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Anti-biotic resistance – The danger ahead

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Abstract

For more than 60 years, antibacterial drugs have been regarded as the panacea to cure infections, whether or not their use is appropriate, and whether the infection was acquired in the community or in the hospital setting. Already in his Nobel Prize speech in 1945, Alexander Fleming, who discovered penicillin, warned that bacteria could become resistant to these remarkable drugs. Indeed, the development of each new antibacterial drug has been followed by the detection of resistance to it.

The development of resistance is a normal evolutionary process for microorganisms, but it is accelerated by the selective pressure exerted by widespread use of antibacterial drugs. Resistant strains are able to propagate and spread where there is non-compliance with infection prevention and control measures.

In this context, the identification of new potential antimicrobial targets and/or the identification of new chemical entities as antimicrobial drugs are in great demand. To date, among the many possible approaches used to deal with antibiotic resistance is the use of antibiotic adjuvants that hit bacterial non-essential targets. In this review, we focus on the causes of anti-microbial resistance and how to overcome it.

Keywords: Antibiotic Resistance, Antibiotic Adjuvant Therapies; Virulence Factors; Combination Therapy.

Introduction

Use of antibacterial drugs has become widespread over several decades (although equitable access to antibacterial drugs is far from being available worldwide), and these drugs have been extensively misused in both humans and food-producing animals in ways that favour the selection and spread of resistant bacteria. Consequently, antibacterial drugs have become

less effective or even ineffective, resulting in an accelerating global health security emergency that is rapidly outpacing available treatment options.

Resistance is the ability of a bacteria against the antagonizing effect of an antibacterial agent upon reproduction prevention or bactericidal. The development of resistance to antibiotics in bacteria often develop as a result of unnecessary and inappropriate use of antibiotics. Through the intense use of antibiotics, resistant microorganisms have emerged over the years, and problems were started to be experienced for the treatment of these infections emerged with these resistant microorganisms.

Until the 1970s, many new antibacterial drugs were developed to which most common pathogens were initially fully susceptible, but the last completely new classes of antibacterial drugs were discovered during the 1980s. It is essential to preserve the efficacy of existing drugs through measures to minimize the development and spread of resistance to them, while reports to develop new treatment options proceed.

Today, on the one hand trying to develop new drugs, on the other hand, there are difficulties in treatment as a result of development of resistance to these drugs rapidly. The development of resistance to antibiotics is a major public health problem in all over the world. The rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives. Many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat. The antibiotic resistance crisis has been attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements.

The Centers for Disease Control and Prevention (CDC) has classified a number of bacteria as presenting urgent, serious, and concerning threats, many of which are already responsible for placing a substantial clinical and financial burden on the U.S. health care system, patients, and their families. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.

History of anti-microbial resistance

The management of microbial infections in ancient Egypt, Greece, and China is well-documented.4 The modern era of antibiotics started with the discovery of penicillin by Sir Alexander Fleming in 1928. Since then, antibiotics have transformed modern medicine and saved millions of lives.

Antibiotics were first prescribed to treat serious infections in the 1940s. Penicillin was successful in controlling bacterial infections among World War II soldiers.4 However, shortly thereafter, penicillin resistance became a substantial clinical problem, so that, by the 1950s, many of the advances of the prior decade were threatened. In response, new beta-lactam antibiotics were discovered, developed, and deployed, restoring confidence. However, the first case of methicillin-resistant Staphylococcus aureus (MRSA) was identified during that same decade, in the United Kingdom in 1962 and in the United States in 1968. Unfortunately, resistance has eventually been seen to nearly all antibiotics that have been developed (TABLE 1)

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Table 1: year of identification of anti-microbial resistance

Anti-biotics	Year introduced	Resistance identified
Penicillin	1940	1943
Tetracycline	1950	1959
Erythromycin	1953	1968
Gentamycin	1967	1979
Ceftazidime	1985	1988
Levofloxacin	1996	1996
Linizolid	2000	2001
Ceftaroline	2010	2011

Types of anti-biotic resistance

The main four types of resistance to antibiotics develops;

- Natural resistance
- Acquired resistance
- Cross-resistance
- Multi-drug resistance and pan-resistance

Natural Resistance: This kind of resistance is caused by the structural characteristics of bacteria and it is not associated with the use of antibiotics. It has no hereditary property. It develops as result of the natural resistance, or the microorganisms not including the structure of the target antibiotic, or antibiotics not reaching to its target due to its characteristics.

Acquired Resistance: As result of the changes in the genetic characteristics of bacteria, an acquired resistance occurs due to its not being affected from the antibiotics it has been responsive before. This kind of resistance occurs due to mainly structures of chromosome or extrachromosomal (plasmid, transposon.)

Cross Resistance: Some microorganisms which are resistant to a certain drug, that acts with the same or similar mechanism and also resistant to other drugs. This condition is usually observed in antibiotics whose structures are similar: such as resistance between erythromycin, neomycin-kanamycin or resistance between cephalosporins and penicillin's. However, sometimes it can also be seen in a completely unrelated drug groups. There is an example of cross-resistance between erythromycin-lincomycin. This may be chromosomal or extrachromosomal origin

Multi Drug Resistance and Pan Resistance: Multidrug-resistant organisms are usually bacteria that have become resistant to the antibiotics used to treat them. This means that a particular drug is no longer able to kill or control the bacteria. Inapropriate use of antibiotics for therapy resulted in the selection of pathogenic bacteria resistant to multiple drugs

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Causes of antibiotic resistance

1. Overuse

The overuse of antibiotics clearly drives the evolution of resistance. Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains. In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on mobile genetic elements such as plasmids.

This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria. Resistance can also occur spontaneously through mutation. Antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind to reproduce as a result of natural selection. Despite warnings regarding overuse, antibiotics are overprescribed worldwide.

2. Inappropriate prescribing

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria. Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases. Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy.

Subinhibitory and subtherapeutic anti-biotic concentrations can promote the development of antibiotic resistance by supporting genetic alterations, such as changes in gene expression, HGT, and mutagenesis Low levels of antibiotics have been shown to contribute to strain diversification in organisms such as Pseudomonas aeruginosa. Subinhibitory concentrations of piperacillin and/or tazobactam have also been shown to induce broad proteomic alterations in Bacteroides fragile.

3. Extensive agricultural use

In both the developed and developing world, antibiotics are widely used as growth supplements in livestock. An estimated 80% of antibiotics sold in the U.S. are used in animals, primarily to promote growth and to prevent infection. Treating livestock with antimicrobials is said to improve the overall health of the animals, producing larger yields and a higher-quality product.

The antibiotics used in livestock are ingested by humans when they consume food. The transfer of resistant bacteria to humans by farm animals was first noted more than 35 years ago, when high rates of antibiotic resistance were found in the intestinal flora of both farm animals and farmers.

The agricultural use of antibiotics also affects the environmental microbiome. Up to 90% of the antibiotics given to livestock are excreted in urine and stool, then widely dispersed through fertilizer, groundwater, and surface runoff.

4. Availability of few new antibiotics

The development of new antibiotics by the pharmaceutical industry, a strategy that had been effective at combating resistant bacteria in the past, had essentially stalled due to economic and regulatory obstacles

Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry. Because antibiotics are used for relatively short periods and are often curative, antibiotics are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux. The availability, ease of use, and generally low cost of antibiotics has also led to a perception of low value among payers and the public.

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Table 2: anti-bacterial resistance threat

Urgent threats	Serious threats	Concerning threats
Clostridium difficile Carbapenem-resistant Enterobacteriaceae (CRE) Drug-resistant Neisseria gonorrhoeae	Multidrug-resistant Acinetobacter Drug-resistant Campylobacter Fluconazole-resistant Candida (a fungus) Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs) Vancomycin-resistant Enterococci (VRE) Multidrug-resistant Pseudomonas aeruginosa Drug-resistant nontyphoidal Salmonella Drug-resistant Salmonella Typhimurium Drug-resistant Shigella Methicillin-resistant Staphylococcus aureus (MRSA) Drug-resistant Streptococcus pneumonia Drug-resistant tuberculosis	Vancomycin-resistant Staphylococcus aureus (VRSA) Erythromycin-resistant Group A Streptococcus Clindamycin-resistant Group B Streptococcus

Strategies to overcome anti-microbial resistance

Misuse and overuse of these drugs, however, have contributed to a phenomenon known as antibiotic resistance. This resistance develops when potentially harmful bacteria change in a way that reduces or eliminates the effectiveness of antibiotics.

Antibiotic resistance is a growing public health concern worldwide. When a person is infected with an antibiotic-resistant bacterium, not only is treatment of that patient more difficult, but the antibiotic-resistant bacterium may spread to other people

When antibiotics don't work, the result can be

- Longer Illnesses
- More Complicated Illnesses
- More Doctor Visits
- The Use of Stronger and More Expensive Drugs
- More Deaths Caused by Bacterial Infections

Antibiotics Fight Bacteria, Not Viruses

Antibiotics are meant to be used against bacterial infections. For example, they are used to treat strep throat, which is caused by streptococcal bacteria, and skin infections caused by staphylococcal bacteria. Although antibiotics kill bacteria, they are not effective against viruses. Therefore, they will not be effective against viral infections such as colds, most coughs, many types of sore throat, and influenza (flu). Using antibiotics against viral infections.

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- Will not cure the infection
- Will not keep other individuals from catching the virus
- Will not help a person feel better
- May cause unnecessary, harmful side effects
- May contribute to the development of antibiotic-resistant bacteria

Patients and health care professionals alike can play an important role in combating antibiotic resistance. Patients should not demand antibiotics when a health care professional says the drugs are not needed. Health care professionals should prescribe antibiotics only for infections they believe to be caused by bacteria. As a patient, your best approach is to ask your health care professional whether an antibiotic is likely to be effective for your condition. Also, ask what else you can do to relieve your symptoms.

Follow Directions for Proper Use

- Take the antibiotics as prescribed. It's important to take the medication as prescribed by your doctor, even if you are feeling better. If treatment stops too soon, and you become sick again, the remaining bacteria may become resistant to the antibiotic that you've taken.
- Do not skip doses. Antibiotics are most effective when they are taken as prescribed.
- Do not save antibiotics. You might think that you can save an antibiotic for the next time you get sick, but an antibiotic is meant for your particular infection at the time. Never take leftover medicine. Taking the wrong medicine can delay getting the appropriate treatment and may allow your condition to worsen.
- Do not take antibiotics prescribed for someone else. These may not be appropriate for your illness, may delay correct treatment, and may allow your condition to worsen.
- Talk with your health care professional. Ask questions, especially if you are uncertain about when an antibiotic is appropriate or how to take it.
- All drugs have side effects. Let your health care professional know if you have new or unusual symptoms or side effects. You might need to stop the antibiotic causing a troublesome side effect and complete treatment with a different antibiotic.

Conclusion

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. This crisis is global, reflecting the worldwide overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge. Antibiotic-resistant infections place a substantial health and economic burden on the health care system and population. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.

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