteins (PBPs) and are the primary target of penicillin antibiotics.

Penicillins – Mechanism of Action

- Penicillins inhibit transpeptidases and activate autolysins.
- Therefore, penicillins disrupt synthesis of the cell wall and promote cell wall destruction.
- The net result is bacteria take up excess water and die (lyse).
- Thus, penicillins are considered *bactericidal* and are only effective against bacteria that are actively growing and dividing.
- Penicillins are much more effective against gram positive bacteria because they do not have an outer membrane.

Resistance

- Penicillin resistance may be caused by:

    1. Inability to reach its target
    2. Inactivation
    3. Mutation in PBPs that make them have low affinity for penicillins (i.e. methicillin resistant *Staphylococcus aureus*, MRSA)

- The predominant mechanism of resistance is inactivation by enzymes called beta lactamases. These enzymes target the beta lactam ring of penicillins rendering the drug inactive.
- We now have beta lactamase inhibitors, which block this enzyme and help avoid resistance.

Classes of Penicillins

- Narrow spectrum penicillins
- Narrow spectrum penicillinase resistant penicillins
- Broad spectrum penicillins
- Extended spectrum penicillins

Narrow Spectrum Penicillins

- Effective in treating gram positive bacteria.
- Some are destroyed by gastric acid so they must be administered IV or IM.
- Effective in the treatment of pneumonia and meningitis.
- Are generally considered to be safe. Drug allergy is the primary adverse effect.

Narrow Spectrum Penicillinase Resistant Penicillins

- These antibiotics have an altered side chain that makes them not susceptible to inactivation by beta lactamase enzymes.
- Effective in treating penicillinase producing *Staphylococci*.
- Less effective versus non-penicillinase producing bacteria.
- Not effective in treating abscesses or penetrating into bone.
- Some bacteria have emerged that are resistant to this class of drug (i.e. MRSA).

Broad Spectrum Penicillins

- Effective against **both** gram positive and gram negative bacteria.
- Broader spectrum is due to their ability to penetrate the outer membrane of gram negative bacteria.
- They are readily inactivated by beta lactamases.

Extended Spectrum Penicillins

- These drugs are effective against gram positive and gram negative bacteria.
- In addition, they are effective in treating patients infected with *Pseudomonas aeruginosa,* a bacteria that is resistant to all other penicillins.
- Extended spectrum penicillins are also susceptible to degradation by beta lactamase enzymes.

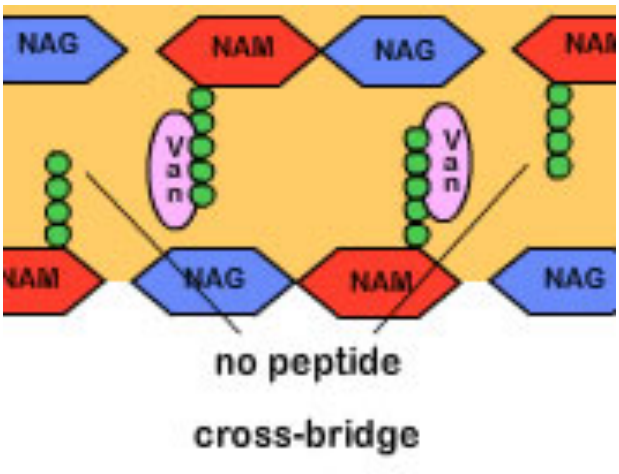
16.5 – Other Antibiotic Drugs

Cephalosporins

- Have the exact same mechanism of action as penicillins since they inhibit transpeptidases and activate autolysins.
- Cephalosporins are *bactericidal* and can be separated into 4 generations:
    - 1st generation
    - 2nd generation
    - 3rd generation
    - 4th generation
- As we move from 1st generation to 4th generation, the drugs tend to increase in terms of their activity against gram negative bacteria, increase resistance to the destruction by beta lactamases, and increase in their ability to penetrate the cerebrospinal fluid.
- Allergy is the most frequently reported adverse effect.
- Cross reactivity of people with penicillin allergy is rare (< 1%) so cephalosporins are a suitable alternative for patients allergic to penicillins.

Vancomycin

- Vancomycin is a potentially toxic drug that is used only to treat serious infections such as those caused by MRSA including osteomyelitis, meningitis, pneumonia, and septicemia.
- Vancomycin inhibits cell wall synthesis but not by binding to PBPs.
- Rather, vancomycin binds to precursors of cell wall synthesis to block the transglycosylation step in cross bridge synthesis.



- Vancomycin may cause ototoxicity, and rapid infusion may cause "red person syndrome" (flushing, rash, itching, hypotension).

Tetracyclines

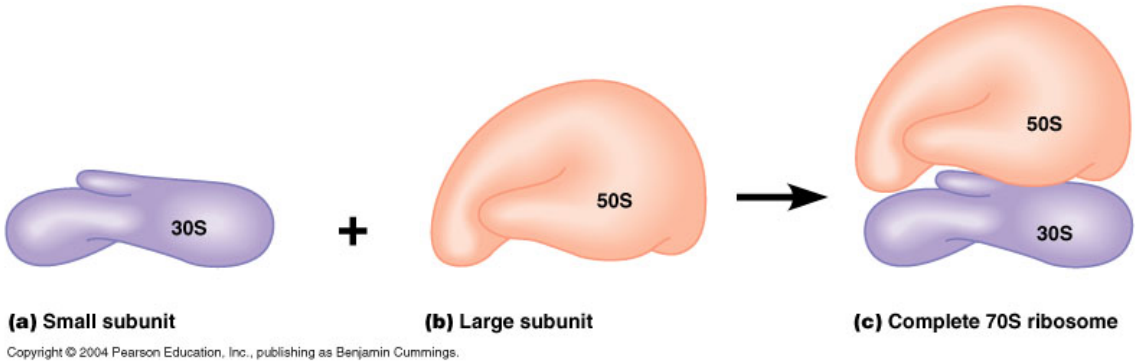
- Are protein synthesis inhibitors.
- They act by binding to the 30S ribosomal subunit of bacteria, and therefore prevent the addition of amino acids to the peptide chain.
- Tetracyclines are broad spectrum antibiotics that are *bacteriostatic*.

- They are effective in treating bacteria that cause typhus fever, chlamydia, and cholera.
- Adverse effects include:

    - GI irritation
    - Photosensitivity – patients must avoid UV (A and B) light and always wear sun block when outside.
    - Susceptible to superinfection.

Macrolide Antibiotics

- Are protein synthesis inhibitors.
- They act by blocking the 50S ribosomal subunit of bacteria, and therefore block the addition of amino acids to the peptide chain.
- Macrolide antibiotics have a broad spectrum and are *bacteriostatic*.
- Adverse effects may include GI upset and QT interval prolongation *(remember Module 10?)*.

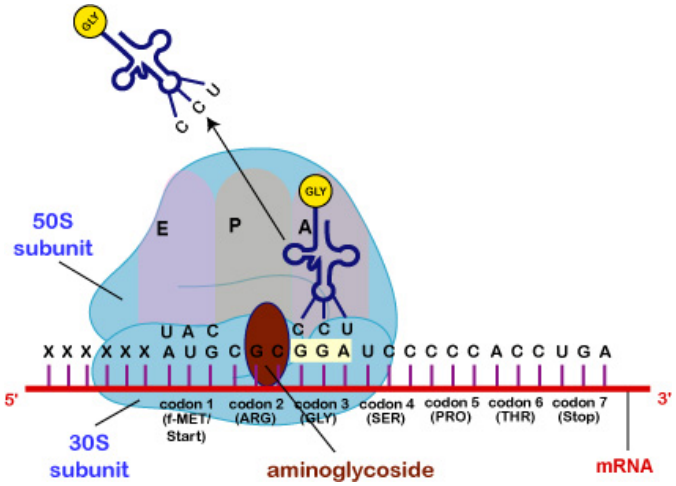


Oxazolidinones

- Are *bacteriostatic* protein synthesis inhibitors.
- They act by binding to a specific region of the 50S ribosomal subunit to inhibit protein synthesis.
- Are narrow spectrum with activity only against gram positive bacteria.
- They are important because they are effective in treating MRSA and vancomycin resistant enterococci (VRE). Use of oxazolidinones should be reserved for MRSA and VRE.
- Adverse effects include may include reversible myelosuppression.

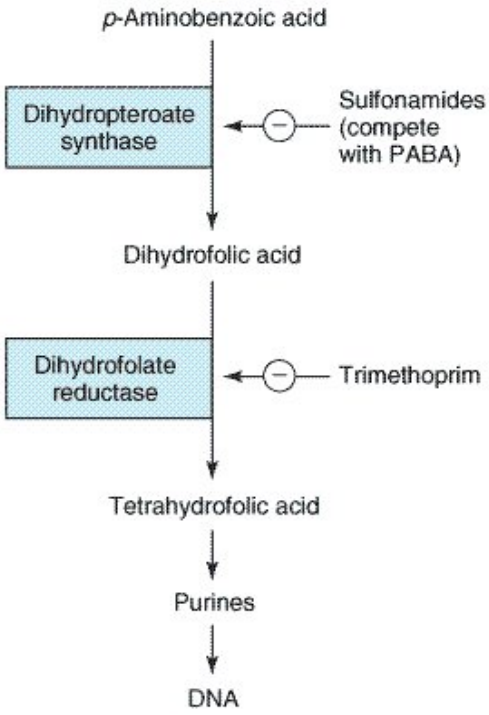
Aminoglycosides

- Are *bacteriocidal*, narrow spectrum (effective vs. gram negative), protein synthesis inhibitors.
- They act by binding to the 30S ribosomal subunit to prevent protein synthesis.
- Aminoglycosides are rapidly lethal to bacteria and the mechanism that accounts for this rapid lethality is unknown.
- Adverse effects include irreversible ototoxicity and reversible nephrotoxicity.

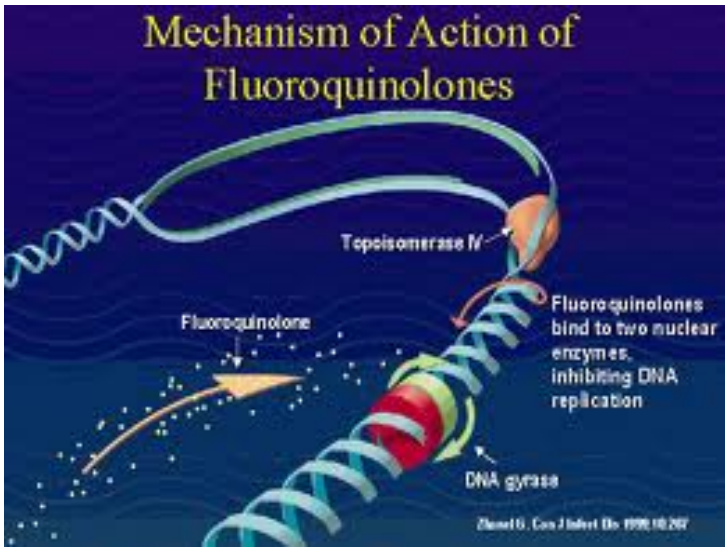


Sulfonamides and Trimethoprim

- Unlike humans who obtain folic acid from our diet, survival of bacteria is critically dependent on the synthesis of folic acid to incorporate into DNA.
- Sulfonamides and trimethoprim act at different stages to block the synthesis of folic acid.
- Often these drugs are given in combination and result in *bactericidal* action.
- The most common use for this combination is for the treatment of UTIs.
- The primary adverse effect associated with this therapy is hypersensitivity reactions such as fever and photosensitivity.
- There is a small risk of severe hypersensitivity reaction called Stevens-Johnson Syndrome.



Fluoroquinolones



- Act by inhibiting DNA replication.
- They inhibit two enzymes, DNA gyrase and topoisomerase IV.
- Fluoroquinolones are *bactericidal* and broad spectrum.
- Fluoroquinolones are effective in the treatment of UTIs, osteomyelitis, and soft tissue infections.
- Adverse effects primarily include GI symptoms (nausea, vomiting, diarrhea).

Isoniazid

- Isoniazid is the primary treatment for tuberculosis.
- It acts by inhibiting the synthesis of mycolic acid, a component unique to the cell wall of tuberculosis-causing bacteria.
- Since mycolic acid is a unique component to *M. tuberculosis* bacteria, isoniazid is only effective in treating tuberculosis.
- Adverse effects of isoniazid include peripheral neuropathy and hepatotoxicity.