Are we entering the post antibiotic era?

Introduction

Antibiotics have been the main course of treatment for microbial infections throughout the years since Sir Alexander Fleming first discovered that *Staphylococcus aureus* colonies could be destroyed by *Penicillium chrysogenum* (Houbraken et al., 2011), leading to the production of Penicillin G Procaine in 1942 by Howard Florey and Ernst Chain (Ligon, 2004). The following years saw improvements being made in the treatment of infectious diseases due to the fact that symptoms were recognized earlier in patients, thus prompting a faster response of treatment. This in turn managed to reduce the mortality rate of the patients that had these illnesses (Tishler, 2005). The reason as to this would be due to the rapidly expanding understanding of the molecular biology of infectious diseases, the mechanisms involved in it and studies done on understanding the pathophysiology of an infectious disease. Further down the road, antimicrobial treatments have evolved rapidly by increasing its safety and efficacy. Antibiotics were able to target the foreign source of infection and is able to eliminate it, thus eliminating the infection. Despite this, antibiotics such as prontosil, the first sulfa drug, penicillin G and streptomycin (Finkelstein and Birkeland, 1938; Houbraken et al., 2011; Bruton and Horner, W. H. 1966) were extremely expensive and were initialy produced to be used for the military in World War I (Tishler, 2005). The cascade of antibiotic discovery continued, causing an increase in the manufacturing of antibiotics, research into the area of antibiotic development was increasing in order to keep up with the types of infections that were appearing in the world. Antibiotics became the only treatment anyone had in mind when a patient

described symptoms that could be of bacterial origin and they were being widely prescribed throughout the world at an alarming rate. Penicillin was one such antibiotic whereby resistance was seen in just 3 years after it was available to the public. A serious number of strains of *Staphylococcus aureus* were becoming resistant to penicillin G (Levy and Marshall, 2004). The problem has escalated to a point where bacteria are mutating and multiplying faster than scientists are able to refine and modify drugs. Such examples of resistant bacteria are *Clostridium difficile, Pseudomonas aeruginosa,* methicillin resistant S. aureus and several other bacteria that initially only caused hospital acquired infection that increased the mortality rate of hospital confined patients, begun spreading to the community, causing infections in what should seem as health individuals (Barrozo, 2003).

Antibiotic Resistance

Just like any other living organism, bacteria also constantly work towards adapting to the environmental conditions that are changing and evolving such as weather and the availability of oxygen in the ‘ survival of the fittest’ pattern (Darwin et al., 1958). Due to bacteria having a remarkable capability to endure harsh environments and evolve alongside it, they have been able to develop various methods of resistances to several antimicrobials that in turn make these drugs ineffective as first choices for treatments caused by these pathogens. As mentioned earlier, certain bacteria do cause hospital acquired infections but they are also able to stay viable in the clinical environment. The chronology of the development of antibiotic resistant strains of bacteria is impressive seeing as it has been occurring since the 1930s where *S. aureus* begun showing resistance to penicillin and

sulphonamides such as sulfamethoxazole (Suvorov et al., 2007). *Neisseria gonorrhoea* and *Haemophilus influenza* were the next to follow suit by becoming resistant to penicillin (Lind, 1990). *S. aureus* also became resistant to methicillin in the late 1970s. That was also the same period where *Mycobacterium tuberculosis* became resistant to several drugs (Soini and Musser, 2001). The next group to have resistance was Group A Streptococci that build resistance towards macrolides like erythromycin (Martin et al., 2002). Several other antibiotics have experience resistance during treatment regime such as vancomycin whereby enterococci have become resistant to it (Donskey et al., 2000).

Mechanisms of resistance

There are various classes of antibiotics that have been produced and marketed worldwide, to name a few, quinolones, macrolides, penicillins and cephalosporins of several generations. Despite this, bacteria have developed at least one way of resisting each of those classes of antibiotics. *Mycobacterium tuberculosis* has even developed resistance to both rifampicin and isoniazid which are the first line treatment for tuberculosis (Weinstein and Hooper, 2005). This increases the difficulty in choosing a suitable regime for treatment, it also increases the cost and morbidity in the community. The world has seen the emergence of acquired immunodeficiency syndrome (AIDS), severe acute respiratory syndrome (SARS) and quite recently in the past year, Middle East respiratory syndrome (MERS) (de Groot et al., 2013) despite the existence of antimicrobials. The trend that is noticed here is that bacteria, even common bacteria are developing resistance to multiple drugs and the types and frequency of

infectious diseases in the population are also increasing, bringing about the problem of treatment seeing as the number of effective antimicrobials are decreasing. In order to understand and develop effective targeted treatment, scientists must first understand the mechanisms in which a bacteria becomes resistant (Sefton, 2002). In most instances of resistance, it occurs in the genetic level whereby the genetic makeup of the bacteria evolves thus modifying the biological action of the bacteria that in turn determines the resistance type in the bacteria.

In the development of antibiotic resistance, a specific antibiotic's presence is required as well as the targeted colony of bacteria, that has the genetic capability to develop resistance (Sefton, 2002). Once treatment is administered, susceptible colonies die while resistant strains survive and catalogue the resistance magnitude that is to be depicted in the cell. These genes are usually located in the transposons that make genetic information transfer between plasmids easier. Multidrug resistance usually occurs when the resistant strains of bacteria contain an integron in the transposons in their DNA that facilitates the integration of multiple antibiotic resistant genes. Both gram-positive and gram-negative bacteria have been identified to have integrons in their genetic makeup. Once a change in DNA has occurred, the genetic material is transferred amongst bacteria. The first method of transfer would be conjugation whereby a pilus forms between close lying bacteria that links them for a short while to transfer the DNA fragments (Sefton, 2002; Leclercq, 2002). A second form of transmission is known as transformation where naked DNA from dead bacteria travel to a nearby bacteria and the DNA is subsequently taken up into the cytoplasm to

be incorporated into the living bacteria. Transduction is also a popular methods of genetic methods of resistance whereby a vector is used to transfer the genetic material from one bacteria to another by infecting the bacterial cell. The vectors are usually bacteriophages (Patterson, 2001). The biological action that follows the transfer of genetic material determines the ability of the bacteria to express the transferred gene. One of the mechanisms is by the destruction of the antibiotic which occurs when enzymes produced by the bacteria chemically modify the drug rendering it inactive. An example of this mechanism is seen in the production of β-lactamases in *S. aureus, P. aeruginosa, Klebsiella pneumoniae* and several other microorganisms that work against β-lactam drugs such as penicillins and cephalosporins. Another mechanism that makes bacteria resistant specifically towards tetracyclines and fluoroquinolones is the antibiotic active efflux where it occurs when the bacteria develops a mechanism of active transport in order to remove the antibacterial component inside the bacterial cell until it the concentration decreases to a point where bactericidal activity stops (Moise et al, 2008).

Risk factors associated with antibiotic resistance

One of the main reasons as to why resistance is an issue to begin with would be that antibiotics are being prescribed to patiently both hospitalized and outpatients in an excessive and alarming manner, not just for treatment but also for prophylactic use. After being prescribed a fairly broad spectrum antibiotic, as the practice is nowadays, most colonies of bacteria in the patients, including commensals, leaving resistant strains in the body to grow and multiply and eventually use the host as a reservoir (Gonzales et al.,

2001). This is one reason as to why the prescription of antibiotics should be controlled and only given to those who absolutely need it. The increase in invasive procedures that utilise prosthetics such as valve replacements, pacemaker implants and plastic surgery, whereby foreign bodies may cause infections.

New drugs?

As scientists understand the pathology of diseases and the molecular biology of it, the knowledge of new drug targets and different substances that have the potential of eradicating these diseases have come to light. Also, pharmacology companies have moved their focus from infections to designing drugs for other chronic diseases that affect the daily lifestyle of a patient such as osteoporosis and because of this diversion, the interest in developing new antibiotics that work against resistant strains has waned. The development of antiretroviral drugs have also caused divisions of infectious diseases research groups to have limited funding in their studies as more importance is placed on obtaining a cure for AIDS. New technological approaches that have emerged such as high throughput screening and genetic engineering has failed to actually give us a new class of antibiotics that could be utilised (Barett, 2005). The creation of novel classes of antibiotics would exhaust resources, would be extremely expensive and would be time consuming when compared to tweaking drugs that are already in the market, due to the waning interest in novel antibiotics, it is important that different platforms of society, i. e government, academics and pharmaceutical companies come together to collaborate on these projects. Alongside this, it is important to instil basic

hygiene practices to control infections in the hospital and healthcare setting. Practices such as washing hands, proper disposal of clinical waste amongst other would ensure that the spread of infection in a healthcare setting is curbed (Shlaes and Moellering, 2002). Despite these measures being practical, the development of antibiotics is still deemed to be unprofitable due to the growing investments in other areas of scientific research that is deemed more important. If scrutinized properly, one does notice that investment in discovering new antibiotics and their subsequent production have been solely carried out by private pharmaceutical companies (DiMasi et al., 2003). Pharmaceutical companies currently do spend a huge amount of money in discovering and developing suitable new drugs. The growing costs of carrying out scientific experiments and sourcing the materials required, not to mention the overall time frame of drug discovery and development of around 10 to 20 years do cause pharmaceutical companies to rethink the need to focus on antimicrobials. Unless attractive incentives are offered to pharmaceutical companies, it is unlikely that these companies are going to show an interest in the development of antibiotics in the near future due to the reasons explained above. As of now, several tertiary research group have taken the initiative to involve the government and administrative force to collaborate with them and to include incentives towards pharmaceutical companies that do indulge in the development of potential antibiotics (Talbot et al., 2006).

Conclusion

I would say that creating newer antibiotics will not solve the overall problem of resistance towards antibiotics seeing as microorganism will continue

mutating and evolving in accordance to their need to survive, thus continuing to build resistance towards antimicrobials. Despite this, antibiotics will still be prescribed until a different form of treatment can be solidified and distributed to the public. It is now up to the scientists, clinicians, the pharmaceutical industry and governments worldwide to collaborate in preventing the occurrence of infection, controlling an outbreak of infection that is aided by the development of diagnostic tools as well as identifying patients that truly need antibiotics to begin with. Even in this case, patients should always be given a narrow spectrum medication unless multiple infection is detected to prevent the occurrence of multidrug resistance. More vaccines should also be created to prevent infections to begin with.

We are not living in the post antibiotic world yet, but it doesn’t seem far off unless collaborations are done to develop new antibiotics. Not only would it be harder to treat infections, but many other aspects of medicine would suffer as well, such as cancer therapy, organ transplantation that heavily rely on immune system suppression. We will also not be able to treat trauma patients who have been in a car crash for instance as antimicrobials would be needed as well. Childbirth would also be a problem as there are occurrences of postpartum infections. We are heading to a post antibiotic era unless measures are taken to develop new antibiotics or alternative form of treatment that is efficient.