Current Research in Microbiology

Chapter 6

The Emerging Prospects of Global Anti Microbial Resistance: Pros and Cons

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Keywords: Antimicrobial Resistance; MDR; XDR; PDR; Antibiotic; Transposons; Integron; Plasmids

Abstract

In the past years infections caused by multidrug-resistant (MDR) microorganism have dramatically increased in all parts of the world. Novel resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. Although MDR is typically credited to chromosomal mutations, resistance is most commonly associated with extrachromosomal elements acquired from other microorganism in the environment. These include altered types of mobile DNA segments, such as plasmids, deletion and insertion sequences, transposons, and integrons. However, inherent mechanisms includes decreased cell wall permeability to antibiotics, alternative relying on a glycoprotein cell wall, altered target sites of antibiotic, enzymatic deactivation of antibiotics, efflux pumps that expel multiple kinds of antibiotics are now recognized as major contributors to resistance in microorganisms. In present scenario, combating with emergence and spread of antibiotic-resistant microganism is one of the major global issues.

1. Introduction

In the last decade we have witnessed a dramatic increase both in the proportion and absolute number of bacterial pathogens presenting multidrug resistance to antibacterial agents [1]. Organizations such as the US Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) are considering infections caused by multidrug-resistant (MDR) bacteria as an emergent global disease and a major public health problem [2].

"There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring 'fastness' [resistance]."

Alexander Fleming, 1946

2. Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) is recognized as a growing global threat. AMR develops when micro-organisms – bacteria, parasites or viruses – no longer respond to the drug or drugs designed to treat them. AMR is a way for any bacteria that has been exposed to an antibiotic to develop resistance or modify its genetic footprint in order to survive [3]. Antimicrobial resistance occurs everywhere in the world today, compromising our ability to combat infectious diseases, as well as undermining many other advances in health and medicine. AMR also increases the costs of health care. When infections become resistant to first-line drugs, more expensive therapies must be used to treat them. Lengthier treatment, often in hospitals, substantially increases health care costs as well as the economic burden on families and societies [4].

2.1. Antibiotic resistance

Microbes are small organisms which can not see by necked eye. There are various types of microbes as, bacteria, viruses, fungi, and parasites. Although most microbes are harmless and even useful to living organisms, some can cause disease. These disease-causing microbes are called pathogens. Microbes have the ability to develop resistance to the drugs becoming drug-resistant organisms. An antimicrobial is a kind of drug that destroys or rests the growth of microbes, as bacteria, viruses, fungi, and parasites [5]. Antibiotic resistance is the ability of bacteria to resistance the effects of an antibiotic, so the bacteria are not destroyed and their growth still occur. Resistant bacteria to the antibiotic lead to rapid growth of microorganisms and spread them in to other organs. Furthermost infection-causing bacteria can become resistant to at least some antibiotics. Bacteria that are resistant to numerous antibiotics are known as multi-resistant organisms (MRO). A number of bacteria are naturally resistant to some antibiotics such as bacteria in gut [6,7].

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3. Terminology Related to Antimicrobial Resistance

3.1. Multiple drug resistance (MDR)

Multidrug resistance or multiresistance is antimicrobial resistance shown by a species of microorganism to multiple antimicrobial drugs. In literal terms, MDR means 'resistant to more than one antimicrobial agent. Many definitions are being used in order to characterize patterns of multidrug resistance in Gram-positive and Gram-negative organisms. The definition most frequently used for Gram-positive and Gram-negative bacteria are 'resistant to three or more antimicrobial classes of antibiotics' [8,9] (**Figure-1**).

3.2. Extensively drug-resistant (XDR)

XDR microbes that are classified as XDR are epidemiologically significant due not only to their resistance to multiple antimicrobial agents, but also to their ominous likelihood of being resistant to all, or almost all, approved antimicrobial agents. In the medical literature XDR has been used as an acronym for several different terms such as 'extreme drug resistance', 'extensive drug resistance', 'extremely drug resistant' and 'extensively drug resistant'. Initially, the term XDR was created to describe extensively drug-resistant Mycobacterium tuberculosis (XDR MTB) and was defined as 'resistance to the first-line agents isoniazid and rifampicin, to a fluoroquinolone and to at least one of the three-second-line parenteral drugs (i.e. amikacin, kanamycin or capreomycin)' [10]. Subsequent to this, definitions for strains of non-mycobacterial bacteria that were XDR were constructed according to the principle underlying this definition for XDR MTB (i.e. describing a resistance profile that compromised most standard antimicrobial regimens) [11] (**Figure-1**).

3.3. Pandrug resistant (PDR)

PDR From the Greek prefix 'pan', meaning 'all', pandrug resistant (PDR) means 'resistant to all antimicrobial agents' [12]. Definitions in the literature for PDR vary even though this term is etymologically exact and means that, in order for a particular species and a microbes isolate of this species to be characterized as PDR, it must be tested and found to be resistant to all approved and useful agents. Examples of current definitions are: 'resistant to almost all commercially available antimicrobials', 'resistant to all antimicrobials routinely tested' and 'resistant to all antibiotic classes available for empirical treatment', making the definition of PDR subject to inconsistent use and liable to potential misinterpretation of data [13] (**Figure-1**).

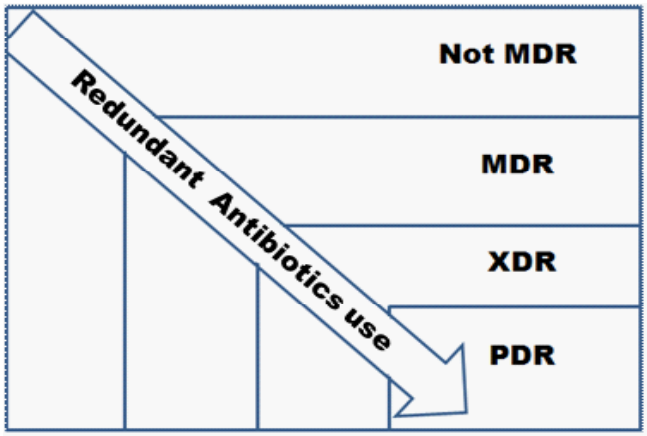

Figure 1: An epidemiological correlation between MDR, XDR and PDR

4. Diversified Microbial Resistance

4.1. Resistance in bacteria

Various microorganisms have survived for thousands of years by their ability to adapt to antimicrobial agents. They do so via spontaneous mutation or by DNA transfer. This process enables some bacteria to oppose the action of certain antibiotics, rendering the antibiotics ineffective [14].

Commonest multidrug-resistant organisms (MDROs)

- Multi-drug-resistant Tuberculosis(15).
- Methicillin-Resistant Staphylococcus aureus (MRSA)(16).
- Vancomycin-Resistant Enterococci (VRE).
- Extended-spectrum β-lactamase (ESBLs) producing Gram-negative bacteria.
- Klebsiella pneumoniae carbapenemase (KPC) producing Gram-negatives
- Multidrug-Resistant gram negative rods (MDR GNR) MDRGN bacteria such as Enterobacter species, E.coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa (17).
- A group of gram-positive and gram-negative bacteria of particular recent importance have been dubbed as the ESKAPE group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species) (18).

4.2. Resistance in fungi

Some yeasts species like Candida can become resistant under long term treatment with azole preparations, requiring treatment with a different drug class. Scedosporium prolificans

infections are almost uniformly fatal because of their resistance to multiple antifungal agents [19,20].

4.3. Resistance in viruses

In 2010, an approximate 7% of people starting antiretroviral therapy (ART) in developing countries had drug-resistant HIV. In developed countries, the same figure was 10–20%. Some countries have recently reported levels at or above 15% amongst those starting HIV treatment, and up to 40% among people re-starting treatment [21]. HIV is the prime example of MDR against antivirals, as it mutates rapidly under monotherapy [22]. Influenza virus has become increasingly MDR; first to amantadenes, then to neuraminidase inhibitors such as oseltamivir, (2008-2009: 98.5% of Influenza A tested resistant), also more commonly in people with weak immune systems [23,24]. Cytomegalovirus can become resistant to ganciclovir and foscarnet under treatment, especially in immunosuppressed patients [25]. Herpes simplex virus rarely becomes resistant to acyclovir preparations, mostly in the form of cross-resistance to famciclovir and valacyclovir, usually in immunosuppressed patients [26].

4.4. Resistance in parasites

In July 2016, resistance to the first-line treatment for P. Falciparum malaria (artemisinin-based combination therapies) has been confirmed in 5 countries Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam) [27]. The prime example for MDR against antiparasitic drugs is malaria. Plasmodium vivax has become chloroquine and sulfadoxinepyrimethamine resistant a few decades ago, and as of 2012 artemisinin-resistant Plasmodium falciparum has emerged in western Cambodia and western Thailand. Toxoplasma gondii can also become resistant to artemisinin, as well as atovaquone and sulfadiazine, but is not usually MDR. Antihelminthic resistance is mainly reported in the veterinary literature, for example in connection with the practice of livestock drenching and has been recent focus of FDA regulation [28].

5. Genetics of Multidrug Resistance

Bacterial antibiotic resistance can be attained through intrinsic or acquired mechanisms. Intrinsic mechanisms are those specified by naturally occurring genes found on the host's chromosome, such as, AmpC β-lactamase of gram-negative bacteria and many MDR efflux systems [29]. Acquired mechanisms involve mutations in genes targeted by the antibiotic and the transfer of resistance determinants borne on plasmids, bacteriophages, transposons, and other mobile genetic material. In general, this exchange is accomplished through the processes of transduction (via bacteriophages), conjugation (via plasmids and conjugative transposons), and transformation (via incorporation into the chromosome of chromosomal DNA, plasmids, and other DNAs from dying organisms). Although gene transfer among organisms within the

same genus is common, this process has also been observed between very different genera, including transfer between such evolutionarily distant organisms as gram-positive and gram-negative bacteria [30]. Plasmids contain genes for resistance and many other traits; they replicate independently of the host chromosome and can be distinguished by their origins of replication [31]. Multiple plasmids can exist within a single bacterium, where their genes add to the total genetics of the organism. Transposons are mobile genetic elements that can exist on plasmids or integrate into other transposons or the host's chromosome. In general, these pieces of DNA contain terminal regions that participate in recombination and specify a protein(s) (e.g., transposase or recombinase) that facilitates incorporation into and from specific genomic regions [31,32]. Conjugative transposons are unique in having qualities of plasmids and can facilitate the transfer of endogenous plasmids from one organism to another. Integrons contain collections of genes (gene cassettes) that are generally classified according to the sequence of the protein (integrase) that imparts the recombination function. They have the ability to integrate stably into regions of other DNAs where they deliver, in a single exchange, multiple new genes, particularly for drug resistance. The super-integron, one which contains hundreds of gene cassettes), is distinct from other integrons; it was first identified in Vibrio cholera [33, 34].

6. Mechanism of Action of Multidrug Resistance

Once exposure to bacteria occurs, infection and bacteria spread occur, so, treatment with suitable drugs as antibiotics must begin. Antibiotics responsible for stop the growth of bacteria and prevent bacteria multiply, so kill them, hence use in treatment of disease. While in the other cases antibiotics loss their ability to stop growth of bacteria, hence multiplication of bacteria increase and this lead to spread antibiotics resistance bacteria and development of disease. Antibiotic resistance can be occurring through various types of mechanisms as shown in **Figure-2**.

6.1. Drug inactivation or modification: for example, enzymatic deactivation as in penicillin G in some penicillin-resistant bacteria through the production of β-lactamases. Protecting enzymes manufactured by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will diminish its capacity to bind to the bacterial ribosomes and disrupt protein synthesis [35,36] (**Figure-2**).

6.2. Modification of target or binding site: for example, alteration of PBP-the binding target site of penicillin's-in MRSA and other penicillin-resistant bacteria, or modification in structure of ribosomal protection proteins. These proteins guard the bacterial cell from antibiotics through changes its conformational shape. Change of proteins conformational shape allows these proteins to loss their activity so, prevent inhibit protein synthesis, and this help in grow of bacteria and spread it [37,38] (**Figure-2**).

6.3. Alteration of metabolic pathway: for example, absence of paraaminobenzoic acid (PABA), this is precursor for the synthesis of folic acid and nucleic acids [39].

6.4. Reduced drug accumulation: By decreasing drug permeability or increasing active pumping out of drugs through cell membrane.

6.5. Efflux Systems: Altered Membranes mechanism also operates in antibiotic resistance for example Porins [40] (**Figure-2**).

6.6. Mutation rate: Increased mutation rate as a stress response leads to evasion of antibiotics.

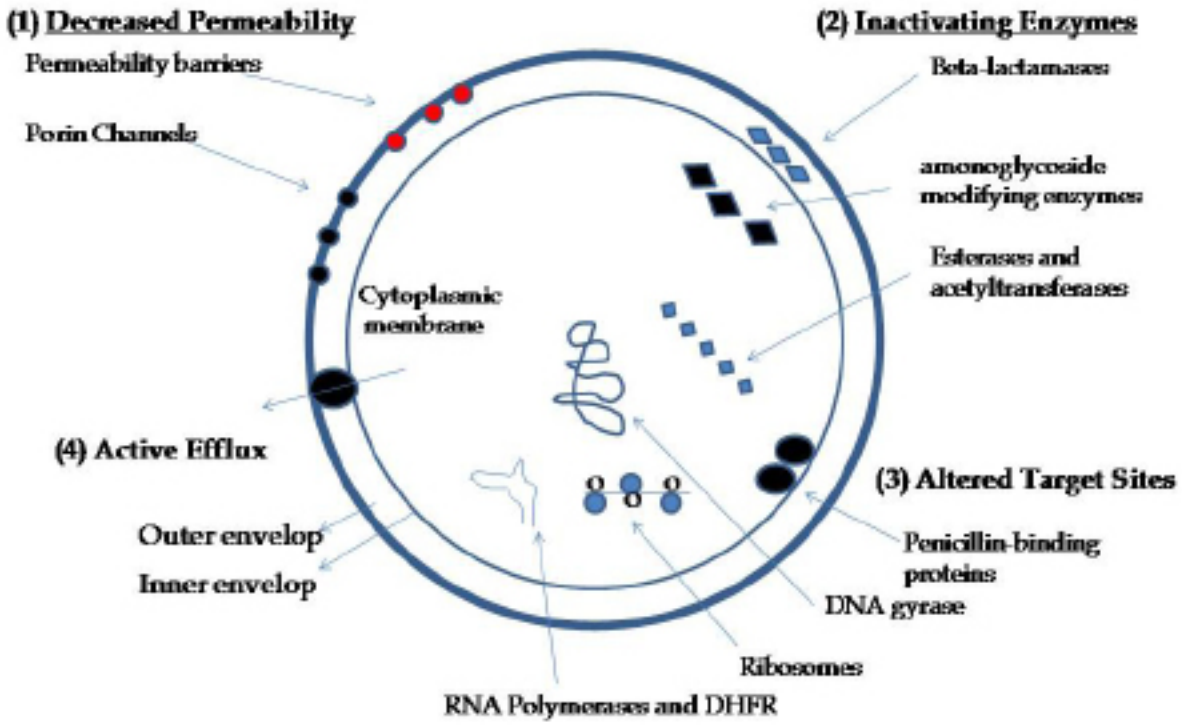

Figure 2: Schematic representation of various aspects of action mechanism of multidrug resistance.

7. Prevention and Control Measures of Microbial Resistance

Antibiotic resistant microbes can be transfer from person to person inside the community. This is becoming more common. With the emergence and spread of antimicrobial resistant pathogens, antimicrobial resistance surveillance is becoming an important task of the Microbiology Laboratory. Antimicrobial resistance surveillance is a ongoing (and organized) data collection that after being analyzed and reported provides useful information for empirical antimicrobial therapy. The following measures can be taken to prevent the emergence and spread of antibiotic resistance worldwide [42,43].

7.1. Prevention and Control: Manual Level

Antimicrobial resistance is a complex problem that affects all of society and is driven by many interconnected factors. Single, isolated interventions have limited impact. Coordinated action is required to minimize the emergence and spread of antimicrobial resistance [44].

WHO is providing technical assistance to help countries develop their national action plans, and strengthen their health and surveillance systems so that they can prevent and manage antimicrobial resistance [45]. The following manual way should be taken to combat the emergence and spread of antibiotic resistance worldwide described in **Figure-3**

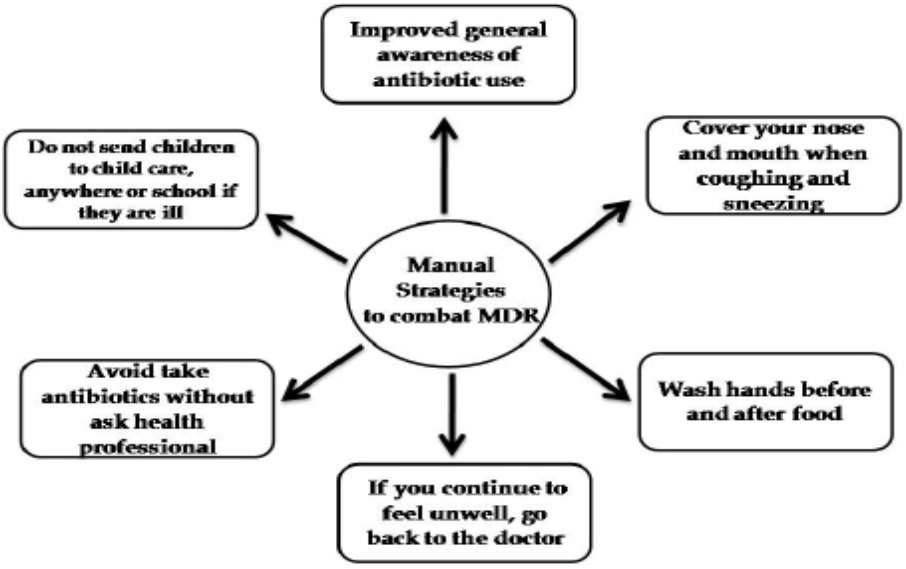

Figure 3: Diagrammatic representation of manual stratgies to combat multidrug resistance.

7.2. Prevention and Control: Molecular Level

Greater innovation and investment are required in molecular research and development of new antimicrobial medicines, vaccines, and diagnostic tools. A better understanding of the molecular basis of antimicrobial resistance has facilitated the development of bioinformatic tools to identify antibiotic resistance genes in bacterial genomes [46,47]. It has defined a strategic research agenda under the assumption that only a collaborative effort will provide the necessary critical mass and scientific expertise to answer the most important and urgent research questions related to antimicrobial resistance [48,49,50]. The following molecular stratgies should be taken to combat the emergence and spread of antibiotic resistance worldwide described in **Figure-4** [51].

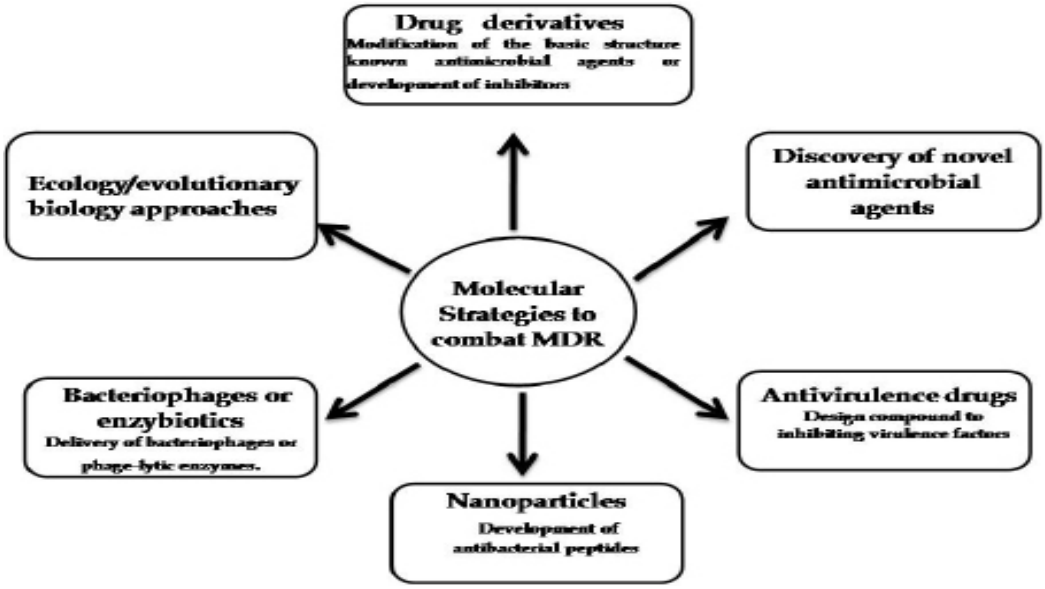

Figure 4: Diagrammatic representation of molecular stratgies to combat multidrug resistance.

8. Future Prospects and Concluding Remark

The presence of multiple drug-resistant bacteria is responsible for spreading various diseases in the world. Traditional technique fails to solve this problem. The prompt identification of the antimicrobial susceptibility of a microorganism, on the other hand, ensures the administration of the correct treatment and reduces the need for broad-spectrum drugs, limiting the emergence of antimicrobial resistance. Molecular technique like mass spectrometry, Crystallography, NMR, 2 Dimensional electrophoresis have shortened the time to detect specific resistance mechanisms and the development of next generation sequencing technologies has increased the number of sequenced bacterial genomes at an exponential rate. A better understanding of the molecular basis of antimicrobial resistance has facilitated the development of bioinformatic tools to identify antibiotic resistance genes in bacterial genomes. Similarly, advanced applications of nanoparticles and bacterial microencapsulation to clinical are very promising and might be fully developed in the years to come. Phage therapy is an important alternative to antibiotics in the current era of drug-resistant pathogens. Bacteriophages have played an important role in the expansion of molecular biology, not only, but also play important role in overcome antibiotic resistance.

A global and coordinated initiative to tackle antibiotic resistance will be needed to persuade the general population and policy makers of the advantages, both medical and economic, of combating the threat of antimicrobial resistance.

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