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REVIEW ARTICLE

Antibiotic Resistance: A Global Threat

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ABSTRACT:
Antibiotics are the chemotherapeutic agents that kill or inhibit the pathogenic microorganisms. Resistance of microorganism to antibiotics is a growing problem around the world due to indiscriminate and irrational use of antibiotics. Data from across the world have shown an overall decline in the antibiotic pipeline and continually rising resistance to all first-line and last-resort antibiotics. The gaps in our knowledge of existing prevalence and mechanisms of antibiotic resistance are all too well known. Several decades of antibiotic abuse in humans, animals, and agricultural practices have created health emergency situations and huge socio-economic impact. The present review article attempts to discuss the various aspects associated with antibiotic resistance including the basic concepts, causes of antibiotic resistance, antibiotic resistant microorganisms, challenges associated with antibiotics resistance, and ways to prevent antibiotic resistance.

Key words: Antibiotic resistance; drugs; infections; public health.

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Introduction

The resistance of a bacterium to a drug can be determined by minimal inhibitory concentration (MIC), that is, the lowest concentration that completely inhibits growth of a clonal culture.[1,2] An increase in antibiotic resistance occurs when the population can grow even in the presence of higher concentrations of antibiotic. Resistance (a genetically inherited trait) can be acquired by bacteria via any of the processes i.e. spontaneous de novo mutations, or horizontal gene transfer.[1,3,4]In spite of this fact, the level of resistance can be heterogeneous within a population, depending upon various factors like the environment, the population structure, or the physiological state of the cell.[1,5,6]

The efficacy of antibiotics is endangered by the rapid emergence of resistant bacteria worldwide.[7,8,9] As a result of this, the bacterial infections have again become a threat.[7,10]Overuse and misuse of medications and a lack of new drug development by the pharmaceutical industry has contributed towards increased antibiotic resistance.[7,8] Antimicrobial resistance is associated with high morbidity and mortality. Multidrug resistant patterns in gram-positive and gram-negative bacteria have resulted in difficult-to-treat or even untreatable infections with conventional antimicrobials. Due to absence of the facility of early identification of causative microorganisms and their antimicrobial susceptibility patterns in many healthcare settings, broad spectrum antibiotics are being used in an inappropriate manner. Moreover, there is lack of availability of updated epidemiological data on antimicrobial resistance in frequently encountered bacterial pathogens.[11,12]

Classification of a number of bacteria for developing multidrug resistance overtime against antibiotic drugs has been given by The Centers for Disease Control and Prevention (CDC).[13]These antibiotic resistant bacteria can spread to humans or animals. Some examples of commonly encountered antibiotic resistant pathogens include*Methicillin-Resistant Staphylococcus aureus (MRSA), Extended-Spectrum b-lactamase and carbapenemase-producing coliforms, Toxin Hyperproducing Clostridium difficile*.[14,15]

At present, there is an urgent need to discover newer antibiotics to combat the growing menace of antibiotic resistance.[14,15] This goal can be achieved viamulti-disciplinary research work at the national and international level. This can be supplemented by increasing awareness about self-medication and the side effects of antibiotic overuse.[15,16]

Historical Perspective

Resistance has long been with us. Bacteria possess a remarkable number of genetic mechanisms for resistance to antibacterials and there is a substantial pool of antibiotic resistance genes in nature that have evolved over millions of years.[17]The management of microbial infections in ancient Egypt, Greece, and China is well-documented. Sir Alexander Fleming is credited with starting the modern era of antibiotics. Antibiotics were first prescribed to treat serious infections in the 1940s. Penicillin was successful in treating bacterial infections

during World War II. However, shortly thereafter, penicillin resistance came to the fore.Thus, new beta-lactam antibiotics were discovered, developed, and used. However, soon thereafter, methicillin-resistant Staphylococcus aureus (MRSA) was also identified.[7,10,18]
Analysis of organisms and epidemiological data suggest that the evolution and spread of multidrug-resistant organisms have accelerated dramatically over the past 50 years. This time period coincides with the discovery and increasingly widespread use of antibacterial agents.[17,19]
Unfortunately, resistance has eventually been seen to nearly all antibiotics that have been developed.[7]

Parameters Used to Define Potency of Antibiotics

Relatively accurate information about the bioactivity of a given antibiotic can be obtained using microbiological assays. Several in vitro parameters can be used to determine the potency of antibiotics, including MIC, minimum bactericidal concentration (MBC), mutation prevention concentration (MPC) and critical concentration (Ccr).[20]
MIC is regarded to be the standard parameter to determine the susceptibility of microorganism to antimicrobial agents. MIC can be defined as the lowest concentration of an antimicrobial agent that can inhibit the visible growth of microorganisms after overnight incubation.[20,21]MBC is considered as the standard quantitative index of the bactericidal potency of antimicrobial agents. MBC is defined as the lowest concentration of antimicrobial agent that prevents the growth of a microorganism after subculturing to an antibiotic free medium.[20,22]MPC is the antibiotic concentration that allows no mutant to grow, or a concentration above which bacterial cells require the presence of two or more resistant mutants for growth.[20]Ccr is the minimal concentration of antibiotic that inhibits microorganism growth and prevent bacterial concentration to reach critical point.[20,23]

Causes of Antibiotic Resistance

One of the major reasons for antibiotic resistance is the overzealous use of antibiotics. Based on epidemiological data a direct relationship has been demonstrated between antibiotic consumption and the emergence and dissemination of resistant bacteria strains.In spite of warnings regarding overuse, antibiotics are overprescribed worldwide.[7,24,25]
The use of antibiotics as growth supplements in livestock is also one of the cause of increasing antibiotic resistance. The transfer of resistant bacteria to humans by farm has been demonstrated by molecular detection methods.The sequence of events which occur in transfer of resistant bacteria from farm to humans is as follows: a) antibiotic use in food-producing animals kills or suppresses susceptible bacteria, allowing antibiotic-resistant bacteria to thrive; b) resistant bacteria are transmitted to humans through the food supply; c) these bacteria can cause infections in humans that may lead to adverse health consequences.[7,28,29]
Another pertinent reason for increased antibiotic resistance is inappropriate prescribing for antibiotics. It has been demonstrated that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases.[26] Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy. This can promote the development of antibiotic resistance by supporting alterations in genes. This can increase virulence, while increased mutagenesis and HGT promote antibiotic resistance and spread.[7,27]
The development of new antibiotics by the pharmaceutical industry has essentially come to a halt. Furthermore, there has been a drastic reduction in the number and diversity of research teams as a result of merger between pharmaceutical companies. Due to economic crisis there has been a reduction in the money spent on antibiotic research in academia. A major reason responsible for this is that most of the antibiotics are used for relatively short periods of time. Also obtaining regulatory approval for new antibiotics from regulatory agencies is often an obstacle.[7,29,30]

Antibiotic Resistant Microorganisms

S. aureus

S. aureus is one of the most important human pathogen. It is responsible for causing infections in the community and healthcare settings. Although much of the attention is focused on MRSA, its methicillin-susceptible counterpart (MSSA) remains a prime species in infections. *S. aureus* has evolved rapidly in recent years. Scientific literature shows that MRSA represents a global problem with an increase in mortality and the need for expensive last-resource antibiotics. Although, newer anti-staphylococcal drugs have been developed, however, their clinical use has been very limited so far. Molecular typing techniques have allowed identification of the major successful clones and lineages of MSSA and MRSA, including high-risk clones, and tracing their diffusion.[11,31]

Vancomycin-Resistant Enterococci (VRE)

A major therapeutic challenge is presented by VRE. Enterococci can cause a wide range of illnesses. VRE infectionsare often caused by *Enterococcus faecium* and *Enterococcus faecalis*.Limited antimicrobial options are available to treat VRE. These include linezolid and quinupristin/dalfopristin, while the role of daptomycin and tigecycline needs to be further documented in scientific literature. As VRE poses a major threat, there is tremendous interest in developing newer therapeutic drugs that could have bactericidal activity against VRE.[7,28,32]

Drug-Resistant Mycobacterium Tuberculosis

Drug-resistant *M. tuberculosis* infections are a seriousthreat worldwide. Air is the most common mode of spread of *M. tuberculosis*. Lungs are the most common site affected by *M. tuberculosis*. Although, most of the tuberculosis infections are curable with available first-line drugs, however, sometimes, *M. tuberculosis* can be resistant to one or more of these first-line drugs. Limited treatment options are available for extensively drug-

resistant tuberculosis as it is resistant to most tuberculosis drugs, including isoniazid and rifampicin, fluoroquinolones, and also the second-line injectable drugs.[7,18,28]

Carbapenem-Resistant Enterobacteriaceae (CRE)

CRE are a group of bacteria that have become resistant to "all or nearly all" available antibiotics, including carbapenems, which are typically reserved as the "treatment of last resort" against drug-resistant pathogens. This resistance is due to presence of an enzyme called New Delhi metallo-beta-lactamase. This enzyme is present in some of the gram-negative Enterobacteriaceae bacteria. This enzyme makes these bacteria resistant to virtually all beta-lactams, including carbapenems. Untreatable or difficult-to-treat infections due to CRE bacteria are on the rise among patients in medical facilities.[7,18,28]

Multidrug-Resistant Acinetobacter

Acinetobacter is a gram-negative bacteriumwhich is responsible for causing pneumonia or bloodstream infections, especially in critically ill patients on mechanical ventilation. Few of the*Acinetobacter* species have become resistant to all or nearly all antibiotics, including carbapenems, which are often considered to be the drug of last resort.[7,28]

Extended-spectrum beta-lactamase (ESBL)- Producing Enterobacteriaceae

*ESBL-producing Enterobacteriaceae*possess a broad-spectrum beta-lactamase enzyme. This enzyme enables them to become resistant to a wide variety of penicillin and cephalosporin antibiotics. Some *ESBL-producing Enterobacteriaceae* are resistant to nearly all antibiotics in the penicillin and cephalosporin classes. In such cases, the remaining treatment option is an antibiotic from the carbapenem family.[7,28]

Multidrug-Resistant Pseudomonas Aeruginosa

Pseudomonas aeruginosa is one of the common causative agents of hospital acquired infections. Some of the strains of multidrug-resistant*Pseudomonas aeruginosa* have been found to be resistant to nearly all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems.[7,28]

Challenges Associated with Antibiotics Resistance

In hospitals, the chances ofoccurrence of infections related to antibiotic resistant pathogens is high as highly vulnerable patients are clustered together and there is a high use of antibiotics in such settings along with invasive procedures. In the current scenario the need of the hour is to educate people about antibiotics, its side effects, and to encourage them to stop the misuse of antibiotics. As a matter of fact, lack of knowledge about self-medication is the prime reason for mass scale antibiotic resistance tragedy.[15]

Another challenge associated with antibiotic resistance is that even educated population of some developing countries has a tendency to indulge in self-medication.[15,33] This fact makes us to believe that even after the diagnosis of a chronic ailment, patients seek only occasional professional advice, and consider them competent to manage and maintain their own health. Thus, in order to curb antibiotic resistance from emerging as an even bigger global crisis it is important to educate people about the emergence of antibiotic resistance in bacterial pathogens.[15,34]

Ways to Prevent Antibiotic Resistance

If we are successful in decreasing resistance gene frequency at the local level and antibiotic use is regulated, it can prevent the global antibiotic crisis from growing even bigger.[15,35]We need to highlight incomplete knowledge and misperceptions about the use of antibiotic and the subsequent consequences of its misuse. Health practitioners should take up the responsibility of providing proper instructions about the usage of antibiotic such as dose, frequency of dose, treatment course and the harmful effects of its misuse.[15,36]

Lack of compliance to the antibiotic treatment course and improper self-medication are major reasons for the increase in drug-induced diseases and development of antibiotic resistance crisis.[15,36]Counselling should also be done about the psychological factors that can assist patients in enhancing the adherence to medication such as enhancing motivation, patient education, formulating health goals and increasing social support.[15]

CONCLUSION

Antibiotics are a type of antimicrobial agents that are used in the treatment and prevention of numerous bacterial infections. Antibiotic resistance is one of the most serious problems which is faced around the globe. Correct measurement of potency and bioactivity of antibiotics is essential to overcome the resistance problem and to safely use antibiotics.[20]The selection of resistance in one organism in one part of the world may have long-term and important implications for human health globally.[17]There is a requirement for more multi-disciplinary research efforts to manage the antibiotic crisis.[7,15]

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