Acta Scientific MICROBIOLOGY (ISSN: 2581-3226)

Volume 5 Issue 9 September 2022

Review Article

Emerging Threats to Community Due to Antimicrobial Resistance: Mechanism and Facts

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DOI: 10.31080/ASMI.2022.05.1131

Received: July 22, 2022

Published: August 05, 2022

Abstract

Due to emerging resistance mechanisms imposed by the microbes, antimicrobial resistance creates a danger to our ability to treat the prevalent infections. It is particularly concerning to see how the multi-drug resistant microorganisms which are also known as "superbugs," are expanding across the globe and causing diseases that are drug resistant. Clinical trials for new antibiotics are increasingly running out. Out of thirty two antibiotics, six were classified as novel by WHO in 2019. The scarcity of top-notch antimicrobials continues to be a major problem. The lack of antibiotics is wreaking havoc on developing nations, especially for the healthcare industry. As drug resistance grows globally, antibiotics are becoming more and more valuable. Because AMR reduces the patient's recovery or caregiver's productivity by requiring longer hospital period for more intensive and expensive treatment affecting economic and health care cost. Therefore, there should be rationale use of antimicrobials and hence the antimicrobial prescription has to be updated periodically and followed.

Keywords: Anti-bacterial; Antibiotics; Drug-Resistance; Antimicrobial Resistance (AMR); Multi-drug Resistant Bacteria; Anti-fungal; Anti-viral; Anti-tubercular

Introduction

Hope that illnesses could be controlled and prevented arose with the discovery of antibiotics. On the other hand, infections continue to remain the main reason for death in underdeveloped countries. This is brought about by the resurgence of previously treated diseases, the advent of novel diseases, and most importantly, the growth of antibiotic resistance [1]. Antimicrobial resistance (AMR) is the phenomenon in which bacteria, viruses, fungi, and parasites develop antibiotic resistance over time, making infections more challenging to treat and raising the risk of disease transmission, life-threatening sickness, and death [2,3]. Due to drug-resistant microbes that have created new resistance mechanisms, antimicrobial resistance still poses a danger to our ability to treat prevalent diseases. Antibiotic effectiveness declines as medication resistance increases. Illnesses caused by gram-negative bacteria that are carbapenem-resistant, are on the WHO priority pathogen list. These new medicines will eventually become outdated, just like current antibiotics have unless people adjust how they are now utilized [6]. Antimicrobial resistance is primarily brought on by the misuse and overuse of antibiotics, a lack of clean water, sanitation, and hygiene (WASH) for people and animals, inadequate infection and disease prevention and control in hospitals and farms, a lack of effective, reasonably priced drugs, vaccines, and diagnostics, a lack of awareness and knowledge, and a lack of law enforcement. Urinary tract infections, sepsis, and sexually transmitted infections are among the prevalent bacterial illnesses that frequently exhibit antibiotic resistance [5,7]. For instance, among nations reporting to the World Health Organization, resistance to the common antibiotic ciprofloxacin,

which is used to treat urinary tract infections, ranged from 8.4 - 92.9 percent in countries reporting to Global Antimicrobial and Use Surveillance System (GLASS). Life-threatening infections in the intestine can be brought on by a kind of bacteria called *Klebsiella pneumonia*. The global rise of *K. pneumoniae's* resistance to last-resort drugs (carbapenems) is alarming. Hospital-acquired infections are frequently brought on by *Klebsiella pneumoniae*. More than half of patients treated for *K. pneumoniae* infections in different regions do not respond to carbapenem medicines because of resistance [8,9]. Fluoroquinolone medications, which are used to treat urinary tract infections, are highly resistant to *E. coli*. More than half of the people taking this medication in different parts of the world no longer experience any benefit. Life-threatening carbapenem-resistant *Enterobacteriaceae* infections can only be treated with colistin (i.e. *E.coli, Klebsiella*, etc.). Bacteria that are resistant to colistin have also been found in various locations [10]. Our skin's natural bacteria, *Staphylococcus aureus*, is a major cause of sickness in both the general population and the hospital system. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have a 64% higher mortality rate than infections with bacteria that are susceptible to antibiotics [11,13].

In 2019, an antimicrobial resistance indicator was added to the SDG monitoring framework. This indicator helps to measure the number of bloodstream infections caused by MRSA and *E. coli*. Both are resistant to third-generation cephalosporins. GLASS received information on MRSA causing bloodstream infections from 25 as well as information on *E. coli* causing bloodstream infections from 49 nations [12]. MRSA prevalence was 12.11%. Despite the fact that the data do not cover the entire country, 36% of *E. coli* is found to be resistant to third-generation cephalosporins. Management of gonorrhea was hampered due to widespread resistance in incredibly diverse strains of *N. gonorrhoeae*. There has been a rapid rise in resistance to the following antibiotics such as beta-lactam antibiotics, tetracyclines, macrolides, and fluoroquinolones (Table 1). The only empiric treatment for gonorrhea is typically ceftriaxone, an injectable extended-spectrum cephalosporin (ESC). There is an urgent need for novel antibiotics to treat bacterial infections caused by carbapenem-resistant microorganisms. These new medicines will eventually become outdated, just like current antibiotics have unless people adjust how they are now utilized. If effective methods for preventing and treating drug-resistant diseases are not proposed, the mortality rate due to infections caused by drug-resistant micro-organisms will eventually rise. The risks associated with organ transplants, cancer chemotherapy, and surgical operations including cesarean sections and hip replacements will increase [19].

Current scenario

Anti-bacterial resistance

The major antimicrobials which are used to treat common diseases, such as urinary tract infections, sepsis, sexually transmitted diseases, and gastroenteritis, have been showing an increasing rate of drug resistance which has been documented globally, imposing an alert that we are running out of effective antibiotics. In countries reporting to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the Ciprofloxacin resistance rate is found to be ranged between 8.4%- 92.9% for *Escherichia coli* and 4.1% to 79.4% for *Klebsiella pneumoniae* [12].

Common gut bacteria called *Klebsiella pneumoniae* can result in illnesses that are fatal. Over the globe, *K. pneumonia* has developed resistance to the drugs that used as a last resort (carbapenems). *K. pneumoniae* is a significant contributor to hospital-acquired illnesses including pneumonia, bloodstream infections, infections in infants, and infections in patients in intensive care units. More than 50% of patients who are treated for *K. pneumoniae* infections do not respond to carbapenem drugs due to emerging drug resistance [15,20].

Fluoroquinolone medications, which are used to treat urinary tract infections, are widely resistant to *E. coli*. More than half of patients receiving this medication are no longer responding in several nations throughout the world [16].

Life-threatening infections brought on by *Enterobacteriaceae* that are resistant to carbapenem can only be treated with colistin as the last resort. There is also an alert for colistin-resistant bacteria which have been found in various countries causing diseases for which there is no treatment option available [17,18].

Our skin is habitat to the bacterium *Staphylococcus aureus*, which also frequently causes infections in healthcare set-up as well as in the community. It has been seen that methicillin-resistant *Staphylococcus aureus* (MRSA) causing infections increase the mortality rate by 64% compared to infections that respond to treatment [19,21].

Anti-tubercular resistance

Over the globe, the TB epidemic is being threatened by new *Mycobacterium tuberculosis* strains which show resistance to anti-tubercular drugs. According to WHO estimates, there were over 500,000 new cases have been found which are rifampicin-resistant tuberculosis (RR-TB). The majority of these cases were multi-drug resistant tuberculosis (MDR-TB), a type of disease that is resistant to the two most potent anti-tubercular drugs [11,21]. In 2018, one-third of the 500,000 cases who got MDR/RR-TB were identified and reported. Treatment regimens for MDR-TB are much more expensive, time-consuming, and ineffective. Approximately, 60% of the patients with MDR/RR-TB who got treated were successfully cured. MDR-TB was present in 18% of previously treated cases and 3.4% of newly diagnosed cases of TB in 2018 [22].

Anti-viral resistance

Resistance to antiviral drugs is a growing concern in immunocompromised patients because persistent viral replication and extended drug exposure select resistant types of viruses. The majority of antivirals, including antiretroviral (ARV) medications, have developed resistance [19]. Due to the advent of drug-resistant HIV, all antiretroviral (ARV) medications run the risk of going partially or completely inactive (HIVDR). HIVDR can develop in patients undergoing antiretroviral medication, and persons can contract HIV that is already drug-resistant. Countries in Africa, Asia, and Latin America have imposed pre-treatment HIVDR (PDR) to non-nucleoside reverse-transcriptase inhibitors (NNRTIs). PDR is frighteningly prevalent in young children.

In Sub-Saharan Africa, more than 50% of newborns with newly discovered HIV are infected with a virus that is resistant to NNRTI. The most recent WHO ARV guidelines currently suggest using the new medicine dolutegravir as the optimal first-line treatment for both adults and children in light of these findings. In order to prevent the unfavorable effects of NNRTI resistance, the use of this medication is especially necessary [22].

Rising levels of resistance have significant economic repercussions due to expensive second and third line of drug regimens. The HIV drug resistance programme of WHO keeps track of the spread and emergence of resistance to both older and more recent HIV medications worldwide [23].

Anti-parasite resistance

One of the biggest threat to controlling malaria is the evolution of drug-resistant parasites, which increases malaria morbidity and mortality. Most nations with high rates of malaria employ artemisinin-based combination treatments (ACTs), which are advised as the first-line treatment for *P. falciparum* malaria that is not complex. Artemisinin and a companion medication are combined to form ACTs. Studies carried out performed between 2001 and 2019 in Cambodia, Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam have confirmed partial resistance to artemisinin and resistance to a number of the ACT partner medications in these countries [21,24]. This makes choosing the best course of treatment more difficult and necessitates careful observation. Artesunate-sulfadoxine-pyrimethamine failures in some nations were caused by *Plasmodium falciparum*, resistance to sulfadoxine-pyrimethamine, prompting a switch to a different ACT. Evidence indicating the occurrence of mutations linked to partial artemisinin resistance in Rwanda has just been published in Africa. The tested ACTs are still very effective as of right now. However, increased resistance to artemisinin and the ACT companion medications could endanger significant advancements in malaria control and present a serious public health concern [25].

Anti-fungal resistance

Resistance to antifungal drugs is becoming very common, which makes the already challenging treatment environment worse. For individuals who also have other underlying diseases, many fungal infections have existing treatability difficulties including toxicity. One of the most prevalent invasive fungal diseases caused by *Candida Auris*, is already pervasive, with increasing reports of resistance to Fluconazole, Amphotericin-B, Voriconazole as well as growing resistance to Caspofungin. This results in fungal infections that are more challenging to treat, treatment failures, and lengthier stay in hospital which subsequently increases treatment expenses. WHO is conducting a thorough investigation of fungal diseases around the world which will help to outline the important list of fungal pathogens along with an evaluation of antifungal drug development [21,26].

Methods

Peer-reviewed articles were searched and referred for the various cases causing antibiotic resistance. Articles from the

Antibiotic class	Type of resistance	Mechanism of resistance
Aminoglycoside	Decrease in uptake Increased modification	Changes in outer-membrane Aminoglycoside modifying enzymes
Beta-lactams	Altered Penicilin Binding Protein (PBP) Enzymatic degradation	PBP-2a Penicillinase which is classified as per ambler classification
Glycopeptide	Target alteration	D-alanyl-alanine is changed to D-alanyl-D-lactate
Macrolides	Target alteration Efflux pump	Methylation of the ribosomal active site with reduced binding. Macrolide efflux (Mef) -type pump
Oxazolidinones	Target alteration	Mutation in the active site leads to a decrease in binding
Quinolones	Alteration in target Efflux pump	The mutation leads to reduced binding to the active site. Membrane transporters
Tetracycline	Efflux Alteration in target	New membrane transporters Alteration of proteins that bind to ribosomes and alter the conformation of the active site.
Chloramphenicol	Antibiotic inactivation Efflux pump	Chloramphenicol acetyltransferase New membrane transporters
Sulfa drugs	Alteration in target	Genetic mutation which encodes DHPS (Dihydropteroate synthase)

Table 1: Mechanism of Antibiotic Resistance.

past three decades were considered, including PubMed, Scopus, and Google Scholar. A review template was developed to extract information from the literature identified for the structured literature reviews.

Discussion

Drug molecules can enter a cell through self-uptake, diffusion through porins, or diffusion across the bilayer. Porin channels are present in gram-negative bacteria's outer membrane (OM). Small hydrophilic compounds like β-lactams and quinolones can only pass through the OM via porins. Since there are fewer porin channels, less fluoroquinolones (FQ) and less β-lactam antibiotics can enter the cell, which increases the likelihood of antibiotic resistance (Figure 2). Low OM permeability in Pseudomonas aeruginosa causes acquired resistance to all antibiotic classes. Efflux pumps, membrane proteins that maintain low intracellular concentrations, transfer antibiotics outside of the cell. Antimicrobials are prevented from reaching their target by efflux mechanisms, which remove them from the body at the same rate that they enter the cell. Efflux mechanisms force antimicrobials out of the cell (Figure 1).

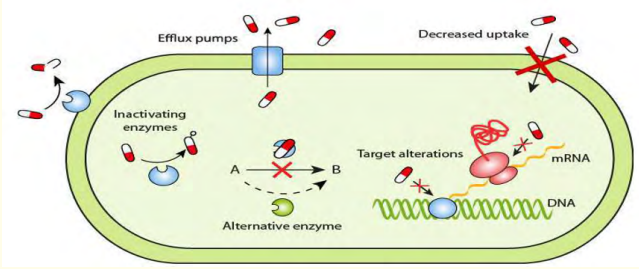

Figure 1: Mechanism of antibiotic resistance (Efflux pump).

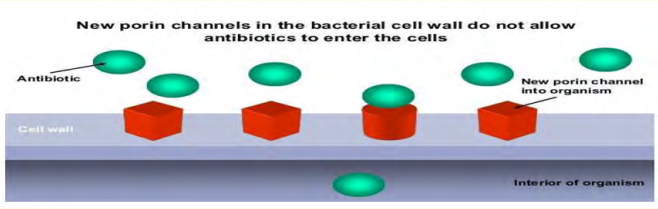

Figure 2: Mechanism of antibiotic resistance (Porin Channel).

Unlike porins, which are located in the OM, these pumps are situated in the cytoplasmic membrane. All types of antibiotics—aside from polymyxin—are prone to activating the efflux mechanism. Pumps for antibiotic efflux are available. The majority of them are multidrug transporters, which are important in the development of bacterial multidrug resistance since they may transport a variety of unrelated antibiotics, including macrolides, tetracyclines, and FQ. Target molecule modification: Common mechanisms of resistance include innate or acquired alterations in the antimicrobial target sites that impair medication binding. The target area regularly changes as a result of spontaneous mutation in bacterial genes. Because antibiotic interactions with target molecules are so exact, even slight changes to the target molecule can have significant effects. Three enzymes, β-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferases, are involved in the inactivation of antibiotics (AACs).

Conclusion

When antibiotics were discovered, people exhale a sigh of relief because they realized that bacteria would no longer exist. Bacterial resistance to antimicrobial treatments has been brought about by the evolution of bacteria into more intelligent organisms and by the extensive use of antibiotics in therapeutic settings. The biochemical forms of resistance mechanisms exploited by bacteria include antibiotic inactivation, target modification, altered permeability, and metabolic pathway "bypass". It is advantageous to identify the mutations that produce bacterial resistance to drugs (phenotypes) across all antibiotic classes (genetic analyses). A deeper comprehension of the mechanisms underlying antibiotic resistance as they relate to the use of antibiotics in various circumstances will be advantageous to clinicians.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

The authors declare no conflicts of interest.

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