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Antimicrobial Resistance: A Tale of the Past becomes a Terror for the Present

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Review Article

Abstract

Multidrug resistance is a state of insensitivity or resistance (natural or acquired) of a microorganism to the administered antimicrobial drug, making these drugs ineffective. At present, Antimicrobial Resistance has become a global crisis endangering the efficacy of antibiotics which had once transformed the medical history, saving millions of lives. In accordance to WHO report, the treatment regime for diseases like Tuberculosis, HIV, Influenza, Pneumonia etc. have become ineffective due to the emergence of resistant mutant strains. This review focuses on the mechanism, growing risk, causes of MDR and possible alternatives which could be the major need in the present scenario.

Keywords: Multidrug resistance; Antimicrobial Resistance; Penicillin; Intrinsic resistance; Acquired resistance.

1. Introduction

During the last few decades, the incidence of microbial infections has increased dramatically. Continuous deployment of antimicrobial drugs in treating infections has led to the emergence of resistance among the various strains of microorganisms. Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial drug (which are structurally unrelated and have different molecular targets) despite of earlier sensitivity to it [1,2].

Antibiotics are considered as the most important therapeutic discoveries in the history of medical science. It has revolutionized the methods to treat people for various pathogenic infections like those from bacteria, fungi, protozoa, etc. They to a greater extent reduced the mortality and morbidity rates caused due to bacterial infections. But this miracle scenario has changed in the recent few decades. Antibiotic Resistance has now become an explosive global issue endangering the efficacy of antibiotics which had once transformed the medical history, saving millions of lives [3,4].

World Health Organization (WHO) defines Antimicrobial Resistance (AMR) as the state at which a microorganism becomes resistant to a particular antimicrobial drug that was once able to treat the infection caused by that microorganism [5,6]. Resistance is the property acquired by the microorganism and not the person who is infected by the organism [7].

The whole history of antibiotics started from the accidental discovery of penicillin long back in1928 by Sir Alexander Fleming. Penicillin gave a new definition to the modern medicine saving millions of life. Shortly after the World War II, penicillin resistant organisms evolved thus initiating the problem of microbial resistant organisms [8-10]. Considering it as a miracle discovery of the century earned a name as “miracle drug” was soon available to the public easily, despite the warnings by Alexander Fleming, because bacteria had the ability to transfer their genes horizontally from one bacterium to the other (ability to share the resistance) which went unheeded by the scientist and doctors of those times. In 1976, Stuart Levy a physician and researcher at Tufts University, known to be one of the first to identify antibiotic resistance due to its use in animals, and to clamour for greater awareness of the problem. He worked on a study that examined how small amounts of tetracycline in animal feed could cause resistance in humans [11].

A general question that why antibiotics resistance has become a threat in the recent decades. This is mainly because of the misuse and overuse of these medication and also the lack of new drug discoveries by the pharmaceutical research industries [8,12,13]. Microorganisms on the other hand are becoming capable of producing potentially resistant strains against these antibiotics. This is acquired by any of the three ways like gaining natural resistance in certain types of bacteria or by genetic mutation or by one species acquiring resistance from another [14]. Few examples of microorganisms exhibiting AMR are listed in Table 1 [15].

Table 1. Common drug resistant microbes and diseases caused by them.

Antimicrobials class	Drug(s)	Resistant Species	Site of Action	Typical diseases
Bacteria				
β-Lactams	Penicillins (ampicillin)	*Streptococcus pneumoniae*	Peptidoglycan biosynthesis	Pneumonia, meningitis and otitis
	Cephalosporins (cephamycin)	*Escherichia coli*		Urinary tract infections and blood stream infections
	Penems (meropenem)	*Klebsiella pneumoniae*		Pneumonia, blood stream, and urinary tract infections
Quinolones	Fluoroquinolones	*Mycobacterium tuberculosis*	DNA replication	Tuberculosis
Fungi				
Sulfonamides	Sulfamethoxazole	*Aspergillus* spp.	C1metabolism	Aspergillosis
Virus				
Ganciclovir	Acyclovir, famciclovir, and valacyclovir	Herpes Simplex Virus (HSV)	DNA polymerase	Herpes simplex
Lamivudine	Lamivudine	Hepatitis B virus (HBV)	DNA replication	Hepatitis B

2. Present Scenario of Antimicrobial Resistance

India, has always been a real threat to public health in terms of Infectious diseases, because of the emergence of AMR pathogens like *Klebsiella pneumoniae*, *Providencia stuartii*, *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and other few species of *Shigella* are resistant to some or the other antibiotic classes commonly used for the treatment, leading to an era of AMR [16-18]. The scenario has never changed despite of the alarming increase in the prevalence of AMR bacterial pathogens, information available to the general public regarding the current scenario of resistant pathogens and their molecular identity remains unheeded [18,19]. In a study, Kumar et al. made an attempt to analyse the antibiotic susceptibility of around 654 Gram-negative enteric pathogens from two metropolitan Centres in India, Kolkata and Delhi. This comprehensive study, made clear the possible mechanisms of dissemination among bacterial cells [20].

WHO's 2014 report on the global scenario of antimicrobial resistance states that the problem of antibiotic resistance is no longer a problem of the future but rather the present, an on-going situation causing a risk in the ability to treat common infections in the hospitals [21-24]. Without immediate and urgent coordinated action, the world would lead towards a post-antibiotic era, in which common infections and minor injuries treatable for decades can once again kill [25]. A few infections which gained resistance are mentioned below:

- Resistance is found against the most widely used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* - fluoroquinolones-are very widespread [26].
- Resistance to first-line of drugs to treat the infections caused by *Staphlylococcus aureus* is also widespread [27].
- Resistance to the treatment of a life-threatening infections caused by a common intestinal bacteria-carbapenem antibiotics-has spread to all regions of the world [28].

2.1 Tuberculosis

In accordance to the report published in 2013, an estimate of 480,000 new cases of multi-drug-resistant tuberculosis (MDR-TB) was recorded globally. Among these cases, nearly 3.5% were new cases and 20.5% were previously treated for MDR-TB. In addition to this data nearly 100 countries from around the world were identified to report extensively drug-resistant TB (XDR-TB) [24,29,30].

2.2 Human immunodeficiency virus (HIV)

HIV drug resistance occurs when the virus replicates inside an infected person who is undergoing Antiretroviral Therapy (ART). With the use of well-managed ART, the resistance scenario is emerging rapidly. Some studies reported that increase in access to ART will eventually lead to the rise in HIV drug resistance. The situation is in such a level that the first-line and second-line ART will be rendered ineffective, threatening the lives of people [31,32]. Even-though USA is the biggest national funder for HIV research, it discovers approximately 50000 new infections each year, facing the major HIV epidemic [33].

2.3 Influenza

In the past 10 years the use of antiviral drugs was an important tool for the treatment of epidemic and pandemic influenza. This lead to the trend of piling up the stock medicine for the pandemic preparedness, but the constantly evolving nature of influenza is gaining resistance over these drugs. Antiviral susceptibility is constantly monitored by the WHO Global Surveillance and Response System.

2.4 Pneumonia

The increasing incidence of multiple-antimicrobial resistance among *Streptococcus pneumoniae* isolates is becoming a problem throughout the world [34,35]. Penicillin resistance has become widespread and is a worldwide occurrence. Resistance to other classes of antibiotics traditionally used as alternatives in the treatment of pneumococcal infections has also increased markedly during recent years. In some areas of USA, Europe and East Asia, prevalence of macrolide resistance has been reported recently as high as 35%. From the clinical standpoint, a growing number of failures following the use of these agents has been described [36,37].

3. Classification of Drug Resistance

Drug resistance is generally classified into two types, Intrinsic and Acquired. The classification is based on whether the organism or cell was resistant before the treatment began or it was initially drug sensitive but developed resistance during treatment. The former is known as intrinsic resistance or natural resistance while the latter is known as Acquired or *de novo* resistance [38].

3.1 Intrinsic resistance

The natural property of microorganisms to resist any drug due to evolution is known as intrinsic resistance [39]. This type of resistance is present in all bacterial species. It may be due to the structure of cell membrane, presence or absence of the drug binding protein, the absence of a biochemical pathway, presence or absence of drug metabolizing enzyme, the expression of specific stress response proteins or high repair capacity, etc. [38]. Apart from bacterial outer membrane and active efflux, intrinsic resistance is also mediated by a number of additional genes and genetic loci [40]. Enterococcii are naturally resistant to cephalosporins because they do not have the peptidoglycan binding protein to which the drug binds. *Klebsiella* are resistant to ampicillin due to the production of beta lactamase, that destroys the drug before it can reach its target [41,42]. In many microbes, the low permeability of its cell wall or its unusual structure plays a major role in drug resistance. Thus lipid bilayer of unusual fluidity and abnormal thickness possibly slows down lipophilic drugs [43,44].

3.2 Acquired resistance

Acquired resistance can be defined as the resistance developed by a microorganism against the activity of a particular antimicrobial agent, to which it is previously sensitive. This type of resistance is developed due to gene mutations and extra chromosomal segments resulting in gene exchange [39]. Three types of genetic changes are possible: mutation and amplification of the mutated gene which is involved in the pathway responsible for resistance, gene mutation causing altered expression of proteins involved in stress response processes, and gene transfer [38]. While in many bacteria, acquired resistance is generally obtained through horizontal gene transfer, in mycobacteria it occurs mainly by spontaneous mutation in targeted genes. Alterations in drug efflux mechanisms are a common cause of multidrug resistance. In Gram-positive bacteria, association between efflux pump overexpression and MDR has been reported. In *S. aureus* strains, overexpressing efflux pumps were common and they show resistance to methicillin [45-47]. Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections are mostly reported due to unhealthy hospital environment and poorly maintained ICU conditions, causing simple skin infection to deadly infections example pneumonia, osteomyelitis [33].

In bacteria and fungi, cell wall has an important role in their survival. Antimicrobial drugs inhibit cell wall synthesis by binding to peptidoglycan layer of bacteria (e.g. Cephalosporin) or by inhibiting ergosterol synthesis in fungus (e.g. Fluconazole). These microbes undergo chromosomal mutation or through conjugation or transformation (e.g. *K. pneumoniea*) exchange their extrachromosomal DNA, altering cell membrane composition, example; reduction in ergosterol content in plasma membrane [48,49]. This reduces cell membrane permeability and decreased drug intake [1,50-52]. This also results in decreasing active target sites for drugs. Beta lactamase producing microbes inactivate or degrade antimicrobials by hydrolysing their ester or amide bonds. The resistant strains of different microorganisms either oxidise or reduce the antimicrobial drugs to inhibit their interaction with the target sites [51].

Antiviral drugs generally target viral DNA polymerase with reverse transcriptase activity. Resistant microbes have mutated gene responsible for reverse transcription, inhibiting the interaction between drug and the enzyme. The protozoan parasites like *Plasmodium* spp. and *Toxoplasma gondii* also undergoes mutation (point or substitution), altering the drug targeted sites, altering calcium homeostasis in endoplasmic reticulum [53]. This results in expulsion of drugs like atovaquone, antifolate combination drugs out of the cell [54,55]. Overall drug efflux pumps are the predominant mechanism of MDR. Overexpression of genes encoding ATP-Binding Cassette (ABC) transporter membrane proteins (e.g. P-glycoprotein), also known as the multidrug efflux pumps, responsible for export or expulsion of drugs out of the cell, generates MDR and allows normal cell functioning without any interference [49,56]. In *Entamoeba* spp. and *Leishmania* spp. membrane, overexpression of P-glycoprotein or multidrug resistant proteins (MRP) alters the fluidity and permeability causing ATP-dependent efflux of the antimicrobials and thereby decreasing their intracellular concentration [15,57,58]. *E. coli* efflux system AcrAB-TolC has shown to be able to expel chloramphenicol, fluoroquinolone, tetracycline,

novobiocin, rifampin, fusidic acid, nalidixic acid and β-lactam antibiotics [59].

4. Role of Environment in Antimicrobial Resistance

Change in natural ecosystem, as a consequence of human activities has led to increase in the resistance of human pathogens. Overuse of antibiotics is one of the major causes of increasing multi drug resistance [60]. Lack of measures for infection prevention and control, poor hygiene has contributed equally to the proliferation and rapid spread of resistant strains. Hospitals, where most drugs are used and prescribed, are the places where most drug resistant strains are observed (e.g. sulfonamide-resistant *Streptococcus pyogenes,* penicillin-resistant *Staphylococcus aureus*) [61].

In tropical countries due to warm and moist climate and close proximity of non-human vectors, the possibility of survival of pathogenic and commensal bacteria is more. World's fastest growing cities are located in the developing countries and overcrowding in these places and lack of clean water and proper sanitation is increasing the chances of amplification of the resistant strains [62].

Food preservatives used nowadays, targets to increase the lag phase of bacteria to decrease or inhibit bacterial growth but these preservatives in turn making these bacteria resistant by increasing their genetic and phenotypic adaptations. This in turn is increasing the genetic diversity and the chances of survival for the pathogens [63,64].

The contamination of water by the hospital effluents and or livestock farms is responsible for rapid amplification of resistant strains of enteric bacteria. Recycled sewage sludge used for agricultural purpose contains numerous antibiotic resistant strains. Similarly, manure from animal farms, contain antibiotics. Bacteria getting exposure to these antibiotic residues become resistant eventually and horizontal transfer of antibiotic resistant gene increases the frequency of these antibiotic resistant bacteria [65].

Plasmid encoded *qnr* genes in *Aeromonas* spp. has been reported. The same plasmid containing the same *qnr* gene has been found in different distant locations, which indicates that if these resistant genes get encoded in the gene transfer element, they can be easily disseminated [66].

5. Step Forward for a Solution. What could be done?

AMR developed into a complicated issue waving a path to become an international dreadful concern. In order to get a hold on this issue of AMR, cooperative efforts (Figure 1) from different individual sectors is the need of the Era [1,48,67]. As a part of this, various Antimicrobial Stewardship Programs (ASPs)

Figure 1. Key role players that could reduce the effect of antimicrobial resistance.

are organised these days for optimizing antimicrobial therapy thereby also focussing on reduced treatment-related cost and also improving clinical outcomes and safety, thus minimizing or stabilizing AMR [68].

The major way to preserve the potency of these existing antibiotics is by decreasing the overall antibiotic use, which is to be individually taken care by Physicians, pharmacists and the general public.

- Antibiotics must be prescribed only for bacterial infections and in the proper dose for the correct amount of time.
- Narrow spectrum drugs should be chosen by doctors whenever possible to avoid destroying populations of beneficial bacteria along with the disease-causing bacteria.
- In addition, non-therapeutic uses of antibiotics in farm animals and agriculture should be eliminated.

The epidemic of resistant bacteria has spurred among researchers in finding novel antibiotics, but on the other hand the process of producing a new antibiotic is long and expensive process requiring approximately ten years in addition to that nearly $300 million to bring a new antibiotic to market. Many a times, the efforts to find novel drugs in fungi and soil microorganisms results in compounds that are either same or similar to the previously discovered antibiotics, thus resistance to these new antibiotics eventually develops, and emergence of resistance is evident in as little as two years. Nevertheless, the searching for new antibiotics is still an on-going process [69].

One approach taken by researchers to combat antibiotic resistance is to strengthen the action of

existing antibiotics by modifying them so the bacterial enzymes that cause resistance cannot attack them. Alternately, "decoy" molecules can be used along with the antibiotic, so that the bacterium's resistance enzyme attacks the decoy molecule rather than the antibiotic. Decoy molecules such as clavulanic acid or sublactam are already in use for blocking the beta-lactamase enzymes that destroy the penicillin family of drugs [70].

An alternative approach to the antibiotic resistance problem is to interfere with the mechanisms that promote resistance, rather than the attempt to kill the bacteria. For example, interfering with the duplication or movement of a bacterium's genetic material would eliminate the transfer of resistance genes between bacteria [71].

These interventions by the ASPs aims to either restrict the availability of selected antimicrobial agents, termed as “front-end,” or by examining broad spectrum use of antibiotics and then streamlining or discontinuing it, known as “back-end” [72]. Therefore, there is an urgent need of support and coordination at the global, regional, sub regional and national level to serve in future progress [48].

6. Conclusion

Drug resistance is emerging as a worldwide threat. Over the time many infectious microbes are becoming resistant to the drug designed to kill them, making the drugs infective. As most microbes divide and evolve rapidly, they become resistant to these drugs. Lack of new drugs to combat MDR threat is leading to global crisis.

Overuse and misuse of these drugs, enhances the resistance of these microbes. Development of resistant strains is inevitable but a coordinated way to avoid overuse, increasing public awareness, maintaining hygienic waste disposal from hospitals and farms may help in controlling the rapid development of microbial drug resistance [73]. To increase the effectiveness of antimicrobial drugs, Physicians may prescribe Decoy molecule which mimics the antibiotics giving a way for the drug to reach their site of action.

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