Disease treatments:

I. treat symptoms:

For some diseases, this is all that can be done. The common cold, for instance.

- Some evidence that for rabies this may eventually lead to a treatment/cure (coma induction seemed to work for a girl in Wisconsin in 2004.

Often this is the primary line of defense:

- lowering extreme fevers

- dealing with severe dehydration (rehydration)

- etc.

- symptoms can be so severe that they obviously must be dealt with.

II. Try to kill causative agent:

Main problem here is that it's not as easy as it sounds.

- How to kill the pathogen and not the host?

- Many early treatments for diseases were extremely dangerous. For some diseases (e.g. sleeping sickness), this is still the case.

- salvarsan was discovered in 1910 - effective against syphilis, though it is also toxic (made up in part of arsenic).

- this was a serious problem until the discovery of antibiotics like penicillin.

Antibiotics

- First antibiotic discovered was penicillin, in 1897, though this was ignored until Alexander Fleming rediscovered penicillin in 1928. But it wasn't until WW II that the British, then Americans, accelerated research into penicillin, which finally became more widely available.

- Today it is easy to find antibiotics, but the problem is that many are highly toxic, or have some other unsuitable characteristics.

- Although many antibiotics are fairly safe, most do have some side-effects, sometimes surprising:

- pseudomembranous colitis is caused a bacteria that normally lives in the gut. It is usually kept under control by other bacteria in the gut.

- antibiotics can kill a large number of beneficial gut bacteria

- this can cause *Clostridium difficile* (our problem bacteria) to rapidly grow. In large numbers it is toxic - causes diarrhea, abdominal pain, fever, fatigue, loss of appetite. It can kill.

- Some antibiotics are more likely to cause this than others.

Incidentally, is it obvious why diarrhea is a common side effect of many antibiotics??

Antibiotics are divided into two broad categories:

- Those that are bactericidal (kill the bacteria)

- Those that are bacteriostatic (prevent them from growing - this allows the hosts defense mechanisms time to take over).

Other ways of classifying antibiotics include:

Broad vs. narrow spectrum:

Broad spectrum - work against a wide variety of antibiotics.

Others are narrow spectrum - work only against a few types.

Gram positive vs. gram negative:

Due to the different characteristics of the cell membrane in positive and negative gram bacteria, this makes a big difference in whether or not an antibiotic is effective.

Aerobic vs. non-aerobic:

The basic metabolism of these bacteria can be different, so the antibiotics that are used are often different as well.

Five main modes of action:

- inhibit cell wall synthesis - works because human cells usually don't have the components of bacterial cell walls that are attacked by antibiotics.

- inhibit protein synthesis - bacterial ribosomes (which make proteins) are different enough from human ribosomes so this works without affecting humans too much.

- damage the plasma membrane - similar to the first one, but the actual cell membrane is damaged. Some antifungal drugs work this way as well.

- inhibition of DNA replication and transcription - works, but many are dangerous or not terribly useful because they interfere with human DNA replication and transcription.

- interfere with making essential metabolites (think mostly "enzymes"). Without these, bacteria can't survive, so they die. Even though we often need the same products, we make them differently, so this works.

Many, many types of antibiotics. We will not go through all of these, since this is not a microbiology class.

- But, if you're researching a bacterial disease, be sure to talk about treatments, and why or why they are not effective.

- Antivirals

It is estimated that up to 90% of the population in the U.S. has had some kind of viral infection in the last year.

It is only recently that this class of drugs has started to become developed.

- The main impetus has been AIDS, and many AIDS drugs are antiviral drugs.

The main problem in developing an antiviral drug is that the virus is inside the host cell.

We're not good enough to do what the immune system can do, which is to recognize infected body cells, and only kill those.

So how do we kill the virus without killing the host cell???

- In general, antiviral drugs interfere with some stage of protein, RNA or DNA production (for example, by having the viral genetic material make "false" DNA which doesn't work).

A few antiviral drugs have been approved for diseases other than AIDS; for example, the flue (oseltamivir - Tamiflu, or zanamivir - Relenza), or hepatitis B.

Interferons are also classified as antivirals (and may work against the common cold, though only if treated early during the incubation phase - also has bad side effects).

Hopefully a lot more antiviral drugs will come on line in the future.

- Antifungals

The problem here is that fungi are eukaryotes. Their cells are a lot more similar to ours than prokaryotes, so it's much more difficult to develop effective treatments.

Still, there are some out there:

Many work based on the fact that our cell membranes are a bit different (fungi use ergosterol and we use cholesterol as the principal sterol in our cell membranes)

(Sterols are used for messaging and help control the fluidity in our membranes).

Even so, many antifungal compounds are toxic, so have to be monitored carefully.

- Antiprotozoans & Antiparasite

Several drugs are out there that help treat protozoan diseases. For some we don't even know how they work.

- drugs are available for such diseases as malaria, giardiasis, amebiasis, etc.

Drugs are also available to treat infections with worms. For example, tapeworms, flukes, and even things like mites and ticks.

- some seem to work by affecting the cell membranes of worms, some work by exposing antigens to the immune system (which can then attack the parasite), some interfere with ATP synthesis, but some work in ways we don't understand yet.

III. Pathogens fighting back: Evolution!

Briefly, evolution is defined as “the change in the genetic makeup of a population over time”.

Usually this is by natural selection, but sexual selection & artificial selection are viable alternatives to natural selection.

Natural selection:

- 1) Organisms are different from one another (even members of the same species).

- 2) All organisms produce more offspring than can survive.

- 3) Therefore, only some survive - those most suited to their environment.

Unfortunately, this has been causing havoc in medicine (and agriculture).

Bacteria have evolved resistance to many types of antibiotics. There are some bacteria out there that are resistant to almost any antibiotic known!

If we're not careful, we'll soon be back to the days where bacteria were killing vast numbers of people:

- plague, whooping cough, leprosy, tuberculosis, etc.

Main problems come from several sources:

- people demanding antibiotics from doctors when they are not needed (e.g. for the common cold).

- people do not take antibiotics long enough, allowing surviving bacteria to propagate.

- in some parts of the world, antibiotics are available without a prescription - their use is not controlled.

- the livestock industry is particularly notorious:

    - will feed vast amounts of antibiotics to cattle, pigs, etc. in order to keep them healthy.

        - these animals are not even ill, it's just preventive maintenance.

        - OR, worse, they promote growth (probably by inhibiting some bacteria normally found in the guts of these animals).

            - as a result there are numerous antibiotics in the environment which causes strong selective pressure on bacteria.

    - Recently the livestock industry petitioned the government to be allowed to use cefquinome.

        - The AMA and numerous consumer groups vigorously oppose this move, since cefquinome is one of the last few effective antibiotics out there (evidence from Europe has shown an increase in cefquinome resistance after its use in cattle).

        - The FDA doesn't seem to care, and appears to be on track to approve the use of cefquinome.

            - this was the state a year ago. Haven't been able to find out what's happened since then.

        - As an aside, the FDA seems to have been gutted recently in their effectiveness. Yes, there are a lot of problems with the FDA, but what is happening now is unconscionable.

    - The pharmaceutical industry generally supports the livestock industry since it means increased sales of antibiotics.

Drug companies have little interest in developing new antibiotics because profit margins are too low.

Could be one of the most serious issues facing us in upcoming years.

The infectious diseases society of America is urging legislation and tax incentives to re-start the development of new antibiotics.

Incidentally, this is a problem not just with antibiotics, but antivirals, antifungals, etc.

- Malaria has become widely resistant to the drug of choice, chloroquine.