DIVISION OF MEDICAL ETHICS
HIGH SCHOOL BIOETHICS PROJECT

Antibiotic Resistance

Overview

Antibiotics are a class of medications that target specific bacterial structures or processes. They are prescribed to inhibit or kill the growth of bacteria and fungi. Unfortunately, with increased use and misuse of antibiotics, certain bacterial strains have evolved to develop antibiotic resistance to the drugs that were originally used to treat them. If people continue to misuse antibiotics, and doctors keep unnecessarily prescribing them, a completely resistant bacterial strain may set back modern medicine to a time without antibiotics. There are different solutions proposed in this module, which can aid in slowing down the evolution of these "superbugs." However, there are a few ethical dilemmas regarding viable solutions. For example, is it better to treat patients now with antibiotics right away and in high dosages, while risking the development of a resistance to the treatment? Or is it better to treat current patients with alternatives to antibiotics and in lower dosages so as to prevent future generations of patients from having to deal with higher frequencies of resistant bacteria? Should we be making it easier to develop drugs in order to promote the production of new antibiotics? The goal of this module is to educate students on how to properly assess the use of antibiotics as well as equip them with the tools necessary to discuss the different solutions to combating antibiotic resistance.

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Learning Outcomes

1. Understand the purpose and function of antibiotics and how resistance occurs
2. Develop an understanding of the benefits and risks associated with antibiotic use
3. Analyze different ethical arguments and discussions surrounding antibiotic use as it is now and proposals for the future
4. Consider the most efficient way to administer antibiotics while keeping in mind the threat of antibiotic resistance

Procedures and Activities

This unit uses a student-centered and interactive approach to teaching. Activities are designed to allow for student participation and are marked as an individual, partner or group activity.

1. Introduction to Topic

Individual Activity

Questions: Agree or disagree? This activity should be done individually by each student to assess their knowledge/opinion at the beginning and then again at the end.

- You can stop taking antibiotics as soon as your symptoms go away

- Antibiotics treat viruses and bacteria such as the common cold
- Antibiotics should always be the first line of defense in the emergency room
- Antibiotics can have severe side effects
- Antibiotics are added to food for farm animals
- You can take antibiotics without the prescription of a doctor
- Antibiotics can kill viruses

Now the teacher should read aloud the questions and take tallies for how many students agreed or disagreed with the statement. No one is right or wrong; this is about assessing knowledge and opinion to make the students aware before beginning.

Binary fission is a form of asexual reproduction in which a single bacterium will grow to twice its size and make a copy of its DNA so that it can essentially split in two at a precise moment to create a new, identical, bacteria cell. This process aids in the buildup of resistant bacteria because it allows bacteria to replicate at a fast pace and increase the population exponentially.

Horizontal gene transfer is a way for one bacterial cell to transfer DNA to another within the same generation. One method is called conjugation, in which the two cells physically connect to exchange genetic information. The first cell will have a piece of DNA packaged into a plasmid so that it can then be absorbed by another bacterium. Plasmids are cyclical segments of DNA picked up by bacteria from their environment and can then be inherited or transferred to other bacteria.

Antigens are foreign substances that are detected when they enter the body and provoke an immune response.

Antibodies search for specific antigens and bind to them so that they can be detected by another part of the immune system. They can also neutralize the antigen by impeding certain functions when it binds to the antigen. Antibodies are shape specific, meaning that the binding mechanism is special to the antigen it binds to.

Transposons are DNA sequences that are able to change their locus (location) within a genome.

Symbiotic relationship is a relationship in which both parties involved equally benefit from each other.

Explanation of Antibiotics & Resistance

Before discussing the impact of antibiotic resistance, it is important to first understand how resistance develops and how antibiotics function.

I. Antibiotics and Your Immune System

Your immune system is divided into two main parts, the innate and the acquired. The innate immune system comprises methods of immunity with which a person is born. For example, mucous membranes act as defense barriers, trapping bacteria and other small particles from entering your body. Coughing, as well, can be a function of your innate immune system as it occurs to block and/or remove an alien particle from entering your respiratory system. Your acquired immune system, on the other hand, adapts over time to specific microbes. In response to specific antigens, your body will produce antibodies designed to fight the specific invader. Your body will then be able to produce that specific antibody when it is presented with that antigen later, which creates immunity to a particular microbe. Lymphocytes, which are a type of white blood cell, produce antibodies.

Sometimes, the body does not respond quickly enough to invaders, so antibiotics are introduced to wipe out specific bacteria that cause disease. They work by targeting specific features and functions of the bacteria such as their cell walls, their protein production (ribosomes), or their DNA replication pathways. One common bacterial infection you may have experienced is a urinary tract infection (UTI), which is an infection of any part of the urinary system. The uncomfortable but not dangerous symptoms of a bladder infection include a burning sensation while urinating, cloudy urine, strong-smelling urine, and frequent and strong urge to urinate. However, there are serious complications associated with a potentially subsequent infection in the kidneys. Most of the time, a UTI will resolve on its own. However, antibiotics are a common treatment prescribed by doctors, with a course of only about a week or two for simple cases.

II. Antibiotic Resistance

There are two ways bacterial infections become resistant to antibiotics: through random genetic mutations or by acquiring a plasmid that encodes for resistance from another bacterium.

The former is an extension of natural selection, a law of evolution which states that organisms within a species most strongly adapted to their environment will survive in order to pass down their traits to future generations. For bacteria, that means that if one bacterium has developed a mutation that protects it from being killed by an antibiotic, that bacterium will survive and be able to pass down that trait to future generations until the resistance is so frequent in the gene pool that the antibiotic becomes ineffective.

The latter occurs through a process called conjugation, during which a bacterium transfers genetic information through plasmids and transposons to another bacterium as a type of horizontal gene transfer. Instead of sharing genetic material from one generation to another as occurs in sexual reproduction, they can also exchange genetic material within a generation.

Group Activity

To be done in groups of approximately four students to demonstrate how antibiotics target bacteria and how resistance occurs and is transferred until antibiotics are ineffective. (Adapted from Antibiotics: Peer Education, by Dr. Carwyn Watkins)

- Get two different color balloons. This example uses red and yellow.
- Start with 4 yellow and 1 red, but put a piece of duct tape over one part of the red balloon (This symbolizes the resistance to the antibiotic).
- Now, use a pin to try and pop one yellow and the red, the yellow should pop, but not the red.
- Next, double the amount of each balloon so there are 6 yellow and 2 red. Both red balloons should be taped.
- Again, try to pop 4 yellow and 2 red, and then double the remaining balloons.
- This time however, put a piece of tape on a yellow balloon to simulate horizontal gene transfer.
- Try to pop all the balloons.

- Have students connect parts of the activity to corresponding aspects of antibiotic resistance by drawing lines between the left and right column:

● Red Balloon	Antibiotic
● Yellow Balloon	Bacteria
● Tape	Mutated Bacteria
● Pin	Conjugation
● Yellow balloon with tape	Mutation

Discussion

- How can not taking a full dosage of antibiotics allow for resistant bacteria to grow in number?
- Should we continue to rely heavily on antibiotics? Also, should antibacterial cleaning supplies (soaps, etc.) be used in households?
- What do you think will happen if humans continue to rely on antibiotics?

History of Resistance & Antibiotics

I. First Applications of Antibiotics

After the discovery of penicillin in 1928, it took almost a dozen years for researchers to embrace and appreciate its effects and potential. Up until March of 1942, it had only been used in the battlefield minimally to treat and prevent wound-related infections, and on mice for research. However, as Anne Sheafe Miller lay on her deathbed, suffering from a severe streptococcal infection, her doctors became desperate. In a last-ditch effort to save her life they administered penicillin, an experimental drug at the time. Her doctors began seeing improvements overnight. Just as in Anne's case, penicillin went on to save many people and was used heavily on the battlefield during World War II to prevent soldiers from acquiring life-threatening bacterial infections.

II. MRSA Case Study

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an antibiotic resistant strain of *Staphylococcus*, known colloquially as "staph," which is a common skin infection that is particularly prevalent in hospitals. Methicillin was first introduced as an antibiotic in 1959, and MRSA subsequently started appearing as early as 1961 in English hospitals. It then appeared in America when a patient acquired a MRSA infection in a Boston hospital in 1968. MRSA is becoming much more common in hospital settings as infections are easier to spread through open wounds, unclean conditions, and contamination of personal items. A more recent outbreak in UC Irvine Medical Center in December of 2016 shows how hospital conditions can easily foster an outbreak. This California hospital reported 10 cases of infants being treated in the neonatal intensive care unit who tested positive for the same MRSA strain, starting in December of 2016 with the last one being tested in March.

III. 2016 Olympics Water Issue

Drug-resistant bacteria are not only a concern in hospital settings. During the 2016 Olympics Games in Rio de Janeiro, Brazil, drug-resistant bacteria was found in one of the bodies of water prepared for use by the rowing and canoe teams. This issue stems from sewage contaminating Rio's waterways, allowing for the breeding of bacteria and viruses in bodies of water surrounding the city. This example, if it becomes a trend around the world, poses a big threat of future drug-resistant bacterial outbreaks. Hospitals, presumably, have decontamination protocols that attempt to prevent such outbreaks. Once these resistant bugs appear in the environment and infect water sources, however, outbreaks will be much harder to control as resistant bugs can infect humans and transfer genetic material to non-resistant bacteria.

IV. SARS-CoV-2

There are also concerns that the Coronavirus pandemic could be advancing this problem. According to the Oxford University Journal of Antimicrobial Chemotherapy, around 70 to 80 percent of patients infected with the Coronavirus received antibiotic therapy even before a bacterial infection was confirmed. What is more shocking is that the novel Coronavirus is a non-living virus, therefore unaffected by antibiotics. This is clearly a misguided usage of antibiotics, which can exacerbate resistance of antibiotics.

V. Where Are We Headed? (Discuss this question first, and then share the statistic).

In 2013, the CDC reported that at least 2.8 million people are infected with antibiotic resistant bacteria a year, and at least 35,000 die because of this. It was then projected that by 2050, antibiotic resistance will kill 10 million per year if changes aren't made.

Human Impact on the Development of Resistance Against Antibiotics

Teacher-Directed Class Discussion

Discuss this question first with the class. Have students make a list of ways they believe that they, or someone they know, could have been in circumstances that contributed to the development of antibiotic resistance. Make it clear that this does not mean they have personally caused resistance to occur in any bacteria. Then have everyone vote for the top 4 ways in which human activity contributes to antibiotic resistance. What were the top 4 picked by the students? Ask

Correct suggestions may be, but are not limited to:

- People misusing their antibiotic prescription
- Doctors too quick to prescribe and prescribe too often
- First line of defense in emergency rooms
- There are many symptoms that prompt the premature use of antibiotics when they could just as easily be indicative of a virus
- 9 times out of 10 a sore throat is caused by a virus
- At least 30% of antibiotics prescribed in doctors' offices, emergency rooms, and hospital clinics are unnecessary
- Overuse and misuse with animal and food production
- Patient self-diagnosis and easy access to antibiotics (More so in developing countries)
- Not enough funding and research going into developing new drugs to keep up with the fast rate of resistance

Pros to Antibiotic Use

Individual Activity

Think about, and respond to the questions: Why are antibiotics so important? Why are they used so often?

The word "antibiotics" has become a common household term since the discovery of penicillin in 1928 by Dr. Alexander Fleming. Now, the prescription of antibiotics is a common response to many symptoms, and antibiotics are used worldwide to treat a plethora of diseases and infections. They have greatly helped decrease the frequency of some once deadly diseases as well as make many diseases treatable with only a prescription. Through the use of antibiotics, we have been able to make horrible diseases such as tuberculosis go from one of the leading causes of death in the US in 1900 to only causing 493 deaths in 2014.

Antibiotic use has extended further than fighting human infections. They are now commonly used to treat and prevent disease in livestock. Why might we care what medical treatment a pig or cow receives? Antibiotics in livestock are used to improve animal's welfare and prevent an increase in euthanasia. Similarly, there is a direct positive correlation between an increase in animal disease and human disease rates, making the use of antibiotics not only helpful for animals, but humans as well. Additionally, because many farms have such cramped and unsanitary living conditions for the animals, antibiotics help prevent the spread of disease between animals.

Cons to Antibiotic Use

After all antibiotics have done for us, why are so many people doubting them so much now? First, because of misuse and overuse of antibiotics at home and in the clinic, we may soon be facing a world where the biggest con of using antibiotics is that they no longer work. Most antibiotics (like all drugs) have side effects, which can range from minor rashes to anaphylactic shock or kidney issues. Thus, doctors should discuss these risks with patients, and patients should decide if the benefit of taking the antibiotic is worth doing, given the risks. In addition to the risk of unwanted side effects, antibiotics are able to kill other bacteria that are beneficial for your health, not just the invader bacteria that causes disease. In your gut, there exists a whole biome of bacteria. These gut bacteria are necessary to your digestive system and have evolved to have a symbiotic relationship with us. Unfortunately, at the moment, there is no way to tailor an antibiotic so that it will only attack a very specific bacterial strain in a clinical setting. There is research being done at an earlier stage in labs in which scientists have been able to take a specific bacteria's immune defense mechanism and use it to target itself. This process could allow scientists to only target one strain of bacteria, even among others that share 99% of the same DNA. This can help prevent healthy bacteria to avoid being attacked by antibiotics as well as possibly help with reducing the risk of developing antibiotic resistance. However, as of now there is no clinical application of it yet, which means regular antibiotic use may cause the healthy bacteria in your gut to be at risk of disappearing when you take antibiotics. If the antibiotic is not too strong and doesn't do too much damage, you can take probiotics to help replace your healthy bacteria. However, repeated antibiotic use can hurt your gut bacteria and cause different digestive, metabolic, and other health complications. For example, *C. difficile* is a type of bacteria that can cause diarrhea, as well as more serious complications such as swelling of the colon and kidney failure. *C. difficile* is associated with overuse of antibiotics because some types can weaken your gut bacteria, creating an environment in which *C. difficile* can thrive. Originally, *C. difficile* was mostly seen in healthcare and assisted living settings where errors in sanitation and hygiene helped spread it amongst patients and practitioners.

When discussing use of antibiotics on livestock, there are many downsides. Animals are routinely over-prescribed antibiotics, which can end up in water run-off. Additionally, if you eat meat, you may also be consuming small quantities of antibiotics. Every day, drug makers sell at least 4 million pills worth of antibiotics to industrial farms. This also breeds superbugs, which can end up in our food and water sources. Finally, antibiotic production generates a lot of pollution, especially in water systems from chemical runoff. For example, an Indiana wastewater facility 45kg (99lbs) of ciprofloxacin was released into a nearby river each day. That is about the same as the total amount consumed by Sweden over 5 days. This pollution is not only bad for the waterways, but can aid in the buildup of resistance to those antibiotics.

Possible Solutions

I. Stewardship Programs in Hospitals and for Doctors

Stewardship programs are being implemented in hospitals and healthcare practices to provide practitioners and healthcare staff with tools to help prevent antibiotic resistance. These programs usually have various components, such as diagnosis guidelines, steps to determine the best intervention for various kinds of infections, sanitation practices, restrictions on specific antibiotics, and the roles of different healthcare providers in the process of patient care (i.e., clinicians, department heads, nurses, technicians, etc.) In 2015, the World Health Assembly adopted a global action plan on antimicrobial resistance with the aim of limiting antibiotic misuse and altering the future of antibiotic use and research. On top of lowering rates of antibiotic-resistant bacteria, these stewardship programs have the potential to save millions of dollars, making research more accessible.

Group Activity

Activity: Have students split into groups to create a public service announcement
(either posters or video commercials) about one component of antibiotic Resistance that the public should know.

Example: Asking your doctor about alternatives to antibiotics and/or what dose is
necessary, guidelines to taking antibiotics, common cold or bacterial infection, hygiene practices, etc.

II. Drug Pipeline Running Dry

One big threat in the world of antibiotics is the lack of new drugs being developed. The drug pipeline is running dry just as bacteria are developing resistance to the drugs we have now. One way to combat resistance is to develop new and stronger drugs after bacteria develop resistance to current drugs. The lack of new drugs to treat infections is concerning; however, some new pieces of legislation in the United States address this worry.

The GAIN Act was signed into law in 2012, and it contains provisions that fast-track the review and distribution of drugs aimed to treat serious infections. In one year, the GAIN Act allowed 16 antibiotics to be approved by the FDA and to be labeled as "qualified infectious disease products."

More recently, the 21st Century Cures Act that was signed into law in 2016 allocates funding for public health concerns such as cancer research and the opioid epidemic. It also reforms some aspects of the way in which drugs are approved. To help address the need for new antimicrobial drugs, the Cures Act allows for smaller groups of people to be enrolled in a study when testing a new drug aimed at treating microbial infections. This provision will greatly help in the development of antibiotics meant to target antibiotic-resistant bacteria. A small trial size is crucial in the production of these drugs because the population of people affected by drug resistant bacteria is quite small, making it difficult under previous rules to conduct human participants research.

In October of 2020, the White House announced a 5-year national plan to combat antibacterial resistance and to improve the health and the wellbeing of all Americans. The plan's main goals are to (a) slow the emergence of superbugs (b) allocate funds to help aid research and developments of new antibiotics, and (c) develop diagnostic tests to identify and classify bacteria that are resistant to antibiotics.

III. Antibiotic Use in Food Production

While we cannot completely stop the use of antibiotics in food production, we can limit and track it. For instance, antibiotics should only be used to treat infections that animals acquire, not to prevent their growth or as a precaution against disease. Also, antibiotic use should be more closely tracked and recorded to ensure animals are not being given doses that are too high. Keeping farm facilities more hygienic will decrease the spread of disease and keep farmers from having to use as many antibiotics (this applies to human care as well). Finally, more research should go into antibiotic alternatives for animals.

Finally, it's important to hold yourself and your doctor accountable. Make sure you take the recommended dosage and not take antibiotics that weren't prescribed to you. Also, ask your doctor if you are unsure about your course of treatment or get a second opinion if you're unsure about the treatment that's been prescribed to you.

Ethics

Group Activity or Individual Activity

When approaching the antibiotic discussion, there are a few key ethical dilemmas to examine. Brainstorm a few ethical issues you can see being raised when talking about antibiotics and antibiotic resistance.

I. Who is responsible for fighting antibiotic resistance?

Should it be the doctor's job to monitor prescription rates and have more frequent post-treatment check-ups to make sure the antibiotics are being taken properly? Or is it the role of the patient to ask the doctor for alternatives and to take their prescription properly? And on a larger scale, are wealthy countries responsible for covering the costs of research aimed at new drugs to fight resistant bacteria, even when there are much higher rates of resistance in developing countries?

II. Current Patient vs. Future Patient

Secondly, when it comes to limiting the amount of antibiotics being prescribed, we have to ask: Whose health is more important, the current patient or the future patient? Who will be impacted by the present patient's treatment? In the case of antibiotic usage, should society focus more on the wellbeing of current patients or the wellbeing or future generations of patients who may be harmed later by the overuse of antibiotics? Should doctors only be concerned with their patients, or is it more important for them to keep in mind a wider set of risks and complications for overall present and future population health?

What control should patients have over their healthcare? If a doctor is reluctant to prescribe an antibiotic for some symptoms, should the patient be able to convince the doctor to change his or her mind? And should patients be allowed to seek out another doctor who will prescribe antibiotics if they really want to take them or at least be able to dispute a prescription given by a doctor?

III. Legislation

Finally, with new laws like the GAIN Act and Cures Act, there are concerns about fast tracking pharmaceuticals. Expediting the drug testing process could lead to more uncertainty about some of their side effects, as well as how effective they are to treat the disease for which they are developed. Is the situation so dire that we are willing to take risks that may harm future patients? Or should we consider fast-tracking a preventive measure? If the latter is true, should we engage in it now as well as exercise other possible solutions?

Conclusion and Discussion

Group Activity

Have a discussion and/or have students choose a solution they think will make the greatest impact, or have them create a solution that hasn't been discussed in this module. Have students present the solution as they would to a lawmaker who is able to write a new law that would address antibiotic resistance. Why is this one solution so important? Is this easy or hard to get done compared to the others? How would you go about getting it done or starting it? Have students defend their solution and address arguments against their solution.

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