2015

Antibiotic Resistance Mechanisms, Problems, and Solutions

Andrea Sageman
Grand Valley State University

Antibiotic Resistance Mechanisms, Problems, and Solutions

Andrea Sageman

Grand Valley State University

Introduction

Antimicrobial resistance is a growing problem in the world today. The Center for Disease Control cited antimicrobial resistance as the second-most significant health threat in 2014 ("CDC year in review: 'Mission: Critical,'" 2014). It is estimated that 23,000 people die from infections caused by antibiotic resistant bacteria every year, and many more people are hospitalized due to drug resistant strains of microorganisms. Antimicrobial resistance makes treatment of infections more difficult, expensive, and dangerous. ("Antibiotic/Antimicrobial resistance," 2010) The problems caused by drug resistant bacteria will affect almost everyone working in health care in some capacity, and this issue will likely only become more important in the future. Drug resistance is an issue that has developed over decades, as an inevitable and natural process of over administering and over-utilizing antimicrobial drugs. It is important for health care workers to understand how an antimicrobial agent functions, the mechanisms of drug resistance, how resistance develops, the problems caused by antimicrobial resistance, and the possible solutions to this problem.

Section 1- Antibiotic Mechanisms of Action and Mechanisms of Resistance

Antimicrobial agents are substances that are capable of killing or inhibiting the growth of microorganisms. The term "antimicrobial" includes antibiotics as well as other chemicals and compounds that may be used to kill microorganisms. The term "antibiotic" refers to substances that are naturally produced by certain fungi and bacteria, as well as similar substances that are created synthetically. (Mahon, Lehman, & Manuselis p. 260-263, 2011). Antimicrobials and antibiotics can be classified as either bacteriostatic or bactericidal. Bacteriostatic substances, such as tetracyclines and sulfonamides, function by preventing the replication of microorganisms. If used to treat an infection, these substances can prevent an organism from

increasing in number, but the immune system of the host needs to be able to clear the already existing organisms. If the concentration of the drug decreases, the organisms will still be able to reproduce and continue the infection. Bactericidal compounds, such as fluoroquinolones or beta-lactams, result in the irreversible death of the organism. (Bauman p. 293-295, 2011).

There are several different mechanisms through which antibiotics inhibit or kill microorganisms. Because bacteria become resistant to antibiotics by disrupting or rending these mechanisms ineffective, it is important to understand the different ways antibiotics function. It is also important to consider that while a good antibiotic should destroy the microorganism it targets, it would ideally not be harmful to human cells. One of the most common mechanisms of action is of targeting the cell wall, which is present in bacteria (or prokaryotic cells) but absent in humans (or eukaryotic cells). In bacteria classified as gram positive, the cell wall is composed of a layer of peptidoglycan and an internal cell membrane. Gram negative bacteria also have an internal membrane and a cell wall made of peptidoglycan, but they possess an additional external cell membrane as well. This external cell membrane can sometimes help to shield gram negative bacteria from antibiotics that can disrupt the peptidoglycan that composes the cell wall (Young, 2011).

Peptidoglycan is a compound that is not present in human cells, so it is an ideal target for antibiotics. The beta-lactam antibiotics function by disrupting how the peptidoglycan molecules link together to form the cell wall. Penicillins and cephalosporins do this by binding to enzymes that assemble the precursor components of the peptidoglycan molecule. Other antibiotics, such as cabapenems, prevent peptidoglycan molecules from linking together to form the cell wall. Vancomycin functions by binding to a precursor molecule to peptidoglycan, which disrupts the microorganism's ability to create new peptidoglycan molecules. Due to vancomycin's large size,

it cannot cross through the porins of the outer cell membrane of gram negative bacteria, so it is only used to treat infections caused by gram positive organisms. (Mahon et al., p. 264, 2011). Disrupting the formation or linking of the peptidoglycan molecules disrupts the structural integrity of the cell, an action that can lead to a collapsing or bursting of the cell wall, resulting in the death of the microorganism. For this reason beta-lactams are classified as bactericidal drugs ("MIC test strip technical sheet," 2013).

Like beta-lactams, polymyxins also disrupt the structural integrity of the cell and are bactericidal, but polymyxins function by targeting the outer cell membrane of gram negative bacteria ("MIC test strip technical sheet," 2013). A compound called lipopolysaccharide is a structural component of the outer cell membrane. This compound is negatively charged. It is normally stabilized by calcium and magnesium, which possess a positive charge. Polymyxins have a positive charge that is stronger than the charge of calcium or magnesium, so this drug can bind to the lipopolysaccharide with a stronger affinity than calcium and magnesium. When the drug binds, it removes the calcium and magnesium, causing a disturbance in the cell membrane. Cell death occurs due to the loss of integrity of the outer cell membrane (Falagas & Vardakas, 2010).

In order to create proteins or cellular products that the cell requires to survive, all cells must first copy their DNA into an RNA molecule that can be translated into a protein. Many antibiotics function by disrupting the process of DNA replication. Initially, a DNA strand is unwound by an enzyme called helicase. Topoisomerase II (DNA gyrase) helps to stabilize the DNA molecule and relieve the strain from being unwound by helicase. A class of antibiotics called the Quinolones target the complex of DNA and topoisomerase II. The drug binds to this complex and prevents further DNA replication from occurring. Normally, after a DNA strand is

unwound, an RNA copy is made of the DNA in the nucleus. This process is facilitated by RNA polymerase. While both human cells and bacterial cells utilize RNA polymerase, the bacterial RNA polymerase differs slightly from that found in eukaryotic cells. The drug Rifampin works by binding the RNA polymerase molecule, thus preventing the RNA chain of nucleotide bases from elongating. Rifampin is the only drug currently available that is able to bind RNA polymerase, and stop the transcription of RNA. Rifampin can be bactericidal or bacteristatic depending on the concentration of the drug that is administered ("Rifadin (Rifampin) drug information," 2013).

After the DNA is copied into a complementary RNA strand, the RNA exits the nucleus and complexes with ribosomes, which are capable of converting the RNA code of nucleotide bases to a functional protein molecule. Bacterial cells contain ribosomes that are composed of the 30S and the 50S ribosomal subunit, while eukaryotic cells contain ribosomes that are made from a 40S and a 60S ribosomal subunit. Antibiotics can target the 30S or the 50S ribosomal subunit. Aminoglycosides and Tetracyclines target the 30S subunit. The binding of an aminoglycoside to the 30S subunit prevents the docking of transfer RNA, which leads to incomplete or incorrect proteins. Tetracyclines block how the RNA molecule rotates into the ribosome, which causes the RNA molecule to be released prematurely, leaving an incomplete peptide. It is important to note that these effects are reversible, and if the drug concentration diminishes in the patient, then the microorganisms will be able to function as normal. Thus, these drugs are bacteristatic. (Mahon et al., p. 266-274, 2011).

Sulfonamides also function by disrupting the production of DNA and RNA, but in a different way. Folic acid is a compound that is used in the synthesis of nucleotides. Many bacteria convert para-aminobenzoic acid to folic acid. Sulfonamides are very similar in structure

to para-aminobenzoic acid, therefore, they are capable of binding to an enzyme that is involved in the conversion of para-aminobenzoic acid to folic acid. This slows the cell's production of folic acid, and thus the production of DNA and RNA, an action that can restrict the growth of the microorganism (Henry, 1943). Trimethoprim functions very similarly to the sulfonamides, but it binds to a different enzyme involved in the production of folic acid. Both of these antibiotics disrupt the production of a metabolic product the microorganism needs and they are both bacteriostatic (May, 2015).

While there are many different ways in which antibiotics can kill or inhibit microorganisms, there are also many mechanisms of resistance that microorganisms innately possess or have developed over time. It is possible that through one mechanism, an organism can become resistant to many different classes of antibiotics, especially if the antibiotics function in a similar way. Sometimes resistance can be shared between individual bacteria through the production of "resistance plasmids," which are pieces of DNA capable of being transferred from one cell to another (Clewell, 2014). Understanding these mechanisms of drug resistance is essential to understanding why drug resistance is a growing problem.

One way a cell may gain resistance to an antibiotic is by making an enzyme that renders the drug inactive, or that decreases the functionality of the antibiotic. An example of this are beta-lactamases, which are capable of breaking the beta-lactam rings of penicillin and other beta-lactam antibiotics. Breaking the beta-lactam ring stops the antibiotic from being able to attach to the peptidoglycan precursors. It will be less likely that penicillin or other similar drugs will be able to disrupt the integrity of the cell wall, as long as the organism produces beta-lactamases. This method of resistance can be transferred from one bacteria to another through the production

of R-plasmids, and is common in strains of methicillin-resistant *Staphylococcus aureus* (MRSA) (Holcomb et al., 2008).

Another common way of interfering with antibiotics is by preventing the entry of the drug into the cell. Gram negative bacteria have an external cell membrane, and drugs must pass through the cell porins, which are channels that span the outer membrane and allow the entry and exit of materials into or out of the cell. In order to enter the cell or interact with the cell wall, the drugs must be able to pass through the porins. A gene mutation can result in altered porins, usually by changing the electrical charge or the physical structure. These changes can make it more difficult for an antibiotic to enter the cell. The antibiotic is still functionally active, but it is now unable to reach its target site. A microorganism can develop resistance to multiple drug classes at once in this manner. Gram negative bacteria are innately resistant to large drugs like vancomycin, which is too large to pass through the porin even before a mutation occurs (Galdiero et al., 2012).

Many antibiotics act by binding to a target molecule that is a component of the microorganism. A microorganism can decrease the effectiveness of a drug if the target molecule changes slightly in its structure. If the structure of the target changes, then the antibiotic may no longer be able to bind to the target molecule. For example, tetracyclines block the transfer RNA access site by binding to it. Slight changes in the access site may result in microbial resistance to tetracyclines. Another mechanism through which microorganisms can become resistant to tetracyclines is by utilizing an efflux pump. An efflux pump is a biological pump that can force the antibiotic out of the cell, so that it cannot reach or stay in contact with its target. This method of antimicrobial resistance may often create resistance to more than one class of antibiotics (Speer, Shoemaker, & Salyers, 1992).

If an antibiotic functions by competing for an enzyme binding site to disrupt the production of a product, a microorganism could develop resistance by producing more of the enzyme the antibiotic binds to. This will increase the concentration of the enzyme, so that even if all antibiotic molecules bind to an enzyme, there will still be enough to create the metabolic product. Additionally, a microorganism could obtain the compound that it needs to survive from another source. For example, sulfonamides bind to an enzyme in order to disrupt the production of folic acid. Microorganisms can render sulfonamides ineffective by taking folic acid from the external environment, like human eukaryotic cells do (Huovinen et al., 1995).

It is possible for one organism, *Mycobacterium tuberculosis*, to inactivate fluoroquinolones and quinolones by protecting DNA gyrase with a protein the bacteria can synthesize. This protein is known as MfpA protein, and it functions by binding to DNA gyrase. This prevents the antibiotics from being able to access their normal binding site. The MfpA protein does not seem to have another function, besides disabling these antibiotics. Like other mechanisms of resistance, this one works by preventing the antibiotic from binding to the target as the MfpA protein takes the place of the antibiotic, and it is unique in that the target itself is not altered. This mechanism is perhaps especially important because tuberculosis is an infection that can take months, or even years, to cure with antibiotics. It is also significant that this is a method of antibiotic resistance that is unique to this Mycobacterium. (Bauman p. 298, 2011)

Now that the mechanisms of antibiotic action and resistance have been discussed, it may be helpful to consider how microorganisms acquire and develop resistance over time. By chance, genetic mutations can sometimes occur when the DNA of an organism is copied. In a large population of a single species of a microorganism, it is possible that some sort of a genetic mutation may have randomly occurred in a small percentage of the population. Prokaryotic cells,

which include bacteria, can copy DNA more quickly than eukaryotic cells, but there is an increased risk of mutation (Taylor, 2011). This potential mutation may have no phenotypical effect or have a harmful effect on the microorganism. However, it is possible that the mutation has occurred in such a way that the organism has a slightly altered porin, or is able to produce a new enzyme or product. If this happens, then the mutation might lend this individual bacterium some resistance to an antibiotic. Sometimes, mutations can be shared between individual bacteria through the production of R-plasmids, which are pieces of DNA capable of being transferred from one cell to another. If the organism is not causing an infection, and if antibiotics are not administered, then this organism must compete for space and resources with other microorganisms near it, as it is just one microorganism out of many. In normal conditions, it is unlikely that this mutation will give this organism and its descendants an advantage over the organisms around it. Therefore, the percent of the overall population that has this mutation will probably remain low.

If, however, an antibiotic is administered that kills the rest of the population but leaves all organisms with the mutation alive, then they are afforded a large advantage. With the normal strain of the organism inhibited, the resistant strain of the organism is able to grow with little competition, if it is able to survive the immune response of the host. Eventually, most or all of that organism's species in the host will be resistant to the antibiotic that was administered. The antibiotic that was initially effective at subduing the infection will not be very effective against the now resistant strain of organisms. The patient's immune system or another antibiotic may be needed to treat this infection. The host is also now carrying the resistant strain, which could potentially be spread to other people. In this way, an infectious, antibiotic resistant strain of an organism can emerge due to antibiotic use.

Section Two: The Development of Antibiotics and Bacterial Resistance

It is undeniable that the discovery of antibiotics has had a hugely positive impact on the health of the human species. The discovery of the different classes of antibiotics has required the work and dedication of many great scientists over the last century, and it still continues today. One of the first notable antimicrobial discoveries was the discovery of Sulfa drugs, by Paul Ehrlich. Dr. Ehrlich was interested in the idea of a "magic bullet," a compound that could target and destroy infection while leaving the host unharmed. Dr. Ehrlich and his team of researchers synthesized Salvarsan from an arsenic compound in 1909, and Neosalvarsan in 1912. This was an important step in the development of antibiotics as we know it today, and eventually led to the production of Prontosil, the first sulfonamide, in 1935 ("Paul Ehrlich," 2010).

In 1928, Doctor Alexander Fleming left cultures of *Staphylococcus aureus* to grow while he went on vacation. When he came back, he found that his cultures had been contaminated with a mold. Upon examining his cultures, he realized that the mold inhibited the growth of *Staphylococcus aureus.* This mold was *Penicillium notatum*. Dr. Fleming wrote and published a paper to summarize his findings. This paper caught the attention of Dr. Howard Florey. Dr. Florey purified penicillin from the mold, and tested the compound on mice, to see if it could control infection. His findings were promising, and he and his colleagues worked to mass produce this compound. In the 1940's, millions of units of pure penicillin were manufactured and used to treat infection. Fleming warned that the overuse of penicillin may lead to the development of bacterial resistance when he received the Noble Prize in 1945 for his contributions to the discovery of penicillin (Markel, 2013).

The success of penicillin in treating infection encouraged the search for other antibiotics. Streptomycin, the first aminoglycoside, was discovered by a graduate student named Albert Schatz in 1943 (Sharrer, 2007). Soon after, in 1945, the first tetracycline, chlortetracycline, was isolated from *Streptomyces aureofaciens*. The time period following this, starting in the 1950's and continuing through the 1970's, is considered the golden age of antibiotics. During this time, the polymyxins, cephalosporins, and quinolones were discovered. More recently, the carbepenems were discovered in 1985, and the second generation fluoroquinolones in 1987 ("Table 1, 2013"). Development of new synthetic compounds continues to the present day, as scientists search for new solutions to safely and affordably fight the spread of infection.

Throughout the years as more antibiotics have been synthesized and discovered, resistance has grown and developed as well. The issue of antibiotic resistance is a multifaceted problem, and many different factors and industries have contributed to this problem. While there is not a single event that can be blamed for the spread and development of antibiotic resistance, it may be helpful to consider the environmental and social factors that may have contributed to this problem.

The over prescription of antibiotics is one of the most important factors that contributed to the development of antibiotic resistant bacteria. Obviously, all health care workers strive to help patients recover as quickly and safely as possible. However, not all infections can be treated with antibiotics. Bacterial infections can be treated with antibiotics, but viral infections cannot ("Combating antibiotic resistance," 2015). Therefore, doctors should be hesitant to prescribe antibiotics for certain kinds of illnesses. For example, only about ten percent of bronchitis infections are caused by bacteria; bronchitis is typically caused by a virus. In a study conducted at the Brigham and Woman's Hospital in Boston, Dr. Michael L. Barnett and Dr. Jeffrey A.

Linder found that the antibiotic prescription rate for bronchitis was at 73%, much higher than what one might expect (Barnett & Linder, 2014). By administering antibiotics to a patient with a viral infection, doctors risk disrupting the patient's normal flora, which leads to a greater risk of infection by bacteria such as *Clostridium difficile*, an opportunistic intestinal pathogen which is normally unable to attach to the intestinal wall due to the presence of the patient's normal flora. ("C. diff, causes, symptoms, and treatments," 2005). The use of unnecessary antibiotics also increases the cost of treatment for the patient, and may contribute to the development of antibiotic resistance.

Another possible problem is that physicians in the hospital, as well as primary care doctors, may feel pressured to administer antibiotics even when it is not absolutely necessary. In an article published in *Holistic*, Dr. Malepati claimed that "Patients often pressure us to prescribe. They get angry if we don't give them their Z-Paks." (Goldman, 2014). If patients are refused an antibiotic, there is nothing to stop them from going to another clinic and asking for one again. Dissatisfaction with their doctor's views on antibiotic prescription may cause them to change providers. Doctors may feel that they need to prescribe antibiotics if a patient requests them, in order to avoid upsetting the patient and losing business.

Patients also are involved in the development of drug resistance in another way. Not everyone understands how important it is to take medication as directed by the doctor. It may be tempting for patients to take the antibiotic until they feel better, and not finish the whole prescription. It is also possible that people may keep remaining antibiotics in their home to use when they are feeling sick, or take the prescription of someone else without seeing a doctor. The FDA urges people to "take the medication exactly as directed," and "talk with your health care professional," ("Combating antibiotic resistance," 2015). By failing to take the antibiotics as

directed, it is possible that the antibiotic will not treat the patient as the doctor had hoped. This failure to follow the physicians instructions can lead to an increased cost of treatment and other complications. Also, by exposing pathogenic bacterial infection to antibiotics for too short of a time, patients may be contributing to the development of resistance.

The medical laboratory may also contribute to the development of antibiotic resistance bacteria. If the microbiologist reports antibiotic susceptibility testing results to the doctor, then the doctor most likely will treat the infection with the antibiotics that inhibited growth of the organism. This is appropriate only if the susceptibility results were reported on the organism actually causing the infection. If the culture that the microbiologist used to complete the testing is contaminated, then the results might not really be useful in treating the infection. For example, if a urinary tract infection is suspected, then a urine culture may be set up. It is important that the microbiologist is able to recognize whether or not the culture is contaminated, or just growing the normal skin flora of the patient. If the microbiologist is unable to recognize a contaminated culture, then antibiotics may be administered while no infection was present in the patient (Franz & Horl, 1999).

The agricultural industry has also had an impact on the development of antibiotic resistant bacteria. Animals that are raised for human consumption are treated with antibiotics such as fluoroquinolones and tetracyclines. The livestock are treated with antibiotics regularly even when they are free of disease. Losing an animal to illness can be a financial disaster for small family-run farms and factory farms alike. The animals are administered antibiotics as a way to decrease the likelihood of an infection. In some countries, the amount of antibiotics administered to livestock is greater than the amount administered to humans. This widespread, continuous use of antibiotics increases the chance that drug resistant bacteria will develop.

Strains of *Salmonella* and *Campylobacter*, which cause intestinal infections in humans, have developed a resistance to the fluoroquinolones, likely because of the use of antibiotics in agriculture ("Consequences of antibiotic use in food animals," 2012).

There may also be a financial component to the problem of drug resistance. Developing different and new antibiotics may be a partial solution to this problem of bacterial antibiotic resistance. However, developing new antibiotics is very costly, and pharmaceutical companies may not see as much of a return on their investments as they might with other types of drugs. Also, the price of antibiotics may influence which antibiotics are prescribed. Jeffrey Stein, executive of Trius Therapeutics, claims that antibiotics are the "only therapeutic area where prescribing decisions are made based on price rather than efficacy,"(Herper, 2014). Even if a pharmaceutical company is successful in developing a new antibiotic, it may be too expensive to use often. This makes antibiotic research less lucrative for pharmaceutical companies than other areas of research.

The development of antibiotics in the 20th century has surely had an enormous impact on the health-care industry, as well as the way we as a society view infection today. While no one industry is necessarily to blame for the development of antibiotic resistant strains of bacteria, certain actions by physicians, patients, and businesses have increased the incidence of drug resistant bacteria. It is important to recognize the impact that society has had on this phenomenon, so problems and solutions can be understood.

Section Three: Clinically Significant Problems and Possible Solutions

Antibiotic resistance is in many ways a very frightening issue, and finding solutions to problems caused by these infections can be a daunting task. Some organisms cause such damage to patient health and safety, that I feel all health care workers should know about them. There are also many organizations and researchers who work to minimize the damage caused by antibiotic resistance. By examining the ways antibiotic resistance can be minimized and controlled, we can hope for a healthier and safer future.

One very important factor that can affect how dangerous and expensive an infection will be is the location where the infection was acquired. Nosocomial infections, or infections that are acquired at a hospital, are often caused by bacterial strains that have developed some form of drug resistance. Drug resistance is more prevalent in a hospital setting because antibiotics are frequently administered there. The bacterial population in the hospital environment is continuously exposed to antibiotics and disinfectants in an effort to destroy the majority of microorganisms. The disinfecting that goes on in a hospital is necessary to prevent infection, but drug resistance may develop as an unfortunate side effect. Some hospitals will rotate the types of antibiotics they use to treat infection, in an effort to slow drug resistance in the hospital. This drug resistance causes the average nosocomial infection to be more difficult to treat than the average infection acquired elsewhere. This is especially problematic because patients in the hospital are usually more vulnerable; many of them may be recovering from surgery, already fighting another infection, or receiving treatment for disease that may weaken the immune system. The drug resistance may make the infection much more difficult to treat. Other, possibly

more expensive antibiotics may need to be utilized, and it may take more time for the patient to recover, which increases the cost of the patient's hospital stay (Inweregbu, 2005). That greater numbers of drug resistant bacteria exist in the hospital, where people are already battling other illnesses, is a disturbing trend.

Another problem that should be considered is the existence of multi-drug resistant organisms. These organisms either innately possess or have acquired resistance to multiple classes of antibiotics. This is a problem because physicians may struggle to find an antibiotic that can fight the infection. Incidence of infections with multi-drug resistant organisms are higher in the hospital environment, but fortunately, the number of infections caused by these organisms is relatively low. The infections multi-drug resistant organisms do cause, however, are usually associated with severe illness and death. An example of a multi-drug resistant pathogen is vancomycin resistant *Enterococcus* (VRE), which can cause infection in many parts of the body. Researcher Jane Siegel found that vancomycin resistant *Enterococcus* "was associated with increased mortality, length of hospital stay, admission to the ICU, surgical procedures, and costs when VRE patients were compared with a matched hospital population" (Siegel, 2006). Until the 1990's, there were almost no antibiotics capable of treating vancomycin resistant *Enterococcus*. The development of new antibiotics is a slow and expensive process, which makes the existence of multi-drug resistant pathogens more frightening.

Another example of a multi-drug resistant pathogen is methicillin resistant *Staphylococcus aureus* (MRSA). *Staphylococcus aureus* is a common bacterium that causes urinary tract infections, wound infections, skin infections, bacteremia, and other complications. It is also one of the most common nosocomial infections, and one in twenty health care workers are colonized with MRSA (Smith, 2008). MRSA has a higher rate of causing symptomatic or fatal

infections than methicillin-susceptible *S. aureus* (Siegel, 2006). In addition to MRSA, some strains of *S. aureus* have developed a resistance to vancomycin as well, which severely limits the antibiotics available for treatment ("Is MRSA the godzilla of superbugs?" 2013).

While there are many problems associated with drug resistance, researchers and physicians consider and utilize possible solutions. One idea that could help to slow the development of drug resistance is the practice of using multiple antibiotics to treat infection. This helps to slow the development of antibiotic resistance because even if a strain of an organism develops resistance to one class of drug, it might be susceptible to another class of antibiotics. If multiple antibiotics are used at once, the resistant strain is more likely to be killed off, instead of surviving, and perhaps spreading. Another benefit to using multiple drugs at once is the concept of antibiotic synergism. Sometimes when two antibiotics are used together, they each increase the activity or effectiveness of the other, which results in the combined drug being more effective at treating infection than either of the individual antibiotics (Kamill, 1965).

Hospitals have not ignored the problem of antibiotic resistance. Many hospitals throughout the country have developed "antibiotic stewardship" programs at the recommendation of the Centers for Disease Control. The CDC recommends that hospitals monitor the resistance patterns in infections, so that the hospital can be aware what to suspect as a nosocomial infection. The education of the hospital staff about these infections is also very important. The CDC also recommends that a pharmacist be employed at the hospital who can specifically focus on antibiotic use and make decisions about how the antibiotics should be used and managed (Core elements of hospital antibiotic stewardship programs, 2014).

Another extremely important way to fight the spread of antibiotic resistant bacteria is also one of the simplest; encouraging proper hand-washing techniques is an easy and affordable way to prevent the spread of antibiotic resistant bacteria, especially in a hospital setting. Many infections can be spread from one person to another, but by practicing safe hygiene practices, the chance of spreading a disease is reduced. Many hospitals have hand washing tutorials during employee orientation to encourage proper hand-washing in the workplace (Odigwe, 2015).

Conclusion

Ever since antibiotics began to be widely used to treat infections in the 1940's, the incidence of antibiotic resistant strains has increased. These organisms cause a plethora of serious issues including longer illnesses, more fatalities, and increased cost of treatment. Frighteningly, certain organisms are becoming difficult to treat at all as vancomycin, usually considered the “last resort” drug, is becoming less effective. The issue of drug resistant bacteria has received a lot of attention from the government, the public, researchers, and hospital personnel. Policies such as antibiotic stewardship programs have developed in many hospitals in order to analyze and attempt to control the spread of antibiotic resistant infections. It is important for anyone working in health-care to have at least a basic understanding of the issue of antibiotic resistance. By knowing how antibiotics and drug resistance mechanisms function, how and why resistance develops, and the problems associated with antibiotic resistant infections, health-care workers will be better equipped to work with the problem of antibiotic resistance.

References

Antibiotic/Antimicrobial resistance. (n.d.). In *Centers for Disease Control and Prevention*. Retrieved July 19, 2010, from http://www.cdc.gov/drugresistance/about.html

Barnett, M. L., & Linder, J. A. (2014, January). Antibiotic prescribing to adults with sore throat in the United States, 1997-2010. In *JAMA Internal Medicine*. Retrieved from http://archinte.jamanetwork.com/article.aspx?articleid=1745694#Results

Bauman, R. W. (2011). *Microbiology With Diseases By Taxonomy* (Third ed., pp. 290-298). San Francisco, CA: Pearson Education, Inc.

C. diff, causes, symptoms, and treatments. (2005). In *WebMD*. Retrieved from http://www.webmd.com/digestive-disorders/clostridium-difficile-colitis

CDC year in review: "Mission:Critical". (2014, December 15). In *Centers for Disease Control and Prevention*. Retrieved from http://www.cdc.gov/media/releases/2014/p1215-2014-year-in-review.html

Clewell, D. B. (2014, February). Antibiotic resistance plasmids in bacteria. In *Wiley Online Library*. Retrieved from http://www.els.net/WileyCDA/ElsArticle/refId-a0001491.html

Combating antibiotic resistance. (2015, March 23). In *FDA*. Retrieved from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm

Consequences of antibiotic use in food animals. (2012). In *Lumibyte*. Retrieved from http://lumibyte.eu/food/consequences-of-antibiotic-use-in-food-animals/

Core elements of hospital antibiotic stewardship programs. (2014, March 4). In *CDC*. Retrieved from http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

Falagas, M. E., & Vardakas, K. Z. (2010). Polymyxins. In *antimicrobe*. Retrieved February 10, 2015, from http://www.antimicrobe.org/d05.asp

Franz, M., & Horl, W. (1999). Common errors in diagnosis and management of urinary tract infection. . In *Oxford Journals*. Retrieved from http://ndt.oxfordjournals.org/content/14/11/2746.full

Galdiero, S., Falanga, A., Cantisani, M., Tarallo, R., Pepa, M., D'Oriano, V., & Galdiero, M. (2012, December). Microbe-host interactions: Structure and role of gram-negative bacterial porins. In *US National Library of Medicine*. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706956/

Gall, K. (1965, October 16). Combined antibiotic therapy. In *Canadian Medical Association*.

Garzoni, C. (2009, December 16). Multiply Resistant Gram-Positive Bacteria Methicillin-Resistant, Vancomycin-Intermediate and Vancomycin-Resistant Staphylococcus aureus (MRSA, VISA, VRSA) in Solid Organ Transplant Recipients. In *Wiley Online Library*. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2009.02892.x/full

Goldman, E. (2014, November 23). What to do when patients demand unnecessary antibiotics. In *Holistic: Primary Care*. Retrieved from http://www.holisticprimarycare.net/topics/topics-h-n/infectious-disease/1657-what-to-do-when-patients-demand-unnecessary-antibiotics.html

Henry, R. J. (1943, December 7). The mode of action of sulfonamides. *US National Library of Medicine*, 177-196.

Herper, M. (2014, January 27). How to avert an antibiotic apocalypse . In *Forbes*. Retrieved from http://www.forbes.com/sites/matthewherper/2014/01/27/how-to-avert-antibiotic-apocalypse/

Holcomb, H. G., Durbin, K. J., Cho, M., Choi, K. J., Darling, N. D., & Angerio, A. D. (2008, December). Methicillin-resistant Staphylococcus aureus as a threat to public health: A cellular approach. In *Georgetown University Journal of Health Sciences*. Retrieved from https://blogs.commons.georgetown.edu/journal-of-health-sciences/issues-2/previous-volumes/vol-5-no-2-december-2008/methicillin-resistant-staphylococcus-aureus-as-a-threat-to-public-health-a-cellular-a

Huovinen, P., Sundstrom, L., Swedberg, G., & Skold, O. (1995, February). Trimethoprim and sulfonamide resistance. *American Society for Microbiology*, *39*(2), 279-289.

Inweregbu, K., Dave, J., & Pittard, A. (2005, February). Nosocomial infections. In *Oxford Journals*. Retrieved from http://ceaccp.oxfordjournals.org/content/5/1/14.full

Is MRSA the godzilla of superbugs?. (2013, May 17). In *takepart*. Retrieved from http://www.takepart.com/article/2013/05/17/superbug-mrsa-vrsa-antibiotic-resistance

Mahon, C. R., Lehman, D. C., & Manuselis, G. (2011). *Textbook of Diagnostic Microbiology* (Fourth ed., pp. 260-274). Maryland Heights, MO: W.B. Saunders Company.

Markel, H. (2013, September 27). The Real Story Behind Penicillin . In *PBS Newshour*. Retrieved from http://www.pbs.org/newshour/rundown/the-real-story-behind-the-worlds-first-antibiotic/

May, D. B. (1943, March 7). Trimethoprim-sulfamethoxazole: An overview. In *UpToDate*. Retrieved from http://www.uptodate.com/contents/trimethoprim-sulfamethoxazole-an-overview

MIC test strip technical sheet cidal-static. (2013, June 5). In *Liofilchem*. Retrieved from http://www.liofilchem.net/login.area.mic/technical_sheets/MTS30.pdf

Odigwe, O. (2015, March 31). Good personal hygiene: A fight against the spread of infectious diseases. In *MedCrave*. Retrieved from http://medcraveonline.com/MOJPH/MOJPH-02-00019.pdf

Paul Ehrlich. (2010). In *Chemical Heritage Foundation*. Retrieved from http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/preventing-and-treating-infectious-diseases/ehrlich.aspx

Rifadin (Rifampin) drug information. (2013, March 13). In *RxList*. Retrieved from http://www.rxlist.com/rifadin-drug/clinical-pharmacology.htm

Sharrer, T. (2007, August 1). The discovery of streptomycin. In *The Scientist*. Retrieved from http://www.the-scientist.com/?articles.view/articleNo/25252/title/The-discovery-of-streptomycin/

Siegel, J. D., Rhinehart, E., Jackson, M., & Chiarello, L. (2006). Management of multidrug-resistant organisms in healthcare settings, 2006. In *CDC*. Retrieved from http://www.cdc.gov/hicpac/pdf/MDRO/MDROGuideline2006.pdf

Smith, M. (2008, April 15). One in every 20 healthcare workers is MRSA carrier. In *Medpage Today*. Retrieved from http://www.medpagetoday.com/InfectiousDisease/GeneralInfectiousDisease/9117

Speer, B. S., Shoemaker, N. B., & Salyers, A. A. (1992, October). Bacterial resistance to tetracycline: mechanisms,transfer, and clinical significance. In *US National Library of Medicine*. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC358256/

Table 1: Timeline of the discovery and introduction of antibiotics. (2013). In *Nature Reviews Drug Discovery*. Retrieved from http://www.nature.com/nrd/journal/v12/n5/fig_tab/nrd3975_T1.html

Taylor, S. (2011). Comparing and contrasting DNA replication in prokaryotes & eukaryotes. *The Classroom*.

Young, K. D. (2011, October 17). Peptidoglycan. In *Wiley Online Library*. Retrieved from http://www.els.net/WileyCDA/ElsArticle/refId-a0000702.html