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Review Article

RESISTANCE TO MULTIPLE DRUGS IN MICROORGANISMS

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Article History	Abstract
Received: 03-04-2024 Revised: 28-04-2024 Accepted: 15-06-2024	Certain microorganisms have the capacity to withstand the effects of several antimicrobial drugs, a phenomenon known as multiple drug resistance (MDR). Those that are resistant to several antibacterial, antifungal, antiviral, and anti-parasitic medications are classified as MDR. Antimicrobial resistance (AMR) is the ability of some microorganisms to engage in actions that are similar to those of a chemical (drug) that would typically kill them or restrict their growth. Primary, secondary, intrinsic, widespread, and clinical resistance are the several categories under which multidrug resistance might fall. Hundreds of thousands of deaths worldwide are attributed to the global problem of multi-drug resistance (MDR) among bacteria. Legislative actions have been taken globally to restrict or outlaw the use of antibiotics in response to the notable rise in MDR bacteria.
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Keywords: Multi drug resistance, Microorganisms, Antibiotic Resistance.	

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Introduction

Multiple drug resistance (MDR) is an antimicrobial resistance exhibited by some microorganisms to multiple antimicrobial drugs. MDR microorganisms are mostly threatening to public health because they resist multiple antibiotics. Other MDR include those that are resistant to multiple antifungal, antiviral, and anti-parasitic drugs. In the present situation, an increase in antibiotic-resistant microorganisms has become one of the most vital threats to the healthcare sector. Multidrug-resistant bacteria (MDR) that are deadly pathogenic are rising day by day and pose a very serious threat to human health.

1. Classification of Multi Drug Resistance:

Administration of appropriate doses of drugs for a particular duration of time, survival of different microbial strains suggests the high levels of resistance developed in them (1). This clinical failure is as a result of not only the antimicrobial resistance but also the suppressed immune function, deprived or poor drug bioavailability, or increased rate of drug metabolism. Multi drug resistance can be classified as primary or secondary resistance.

Secondary resistance: This is also known as “acquired resistance,” this term is used to define the resistance that only occurs in an organism after an exposure to the drug (2). This can also be defined as

resistance that evolve in a patient who has previously received chemotherapy. For example, acquired drug resistance expressed tuberculosis isolated from patients who currently are getting or until that time have received anti-tuberculosis drug treatment for at least one month (3).

It can further be classified as follows;

Intrinsic resistance: Intrinsic resistance is the innate ability of a microorganism to resist activity of a particular antimicrobial agent through its inherent structural or functional characteristics, which allow tolerance of a particular drug or antimicrobial class. This can also be called “insensitivity” since it occurs in organisms that have never been susceptible to that particular drug. Such natural insensitivity can be due to:

- Lack of affinity of the drug for the bacterial target
- Inaccessibility of the drug into the bacterial cell
- Extrusion of the drug by chromosomally encoded active exporters
- Innate production of enzymes that inactivate the drug (4).

For example, Gram-positive bacteria to aztreonam (a beta lactam), Gram-negative bacteria to vancomycin, anaerobic bacteria to aminoglycosides, aerobic bacteria to metronidazole etc (5).

Common Drugs: Victim of Resistance

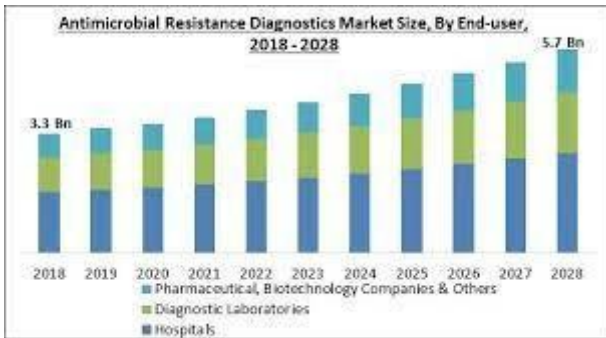


Figure 1: Microorganisms and their resistance mechanism to various Antibiotics.

2. Antibiotic Resistance Mechanisms in Gram Positive Bacteria:

The major threat in the present scenario is an increase in MDR bacteria and the unavailability of novel antibiotics to kill them. Nowadays, the research is mainly focused on searching for novel methods to treat such MDR.

Among such deadly pathogens, β -lactamase-resistant *Streptococcus pneumoniae*, methicillin resistant *Staphylococcus aureus* (MRSA), and vancomycin resistant *Enterococcus faecalis*. There are two main mechanisms through which Gram-positive bacteria develop resistance to antibiotics. These are as follows:

- (i) Secretion of β -lactamases, i.e., responsible for the enzymatic breakdown of antibiotics
- (ii) By reducing the affinity and susceptibility of their target site, e.g., PBP (penicillin-binding protein), through either attainment of exogenous DNA or through mutation among native PBP genes (6)

Different antibiotics have diverse mechanisms of action. A few such examples are given below.

(i) Penicillin-binding proteins were targeted by β -lactams which bring about the end step of cell wall synthesis that ultimately cause cell death. β -lactamases are responsible for the deactivation of the antibiotic and hence develop resistance.

(ii) Vancomycin and teicoplanin are glycopeptides. These antibiotics also inhibit the end step of cell wall synthesis. Attainment of the van gene cluster (VanA, VanB, VanC, VanD, VanE, and VanG) is mainly responsible for the development of resistance that ultimately causes less binding affinity to glycoproteins (7)

(iii) Other antibiotics like quinolones act on the DNA gyrase and topoisomerase IV enzymes and inhibit their function. This results in bacterial death. Resistance to quinolones develops due to the mutations occurring in the subunits of these two enzymes (*grIA/grIB* and *gyrA/gyrB*)

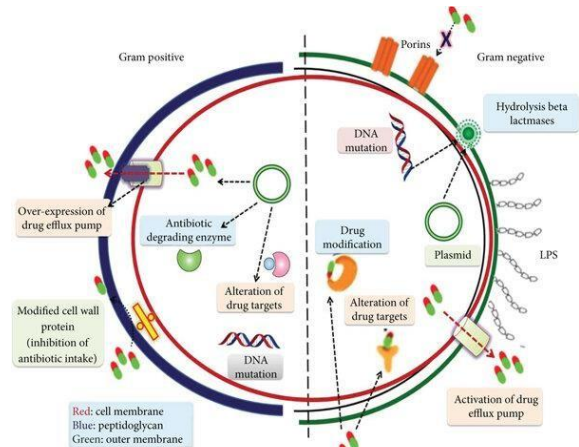


Figure 2 : Resistance mechanism found in Gram-positive and Gram-negative bacteria.

3. Antibiotic Resistance Mechanisms in Gram-Negative Bacteria:

Natural products have been used to cure many ailments since ancient times. For example, the cinchona tree contains quinine, which is used to treat malaria. Since Fleming discovered penicillin in 1929, a plethora of antibacterial medicines have been developed, all of which have had a significant influence on human health and death rates across the world (8). Antibiotics have been overused and misused, resulting in the emergence of new resistant forms.

Screening for Multi-Drug Resistant Bacteria:

Multidrug resistant (MDR) bacteria pose a significant threat to society in general and the safe application of medical care in particular. As drug resistance rises, healthcare-associated infections become an increasing threat to medical practice, because infections caused by MDR bacteria are associated with higher incidences of mortality and prolonged hospital stay (9).

Patients at risk of being colonised with MRSA at admission to hospital have routinely been screened for colonisation since 2000. In 2007, Vancomycin-Resistant Enterococci were added to the list of reportable multidrug resistant bacteria, as well as the multidrug resistant Gram-negative bacteria (MDRGN), such as the gut bacteria *Klebsiella pneumoniae* and *E. coli* that produce Extended-Spectrum Beta-lactamases (ESBLs) and/or carbapenemases. These bacteria are resistant to our most valuable and most used antibiotics (10).

4. Alternative Techniques for Controlling MDR Infections:

4.1. Use of Nanotechnology to Create anti-MDR-Resistant Nano bacterial Agents. According to one study, nanoparticles can be used to replace antibiotics and certain disinfectants. Liposome nanoparticles made of both inorganic and organic materials, such as silver, zinc, gold, and copper, can be used as antibiotics and disinfectants. The polyelectrolyte (PAH) surface-modified gold nanoparticles and silver nanoparticles had a symbiotic repressive effect of about 100% on *Bacillus Calmette-Guerin* and *E. coli*, while the silver nanoparticles

conjugated with curcumin had a combined antimicrobial effect on *Pseudomonas aeruginosa* and *E. coli*. In rat models, monotype chemoattractant protein-1 (MCP-1) nanocoated on orthopaedic implants with interleukin-12 p70 (IL-12p70) and multilayer polypeptide nanoscale coatings with IL-12 powerfully arouse the body's innate defence against open fracture (11).

4.2. Essential Oils and Mono-/Bi-/Tri-Metallic Nanocomposites as Alternate Sources of Antibacterial Agents in the Fight against Multidrug-Resistant Pathogenic Microorganisms. Plants' active phytochemicals, bioactive substances, secondary metabolites, and essential oils are thought to be important in combating antibiotic resistance in pathogenic bacteria. The amount of bioactive components found in various essential oils, for example, has a significant and unique function; essential oils isolated from cinnamon and black pepper, for example, damage cell membranes and inhibit *E. coli* and *S. aureus* metabolic activity (12).

5. Broad overview of current market issues related to AMR/ MDR and trends in R&D for new antibiotics covering both private and public sectors:

There is a lack of new antibacterial medicines and vaccines as the growth in AMR/MDR has been accompanied by a sharp decline in development of new treatments. Over the past three decades only two new classes of antibacterial medicines have been discovered, compared to 11 in the previous 50 years. The number of antibiotics becoming obsolete due to resistance significantly exceeds the number of new, approved treatments (13).

The two new classes of treatments relate to pulmonary multidrug-resistant tuberculosis (MDR-TB), where drug resistance has been on the rise. The first is Otsuka's delamanid, which was granted approval in 2014 by Japan, the Republic of Korea and within the EU (to be used in combination with other anti-TB medicines). In November 2014, WHO issued policy guidance on the use of delamanid, to assist access in developing countries. The second was Janssen Pharmaceutical's bedaquiline, which was granted approval in Peru, the Philippines, the Republic of Korea, the Russian Federation, South Africa and the USA. In 2015 the US Food and Drug Administration (FDA) approved tazobactam by Cubist (fully owned by MSD) and Allergan/AstraZeneca's Avycaz, both for the treatment of complicated urinary tract and intra-abdominal infections, as well as bacterial pneumonia (14).

They called on governments to work with them in developing new and alternate market structures to provide more dependable and sustainable market models. This includes new incentives for R&D, new mechanisms to ensure that the price of antibiotics reflects value, and payment models that reduce the link between profitability and volume of sales. The declaration also sets out the commitment by the companies across three broad areas:

- 5.1. reducing the development of drug resistance
- 5.2. increasing investment in R&D that meets global public health needs
- 5.3. improving access to high-quality antibiotics for all.

6. Global experience:

A review of the literature exposed significant differences in the way countries use antibiotics. For example, in Europe, the Scandinavian countries use comparatively few antibiotics, and consequently have very low levels of resistance (15). On the conflicting, countries like Greece, Italy and a number of Eastern European countries are quite heavy users and hence display pronounced levels of antibiotic resistance. Many other regions and countries, like India, China and the Americas, are weighty users, and also use antibiotics as animal growth promoters. Hence the same vast differences are seen in animal production-related use as some countries are accumulating antibiotics to animal feed as a matter of course. There are significant resemblances within all countries as there is a need for an effective health system. Confirming access and appropriate use depends on multiple factors operating within a well-functioning and well-managed national healthcare system:

- rational selection and use
- reasonable prices
- sustained financing
- reliable health supply systems
- robust regulation and enforcement systems.

GARDP held a provincial workshop in Cape Town, South Africa, in September 2016. Forty- five participants from 11 African countries participated in the meeting (16).

Poor countries often suffer from lack of regulations for antibiotics, leading to access to substandard or falsified antibiotics. Substandard antibiotics often have a lower dosage of the active ingredient that results in increased resistance. It is clear that policies for appropriate supervision and control by regulatory agencies are needed to prevent the supply of expired, substandard and counterfeit medicines.

Evidence suggests that when antibiotics are available the issues are the same for all countries. Overuse leads to greater levels of resistance and hence effective antibiotic stewardship is crucial. However, sustainable access to effective antibiotics, both existing and new, remains a key challenge (17).

7. Access to new-generation antibiotics and stewardship:

Any stewardship framework needs to ensure access for patients who need treatments while preventing inappropriate use. An effective health system is essential for both access and stewardship so that patients can be appropriately diagnosed, treated (being made aware of the crucial importance of medicine adherence), and cured

(18). WHO has produced an options document that details key considerations for the establishment of a global development and stewardship framework. This includes the type of instrument that could be used, scope of medical products, how to define and promote appropriate use, development of new treatments, tools and vaccines and affordable access (19).

The MPP has a similar mechanism with generic producers who are members of the pool. Failure to utilize the license through manufacture and sufficient supply of the associated product ultimately results in withdrawal of the license.

There are opportunities for collaboration between different entities and initiatives where expertise, best practice and networks could be combined to achieve shared goals. For instance, platforms could be explored where various stakeholders could come together for the development of combination treatments or other important formulations (20, 21, 22).

Conclusion

Newer drug development is necessary due to the insufficiency of existing antimicrobial medications. MDR is an inevitable natural occurrence that poses a major global threat to public health; in many instances, up to 100% of food-borne infections resistant to drugs are emerging in developing nations, mostly in Asia and Africa. Deeper understanding of the pathobiology of microbial organisms will be fostered by improved understanding of the molecular mechanisms governing MDR, which should aid in the development of novel medicines to battle these resistant infections. The rapid and effortless dissemination of multidrug resistance among bacteria poses a worldwide risk to both humans and animals. This necessitates the development of both comprehensive drug resistance diagnosis and alternative bacterial control strategies that do not include the use of antibiotics. Consequently, there is a strong need to create new tactics for the management of bacterial infections. In response, bacteriophages, antimicrobial peptides, and combinations of two or more antibiotics have been investigated as potential novel therapeutic approaches.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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