Antibiotic Resistance: A Major Challenge

Introduction

"The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism." [1]

These words were said by none other than Sir Alexander Fleming, shortly after he received the 1945 Nobel Prize in Physiology for his discovery of penicillin. At the time, the world was just starting to recognize the potential that antibiotics had to revolutionize the treatment of infectious diseases. As research progressed, various classes of these drugs were discovered and developed and modern medicine entered the antibiotics era.

Antibiotic resistance refers to the natural or acquired ability of bacteria to withstand the effects of the antibiotics. Although resistance to antibiotics is a natural phenomenon, Sir Fleming was accurate in his prediction that the overuse of antibiotics by humans would lead to disastrous consequences. The widespread use of these drugs has exerted a large selective pressure on resistance and has led to its rapid spread.

At present, antibiotic resistance is the greatest threat to modern medicine. If bacteria lose their sensitivity to available antibiotics, transplants, surgical procedures and even minor wounds could prove to be life-threatening. Antibiotic resistance is a complex challenge to tackle as curbing its spread and overcoming its effects require a coordinated global response, with efforts being made not just by the medical community, but also by governments, pharmaceutical companies, scientists and the general public.

At present, due to poor surveillance, the burden of resistant infections is not accurately known, especially in areas of the world where microbiology services are limited and unreliable. This is particularly worrying in the case of developing nations, where levels of resistance to first line antibiotics are dangerously high and second and third line antibiotics are neither affordable nor available in rural areas. [2] The first task is to develop local surveillance systems so that communities can understand the depth of their problem in order to introduce and monitor proper interventions.

Antibiotic resistance develops as a result of our excessive use of antibiotics, spreads in clinical settings and communities, and threatens to take us back to the pre-antibiotic era because of the current lack of novel drugs. This essay will focus on three main aspects of antibiotic resistance--the development of resistance, the dissemination of resistance, and the absence of new drugs which can treat resistant infections--discuss the challenges associated with each aspect, and mention possible ways in which they can be overcome.

Development of Resistance

Over-prescription of Antibiotics

The need to get quick results often leads physicians to over-prescribe antibiotics. All over the world, antibiotics are frequently prescribed in situations where they are not necessary. Many of these unnecessary prescriptions are for acute respiratory conditions caused by viruses (such as influenza and the common cold) or which may be caused by bacteria or viruses (such as sinus infections and pneumonia). The Centers for Disease Control and Prevention (CDC) reported that in 2016, 44% of outpatient prescriptions in the US were for respiratory conditions and of these, half were unnecessary. [3] The absence of quick and reliable tests to ascertain the origin of infection currently poses a challenge. Efforts should be made to develop inexpensive tests which can be used even in rural settings.

Easy Availability of Antibiotics

The over-the-counter (OTC) availability of antibiotics leads to self-medication. Patients often self-medicate when they have a mild illness, in order to avoid taking the time to see a doctor. Patients are likely to take antibiotics in cases where they are not required, take improper doses or follow an improper course, when they self-medicate.[4] The general public remains highly unaware of the problem of antibiotic resistance and efforts to curb the spread of resistance will be ineffective unless public awareness is increased and self-medication is discouraged.

While there is a global need for strict regulations on the OTC sale of drugs, policy makers in developing parts of the world must keep in mind that antibiotics must remain easily available for the large proportion of the population that lacks access to doctors. In India, the lack of access to affordable antibiotics is attributed to more deaths in children than drug resistance is. [5] The need for a balanced approach is evident.

Another cause for concern is the rampant use of antibiotics in the poultry and pig farming industries. The use of antibiotics as growth promoters has been prohibited in the European Union since 2006. [6] The FDA introduced similar rules in the US in 2017. [7] Other nations are yet to follow suit. For example, in India, colistin, a last-line antibiotic, is still available to farmers OTC for use as a growth promoter.[8] As demand for meat is expected to grow with increasing population, the problem will only worsen if stringent restrictions aren't put into place soon.

Spread of Resistant Infections

At present, there is an urgent need to take measures to prevent the spread of infections in both healthcare facilities and in the community. This will become increasingly important as more and more strains of bacteria become resistant to key antibiotics. Although infection control measures do not directly stop the development of resistance, they can minimize the impact that these pathogens have on the health of a community.

Resistant pathogens are a major problem in hospitals due to the frequent use of antibiotics and the presence of many individuals susceptible to infection, including those undergoing invasive procedures.

Gram-negative bacteria generally show higher levels of resistance and can cause serious infections including hospital-acquired pneumonia, septicaemia, urinary tract infections and surgical site infections. These conditions generally affect neonates, the elderly and immune-compromised patients, with diseases like cancer. Gram positive bacteria like Vancomycin-Resistant Enterococci (VRE) and Methicillin Resistant *Staphylococcus aureus* (MRSA) are also current causes for concern.

The enforcement of strict infection control measures in healthcare settings is required to decrease the incidence of resistant infections. For example, a 54% decline was observed in the incidence of health-care associated MRSA in the US, after infection control measures were implemented.[9] It is important that these steps are taken even at local hospitals. Hospitals must also take up the responsibility of maintaining data on the various types of resistance detected in bacteria and their respective rates of occurrence.

Resistant strains which originate in hospitals can easily spread to the community. This is extremely difficult to control and must be locally monitored. Once a resistant strain reaches the community, it has the potential to spread rapidly across borders and cause serious global health concerns.

Development of New Drugs

At present, the pipeline for new drugs against highly resistant pathogens is dry. As antibiotics have low return on investment, require expensive clinical trials with large sample populations and quickly lose their potency once resistance emerges and spreads, pharmaceutical companies have less incentive to develop them as compared to drugs for chronic diseases.[9]

A 2013 study by the Infectious Diseases Society of America (IDSA), noted that there were "unacceptably few agents" being developed which would be effective against highly resistant gram-negative bacteria. [10] This was reaffirmed in 2017 when the WHO listed 12 families of bacteria as "priority pathogens" for the research and development of new antibiotics. The three pathogens listed as top or "critical priority"-- *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumanii*-- are Gram-negative bacteria with resistance to carbapenems.[11] Gram-negative bacteria acquire resistance at quicker rates than Gram-positive bacteria.[12] A better understanding of their resistance mechanisms is required, if we are to develop new classes of drugs against them.

At the same time, it is important that we actively explore non-antibiotic treatments for infections. Treatments based on quorum sensing inhibition, bacteriophage therapy, and immunotherapy are opportunities for us to break the cycle of development of drugs followed by the development of resistance. These therapies have been proven in vitro and have great potential to evolve into effective treatment methods. [13] Investment in research on these therapies will prove worthwhile.

Conclusion

Antibiotic resistance is a global crisis that requires immediate action. The effects of this phenomenon are dire and irreversible. Without proper measures to curb the overuse of antibiotics and prevent the spread of resistant infections, the antibiotics we currently depend on will lose their potency very soon. We will once again find ourselves in an era where even the simplest of surgical procedures and seemingly minor infections will have the potential to kill.

The responsibility of overcoming this challenge does not rest with the healthcare community alone. Governments, pharmaceutical companies, and most importantly consumers of antibiotics, must realize that they play an integral role in the global endeavour to preserve currently available antibiotics and develop new ones. After all, it is the efforts we make to deal with the present crisis of antibiotic resistance that will determine how successfully we can treat infectious diseases in the future.

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