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Antibiotic resistance: Emergence and solutions

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Perspective

Antibiotic resistance: Emergence and solutions

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Abstract

Antibiotic resistance is one of the leading medical crises in the world today. The antibiotic resistant strains are presenting a serious threat to the health of individuals. The strains of Staphylococcus aureus, which are untreatable by any existing antibiotics, were developed already. According to World Health Organization, 4,80,000 people develop drug resistant tuberculosis each year, globally. Ever since the antibiotics were discovered, the resistant strains have been challenging the efficacy of the developed antibiotics. This crisis has been due to the lack of new drugs and due to the misuse of the existing antibiotics. This review presents the emergence, molecular mechanisms of developing resistance, and strategies for minimizing the resistance.

Introduction

Antibiotics play a major role in the treatment and prevention of bacterial infections. They are also helpful in preventing various postoperative infections, for cancer patients who are receiving chemotherapy, during organ transplantation and for HIV infected patients to prevent pneumonia.[1]

The antibiotic resistant strains are often termed as 'superbugs'. The genes of the superbugs will allow the microbes to survive even in the therapeutic levels of antibiotics. Centres for disease control and prevention (CDC) classified the resistant strains as urgent, severe, and concerning threats. Clostridium difficile (CDIFF) and Neisseria gonorrhoeae strains fall under the urgent threat. Methicillin resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococcus (VRE) are some of the strains, that come under the severe threats. Vancomycin resistant Staphylococcus aureus is the one concerning threat.[1]

The root cause for developing antibiotic resistance include, the misuse and the overuse of antibiotics, incorrect duration of therapy, wrong choice, extensive use of antibiotics in livestock and lack of new antibiotics. The overuse of antibiotics is the primary reason for the development of resistant strains. Improper regulation and dispensing antibiotics over the counter promotes overuse.[2] Prescribing wrong antibiotic will lead to potential side effects. Antibiotics are used in livestock for the prevention of infections and to improve health. These are consumed by humans when they take food, which in turn leads to adverse health consequences. The practice of using antibiotics on fruit trees to act as pesticide will also play a role in developing resistance. Finally, the lack of new antibiotics due to less investment resulted in the development of resistance.

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Emergence

The discovery of penicillin in 1928 started the golden era for antibiotics. They were used to treat severe infections and it saved many lives. Penicillin was successful in treating many bacterial infections.[3] However, the resistant strains to penicillin were developed and became a concerning threat. The discovery of beta lactam antibiotics solved this problem, but MRSA was identified after 10 years. Eventually, the resistance has been developed for all known antibiotics. Vancomycin was developed for treating this MRSA infection.

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Carbapenems are useful in treating multi drug resistant bacteria. They are a class of beta lactam antibiotics and kill bacteria by inhibiting cell wall synthesis. They are broad-spectrum antibiotics, used to treat the infections by resistant strains like Pseudomonas aeruginosa, Escherichia coli, and Acinetobacter species. Yong et. al. described a strain of Klebsiella pneumoniae, that is capable of producing metallo-beta-lactamase enzyme (MBL). Because of this enzyme, it became resistant to carbapenems which made difficult to treat their infection. This strain was identified in Swedish patient of Indian origin who acquired urinary tract infection.[4] This enzyme was named as New Delhi metallo-beta-lactamase-1 (NDM-1) as a patient acquired it from India.

Mechanisms of antibiotic resistance

Antibiotic resistance can be developed by several mechanisms. Broadly, it may be due to modification or inactivation of antibiotic or decreased uptake of antibiotics. The bacteria become resistant to a specific antibiotic either by intrinsic mechanisms or by acquiring resistance genes from other bacteria.[5] Bacteria contain several genes, which would lead to intrinsic bacterial resistance and some bacteria acquire these genes and become resistant. The various mechanisms by which bacteria can acquire resistance is shown in Figure 1.

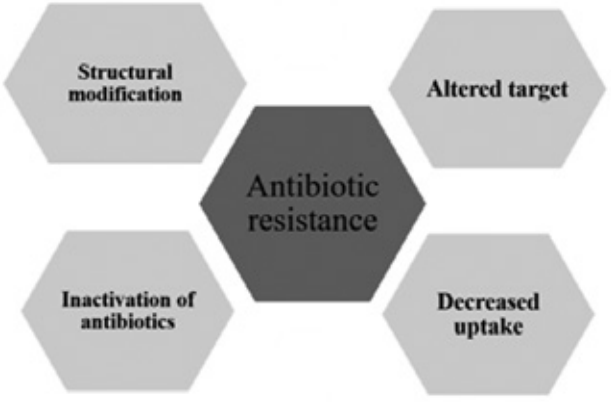

Figure 1: Mechanisms of antibiotic resistance

A. Inactivation of antibiotics

Hydrolysis of antibiotics by enzymes produced by bacteria is the most common way to achieve resistance in bacterial strains. The group of beta lactam antibiotics are prone to lysis by the enzyme beta lactamase. Diverse range of enzymes specifically beta lactamases, have been developed which are capable of lysing cephalosporins, penicillins, carbapenems and monobactams.[6] Transfer of plasmid from one bacteria to another lead to the development of resistance.[7] The resistant strains were developed, which were even capable of degrading powerful member of beta lactam antibiotics group, the carbapenemes. These strains produce MBL-1 to degrade carbapenems. Several classes of enzymes have been characterized, which can degrade aminoglycosides and macrolides.

The beta lactam antibiotics exert their action by binding to penicillin binding proteins (PBP). The PBPs are a group of proteins located on the bacterial cell membrane, and are essential for the cross linking of the bacterial cell wall. The beta lactams when bound to PBPs prevent them from performing their function, thereby leading to the inhibition of cell wall synthesis. The mechanism of beta lactam antibiotics is to bind penicillin-binding protein, which inhibits the cell wall synthesis. Destruction of beta lactam ring results in the loss of ability to bind the penicillin-binding proteins. The examples include penicillin resistant strains of Staphylococci and cephalosporin resistant Enterobacteriaceae.

B. Modification of structure of antibiotic

Accurate binding of antibiotic to target protein depends on the structure of antibiotic. Any change in the structure prevents its binding to target protein.[8] Changes are made by adding chemical groups like phosphate and hydroxyl to antibiotics. These kinds of modifications are particularly seen in aminoglycosides like streptomycin, amikacin, and kanamycin, in which the structure of the antibiotic is modified. Hence, it cannot bind the ribosome and affect the protein synthesis. Example is the resistant species of Mycobacterium.

C. Altered target

The binding regions were altered in resistant bacterial species either by mutation in the genes coding target protein or by modification of target protein. The changes prevent binding to target protein and confers resistance.[9] This kind of resistance

was developed in almost all antibiotic classes like aminoglycosides, quinolones, glycopeptides, and beta lactams due to mutations and transformation. The examples include vancomycin resistant strains of enterococci.

D. Decreased uptake

The decrease in the uptake of antibiotics is due to efflux pumps of bacteria, which drain the antibiotics in the bacterial cell.[10] Overexpression of efflux pumps in a cell leads to the development of resistance in bacteria [Figure 2]. This mechanism particularly confers resistance to Staphylococci against quinolones.

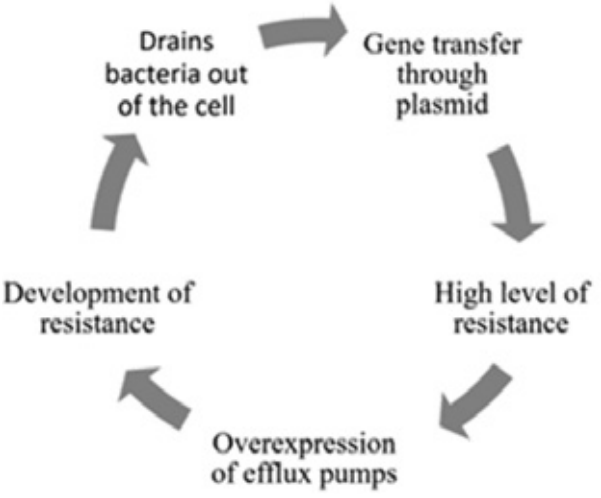

Figure 2: Decreased uptake of antibiotics.

How to resolve antibiotic resistance?

As the antibiotic resistance is posing serious threats to the health of individuals, finding a right solution is very much necessary to save the people.[11] Proper preventive steps have to be taken to decrease the misuse of antibiotics. There is also a need to develop strategies by exploiting advances in molecular biology for finding new ways of treating the resistance strains. The preventive measures include proper education, decrease the use of antibiotics in livestock and control in prescribing antibiotics. Treatment of resistant strains include development of new antibiotics, vaccines, non-antibiotics and use of bacteriophages as described by Ian A Mckay et. al.

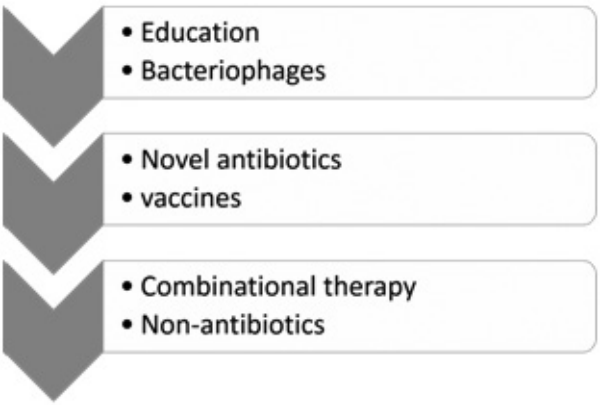

Figure 3: Strategies for overcoming antibiotic resistance.

A. Education

Sensitizing the clinicians and the pharmacists about the pharmacokinetic parameters of drug is very much essential. The inappropriate prescribing of antibiotics leads to patient complications and the inadequate dosing leads to resistance. Alertness about the need of proper prescription of antibiotics is very essential to reduce the overuse and misuse of antibiotics. There is also a need to educate the public regarding hygiene and the need of following the prescription.[12] Multidrug resistance is mainly seen in hospital-acquired infections. Hence, there is a need to educate the health workers about proper disinfection and hygiene.

B. Novel antibiotics

The resistance to antibiotics has started due to using limited class of compounds having very less targets and mechanisms. The development of a new class of antibiotics having complex mechanisms is essential for combating the battle of resistance. The pharmaceutical companies treat the antibiotics as non-profitable drugs compared to the drugs used to treat the chronic diseases, which created a gap in the field of antibiotics discovery. Hence, the pharmaceutical companies need to step up and scale up the research done in the academia. Screening new chemical entities from natural sources like soil and plants helps in isolation of the new natural antibiotics.[13]

Isolation and characterization of animal secretions, which contain antimicrobial agents, can be helpful in treating the resistant strainsThe examples include indolicidin from cow and protegrin 1 from pig.[14]

Even many microbes produce bioactive compounds like antibiotics which on isolation may give a new class of antibiotics.

Table-1: New class of antibiotics[15]

NAME OF THE DRUG	CLASS
Ceftolozane	Cephalosporins
Clazomicin	Aminoglycoside
Eravacycline	Fluorocycline
Brilacidin	-----

C. Bacteriophages

Bactriophages are the viruses that specifically infect bacteria and the studies suggest the use of bacteriophage for the treatment of drug resistant strains, seems promising. The Polish studies based on this has shown that they are effective against systemic infections and mucosal infections. The immunogenicity is less and is having good bioavailability. This therapy is still in early stages of the development and a thorough research is required regarding the physiology of bacteriophages.

D. Virulence factors

Many bacteria release virulence factors which will cause infections. The suppression of virulence factors by using new compounds finds effective in combinational therapy with antimicrobial agents.[16] Suppression does not kill microbe but decreases the emergence of resistance. The examples include the usage of RNA III for neutralization of virulence factors of Staphylococcus aureus. Balaban et. al. described the use of this compound which showed decrease in the size of lesion in mice. The development of vaccine using powerful virulent factor may give good results and used as a synergistic therapy with suitable class of antibiotics.

E. Combinational therapy

Combining the agents having different modes of action has shown a promise. For example, the combination of a macrolide and a fluoroquinolone or beta lactam and a tetracycline has been used in HIV infections. The use of beta lactamase inhibitors along with beta lactam antibiotics is a good strategy. Clavulanic acid is used as a beta lactamase inhibitor.

F. Non-antibiotics

Use of the class of drugs other than antibiotics called non-antibiotics, is a hope for treating the drug resistance. Compound like phenothiazines might enhance the activity of the normal class of antibiotics and useful in eliminating the resistance. In some studies, they have shown activity against the resistant bacterial strains.

G. Disruption of the biofilms

Certain bacteria are capable of producing polymers which can shield them from immune cells. These are called biofilms and the antibiotic resistance conferred due to this is a difficult problem to treat. It is because of the difference in the pattern of resistance in biofilms and conventional microbes.[17] Understanding the mechanisms in resistance hold the key for developing the strategies against it. The matrix surrounding bacteria is essential for their survival. The use of substances that are capable of destroying biofilm can be given as a combinational therapy along with the conventional therapeutic agents.[18] Identifying the polymer in different kinds of bacterial films is essential for choosing the agent to depolymerize it, which is a promising area of research.

Conclusion

The antibiotic resistance is a leading global crisis developed due to the lack of new class of antibiotic drugs and the misuse of the existing antibiotics. The research in the area of development of new classes of drugs like non-antibiotics, vaccines made of potential virulence factors and use of bacteriophages will be helpful in combating the battle of resistance. At the same time, educating the health workers and the public regarding self-medication, self-care, and limiting the irrational prescription, dispensing, and use of antibiotics is highly opted to overcome the biggest challenge of the current century, the antibiotic resistance.

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