Review Article

GROWING ANTIBIOTIC RESISTANCE IS A MASSIVE THREAT TO HEALTH SYSTEM

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ABSTRACT:
Antibiotic resistance has become a worldwide problem and a massive threat to the health system, particularly in developing countries. A number of factors such as excessive use of antibiotics in the dairy industry, poultry industry, dosage effect, non-professional doctors especially in rural areas, self-medication, and misuse of antibiotics are contributing towards antibiotic resistance. The astonishing genetic capacity of bacteria to resist antibiotics is due to over usage of antibiotics and transmission of resistant genes to further generations through horizontal gene transfer. The basic mechanisms of antibiotic resistance are the degradation of different drugs used against bacteria by enzymes, changes in proteins that have to be targeted by antibiotics, and alterations in permeability of membrane toward different antibiotics. The growing antibiotic resistance is a problem not only in underdeveloped countries but also in developed countries. This review addresses different aspects of antibiotic resistance, mechanisms, factors involved, and future impact of growing antibiotic resistance.

Key Words: Antibiotics, Antibiotic Resistance, Enzymes

INTRODUCTION:

Antibiotics can be defined as agents that are used to kill or stop the growth of bacteria.[1] No doubt, antibiotics have revolutionized the field of medicine, but today one of the most emerging problems is antibiotic resistance. The resistance to antibiotics has not only resulted in an increased rate of mortality but has dramatically increased the cost of treatment. Antibiotic resistance can also be defined as a process in which bacteria becomes resistant to specific antibiotics, and the antibiotics no longer kill or inhibit the growth of bacteria. Whenever the antibiotics are administrated, there are three possible outcomes; the bacteria will be killed, growth will be inhibited, or they will continue to multiply and will increase in number.[2] There are many factors that lead to antibiotic resistance through different mechanisms such as, i.e., natural selection, plasmid transfer, and mutation.[3]

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Plasmid transfer is a mechanism in which bacteria can transfer their genetic material directly between each other as this ability is not present in other bacteria. Plasmids are small extrachromosomal circular rings of DNA that function as a vehicle in order to transfer resistance among bacterial species. Plasmids have the capability of spreading bacterial resistance in different regions of the world. The mutation is another phenomenon that leads to resistance in bacteria. Bacterial genome regularly changes in response to the employment of antibiotics. The regular usage of antibiotics causes an increase in mutational levels that leads to an increase in the level of bacterial resistance.[4] Bacteria to get resistance by the degradation of different drugs using enzymes; changes in proteins which have to be targeted by antibiotics and alterations in permeability of membrane toward different antibiotics.

The mechanism of resistance in bacteria has been studied extensively at the molecular level, and there are different mechanisms for the development of resistance in microbes.[5] Some of the most important known mechanisms are described here.

Genetic Jugglery:

Genes of β-lactamase enzymes are most widely distributed, and mutations in these genes result in broad-spectrum resistance in different bacteria toward antibiotics.[6] The genes of β-lactamase are ancient, and these have been found in different environmental conditions[7] with different substrates, which provide sufficient evidence for its contribution toward resistance in bacteria. CTX-M is a novel β-lactamase demonstrated as the first enzyme with the ability to hydrolyze cephalosporin at a high level.[8] CTX-M and its variants are one of the most important factors which are contributing to the potential threat of antibiotics resistance worldwide.[9]

Intrinsic Resistance:

Intrinsic resistance is a mechanism in which resistance results due to the presence of specific genes in a bacterial genome, i.e., quasi and proto resistance. The advancements in recombinant DNA technology, different mutagenic techniques helped to discover the role of these intrinsic genes in bacteria and their microbial resistance. One of the most important routes which cause resistance to trimethoprim[10] and sulphonamides[11] in bacteria is gene amplification. It has been shown that specific resistant strain is produced when there is overexpression of the wild-type gene.

Transmission of Resistant Gene:

It has been documented that accessory genetic elements of the bacterial genome have the ability to take resistant genes and transmit. Mutations that make the bacteria resistant toward antibiotics are transferred at a high rate through horizontal transfer.

Regardless of differences that exist between gram-positive and gram-negative bacteria, the transmission through plasmid is the most common method for transmission of resistant genes.[12] The transmission of resistant genes through conjugation is studied extensively. The rate of transmission varies greatly in different environmental conditions, and the frequency of transmission is quite high in the natural environment as compared to laboratory conditions.[13] Recently, a large number of antibiotic-resistant genes have also been documented in human gut microbes.[14] The interchange of both virulent and pathogenic genes is most frequent in meningococci, streptococci, and their related genera, with transformation being the mechanism for transmission.[15,] Acinetobacter species are most competent to transfer DNA directly from the environment or through horizontal gene transfer.[16] Various mechanisms involved in the transmission of antibiotic resistance genes have been studied in the laboratory, and it is observed that the genetic transmission can take place by methods other than transformation by bacteriophages and plasmids. In complex communities of bacteria, the transmission of resistant genes can take place through the fusion of cell wall.[17] However, gene transmission efficiency and its selective expression are important limitations. On the other hand, the low genetic expression provides them protection from different antagonists.[7] There is enhanced antibiotic resistance when sub-inhibitory concentrations of antibiotics are used. In this case, the activation of the SOS response system of DNA repair system facilitates the transfer of genes.[18]

Risk Factors of Antibiotic Resistance:

Dairy and Poultry Industry

Same types of antibiotics are being used to treat animals and human infections, which is contributing towards increased antibiotic resistance.[19] Since the 1950s, antibiotics are used routinely in the feed of cattle, poultry, and swine to stimulate rapid growth and to avoid infections that may occur in animals that reside in congested and unsanitary conditions.[20] Nowadays, there is an increasing trend of usage of antibiotics in livestock, as almost 80% of all antibiotics are sold for livestock. Tetracyclines, Macrolides, Sulfonamides, and Streptogramins are used in cattle, poultry and swine feed. Penicillins,

Aminoglycosides, and Lincosamides are used only in the poultry and swine feed industry. Antibiotics are being routinely provided to animals regardless of their sickness. Due to this regular provision of antibiotics to animals, bacteria that reside in the gut of animals, skin, and respiratory tract become resistant to those antibiotics.[21] These bacteria can spread to people from livestock operations in different ways, i.e., food, environment, and workers. Antibiotic resistance bacteria are also found on fresh meat.[22]

Dose Effect and Overuse:

Usage of antibiotics contributes to antibiotic resistance, whether the use is appropriate or inappropriate.[23] Antibiotics that help in treating patients suffering from various diseases can be categorized as appropriate antibiotics, while antibiotics that do not help patients in coping against diseases are termed as inappropriate antibiotics. A number of studies predict that usage of antibiotics and antibiotic-resistant bacteria are interrelated.[24] It is also a fact that if we lower the usage of antibiotics, the number of antibiotic-resistant bacteria also decreases significantly.[25] If someone fails to complete the course of antibiotics, some of the infecting bacteria survive and become most resistant to that specific antibiotic. The bacteria that survive give rise to a number of bacteria more resistant to that antibiotic as compared to normal bacteria. So, the infection cannot be treated with that antibiotic.[26] Later on, antibiotics eradicate competitors that are sensitive to drugs and leave behind resistant bacteria that reproduce as a result of natural selection.

Non-Professional Doctors in Rural Areas

Non-availability of highly qualified and professional doctors in rural areas[27] is a common factor for antibiotic resistance in some developing countries. They do not advise patients to have a laboratory test before prescribing any antibiotic and prescribe inappropriate antibiotics.[28] Incorrect antibiotics can contribute to increasing the number of antibiotic-resistant bacteria.[29] Correct prescription of antibiotics is really important because incorrect prescription of antibiotics may pose serious threats, and patients become exposed to many other complications.[30] Another factor contributing to increased resistance in bacteria is the false advertisement of antibiotics by just profit earner people.

Self-Medication of Antibiotics:

The attainment and self-administration of antibiotics in order to treat a perceived infection is known as self-medication.[31] The antibiotics are self-administrated not only in underdeveloped countries but also in highly developed countries.[32] The prescribed antibiotics can also be used for self-medication.[33] People use self-medication with antibiotics in order to save time, money, to avoid consultation of doctor, past successful use for family and friends and leftover medicines.[31] In Pakistan, amoxicillin and metronidazole are the most commonly used self-medicated antibiotics while self-medication with antibiotics is mostly used for complications like fever, pain and respiratory problems.[31,34]

Misuse of antibiotics:

Misuse of antibiotics is widely practiced in developing countries, and this practice is recognized as a serious threat to our public health.[35] Superbugs are a kind of harmless bacteria that can cause serious infection as they have the ability to become resistant to multiple antibiotics.[36] The misuse of antibiotics along with overuse of fluoroquinolones causes an increase in the number of antibiotic-resistant bacteria, and it becomes really difficult to treat infections with antibiotics.[37] Fluoroquinolones when used as a first-line antibiotic, antibiotic sensitivity has decreased with negative effects such as those related with cystic fibrosis.[38]

Inappropriate Prescription:

Inappropriate prescription is another factor that is contributing to increased antibiotic

resistance. Worldwide different reports have demonstrated that duration, treatment indication, and choice of antibiotic is improper in 30% to 50% of cases.[39] It was reported in the U.S that pathogen was detected only in 7.6% out of 17,435 patients who were hospitalized with Community-Acquired Pneumoniae (CAP).[40] Moreover, 30 to 60% of antibiotics which are used in ICU are inappropriate, suboptimal, or incorrect. The sub-therapeutic concentration of antibiotics enhances antibiotic resistance through genetic alterations such as mutagenesis, Horizontal Gene Transfer (HGT) and alterations in genetic expression. Increased virulence is associated with alterations in genetic expression while HGT and mutagenesis enhances the antibiotic resistance and their transmission.[41]

Least or less of new antibiotics:

One of the most effective methods to overcome the resistance in bacteria was the development of new antibiotics which has been delayed due to many regulatory and economic problems.[40] Diversity of research teams has also reduced to significant level due to merges between different pharmaceutical industries.[42] Antibiotics are not considered economically more feasible by pharmaceutical companies because of their short duration of usage as compared to drugs which are used to treat chronic and life-threatening diseases such as gastroesophageal reflux, psychiatric disorders, asthma etc.[43-45] Because medicines used for the treatment of chronic disorders provide more profit to pharmaceutical companies and they prefer to invest in them.[44] Another factor associated with decreased availability of new antibiotics is their low price. The price of new antibiotics is a maximum of 1 to 3 thousand dollars per course as compared to hundreds of thousands of dollars of chemotherapeutic drugs.[44,45] Moreover, when the new antibiotic comes in the market, physicians usually treat it as the last option and prescribe older drugs.[43,44] This behavior leads to decreased use of new antibiotics and thereby reduced investment by companies.[42] Ultimately, when new antibiotics are used, the appearance of resistance can be predicted, but the bacterial evolution is quite uncertain; therefore, the timeline of resistance cannot be predicted. Therefore, manufacturers that invest in the development of new antibiotics may assume that profits are reduced to a significant level when resistant develop against that antibiotic.[44] One additional complication is that suppliers of most antibiotics are generic drug manufacturers, and these drugs are usually off-patent.[45] Due to these and many other factors, only a few antibiotics are being made. Infectious Disease Society of America (IDSA) has reported in 2013 that few new antibiotics are in phase 2 or phase 3 of development with activity against resistance developed in gram-negative bacteria such as Pseudomonas aeruginosa, Enterobacteriaceae and Acinetobacter baumanni.[46]

One of the major problems in the development of new antibiotics is regulatory approval.[42, 44] The approval for antibiotics has been reduced to a significant level between 1983 and 2007.[44.] The most usual difficulties in getting regulatory approval are different requirements of clinical trials in different countries, bureaucracy, clarity issues, inappropriate communication, and changes in licensing and regulatory rules.[42] Different changes in standard made by FDA during two decades have made clinical trials of antibiotics quite challenging.[45] Production of antibiotics is also considered uneconomical because a very large population sample is required.[42,45] In order to fill the gap which is present between discovery and development of antibiotics, small companies are coming forward, but they cannot accomplish the financial demands at phase 3 of clinical trials. Merck in December 2014 attained Cubist Pharmaceutical, which is proposed to speed up the regulatory approval and study of antibiotics.[47] In order to continue the discovery and development of new antibiotics there is need of new regulatory

approaches.[44] The new regulatory pathway for approval (LPAD) has been proposed by IDSA which has gained positive comments from the public. This model will help in fast, smaller and cost-effective clinical trials.[40]

Challenges:

Increased resistance of antibiotics due to their inappropriate usage to treat the patients suffering from chronic and vulnerable diseases is presenting a challenging situation. The rate of death has also risen greatly due to increased resistance, and it has been reported that in 2006, round about 50,000 people died due to increased resistance in two bacterial strains, which cause pneumonia and sepsis.[30] Another challenge associated with increased resistance of antibiotics is the increasing trend of self-medication, especially in developing countries. It has been noted that in Asian countries, even educated people are relying on self-medication.[48,49] Even after a chronic disease has been diagnosed, people consider themselves capable of maintaining their health, and in most cases, they do not take professional advice, and even if they take, they do not take it seriously. It has also been demonstrated that the use of some drugs such as topical corticosteroids, oral contraceptives, histamine H_2-receptor blockers, and antifungals is increasing day by day without any professional advice, which also shows that there is also lack of awareness.[50] The healthcare facilities are expensive in developing countries, and at the same time, these are not upto the mark; therefore, people do not prefer to go to professionals. So, to raise the standard of these health care centers and to make them accessible for everyone is another challenge.[51]

One of the great challenges for the government is to raise the awareness of antibiotics, the consequences of their misuses, and their possible side effects. It is also necessary to educate people about difficulties in the treatment of those diseases which are caused by pathogens in which resistance to different antibiotics has developed. The antibiotic resistance problem is not only a matter of concern for healthcare departments, but it may also damage the economy of the country.[52]

The lack of facilities and funding for the development of new antibiotics is another challenge which is currently faced by many pharmaceutical industries, and the efficacy of antibiotics which are currently available is in grave danger because the bacteria are becoming more and more resistant to them and as result of this resistance, the infections will become fatal. Two major problems associated with the development of new antibiotics are strict regulatory requirements and a shortage of monetary incentives.[30] Also, it has been noted that due to increased resistance in bacteria, the antibiotic therapies are becoming more and more complex and also in serious cases they are quite useless.[50]

Future Perspectives:

At this time, the world is moving toward the post-antibiotic era, and the different infectious diseases which were once considered treatable will not be able to manage again due to enhanced antibiotic resistance in bacteria. At present, around 70,000 people die worldwide annually due to enhanced antibiotic resistance. Due to the overconsumption of antibiotics in Pakistan, the resistant strains are spreading at a very high rate, and the adaptation of bacteria toward these antibiotics is also increasing day by day. The antibiotic usage in animals is increasing day by day in agriculture and poultry, and it has been reported that in order to meet the needs of the growing world the antibiotic usage will increase by 70% till 2050.

Due to increased antimicrobial resistance, there is an increase in the number of patients with such infectious diseases that cannot be treated. Also, there is a significant increase in the number of pathogens that are resistant to different drugs at the same time. Therefore it must be highlighted that is the need of time to develop new antibiotics to which bacteria and pathogens are not resistant.[53]

One of the key factors which are leading toward increased resistance of antibiotics is diagnostic uncertainty, which results not only in an increased number of resistant strains but also increased selection pressure.[54] The absence of appropriate techniques to detect and diagnose at early stages has also made it difficult to initiate therapy at appropriate time especially for those diseases which can be life threatening.[55]

It is proposed that in the future, the selection problem may be reduced by improving the diagnosis of bacterial infections. The indication to start and end the treatment by the development of a new diagnostic test would be a greater accomplishment.[56,57] Also, in the future, diagnostic accuracy can be increased by molecular diagnostics, which would enable the use of more appropriate antibiotic drugs. A scenario has been described by Dunne et al. in which he proposes that by 2050, the clinical samples would be analyzed and detected automatically by the development of sophisticated platforms with real-time amplifiers, and it will enable us to detect any pathogen within 30 minutes.[58] It has also been proposed that through the development of new tools it will be possible to distinguish between different viral and bacterial infections.[59]

The need for antibiotics and ultimately the resistance in antibiotics can be eliminated by developing conjugate vaccines, for example, those which are based on pneumococcus and encapsulated H. influenza. But at the same time, it has also been demonstrated that different problems may be associated with the development and delivery of these conjugate vaccines. Also in immunocompromised people, the commercial strains can be transformed into pathogenic strains and the vaccine activity against these bacteria could result in the destruction of natural immune system.

CONCLUSION:

The importance of antibiotics cannot be denied, and we depend completely on antibiotic therapy for the treatment of many infections. The antibiotics are used not only for the treatment of bacterial infections but also in other processes such as organ transplants. But excessive use of antibiotics results in antibiotic resistance that has threatened the benefits which have been achieved through the usage of antibiotics. There are many factors which are contributing to increased resistance of antibiotics, such as their extensive use in dairy and poultry, poverty, inappropriate prescription, regulatory barriers, over-dosing, lack of medical facilities, and many others. Many pharmaceutical companies are not making new antibiotics, mainly due to a lack of funds. The increased resistance toward antibiotics has also resulted in an increased burden on the economy of countries. It has also been also demonstrated that the rate of inappropriate prescription of antibiotics had been raised up to 88.9%. People usually do not consult doctors or other professionals, and they rely on self-medication. In order to overcome all of these issues, there is a need for increased awareness about the usage of antibiotics, health effects, and resistance. The government should also make new policies to overcome these challenges. Legislative amendments in Pakistan Medical & Dental Council (PMDC) ordinance should be made to prevent misuse and self-medication.

AUTHOR'S CONTRIBUTION:

MSA: Concept and design of the study
MSQ: Editing and final approval of the version
PI: Revision of article
SA: Drafting the article
IG: Data collection and drafting
ZA: Design of study
AH: Critical revision of article

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