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Multiple Drug Resistance In Pathogens: A Surging Public Health Concern Imperative To Scrutinize

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ABSTRACT

Antimicrobial resistance to at least one antimicrobial agent in two or more antimicrobial classes is referred to as multiple drug resistance (MDR), sometimes known as multi-resistance. Antimicrobial classes group antimicrobial substances according to their action mechanism and the target species they are effective against. Multi-drug resistant bacteria are the MDR forms that pose the greatest concern to the healthcare system, additional groups comprise MDR viruses, fungi, and parasites resistant to multiple antivirals, antifungal, and antiparasitic drugs respectively. A variety of "complicated to treat infections" such as catheter-associated urinary tract infections, ventilator-associated pneumonia, surgical site, and numerous other refractory infections have been caused by pathogens with intensifying multidrug resistance characteristics. These infections were initially most common in hospital environments but are also now found in communities. Due to natural and unnatural pressures, antibiotic resistance often originates via spontaneous genetic alterations or is gained by horizontal gene transfer of pathogenicity islands harbouring resistance genes - a genetic mechanism by which antimicrobial resistance can propagate through the transfer of antibiotic-resistant genes (ARGs) across microorganisms. Nevertheless, antibiotic resistance is the product of microbes' genetic adaptation to the environment, improper and irrational utilisation of antimicrobial drugs not only in the health care system but also in the veterinary and agricultural domains plays a critical part in hastening this trend. In healthcare, improper antimicrobial selection, poor adherence to treatment standards, and insufficient antimicrobial dose with acts of self-medication are the leading reasons for pathogen progression to resist antimicrobials. It would not be an exaggeration to state that we have reached the end of the antibiotic era. A step ahead from this age can elevate a basic bacterium to the level of sars-cov-2, whose antivirus we crave.

Keywords: Multiple drug resistance; Antibiotics; Horizontal gene transfer, ESKAPE pathogens, Superbugs.

INTRODUCTION

In the healthcare system, antimicrobial agents are listed in the category of essential medicines [1]. Since the immune system is incompatible with all pathogen incursions, antimicrobials such as antibiotics, antifungals, and antiviruses are frequently introduced to supplement the immune system in exempting the body from lethal infectious pathogens that have taken a toll on human health. Antimicrobial medications have been utilised for decades around the world. Vigilance in various regions across the globe has revealed that too many contagious microbes have evolved significantly, with an alarmingly significant proportion of antimicrobial resistant species resilient to the inhibitory impacts of these medications [2]. Not just one, but nearly all competent invading microorganisms (e.g., bacteria, fungi, viruses, and parasites) have used high degrees of MDR with heightened mortality and morbidity and are hence known as "superbugs" [3]. Tuberculosis, pneumonia, HIV, influenza, malaria, yeast infections, and a variety of other lethal infections are key causes of death in the contemporary period, implying MDR is a critical global public health concern. The prevalence of microbe-associated illnesses has risen considerably in the past few decades. Persistent usage of antimicrobial medications to treat infectious diseases has resulted in the establishment of tolerance amongst diverse strains of microorganisms, and this resilience among various antimicrobial agents has evolved as a terrifying public health concerns throughout the globe [4]. MDR is characterized as a microorganism's tolerance or resilience to antimicrobial medications that are operationally dissimilar and have diverse cellular targets notwithstanding previous sensitivity to them [5]. Resistant microorganisms can combat attacks by antimicrobial drugs via several cellular mechanisms that are evolving. Because of the rapid emergence of novel resistance patterns and the decline in the efficacy of typical antimicrobials in treating common infectious illnesses, there is an increased risk of mortality, episodes of longer sickness, and increased healthcare costs. Antibiotic resistance is on the rise, posing a threat to the aims of sustainable development. Over the last three decades, the rate of resistance has surged dramatically, while the rate of introducing new antimicrobials to the repertoire of current medications has decreased. This public health concern has such a gigantic face that WHO has committed a weak awareness campaign to evaluate it [6]. Nonetheless, the emergence of MDR is a natural process and a part of the survival of the fittest phenomena, erroneous antimicrobial medication usage in healthcare, veterinary and aquaculture, insufficient hygienic conditions, improper food management, and imprecise prevention and management methods all contribute to speed-up and spread of MDR [2, 7]. Furthermore, an increase in the prevalence of immunocompromised situations, such as HIV infection, diabetics, and organ transplant recipients, renders the body an ideal target for hospital-acquired acquired infections, adding to the further spread of the MDR microbes [8]. The degree of effectiveness of modern clinical applications such as organ transplantation and surgical procedures has also contributed

significantly to the emergence of MDR [9]. Tackling developing multidrug resistance issues is a public health crisis that requires a joint strategy. Given the criticality of MDR, this review addresses the challenges connected with MDR as well as the necessity of understanding its relevance and methods for combating it.

GLOBAL SCENARIO

According to recent studies, increased access to antibiotics in both the public and private sectors, as well as increased economic growth, is expected. Daily Defined Doses (DDD) is being used to define antibiotic usage. According to the report, the United States, France, and Italy were the major High-Income Countries (HIC) users of antibiotics in 2015, whereas India, China, and Pakistan were the major Low- or Middle-Income Country (LMIC) consumers [10]. While antibiotic use grew little in the three top HICs, it increased dramatically in the highest-consuming LMICs. "Amid 2010 and 2020, antimicrobial consumption has risen from 3.2 to 6.5 billion Daily Defined Doses (DDDs) (87%) in India, from 2.3 to 4.2 billion DDDs (79%) in China, and 0.8 to 1.3 billion DDDs (65%) in Pakistan," according to the study conducted by Dynamics, Economics & Policy (CDDEP), Princeton University, ETH Zurich, and the University of Antwerp [11]. According to the report, India surpassed the United States as the largest consumer of oxazolidinones (a novel and last-resort antibiotic family, such as Linezolid) in 2012. Amid 2010 and 2020, India recorded the highest rise in antibiotic usage among Low and Middle-Income Countries (LMICs). Expansion of worldwide commerce and tourism leads to a greater possibility for MDR to spread globally and decreases in export and import of numerous items, impacting developing nations' economies [3, 12]

COMMON MULTIDRUG-RESISTANT ORGANISMS (MDROs)

MDR refers to antimicrobial resistance exhibited by pathogenic strains to at least one antimicrobial agent from two or more antimicrobial classes, which are antimicrobial agent categorizations predicated on action mechanism and specificity to target microorganisms [13] MDR bacteria that tolerate multiple antibiotics are by far the most detrimental to the healthcare system, other MDR forms comprise MDR viruses, fungi, and parasites resistant to drugs of a wide chemical variety. To distinguish distinct levels of MDR in bacteria, the terms extensively drug-resistance (XDR) and pandrug-resistance (PDR) have been incorporated. Extensively drug-resistant (XDR) bacteria are those that are resilient to all antimicrobial drugs except in a couple of antimicrobial categories while pandrug-resistant (PDR) microorganisms are resilient to all antimicrobial drugs throughout all antimicrobial classes [6, 14]. Common multidrug-resistant organisms (MDROs) are model contemporary microbes that turned out to be resistant to typical antimicrobials while susceptible to them once. Instances of MDR pathogens infecting humans among bacteria include Vancomycin-Resistant Enterococci (VRE), Methicillin-resistant Staphylococcus aureus (MRSA), Extended-spectrum β-lactamase (ESBLs) producing Gram-negative bacteria, carbapenemase (KPC) producing Gram-negatives, multi-drug-resistant tuberculosis, Multidrug-resistant Gram-negative

rods (MDR GNR) such as Enterobacter species, E.coli, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, [9, 12, 15]. Overlapping with MDRGN, the group of Gram-positive and Gram-negative bacteria dubbed the ESKAPE class has recently gained significant attention. The CDC's 2019 pressing hazard list includes two pathogens from the "ESKAPE" class, carbapenem-resistant Acinetobacter and carbapenem-resistant Enterobacteriaceae, while the prioritized group includes vancomycin-resistant enterococcus faecium (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) [16]. For a decade research reports are showing elevated levels of resistance in bacteria such as Staphylococcus aureus averse to methicillin, Klebsiella pneumonia averse to cephalosporin and carbapenems, Streptococcus pneumonia averse to penicillin, Escherichia coli averse to antibiotics as cephalosporin and fluoroquinolones, salmonella averse to fluoroquinolones, Neisseria gonorrhoeae averse to cephalosporin, nontyphoidal Shigella species averse to fluoroquinolones, and Mycobacterium tuberculosis averse to rifampicin, isoniazid, and fluoroquinolone, producing common afflictions like respiratory tract infections, urinary tract infections, bloodstream infections, pneumonia, wound infections and a high percentage of nosocomial infections [10, 17]. There are only a few fungicides available to manage severe fungal infections. Resilience to azole derivatives like voriconazole, ketoconazole, itraconazole, and fluconazole, polyene macrolides like amphotericin B, DNA and RNA synthesis inhibitors like flucytosine, and 1,3--glucan synthase inhibitors like echinocandins exists in Cryptococcus neoformans , Aspergillus spp., Scopulariopsis spp., Trichosporon beigelii, and Pseudallescheria boydii and is being reported globally [8, 18]. Among opportunistic fungi, yeast species like Candida is developing resistance to long-term azole group of antifungals, necessitating intervention with a distinct drug class. Since Lomentospora prolificans infections are resistant to a variety of antifungal medications, they are increasingly becoming detrimental [19]. Continuous drug exposure and continuous viral multiplication lead to the emergence of resistant strains. Antiviral drug resilience has been evidenced in immunocompromised transplant recipients and cancer patients parasitized with, human immunodeficiency virus, cytomegalovirus, varicella-zoster virus, hepatitis C, hepatitis B virus, herpes simplex virus, or influenza A virus [20]. Since HIV mutates quickly when treated with monotherapies, it serves as the best instance of MDR in the case of antiviral agents [21]. In 2008–2012, 98.5% of influenza A tested resilient to neuraminidase suppressors like oseltamivir. MDR strains of the influenza virus are also increasingly prevalent in individuals with weakened immune systems [22]. Under treatment, cytomegalovirus has also been revealed to develop resistance to ganciclovir and foscarnet, particularly in immunocompromised individuals [23]. Herpes simplex virus rarely becomes resistant to acyclovir preparations, mostly in the form of cross-resistance to famciclovir and valacyclovir, usually in immunosuppressed patients [24]. Multidrug resilience in the case of parasites has been studied in, Leishmania, Plasmodia, Schistosomes, Trichomonas vaginalis, Entamoeba, , , and Toxoplasma gondii [15, 25] averse to anti-parasitic agents like artemisinin, chloroquine, amphotericin B, antimonials, paromomycin, , pentavalent miltefosine, and pyrimethamine. One of the prime examples of disease prone to MDR is

malaria, caused by Plasmodium falciparum. Plasmodium vivax developed resistance to chloroquine and sulfadoxine\pyrimethamine. As of 2012, artemisinin-tolerant Plasmodium falciparum has popped up in western Cambodia and western Thailand [26]. In many tropical and subtropical nations, schistosomiasis and amoebiasis pose a serious public health risk that is now compared to that malaria [27]. Just a few decades ago, antihelminthic resistance is primarily discussed in veterinary studies, such as concerning the practice of drenching livestock, and has recently been the subject of FDA review. All these infectious agents, known as "superbugs," are primary factors of fatal infections, especially in immunosuppressed and critically ill patients. such infectious agents are continuously developing high levels of multidrug resistance (MDR) and are associated with increased morbidity and mortality [28].

PATHOGENS AND RESISTANCE PATTERN

The viability of a eukaryote is based not just on the precise translation of its genes, but also on its freedom from potential pathogens ranging from bacteria to parasites. Whenever any of these pathogens infect a multicellular host, they compete for resources at the cellular scale. The benevolent immune system is the organ system of the body that is constantly striving to safeguard the body against invading pathogens. Without it, a lone virulent prokaryote would damage the millions of interlinked cells of a complex organism [29]. In virulent invasions where pathogen load is at its peak or in immunosuppressed situations, antimicrobials are administrated to complement the activity of elements of the immune system wherein these agents prove toxic to infectious agents and hence lessen the infection load immediately. Pathogens typically adopt a variety of resistance mechanisms as a general rule of natural selection to thrive stress conditions. [30]. Following the exposure to environmental stressors including antimicrobials, pathogens evolve efficiently to construct antimicrobial resistance mechanisms that are mostly reinforced by their genetic makeup. Almost all pathogenic microorganisms, including bacteria, fungi, viruses, and protozoa, have built resistance mechanisms in response to antimicrobial interactions [31]. Resistance is defined as a pathogen's tolerance to an antimicrobial agent when contrasted to other strains belonging to the same species. The tendency of various pathogens to acclimate to antimicrobial agents has allowed them to persist for hundreds of years. Resistances of such type are gained naturally via spontaneous mutations following natural and unnatural pressures or through horizontal transfer of pathogenicity islands that harbour resistance genes [30, 32]. This enables pathogens to fight off the effects of some antimicrobials, rendering them useless. Antimicrobial agents usually retard microbial growth or directly kill them by inhibiting a biosynthetic activity such as nucleotide synthesis, inhibition of DNA/RNA synthesis disrupting protein synthesis, disrupting the cell membrane, or by competitive inhibition, for example, competing enzyme incorporated in the cell wall generation e.g., chitin synthase [33]. Microbes use a variety of strategies to develop multi-drug resistance including, not relying on glycoprotein cell walls anymore, revocation of antimicrobials through enzymes, reduced permeation of the cell wall to

antimicrobials, amended drug binding sites, and strategies for expelling antimicrobials by efflux pumps [20, 34].

Cell walls are essential to the functioning of both fungi and bacteria. Drugs block cell wall synthesis in bacteria by sticking to the peptidoglycan for example penicillins or in fungi by impacting ergosterol synthesis for example polyenes [35], thereby inhibiting cell activities and proliferation. Resistant microbes experience specific chromosomal alterations over time or swap extrachromosomal DNA elements or virulence gene housing pathogenicity islands via conjugation or transformation which are the phenomenon of horizontal gene transfer, and eventually lead to the alteration in the gene expression which in turn results in the composition alteration of the plasma membrane, for example, a decline in the ergosterol level in the fungal cell membranes, which reduces permeation and drug take - up into the cell [2, 9, 36]. A dearth of active binding sites for the antimicrobials such as echinocandins in the case of fungi is caused by modified membrane conformation, such as the 1,3-glucan and lipid material in fungal plasma membranes. [1, 37]. Genetic changes in the target genes induce molecular events which end up in decreasing vulnerability to suppression. Another pathway of multi-drug resistance was discovered to be drug target enzyme increased expression, which leads to target skip because of changes in some metabolic processes such as azoles and allylamines in fungi, resulting in the formation of alternative protein targets, which significantly impacts the ingress of drugs to the target sites. Inhibition or enzymatic breakdown of antimicrobial drugs through hydrolysis of ester or amide bonds like degradation of β -lactams due to β -lactamases, etc. and biological transition of these molecules through acetylation, phosphorylation, adenylation, glycosylation, and hydroxylation have also been identified as contributing to MDR [32, 38]. Tolerant isolates among clinical isolates of pathogens have acquired the capacity to oxidize or reduce antimicrobial agents, preventing them from interacting with their corresponding targets. To impede viral multiplication, antiviral agents typically target viral DNA polymerase with reverse transcriptase function. Mutated drug-resistant viral strains produce mutations in the reverse transcriptase areas of the polymerase gene, that in turn hinder the drug-enzyme interaction. Resilience to the inhibitory properties of antimicrobials upon the enzyme may also develop as a result of structural alterations or distorted substrate linking to the viral polymerase [39]. MDR in parasites is becoming a worldwide public health concern owing to the lack of efficient antiparasitic vaccines and the slow development of novel drugs. Parasites, like Plasmodia spp. and Toxoplasma gondii, endure point mutations that change calcium homeostasis in the endoplasmic reticulum, modify drug target sites and built efflux pumps to expel antiparasitic drugs like chloroquine from the cells [40]. MDR facilitated by drug efflux pumps is still the most common means of MDR development. Upregulation of genes encoding ATP-binding cassette (ABC) transport proteins like P-glycoprotein (Pgp), recognized as multidrug efflux pumps, which are liable for the ejection of antimicrobial agents out of the cell [19, 41], typically ends in drug resistance. Increased expression of P-glycoprotein in the membranes of Entamoeba spp. and Leishmania spp. influences flexibility and

permeation, resulting in an ATP-dependent outflow of drugs [42]. Transformed cells employ MDR as well, limiting the protracted usage of chemotherapeutic agents. An understanding of the pathways associated with chemoresistance, that could arise at the commencement of treatment or amid the treatment course, demonstrates that transformed cells upregulate some multidrug resistance molecules like multiple resistance proteins and P-glycoproteins which stimulate DNA repair processes, suppress programmed cell death, modify drug targets, and alter plasma membrane configuration, along with facilitating enhanced efflux of drugs, deterring appropriate medication dissemination into the cells [43].

PREVENTING THE EMERGENCE OF ANTIMICROBIAL RESISTANCE

Despite the commercialization of several novel antimicrobials, high-level resistance to multiple drugs among pathogens and transformed cells is rising. Ludicrous, imprudent, and chronic use of antimicrobials in healthcare, veterinary, and aquaculture has resulted in the outbreak of multi-drug resistant (MDR) and extremely drug-resistant (XDR) microbial strains worldwide. Almost everywhere, antimicrobials especially antibiotics are consumed by people either without taking into consideration, a professional oversight or accepting pseudo-dosed prescriptions from quacks and OTC sellers. This is assumed to be the main cause of escalation of antibiotic resistance in human health care which renders typical antibiotics ineffective over time [44]. MDR progression is a serious issue and has now become a big global concern. Cooperative efforts are required to reduce the upsurge and propagation of MDR. Furthermore, concentrating on areas prone to antimicrobial misuse through the execution of antimicrobial stewardship designed as coherent interventions aimed at moderating and evaluating the reasonable utilization of antimicrobials is critical. Reforms via antimicrobial stewardship Programmes aspire to either confine the accessibility of specific antimicrobial agents, referred to as "front-end," or to evaluate broad spectrum antimicrobial utilization and then standardize or cease it, termed as "back-end" [45]. So, international, national, regional, and subregional support and collaboration are imperative to serve in future progress. It has been proposed to prevent the emergence of antimicrobial resistance by administration of the proper antimicrobial for the infectious disease, for instance, no antibiotics should be administrated for viral infections, w Whenever feasible, the causative agent should be identified via advanced microbial techniques instead of depending on broad-spectrum antimicrobials, antimicrobial should be chosen via incorporating antimicrobial sensitivity assays so that drug is properly targeted against the specific microbe, the medically precise antimicrobial treatment course should be completed even after symptoms are subsided. Bacteriophages (viruses that kill bacteria) and UV light approaches are developing areas of possible infection management strategies and should be focused more. Because the development of antimicrobial resistance in microbes cannot be entirely avoided, it is crucial to create new antimicrobials over time, and it is critical to employ more biologics and plant-based natural agents to prepare antimicrobials. Alongside the creation of novel antimicrobials, scientific tactics must be employed to safeguard the general public from total resistance [46]. The medical

professionals should provide education and self-regulation antimicrobial stewardship Programmes at hospitals and clinical settings along with cautioning the general public via social media. It has been asserted that, based on the social context, the administration can assist in teaching the public about the significance of antibiotic restriction for human clinical use, however, unlike narcotics, there is currently no regulatory oversight of antimicrobial use anywhere in the communities. Attempts to enhance water and sanitation, as well as the incorporation of timeous immunizations that help prevent infections, are all approaches toward reducing antibiotic intake. Furthermore, it is critical to follow the same regulations when using antimicrobials in veterinary, aquaculture, and plant disease management.

CONCLUSION

Antimicrobial drug resistance is an inevitable natural occurrence that poses a serious global threat to public health due to its association with high mortality and morbidity and high healthcare costs, as well as the fact that it has posed previously unheard-of difficulties for modern civilization. Even the last-resort antimicrobials are ineffective against more than 80% of the pathogenic microbes. Antimicrobial drug development must continue because current options are inadequate. Pathogens frequently use a variety of resistance pathways to enduring unfavorable circumstances. A thorough understanding of the infection pathobiology should be undertaken along with improved knowledge of the molecular pathways regulating MDR, which should make it easier to develop innovative therapeutic strategies to treat these stubborn infections. It is necessary to implement a variety of awareness programs that should facilitate their effective use in reestablishing dominance over diseases. To combat the MDR, a global cooperative effort is necessary. Microbiologists have cautioned that because of the long-term use of antibiotics, many patients have developed an anti-antibiotic stance, making it difficult to treat even the most basic illnesses, which can later develop into fatal ones. By 2030, there won't be any antibiotics left, not even for the most straightforward infections if these problems don't get better. Without antibiotics, antifungals, and antiviruses, cancer chemotherapy, organ transplantation, and routine surgery will be unthinkable, and we will be going to face a future in which a cough or cut can once again be fatal, suggesting that we are returning to the time when antibiotics were not widely available.

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