Review article

Problems, prospect and future of antibiotic resistance

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Abstract

About 90% of deaths due to infection worldwide are caused by antibiotic-resistant microorganisms. Antimicrobial resistance (AMR) is one of the greatest global health threats of the modern age.1,2. .Multidrug-resistant bacteria have become a major health concern. With new generations of virulence and resistant bacteria, we need to improve our understanding and produce novel techniques to control these pathogenic bacteria. Multidrug resistance is amongst the top three threats to global public health and is usually caused by excessive drug usage or prescription, inappropriate use of antimicrobials, and substandard pharmaceuticals. Understanding the resistance mechanisms of these bacteria is crucial for the development of novel antimicrobial agents or other alternative tools to combat these public health challenge. This article reviews the current situation and examines future strategies to tackle the continued threat of bacterial resistance.

Introduction

Antimicrobial resistance is one of the biggest man-made public health threats of modern times. Since the pioneering work of Alexander Fleming, Paul Ehrlich, Gerhard Domagk, and others on antibiotics about 100 years ago, the benefits of these "miracle drugs" for the treatment of infectious diseases have been taken for granted in public health. Unfortunately, a dramatic change has taken place in recent years in terms of efficacy of administered antibiotics. More and more bacteria have developed resistance against antibiotics, and these resistant microorganisms can withstand attack by antimicrobial drugs so that standard treatments become ineffective and infections persist, thereby increasing the risk of spreading to others[3]. Several decades of antibiotic abuse in humans, animals, and agricultural practices have created health emergency situations and huge socio economic impact. Antimicrobial resistance is an important issue when treating patients with various bacterial, fungal, protozoal, and viral infections. However, organisms causing common community-acquired infections have now developed antimicrobial resistance.

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Rationale of the review

As the prevalence of antimicrobial resistance rises, treatment of common infectious diseases, such as respiratory infections and urinary tract infections, becomes increasing 'challenging, and advances made in complex medical therapy, such as organ transplantation, neonatology and intensive care, are also threatened. Compounding this threat is the scarcity of new antimicrobial compounds in the research and development pipeline[4]. Moreover, the treatment of infections due to antimicrobial–resistant organisms places a substantial burden on healthcare systems, and has a major societal and economic impact[1,5]. Finding strategies against the development of antibiotic resistance is a major global challenge for the life sciences community and for public health. Antibiotic-resistant bacteria lose acquired resistant genes more slowly than they were acquired when conditions favorable to antibiotic resistance are removed. If these resistant genes are lost, new generations of the bacteria will respond to antibiotics[6,7].

In this review, we focus on antibiotic-resistant bacteria in developing countries, genes that have mutated in several of the most important antibiotic-resistant bacteria, and ways to prevent infection with these resistant bacteria. This article reviews the current situation and examines future strategies to tackle the continued threat of bacterial resistance.

Methods

A systematic literature search of published articles on antibiotic resistance was conducted. Abstract, full text, experimental studies and review articles that discussed with antibiotic resistance were included.

Discussion

Antibiotic-resistant bacteria cause both community and healthcare associated infections, presenting challenges in treatment and management. The development of new and novel antibiotics, particularly for Gram negative bacteria, is worryingly lacking.

The past decades have seen a dramatic worldwide increase in human-pathogenic bacteria that are resistant to one or multiple antibiotics. More and more infections caused by resistant microorganisms fail to respond to conventional treatment, and in some cases, even last-resort antibiotics have lost their power. In addition, industry pipelines for the development of novel antibiotics have run dry over the past decades.

What is antibiotic resistance?

Antibiotics are often used to treat bacterial infections and are a cornerstone of infectious disease care. However, bacteria evolve in response to their environment. Over time, they can develop mechanisms to survive a course of antibiotic treatment. This "resistance" to treatment starts as a random mutation in the bacteria's genetic code, or the transfer of small pieces of DNA between bacteria. If the mutations are favourable to them, they are more likely to survive treatment and be able to replicate, and are therefore more likely to pass on their resistant nature to future generations of bacteria. When taken correctly, antibiotics will kill most non-resistant bacteria, so these resistant strains can become the dominant strain of a bacterium. This means that when people become infected, existing treatments may be unable to stop the infections.

Antimicrobial Resistance Mechanisms

Antimicrobial resistance can occur via several mechanisms, including: prevention of the ingress of the antibiotic into the target organism's cytoplasm, alteration of or compensatory over-elaboration of the antibiotic target, destruction of the antibiotic, or enhanced function of microbial efflux pumps (wherein the organism pushes the antibiotic out of the cell)[8]. Normally susceptible groups of bacteria may become resistant to antimicrobial agents via random mutation or by acquisition of genetic information that encodes resistance from other, unrelated bacteria. Many bacteria have become resistant to multiple classes of antibiotics via genetic exchange mechanisms8. Antimicrobial resistance genes may be carried on the bacterial chromosome, plasmid, or transposons[9]. Mechanisms of drug resistance fall into several broad categories, including drug inactivation/alteration, modification of drug binding sites/targets, changes in cell permeability resulting in reduced intracellular drug accumulation, and biofilm formation[10-12]. Although resistance of bacteria to antibiotics can be natural, bacteria can also become resistant to an antibiotic through a genetic mutation or by acquiring resistance from another bacterium. One type of mutation, a spontaneous change in the bacteria's genetic material that provides a different type of resistance, is rare and only occurs with a ratio of about 1:106 to 1:107. Mutations can impact bacterial cells in different ways. Some mutatio ns enable bacteria to produce enzymes or other active chemical compounds that inactivate antibiotics, whereas others remove target cells that are attacked by antibiotics, close up entry ports that allow antibiotics inside cells, or produce pumping mechanisms that block antibiotics from reaching their target[13-19]

Framing the problem of antibiotic resistance

The introduction of antibiotics in the mid-20th century was arguably the single most important medical event in recent history with regard to reducing human morbidity and mortality. However, the subsequent and continuing intensive use of antibiotics, both in medicine and in agriculture, estimated to total several million tons worldwide since their introduction[20,21,22], has helped to select a huge increase in the frequency of resistance among human pathogens. High frequencies of resistance significantly reduce the possibility of effectively treating infections. This increases the risk of complications and fatal outcome[23,24], increases the economic burden on health care systems[25,26,27] and may ultimately threaten a postantibiotic era[28-31].

Today, there are about six different deadly bacteria that have strains resistant to all or virtually all antibiotics : Enterobacteriaceae (especially Escherichia coli, Salmonella spp., and Klebsiella pneumoniae), Acinetobacter spp., Pseudomonas aeruginosa, Enterococcus spp., Mycobacterium tuberculosis, and Neisseria gonorrhoeae[32-35] .Antibiotic resistance occurs when strains

of bacteria no longer respond to antimicrobials used to treat infections caused by those microbes. Although some species of bacteria are inherently resistant to one or more classes of antimicrobial drugs, cases of acquired resistance in populations of bacteria that were once susceptible are of greater concern Resistant organisms can also transfer genetic material to other species, which exacerbates the problem by leading to an increased number and variety of microbes demonstrating resistance[8] Populations of antibiotic-resistant bacteria can spread vertically by passing on resistant gene or genes to new generations, or horizontally by exchanging genetic material from one bacterium to another or between different bacterial species. Antibiotic-resistant bacteria lose acquired resistant genes more slowly than they were acquired when conditions favorable to antibiotic resistance are removed. If these resistant genes are lost, new generations of the bacteria will respond to antibiotics[6,7].

In this review, we focus on antibiotic-resistant bacteria in developing countries, genes that have mutated in several of the most important antibiotic-resistant bacteria, and ways to prevent infection with these resistant bacteria.
The future for antibiotics and antibiotic resistance

1. As new antibiotics are discovered and enter clinical use, it will be a matter of time before resistance to these drugs occurs due to the nature of evolution.
2. Strategies to ensure infections remain treatable in the future will need to include.
3. Infection prevention measures.
4. Strict control of antibiotic prescribing.
5. Development of new and different antibiotics.
6. Consideration of new technologies.
7. Developing new antibiotics will require public funding and greater involvement of non-profit making organizations (such as universities), with a focus on the Gram negative bacteria36 Collaborations between microbiologists and biochemists will be essential in supporting the discovery of new classes of antibiotics.
8. Increased infection prevention and control measures in healthcare settings will be necessary to reduce the spread of existing resistant bacteria, but also to reduce all HCAIs and, therefore, reduce antibiotic prescribing. Other preventative measures, such as vaccination, should also be pursued, taking the focus back from one of treatment to one of prevention.
9. Tighter control over antibiotic prescribing is also essential and this can be supported by developing rapid and sensitive diagnostic testing, enabling more timely identification of the bacteria causing infection. This also further supports the use of antibiotics with a small spectrum of activity. Surveillance systems will also be essential for tracking resistance patterns
10. and ensuring that antibiotic policies reflect local antibiotic resistance patterns.

Promising Future

Since the discovery of microbial pathogens, science is developing new antimicrobial agents, and with the new scientific revolution, several methods including molecular techniques have been developed. Identification of the bacteria genome structure provides an accurate understanding of the virulence of pathogenic bacteria and of the properties controlling the pathogens, thereby preventing infection. However, we still need to develop new promising medications including antibiotics and vaccines, and new methods for chemotherapy and organ transplants. With $30 million annual funding over five years[40]. Centers for Disease Control and Prevention Antibiotic Resistance Initiative has succeeded in reducing antibiotic resistance associated with: 50% of C. difficile, which saves 20,000 lives, prevents 150,000 hospitalizations, and reduces healthcare costs by more than $2 billion; 50% of carbapenem-resistant Enterobacteriaceae infections; 30% of multidrug-resistant Pseudomonas, a common cause of infections; 30% of invasive methicillin-resistant S. aureus; and 25% of multidrug-resistant Salmonella infections[37].

New developments

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While a number of antibiotics are in the latter stages of development for Gram positive infections, the only one imminently expected into worldwide use for Gram negative bacteria is faropenem, with development of an oral carbapenem in progress.

These products, together with the other recently launched antibiotics for Gram negative infections, are related to or derivatives of existing groups of antibiotics in which Gram negative bacterial resistance is also present.

The development of new antibiotics is costly and time consuming, giving limited financial return for the outlay associated with their development. In addition, prudent antibiotic prescribing to reduce risk of other infections (such as C. difficile) and the need for antibiotics with a narrow spectrum of activity means their development is not financially viable for the pharmaceutical industry38. This lack of development of antibiotics for Gram negative bacterial infections is a cause of major concern internationally[36].

Other novel technologies, aimed at preventing rather than curing infections, may be useful to reduce antibiotic use and delay the inevitable development of resistance. They have also been shown to have an impact outside of the age group being vaccinated. For example, the pneumococcal vaccine given to children also reduced infection rates in older age groups and an associated reduction in macrolide resistance was seen[39].

Clinical trials of vaccination against P. aeruginosa have taken place. Vaccines against other Gram positive and Gram negative bacteria are in the early stages of development[38].

Since many infections caused by Gram negative bacteria are opportunistic –affecting people with poor immunity due to underlying conditions – cases of Gram negative bacterial infection are likely to increase as advances in medical treatments lead to increased survival of patients with severe underlying disease. Combining this with increasing resistance to commonly used treatments, all available options to preserve the effectiveness of existing antibiotics need to be deployed.

What recommendations does the review make?

The review makes 10 recommendations, outlined below.

1. Launch a massive global public awareness campaign

The issue of antibiotic resistance is still not fully appreciated, especially in the developing world, where antibiotics are often sold without prescription.

2. Improve hygiene and prevent the spread of infection

Improving access to clean water and sanitation, promoting best practice in hospital infection control, and simply encouraging people to wash their hands will all help prevent infection.

3. Reduce unnecessary use of antibiotics in agriculture

The US Food and Drug Administration estimates 70% of medically useful antibiotics are actually sold for use in animals.

It argues that critically important antibiotics should be restricted from animal sales.

4. Improve global surveillance of drug consumption and resistance

Governments need to share data on antibiotic consumption and levels of resistance; Poorer countries should be given assistance in gathering data.

5. Promote new rapid diagnostic tests to

reduce unnecessary use of antibiotics

Many antibiotics are prescribed in cases when a bacterial infection hasn't been confirmed, as a precaution. New types of tests could help prevent this.

The review hopes that by 2020, in wealthy countries antibiotics would only be prescribed if a bacterial infection had been confirmed through testing.

6. Promote the development and use of vaccines and alternatives

Encouraging the take-up of existing vaccines, as well as providing incentives for the creation of new ones, should help reduce the demand for antibiotics.

There also may be alternative interventions that can help prevent infections occurring.

7. Improve the number, pay and recognition of people working in infectious diseases

Infectious disease health professionals tend to be paid less than their peers working in other fields.

A similar pattern can be seen in both private and public sector workers involved in infection research.

8. Establish a Global Innovation Fund for early-stage and non-commercial research

The review recommends that a Global Innovation Fund should be set up to fund "blue sky" research – research that may not have an immediate commercial application, but could lead to breakthroughs in the future.

9. Better incentives to promote investment for new drugs and improve existing ones

There is currently not a great deal of profit in antibiotic research, so pharmaceutical companies should be encouraged by meaningful incentives, such as a reward for bringing a new drug to market.

10. Build a global coalition for real action

Antibiotic resistance is a global problem, so it can only be tackled through global action.

Conclusions

Multidrug-resistant bacteria have become a major health issue. With new generations of virulence and resistant bacteria, we need to improve our understanding and produce novel techniques to control these pathogenic bacteria. In our review, we focused on five pathogenic bacteria with completed genome sequences, which provide a better target for a new generation of antibiotics.

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