Chapter 1: Efflux pumps and Antibiotic Resistance

“Around 700,000 people around the world die annually due to drug-resistant infections. If no action is taken, it has been estimated that drug-resistant infections will kill 10 million people a year by 2050.” -Dame Sally Davies, Chief Medical Officer UK

* 1. Antibiotic Resistance
  2. Low-level to Clinical Resistance
  3. Efflux Pumps

In this chapter, we will focus on exploring the effect of efflux pumps in antibiotics. We will first dive into the meaning and importance of antibiotic resistance itself and the situations in common day medicine. For example, diseases that are presenting this obstacle in clinical settings, the progression of them, and what could be possible outcomes if it is not addressed. We will then direct our attention to the progression itself and the severity of it. The difference of low-level resistance to clinical resistance and what causes that. We will also focus on efflux pumps themselves, how they work, and the outcome of them developing. In this chapter, we will cover some of the most important aspects of efflux pumps and antibiotic resistance in the modern day medicine.

* 1. **Antibiotic Resistance**

Penicillin was introduced in 1943. This began decades of new antibiotic introduction along with beginning antibiotic treatment. After years and years of overuse and misuse, there has begun a period of resistance. An example of drug overuse is parents immediately giving children medicine the second they have a headache or feel sick for years. Another cause of overuse is the point that in lots of other countries, antibiotics are not a regulated or hard to come by drug. Because of the non-regulation and easy accessibility to the cheap and plentiful antibiotics, overuse is promoted. It has also been made possible for people who are in countries where antibiotics are regulated can easily purchase antibiotics from these other countries. This causes the drug to be not as effective in later years of life. Misuse can be thought of using antibiotics for self-treatment or treating a family member without a prescription of doctor referral. These things have caused a serious predicament. Along with the misuse and overuse, there has also been a lack of new drug development. This is caused by the strict guidelines of producing drugs and financial burden to do so. These things put together explain the beginning of antibiotic resistance.

Now that we have established what causes the antibiotic resistance, let’s dive into the “what” it is. Antibiotic resistance is what happens when a bacteria, or even a fungi, begin to be able to defeat the drugs that are usually used to combat them (CDC). The way that bacteria and/or fungi do this is by developing mutations and changes to cause them to be able to continue growing when certain antibiotics are presented. Because of this, infections are beginning to be presented that are much more difficult to treat and sometimes even impossible. This does NOT mean that a person’s entire body is beginning to combat antibiotics or drugs in general. This just means that a certain bacteria is becoming resistance and able to survive against a certain antibiotic that would normally kill them.

Though it may be thought of that antibiotic resistance “probably” occurs only in clinical settings (hospitals, nursing home, urgent care, etc.), it is something that can affect anybody. People of any age or stage of life, as well as humans and animals, are susceptible to this. Because of the abundance of possibilities of who can be affected, it makes antibiotic resistance one of the most pressing health problems. Everyone is a possible target because nobody can completely avoid the risk of coming down with an infection. If nobody can avoid that risk and following that, antibiotics lose their effectiveness, it puts those who are at an even higher risk of infection (those with chronic illnesses) in a spot of possibly not being able to treat them. This begins causing much more serious threats that we then lose the ability to control.

The importance of antibiotics resistance is just as stated above. We lose the ability to control so much in the medical field when it comes to antibiotic resistance becoming more prominent. There are so many situations that antibiotics are used in, such as: joint replacements, organ transplants, cancer therapy, and treatment of many chronic diseases. Some examples of chronic diseases that are treated with antibiotics are diabetes, chronic lung disease, asthma, and rheumatoid arthritis. There are many more, but these are just a few examples. With this being said, the loss of control does not only affect those who are just combating a disease on their own, but also makes it more difficult for healthcare professionals to assist in the treatment.

Another major cause/possibility of antibiotic resistance is extensive use in agriculture. It is estimated that an 80% of antibiotics that are sold within the United States are then used in animals (P&T 279). The process of this is fairly simple. Antibiotics are used in livestock to promote growth and quality of animals and to also aid in preventing infections in them. These antibiotics are used so often that the animals then begin to produce antibiotic resistant bacteria. Once these bacteria are produced and then the livestock are consumed by humans. The antibiotic resistant bacteria are then transferred to the consumer. These bacteria can cause infections in humans and lead to other health concerns. Since they are antibiotic resistant, it is harder to treat these infections.

* 1. **Low-level to Clinical Resistance**

Resistance is something that can develop into being more and more serious over time. It begins as what we refer to as low-level and has the possibility to develop from there. Minimal inhibitory concentration or MIC is defined as the lowest concentration of an antibiotic required to inhibit bacterial growth (Antibiotics). The clinical breakpoint is defined as whether an organism is susceptible or resistant to the antibiotic. For a bacteria to be considered susceptible to an antibiotic being used, its MIC is lower or equal to the clinical breakpoint. While on the other hand, if a bacteria’s MIC is higher than the breakpoint, it is said to be antibiotic resistant.

Take chronic lunch disease for an example. When a patient comes in presenting this disease, healthcare professionals will start treatment using antibiotics. First off, the bacteria are sensitive to the treating antibiotic which means the MIC is below the clinical breakpoint. Once the antibiotics have been used over sometime, there is a possibility that the distribution of these antibiotics may fluctuate, missing some of the bacteria in certain niches. Once these bacteria have been missed, they begin to have the opportunity to develop mutations. Mutations are changes in the bacteria’s makeup resulting in a variant form. These mutations have the chance to be passed on from one generation to the next. When the mutations resulting in antibiotic resistance develop, this means that the antibiotic being used to treat the chronic lung disease is no longer going to be as effective for the patient. With low-level resistance, the antibiotic may still help, but since it will not kill all the bacteria, it will not be a permanent solution for the patient. After the low-level resistance begins to progress and more and more bacteria develop this mutation, clinical resistance advances. These advancements mean that the MIC is now above the clinical breakpoint and the antibiotic has lost its effectiveness on the bacteria. This all together leads to treatment failure for the patient.

The effects of the clinical antibiotic resistance go on and on. Not only is it a hardship in the medical world because healthcare professionals only have so many options when it comes to trying to find an alternated solution, but it can also dramatically affect the patients and their families. Antibiotic resistance leads to a multitude of obstacles. Because of the resistance, patients may face higher medical costs, prolonged hospital stays, and there is even a chance of mortality depending the disease that was trying to be treated. As stated above, healthcare professionals only have so many treatment options and some diseases have less options than others. Another factor is the introduction of new drugs is so low. This is because the cost and guidelines of producing a new drug to the market are so high. Once a company were to pay all the money to create this drug to be presented to the board, there is a possibility that the drug may not meet the guidelines and if it does, it may be too costly. If a drug is produced and too expensive then it will always be the last drug doctors choose to use, making it a money-pit for pharmaceuticals.

More and more attention is being needed to be brought to the attention that clinical antibiotic resistance is an important and increasing issue. Most individuals do not think about the possibility of them or maybe one of their family members developing a resistance to an antibiotic, but with the same antibiotics being used to treat multiple different diseases along with the accessibility of these antibiotics outside of a clinical setting increasing, resistance is becoming more and more prominent. Another obstacle that the persisting antibiotic resistance presents is that of infection spreading. If a patient has an infection or a disease and their bacteria develop this resistance and they stop being affected by the antibiotic being used, then they now have a higher opportunity to spread said infection or disease. With this being a possibility of a big problem, healthcare professionals have to be careful to ensure that antibiotics are working consistently to avoid the spread of a disease that they think they are treating.

* 1. **Efflux Pumps**

Bacteria have multiple methods of reacted to antimicrobial agents. Some of these ways are drug target modification, modified cell wall, drug inactivation, modification (as we have already discussed in the previous section), and (over)expression of efflux pumps (Antibiotics). The best way to think of efflux pumps to understand them is exactly what the name says. They are pumps. They are located in bacteria and pump solutes out of the cell. An efflux pump allows the microorganism it is inside of to control their internal environment. They do this by helping the cell remove toxic substances that do not belong in the cell, including antimicrobial agents, metabolites, and quorum sensing signal molecules, chemicals, or compounds. The difference of expression and overexpression of efflux pumps is exactly as you would assume. There can be an expression of one single efflux pump that can confer multidrug resistance, but the simultaneous expression of more than one of these efflux pumps on the cell surface causes more clinical resistance. They are located in the cytoplasmic membrane of many cells. Efflux pumps require a source of chemical energy to perform their tasks in what they think is protecting the cell they are located on.

Efflux pumps are a huge factor in antibiotic resistance. They can change, overexpress, aid mutations of the bacteria, and more to increase resistance to antibiotics. We will explore what is meant by each of these things that they can do. When it comes to them “changing”, it is meant that the bacteria itself can decrease the specificity of the efflux pump(s) on its surface, causing the number of antibiotics that the pump can and will eliminate from the bacteria to increase. Some efflux pumps are considered to be drug-specific, while others may accommodate multiple drugs with small multidrug resistance, also known as SMR, transporters. When it comes to overexpression of efflux pumps, it means that resistant bacteria may have a greater amount of efflux pumps on the surface of their cells. This goes hand in hand with the aiding the mutations in the bacteria scenario. As explained in the previous section, when the distribution of an antibiotic fluctuates and bacteria in certain niches have the opportunity to develop mutations, a cell can develop low-level resistance to the antibiotic being used. Well not only is the progression of that a route to clinical resistance, but another possibility is the addition of efflux pumps. What is meant by this, is if you take a bacteria that has developed a mutation and begins to be antibiotic resistant, and add efflux pumps to its cell surface, then the bacteria have now progressed into clinical resistance as well. What happens here is that when the efflux pump active only population is tested in a clinical microbiology laboratory, it is still categorized as antibiotic sensitive, causing the chance of the cells that had already developed the low-level antibiotic resistance to evolve into having both mutations and efflux pump overexpression.

There is a “fitness cost” of efflux pump overexpression. This can easily be compared to human population in everyday life. If there is a room full of individuals in their mid-20’s and half of them workout at a high intensity for 1-hr straight, they will naturally be much more exhausted and tired than the other half of individuals in the room that only sat. This applies the same way to the bacteria and their efflux pumps. Cells with an increased efflux pump activity will have the same reduced “fitness” or energy that the other cells in the same population may have without the efflux pump substrate. The difference is that a bacteria cell has the possibility of developing what is called a compensatory mutation. This mutation is similar to what it sounds. It compensates for the fitness and/or energy used by the cells that are constantly having their efflux pumps working. Once this compensatory mutation is attained, the mutated population, even with their working efflux pumps, will no longer be at a disadvantage of the rest of the population when it comes to fitness and energy.

**Chapter 1** In Review

**Section 1.1**

Antibiotic Resistance

Clinical setting

**Section 1.2**

Minimal Inhibitory Concentration

Clinical Breakpoint

Low-level resistance

Clinical resistance

**Section 1.3**

Efflux pump

Small multidrug resistance

Expression vs overexpression

**Overall**

Efflux pumps causing low-level resistance to progress into clinical resistance and the seriousness of clinical resistance itself is real and needs to be more talked about. It is a growing issue in the modern day healthcare field.

**References:**

Ventola, C. L., MS. (2015). The Antibiotic Resistance Crisis [Abstract]. P&amp;T, 40(4), 277-283. Retrieved March 13, 2021, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4378521/pdf/ptj4004277.pdf>

About antibiotic resistance. (2020, March 13). Retrieved March 13, 2021, from <https://www.cdc.gov/drugresistance/about.html#:~:text=Antibiotic%20resistance%20happens%20when%20germs,killed%20and%20continue%20to%20grow>.

Facts-quotes. (n.d.). Retrieved March 13, 2021, from <https://www.combatamr.org/facts-quotes>

Ebbensgaard, A. E., Lobner-Olesen, A., &amp; Frimodt-Moller, J. (2020). Antibiotics. The Role of Efflux Pumps in the Transition from Low-Level to Clinical Antibiotic Resistance, 9(12), 855th ser., 1-7. doi:10.3390/antibiotics