Host Defenses May Need Help

Antibiotics to the Rescue

Bacteria Fight Back
ANTIBIOTIC RESISTANCE
Module Two: What We Will Learn

• Antibiotics
  – How they work
  – How bacteria become resistant
    • Mutations in bacterial genes
    • Selection pressure (evolution)
    • Exchange of genetic material between bacteria

• Strategies for overcoming antibiotic resistance in bacteria
  – Appropriate use to reduce selection pressure
  – Research and development of new antibiotics
What is an Antibiotic?

• A chemical that kills bacteria or stops them from growing
• Antibiotics work only against bacteria, not viruses
Timeline of Antibiotics and Development of Resistance
Antibiotic Timeline

Way B.C.
Bacteria were present before the dinosaurs

1940s
The first antibiotics are mass produced for humans and work well

1950s
Antibiotic resistance that impairs effectiveness appears as the first antibiotics are used

1990s
Current teenagers are born!

Today
Some antibiotics no longer work and few new ones are in the pipeline

2030
Will we have antibiotics that work?

Millions of years later

MARR
Michigan Antibiotic Resistance Reduction Coalition
Key Knowledge About Antibiotics

• The first antibiotics were made from by-products of soil microbes (fungi and bacteria)
• These microbes were competing with other microbes for space to live and grow in the soil
• Chemists developed the first mass-produced antibiotics in the 1940s
• These antibiotics did not maintain their effectiveness very long because some bacteria mutated and thus became resistant and could survive and proliferate
Key Knowledge About Antibiotics

• Chemists then made new, more sophisticated antibiotics
• In a short period of time, bacteria developed resistance to these new antibiotics
• Today some newer antibiotics are engineered by design to jam and kill the resistant bacteria
• Bacteria continue to mutate and survive new antibiotics
Key Concepts to Remember About Antibiotics

• A newly developed antibiotic is most effective when it is first released for human treatment
• Today some bacteria have developed multidrug resistance, and, in some cases, bacteria are resistant to all available antibiotics
• Over time, even fewer antibiotics will be effective, unless newer ones can be developed to replace them
• The development of new antibiotics has slowed, primarily due to the cost of development and lower financial incentive, since the income from an antibiotic taken for 10 days is less than from other drugs that are prescribed for lifetime use.
Types of Antibiotics

• There are dozens of antibiotics used in humans
• Antibiotics fall into several classes or types
• Different types of antibiotics may be active against different types of bacteria
• Bacterial resistance mechanisms may cause resistance to some types but not to others
• Sometimes new types of antibiotics are developed to have activity against some bacteria that are resistant to other types of antibiotics
How Is An Antibiotic Chosen For Treatment?

• Care provider takes a history and does physical exam to determine the site of infection and the likely cause (virus vs. bacteria)

• Specimens collected for lab testing are examined for the growth of bacteria, which are then identified and tested for susceptibility to a range of different antibiotics

• For certain infections (like ear infections), the clinician may treat based on the bacteria that are likely to cause the infection without testing
Selecting the Right Antibiotic For the Bacterial Infection

- Bacteria grown in the lab are swabbed onto the surface of an agar culture plate
- Filter paper disks containing different antibiotics are placed on the surface of the agar plate
- The agar plate is incubated at body temperature overnight
- An effective antibiotic is shown by a “clear zone” on the agar plate where the bacteria were inhibited by the antibiotic as it diffused out from the disk

*The “clear zone” around various antibiotics on this agar plate mean that these bacteria are susceptible to these various antibiotics.

*Bacteria are resistant to this antibiotic.
Narrow- and Broad-Spectrum Antibiotics

- Narrow-spectrum antibiotics are targeted to a limited group of bacterial species
- Broad-spectrum antibiotics are effective against a wide range of bacterial species
- A narrow-spectrum antibiotic should be used to target the specific bacterial infection, preserving the colonizing bacteria and avoiding selection of resistance in these bacteria that might later cause infection
- A broad-spectrum antibiotic is used when you do not know the infecting bacterium and its susceptibility pattern, or when the bacteria are known to be resistant to narrow-spectrum drugs and you don’t have any other choice.
How Antibiotics Work

If you think of bacteria as a lock, then an antibiotic is like a key.
How Do Antibiotics Fight Bacteria?

• Antibiotics disrupt a specific function of a bacterium, preventing its growth and replication by:
  – interfering with DNA or RNA replication
  – disrupting the production of the bacterial cell wall
  – preventing the production of proteins and smaller molecules that are necessary for growth and replication
  – dissolving the cell membrane, causing leakage of cytoplasmic contents
Antibiotic Targets

Cell Wall Synthesis
- Beta-Lactams (penicillins, cephalosporins)
- Glycopeptides (vancomycin)
- D-Cycloserine
- Fosfomycin
- Bacitracin

Ribosomal Protein Synthesis
- Aminoglycosides (streptomycin, gentamicin)
- Erythromycin
- Tetracyclines
- Clindamycin
- Chloramphenicol
- Linezolid

DNA Synthesis
- Fluoroquinolones
- Metronidazole
- Trimethoprim/sulfamethoxazole

RNA Synthesis
- Rifampin

Cell (Cytoplasmic) Membrane
- Polymyxins
- Daptomycin

Cell Wall
- Polymyxins
- Daptomycin

RIBOSOMES

DNA

RNA

Cytoplasmic Membrane
Emergence of Resistant Bacteria

- There are two types of bacterial resistance:
  - **Intrinsic resistance** – existed before antibiotics were introduced, a natural characteristic of the bacterial species
  - **Acquired resistance** –
    - random mutations in bacterial genes resulting in new resistance, or
    - acquisition by a sensitive bacterium of existing resistance genes from an already resistant bacterium
Bacteria Fight Back!

I. Mutations in Bacterial Genes
II. Transfer of Genetic Material Between Bacteria
III. Selective pressure (e.g., evolution)
Bacterial Lock and Antibiotic Key

• Four things can happen:

1. The antibiotic key **unlocks** the bacteria and kills them
2. The antibiotic key can **become damaged** so it cannot open the bacterial lock
3. The bacterial lock can **alter itself (mutate)** so the key (antibiotic) no longer can open the lock
4. The bacterial keyhole can **become blocked** so the antibiotic can not enter
Resistance Against Antibiotics

I. Mutations in Bacterial Genes

• Mutations in bacterial genes can:
  – Make the bacterial outer membrane or cell membrane less permeable, preventing the antibiotic from entering the bacterial cell
  – Pump the drug out of the cell before it gets a chance to work
  – Produce enzymes that inactivate the antibiotic
  – Alter the target site where the drug usually binds to the bacteria, so it can’t bind anymore
II. Transfer of Genetic Material Between Bacteria

Bacteria can transfer their DNA into bacteria of the same or other species
Genetic Acquisition of Antibiotic Resistance by Mutations and by Transfer of Resistance Genes to Susceptible Bacteria

New Resistant Bacteria
III. Selective Pressure

The presence of an antibiotic exerts selective pressure because resistant bacteria continue to grow while susceptible (or sensitive) bacteria are eliminated.
Selection for Resistance

Sensitive and resistant bacteria live together.

Antibiotics kill sensitive bacteria.

The resistant bacteria are left to multiply.
Selection of Bacterial Strains That Have Acquired Resistance by Mutation and/or Transfer of Resistance Genes

Resistant Strains Rare

Antimicrobial Exposure

Resistant Strains Predominant
Other Factors Contributing to Selective Pressure:

1. Patient non-compliance (taking only for a few days or skipping doses)
2. Inadequate dosing (not high enough dose, or doses spaced too far apart)
3. Misuse of antibiotics
   - Overuse (prescribing when not needed)
   - Inappropriate use (patient taking antibiotics prescribed for a different infection)
   - Unnecessary use of broad-spectrum antibiotic (exposing patient to a drug that can affect colonizing bacteria elsewhere in the body)

The use of any antibiotic contributes to the possibility of its loss of effectiveness because of selection of existing resistant bacteria
Important Things to Remember About Antibiotics

• Antibiotics kill bacteria, **not** viruses.
• Taking an antibiotic unnecessarily for colds and flu can select bacteria in the body that are resistant to the antibiotic.
• Never save or share your antibiotics.
• Take your antibiotics as prescribed by your care provider.
Why Should We Be Concerned About Antibiotic Resistance?

- Antibiotic resistance is a serious **global** problem
- Resistant infections are difficult to treat. The bacteria may be resistant to multiple types of antibiotics
- Resistance limits the range of effective antibiotics, sometimes leaving only antibiotics that are expensive, inconvenient to use, or even dangerous (toxic)
Why Should We Be Concerned About Antibiotic Resistance? (cont.)

• It takes 10 years to develop a new antibiotic and over $1B to fund the development
• Newer antibiotics may have more side-effects or may be more expensive and/or less effective than drugs previously developed but now compromised by resistance
• Antibiotics are generally less profitable to drug manufacturers, so there are fewer financial incentives to develop new antibiotics
Additional Environmental Concerns

• Antibiotics have been used to treat meat animals and poultry to prevent infections rather than to treat them, and to promote faster growth; this excessive antibiotic usage can lead to selection of antibiotic-resistant bacteria which can get into humans, either from close contact or consumption of infected meat or dairy products.

• Improper disposal of old or unused antibiotics can pollute the water supply, exposing the general public to low levels of antibiotics which can select for resistance in colonizing bacteria.
Preventing Bacterial Infection is the Best Medicine!

• Wash your hands properly
  – Before eating
  – After using the bathroom
  – After a sneeze or cough
• Cover coughs and sneezes
• Help your immune system by:
  – Eating healthy foods
  – Exercising regularly
  – Getting plenty of sleep every night
• NEVER take an antibiotic for a viral infection, like a cold or flu
What Else Can You Do?

• If you are prescribed antibiotics, take all of the medication as prescribed by your care provider
• Do not stop taking an antibiotic before the end of the treatment course just because you start to feel better; residual bacteria may multiply, causing recurrence of symptoms that may require retreatment increasing the likelihood of selecting resistant cells
• Never share or save antibiotics
• Spread the word, not the resistance
Remember......

• Every time someone takes an antibiotic, resistant bacteria may be selected and then multiply

• Resistant bacteria may then spread to others, compromising the effectiveness of treatment for future infections

• Share what you have learned with your friends and family members
You Can Make a Difference