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Antimicrobial resistance: A major threat to public health

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Abstract
The microbial infections that once were easily treated are becoming untreatable in these days. The major cause for this problem is the growth of antimicrobial resistance among the microorganisms. Antimicrobial resistance possess serious threat to health in India and worldwide. Resistance arise through one of three ways; natural resistance in certain types of bacteria, genetic mutation or by one species acquiring resistance from another. Within four years following the introduction of Penicillin during the Second World War, occurrence of resistance strain was reported. Inappropriate or incorrect use of antimicrobial drugs and premature treatment interruption can cause drug resistance**.** The multiplicity and non-specificity of efflux pumps and occurrence of resistance-conferring genes in non-pathogenic bacteria hint at some other role of antibiotics in evolution. It is also believed that bacteria sense antibiotics as an environmental stress.

Keywords: antimicrobial resistance, multi drug resistance, resistance mechanism

1 Introduction
Antibiotics constitute one of the most significant contributions of modern science. The discovery of these lifesaving drugs transformed the health care scene during the last century. A significant decline in the fatality rate of many diseases was noticed after the introduction of antibiotics into clinical practice. For instance, 20% to 85% death rate due to Pneumonia in US during 1930 came down to about 5% in the 1960. 100% death due to chronic infection of heart value was reducing to 5%. Antibiotic help not only in curing the diseases but also in their prevention. Penicillin for instance, prevent throat infection caused by Streptococcus [1].
Many decades after the first patient were treated with antibiotic, bacterial infection have again become threat [2]. The antibiotic resistance has been attributed to overuse and misuse of these medication, as well as lack of new drug development by pharmaceutical industry due to reduce income incentives and challenging regulatory requirements [3].
Antibiotic resistance or antimicrobial resistance is the ability of microbe to resist the effects of medication previously used to treat them [4].
Resistance arise through one of three ways; natural resistance in certain types of bacteria, genetic mutation or by one species acquiring resistance from another [5]. Within four years following the introduction of Penicillin during the Second World War, occurrence of resistance strain was reported. According to an estimate by The Centers for Disease Control and Prevention (USA), 13300 patients died of antibiotic resistance bacterial infection in USA during 1992. An incredible 150% increase in the occurrence of drug resistance Pneumonia was noted between 1987 and 1994. A 20 fold increase in the frequency of hospital acquired Enterococci; resistance of Vancomycin was seen between 1989 and 1993. The frequency of Methicillin-resistance Staphylococcus score from 2% in 1975 to 32% in 1992 [6].
Bacteria, not human or animal, become antibiotic resistance. The bacteria may infect human and animal, and the infection they cause are harder to treat than those caused by non-resistant bacteria [7].

2. History of Resistance
Antibiotics were first prescribed to treat serious infections in 1940. Penicillin was successful in controlling bacterial infection among World War 2 [8]. However, shortly thereafter, Penicillin resistance became a substantial clinical problem. So that, by 1950, in response new beta-lactum antibiotics were discovered, developed and deployed, restoring confidence. However, the first case of Methicillin-resistance Staphylococcus Aureus (MRSA) was identified during that same decade in UK in 1962 and in the US in 1968 [9]. Vancomycin was introduced into clinical practice for the treatment of MRSA [10]. Streptomycin was found effective for tuberculosis in 1944 but In 1950, scientist Renee Dubos predicted that that bacteria would eventually develop resistance to antibiotics through random mutations [11].

3. Epidemiology
Antimicrobial resistance is one of the most complex global health challenges today. Multidrug-resistance tuberculosis killed as estimate 250,000 people in 2015. People with MRSA are estimate to be 64% more likely to die than people with non-resistance form of the infection. In2010, an estimate 7% of people starting antiretroviral therapy in developing countries had drug-resistance HIV, in developed countries; same figure was 10-20% [12].
In India antimicrobial resistance is high as compare to developed countries due to higher consumption of medicine. However many international agencies like WHO, European Centre For Disease Control and World Health Assembly resolution highlighted the antimicrobial resistance as a major

public health issue. It will be a big challenge to tackle the problem for policy makers and health care providers [13].

4. Resistance to penicillins

4.1 Inactivation of antibiotic by beta-lactamase

The production of beta-lactamase is most common mechanism of resistance. Hundreds of different beta-lactamase have been identified which is produced by Staphylococci, E-coil, etc.

Beta-lactamase chemical opens the beta-lactam ring and inactive the Penicillins (Figure 1). Due to inactivation Penicillins antibiotics do not show their action [14].

4.2 Modification of target penicillin bending proteins (PBPs)

Many bacteria like Staphylococci, Pneumococci and Enterococci are inherently insensitive to Penicillins because in them the target enzymes and PBPs are located deeper under lipoprotein barrier where Penicillins is unable to penetrate or have low affinity for Penicillins [15].

4.3 Impaired penetration of drug to target (PBPs)

Resistance due to impaired penetration of antibiotic to target PBPs occurs only in gram-negative bacteria because of their impermeable outer cell wall membrane, which is absent in gram-positive bacteria. Penicillins like Amipicillin cross the outer membrane and enter gram-negative bacteria via outer membrane protein channels called Porins. Absence of the proper channel or down regulation of its production can greatly impair drug entry into the cell.

4.4 Efflux

Gram-negative bacteria also may produce an efflux pump, which consist of cytoplasmic and periplasmic protein components that efficiently transport some penicillins from the periplasm back across the outer membrane [17].

5. Resistance to cephalosporins

Acquired resistance to cephalosporins could have same basis as for penicillins *i.e.*

a. Alteration in target protein reducing affinity for the antibiotic.
b. Impermeability to antibiotic or its efflux so it does not reach its site of action.
c. Elaboration of beta-lactamase which destroy specific cephalosporin's [18].
d. In enter bacteria, a clear correlation exists between porin quantity and cephalosporin resistance, suggesting that the outer membrane is the sole barrier to drug entry. Such relationships are less Pseudomonas aeruginosa, where the cell may contain additional barrier between the outer membrane and the PBPs. Although elevated cephalosporin resistance often is attributed to single factor an organism response to a drug often reflect the interplay of several factors [19].

6. Resistance to monobactams

Monobactams are monocyclic beta-lactams i.e. they contain a single ring-the beta-lactam ring. Resistance to aztreonam is primarily through hydrolysis by beta-lactamase. Resistance is Due to alteration of Penicillin-binding proteins. Permeability of certain monobactams to bacterial cell decreases [20].

7. Resistance to carbapenems

The overexpression of efflux pumps that expel carbapenems, mostly meropenem, may lead to carbapenem resistance. Enzyme-mediated resistance to carbapenems is due to the production of beta-lactamases that are able to inactivate carbapenems together with other beta-lactam antibiotics. This type of resistance is the most important clinically because their enzymes hydrolyze all or all most all beta-lactams [21].

8. Resistance to sulfonamides

Sulfonamide resistance may occur as a result of mutations that Cause overproduction of PABA, production of a folic acid-synthesizing enzyme that has low affinity for sulfonamide and Impair permeability to the sulfonamide [22].

9. Resistance to quinolones/ fluoroquinolones

Resistance is due to one or more point mutations in the quinolone binding region of the target enzyme or to change in the permeability of the organism. However, this does not account for the relative ease with which resistance develops in exquisitely susceptible bacteria. Most recently two types of plasmid –mediated resistance have been described (Figure 2). The first type utilizes Qnrprotein, which protect DNA gyrase from the fluoroquinolones acetyltransferase capable of modifying ciprofloxacin [23].

10. Resistance to tetracyclines

Resistance to tetracyclines develops slowly in a graded manner. In such bacteria, usually the tetracyclines concentrating mechanism becomes less efficient or bacteria acquire capacity to pump it out. Another mechanism is plasmid mediated synthesis of a protection protein which protects the ribosomal binding sites from tetracycline [24].

11. Resistance to chloramphenicol

Most bacteria are capable of developing resistance to chloramphenicol, which generally emerge in graded manner, as with tetracyclines. Being orally active, broad spectrum and relatively cheap, chloramphenicol was extensively and often indiscriminately used, especially in developed countries, resulting in high incidence of resistance among many gram-positive and gram-negative bacteria. In many areas, highly chloramphenicol resistant S.typhi have emerged due to transfer of R-factor by conjugation resistance among gram-negative bacteria is generally due to acquisition of R-plasmid encoded for an acetyltransferase an enzyme which inactivates chloramphenicol. Acetyl-chloramphenicol does not bind to the bacterial ribosome. In many cases, this plasmid has also carried resistance to ampicillin and tetracycline. Multidrug-resistance S.typhi has arisen [25].

Decreased permeability into the resistant bacteria cells and lowered affinity of bacteria ribosome for chloramphenicol are The other mechanism of resistance. Partial cross resistance between chloramphenicol and erythromycin has been noted, because all these antibiotics bind to 50S ribosomes at adjacent sites [26].

12. Resistance to aminoglycosides

Resistance to Aminoglycosides is acquired by one of the following mechanisms.

a. Production of a transferase enzyme or enzyme inactivates the aminoglycosides by adenylylation, acetylation or phosphosylatin. This is most important mechanism of development of resistance to aminoglycosides.
b. Mutation decreasing the affinity of ribosomes proteins that normally bind the aminoglycosides. This mechanism can confer high degree resistance but operates to limited extent. For e.g. *E.coil* that develop Streptomycin resistance by single step mutation do not bind the antibiotic on the polyribosome. This type of resistance is specific for a particular aminoglycosides (Figure 3).
c. Decreased efficiency of the aminoglycosides transporting mechanism; either the pores in the outer coat become less permeable or the active transport is interfered [27].

13. Resistance to erythromycin

All cocci develop resistance to erythromycin, mostly by mechanisms which render them less permeable to erythromycin or acquire the capacity to pump it out. Resistant Enterobacteriaceae have been found to produce an erythromycin esterase. Alteration in ribosomal binding site for erythromycin by plasmid encoded methlase enzyme is an important mechanism in gram positive bacteria. All the above types of resistance are plasmid mediated, while change in the 50S ribosome by chromosomal mutation has been found. Bacteria that develop resistance to erythromycin are resistance to other marcrolides as well. Cross resistance with clindamycin and chloramphenicol also occur, because the ribosomal binding sites for all these are proximal to each other [28].

14. Multi-drug resistance

Antimicrobial drugs inhibit the cell wall synthesis by binding with the peptidoglycan layer in bacteria and blocking the cell growth and division. These bacteria undergo certain chromosomal mutation or exchange of extra chromosomal DNA elements through conjugation or transformation such as in K. pneumonia, which can cause alteration in the cell membrane composition resulting in decrease permeability and uptake of drugs into cell.

Another mechanism of MDR was found to be an over expression of drug target enzymes leading to target bypass due to modification in certain metabolic pathways, which causes production of alternate target molecules and interference in some protein synthesis. This can influence the access of drugs to the target sites (Figure 4).

Inactivation or enzymatic degradation of antimicrobials has also become increasingly apparent as cause of MDR [29].

15. Multi-drug resistant tuberculosis (MDR-TB)

The two reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person to person transmission. Most people with TB are cured by a strictly followed 6-month drug regimen that is provided to patient with support and supervision. Inappropriate or incorrect use of antimicrobial drugs and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowed setting such as prisons and hospitals. Extensively drug resistant TB (XDR-TB) is a form of multidrug resistant TB with additional resistance to more anti-TB drugs [30].

Some mechanisms of drug resistance are below.

1. Cell wall – The cell wall of M. Tuberculosis contains complex lipid molecules which act as a barrier to stop drugs from entering the cell.
2. Drug modifying and inactivating enzymes. The TB genome codes for enzymes (proteins) that inactive drug molecules. These enzymes usually phosphosylate, acetylate or adenylate drug compounds.
3. Drug efflux system- The TB cell contains molecular system that actively pumps the drug molecules out of the cell.
4. Mutation- Spontaneous mutation in the TB genome can alter protein which is the target of drugs, making the bacteria drug resistant [31].

16. Antifungal drugs resistance

Just like antibiotics cure bacterial infection antifungal drugs save lives by curing dangerous fungal infection and just like some bacterial infections are resistant to antibiotics, some fungi no longer respond to the antifungal drugs that are designed to cure them. This emerging phenomenon is known as antifungal resistance [32].

There are three basic resistance mechanisms to antifungal drugs.

1. Decrease of effective drug concentration with specific mechanisms including increased drug efflux, increased number of targets, drug sequestration of extracellular and intra cellular organs, and poor pro-drug conversion.
2. Drug target alteration.
3. Metabolic bypass.
4. Genome mutations are responsible for these three basic principles. [33]

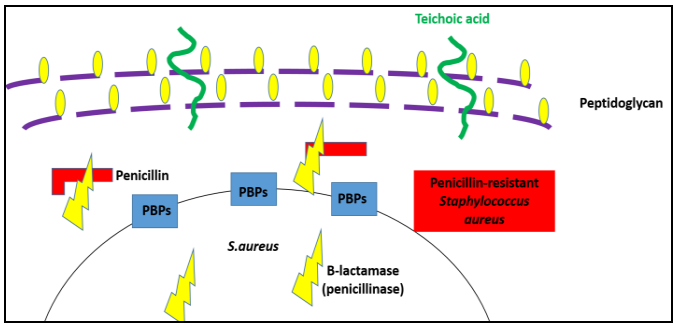

Fig 1: Resistance to Penicillin

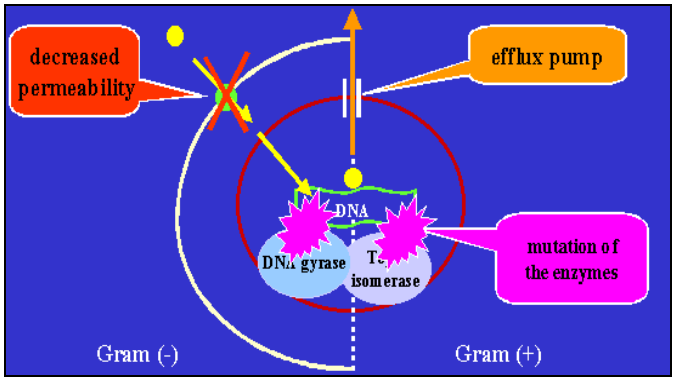

Fig 2: Resistance to Quinolones/Flouroquinolones

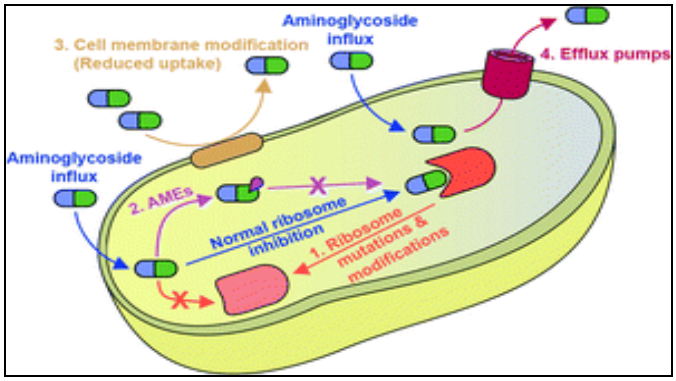

Fig 3: Resistance to Aminoglycoside antibiotics

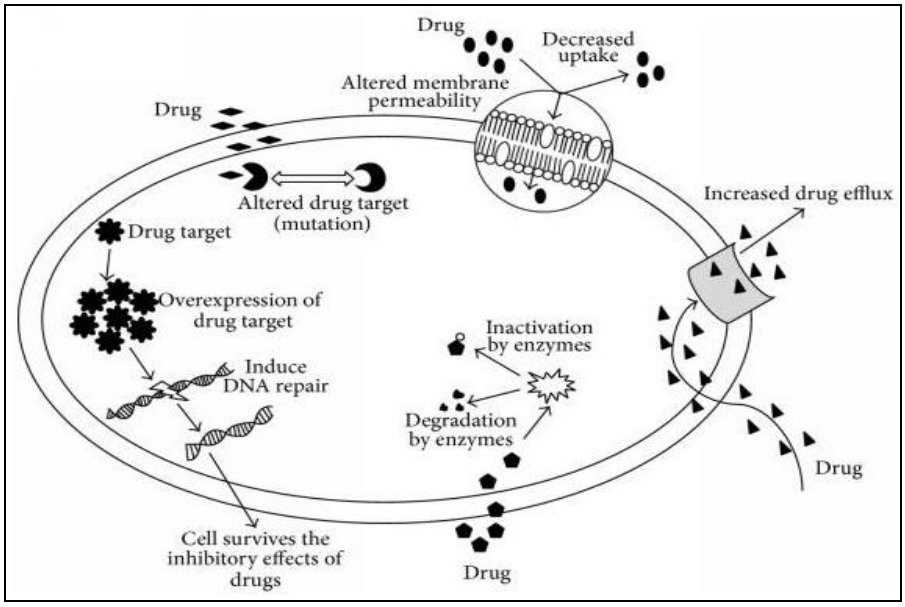

Fig 4: Multi drug resistance (MDR)

17. Summary

The foregoing discussion on antibiotic-resistance in bacteria is focused on the clinical impact of the phenomenon. But there are many other aspects which are overshadowed by its devastating effects on the prospect of chemotherapy. The history of antibiotics as therapeutic agents is less than 100 years old while antibiotic biosynthetic pathways and antibiotic-resistance genes are believed to have evolved thousands of years ago. So in nature both antibiotic biosynthetic pathways and mechanisms involved in antibiotic resistance must have some other significance, which warrants extensive investigations. The multiplicity and non-specificity of efflux pumps and occurrence of resistance-conferring genes in non-pathogenic bacteria hint at some other role of antibiotics in evolution. It is also believed that bacteria sense antibiotics as an environmental stress. Hence there might be some correlation between antibiotic-resistance and stress tolerance of bacteria. Antibiotic-resistance has been detected in many bacteria isolated from extreme environments. Enhanced rate of horizontal gene transfer was observed by some investigators in some food-borne bacteria treated with sublethal levels of stress factors. Therefore, it is obvious that the clinical aspect of antibiotic resistance is only the tip of the iceberg and most of the aspects in the study in antibiotic-resistance of bacteria remain unexplored till now. We hope that thorough investigations will provide more insights in the years to come.

We live in a globalised world. This creates great opportunity but also novel dangers. Resistant organisms can be imported from overseas through international air travel and spread intercontinentally with unprecedented speed. Ultimately, securing global antimicrobial efficacy will therefore require international cooperation, with a role for supranational legislative bodies such as the European Union and United Nations. Leadership from the WHO to coordinate this process, and encourage all UN member states to promote good antimicrobial stewardship, will be crucial.

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