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Upcoming Multi-drug-resistant and Extensively Drug-resistant Bacteria

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ABSTRACT

Background: Multi-drug resistant and extensively drug-resistant bacteria are becoming a serious global health issue, which may soon become untreatable by clinicians. Since then the invention of antibiotics, inappropriate consumption, non-prescribed drugs, overuse, and hoarding have induced the rapid emergence of MDR and XDR bacteria.

Materials and Methods: The ESKAPE pathogens (*Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter* spp.) cause many nosocomial infections and thus escape the biocidal action of the antibiotic. Both gram-positive and gram-negative bacteria have acquired self-defence tools like ESBL, a mutation in porin genes, biofilm production, and many more to acquire multi-drug resistance.

Results: At present, patients' treatment is threatened by antimicrobial resistance (AMR) as it causes high mortality and morbidity rate, economic loss of both patient and country, and prolonged hospital stay.

Conclusion: To combat upcoming multi-drug resistant and extensively resistant bacteria, it is essential to design engineer and novel therapeutic techniques to eradicate such resistant bacteria via burgeoning technologies like nanoparticles, CRISPR-Cas9, genetic engineering, and synthetic biology.

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Introduction

Antimicrobial resistance has become alarming for clinicians in treating patients [1]. According to the latest research, multi-drug resistant (MDR) bacteria and or extensively drug-resistant (XDR) bacteria, vancomycin-resistant *Enterococcus* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) have become a public health menace [2]. It is predicted that antimicrobial resistance acquired from the hospital may soon become an untreatable health problem [3]. In 2011, World Health Organization (WHO) announced the "fight against drug resistance today; otherwise, there will be no treatment tomorrow" [4]. Over the past few years, MDR strains have multiplied [5]. Antimicrobial resistance (AMR) threatens patients' treatment as it causes high mortality and morbidity rate, economic loss of both patient and country, and prolonged hospital stay [6, 7].

The most important clinical isolates that create MDR are *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacteriaceae* family, *Proteus* spp., *Enterococci*, especially vancomycin-resistant *enterococci* (VRE), *Klebsiella pneumoniae*, and methicillin-resistant *S. aureus* (MRSA). "Health for all" was declared by WHO in 2000. Over the last few decades, hospital-acquired infections have become so prevalent that it seems an era of pre-antibiotic times [8]. The Center for Disease Control and Prevention (CDC), the health agency of the USA, and the European Center for Disease Control (ECDC) offered a standardized definition of pan-drug-resistant (PDR), multi-drug resistant (MDR), and extensively drug-resistant (XDR) [9]. PDR condition is defined as nonsusceptibility to all types of antimicrobial drugs. Resistance to three or more antimicrobial drugs is known as MDR. Extensively drug-resistant bacteria show susceptibility to only one or two antimicrobial categories.

Gram-negative bacteria like *K. pneumoniae* and *E. coli* produce ESBL (extended-spectrum beta-lactamase), which clinically destroys antibiotics. The alarming situation is that most people infected with ESBL-producing bacteria are asymptomatic [5]. The top-listed gram-positive species are *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, and *S. aureus*, a silent natural flora of the human body. Meanwhile, it threatens our life by outwitting our immune system. The history of antibiotic chemotherapy reveals that its phenotype is multi-drug resistance, making it a notorious pathogenic bacterium. Since 1940, all antibiotics have been practically conquered by *S. aureus*. The first MRSA strain, Mu50, was isolated in 1961 and prevailed worldwide until it acquired vancomycin resistance [10]. A genuine concern of the medical world is the upcoming resistance toward MDR and XDR bacteria, especially gram-negative types. Advanced-generation antibiotics, which are under clinical development, hold promises to combat severe infections caused by MDR pathogens and enhance the armamentarium of physicians. In the future, nanotechnology is becoming a fast and reliable application to kill antibiotic resistance [11].

Multi-drug resistance

Multi-drug resistance in bacteria results from the mutational changes in genes, and such mutations encode the resistance to particular drugs on the R plasmid. As resistant genes are transferred through integrons, veterinary and human medicine have reduced the therapeutic choice for physicians [12-15]. Few strains of bacteria can maintain their MDR or XDR phenotype and invade the community of the whole world [16]. Over the past few years, microbial infections have significantly increased worldwide. Microbial infections have been treated with antibiotics since the discovery of penicillin in 1928 [17]. The CDC reports that 2000000 people are suffering from antibiotic-resistant infections in the United States every year, adding a direct burden of 20 billion dollars on healthcare costs [18]. According to the latest research, 700000 people died worldwide due to MDR-associated infections, and this death rate will lead to approximately 10 million deaths per year by 2050 [19]. The WHO enlisted MDR microorganisms, their associated disease, and respective drug resistance [20], which is elaborated in Table 1.

Upcoming multi-drug resistant bacteria

Antimicrobial resistance is the largest threat to public health [21], increasing morbidity and mortality due to bacterial infections. Very famous ESKAPE pathogens (*Enterobacter* spp., *S. aureus*, *E. faecium*, *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter baumannii*) cause many nosocomial infections and thus escape the biocidal action of antibiotic [22]. The MDR and XDR microbes are emerging in the medical field due to the frequent and prolonged use of antimicrobials [23]. The therapeutic efficacy of the antibiotic class of carbapenemase-producing *Enterobacterales* (CPE) is also assessed. According to the latest research, many CPE-expressed resistance genes are synergistically affected by antimicrobial drugs. These antimicrobial drugs were used to successfully treat CPE-infected patients. In another research article, two potent antimicrobial combinations for both in-vitro and in-vivo for detecting clinical MRSA infection [24].

Table 1. Multi drug resistant microorganisms, associated diseases and resistance against drugs

Causative Agent (Microbe)	Diseases Caused	Drugs Resistant to
E. coli	Urinary tract infections (UTIs) and systemic infection	Cephalosporins, erythromycin, fluoroquinolones, amoxicillin, penicillin
K. pneumoniae	Systemic infections, abdominal infection, pyogenic liver abscess, pneumonia, UTIs, and meningitis	Cephalosporins quinolones, carbapenems, aminoglycosides, colistin, and tetracycline
Streptococcus pneumonia	Pneumonia, meningitis, and otitis	Trimethoprim-sulfamethoxazole, fluoroquinolones, β-lactams, macrolides, tetracyclines, and lincomycin
S. aureus	Systemic infections, skin, bone, and lung-related infections	Vancomycin, methicillin, and penicillin,
Mycobacterium tuberculosis	Tuberculosis (TB)	Rifampicin, fluoroquinolone, isoniazid

Classification of multi-drug-resistant bacteria

Genetic competency of MRSA to antibiotic resistance

Until now, MRSA has prevailed throughout the world, and in the coming few years, more than 50% of strains of S. aureus will become MRSA, i.e. methicillin-resistant. The staphylococcal cassette chromosome (SCC) was a mobile genetic element to transfer methicillin-resistant gene *mecA* to make susceptible *S. aureus*, MRSA [25]. SCC acts as a site-linked transposon-like element particularly present in the staphylococcal species. The SCC element comprises of *mecA* gene and its regulatory genes like *mecI*, *mecI*, and *ccr*-gene, which encode resistance to methicillin [26].

It comprises two essential genes. One is the methicillin-resistant gene (*mecA*) and its regulators, *mecRI* and *mecI*. Another is a *ccr*-gene group responsible for integration, movement, and excision from the chromosome (Figure 1).

Resistance to vancomycin drug

Some antibiotic resistance to the MRSA phenotype is achieved by spontaneous mutation. The most common examples are the resistance of fluoroquinolone and rifampicin [27]. Moreover, the resistance toward vancomycin is also acquired by mutation, showering a dark shadow over chemotherapy against MRSA. MRSA infection was treated with vancomycin as its last resort for a long time. The MIC concentration of vancomycin for *S. aureus* is 4-8 mg/L [28] (Figure 2).

Internal mechanism of multi-drug-resistant gram-negative bacteria

Generally, the resistance phenomenon in gram-negative bacteria is based on prohibiting the access of antimicrobial drugs to their particular drugs. The bacteria acquire resistance based on multiple mechanisms, and the most common is the multi-drug efflux pump which pushes out most of the drugs to the outside of the cell. Due to less permeability of the outer membrane, there is a slow influx of multiple drugs and efflux of multiple transporters. If the efflux system is over expressed or mutation occurs in the porins through which drugs cross, drug access also reduces. For example, the efflux system in *P. aeruginosa* produces drug resistance to forming periplasmic β-(1–3)-glucans [29]. Another mechanism in gram-negative bacteria is a mutation in porin genes which hinders the permeability of drugs through the outer membrane [30, 31]. It is a non-specific mechanism that interacts with many different classes of drugs with unique monoamine oxidase inhibitors (MAOs). All mechanisms multiply the effect of each other, as in *P. aeruginosa* with *gyrA/parC* mutation, porin genes mutation, and beta-lactamase production in *Enterobacterales*.

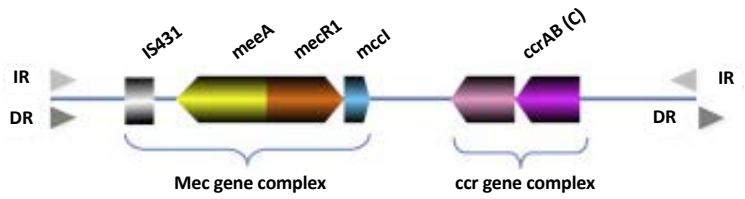

Figure 1. SCC*mec* structure

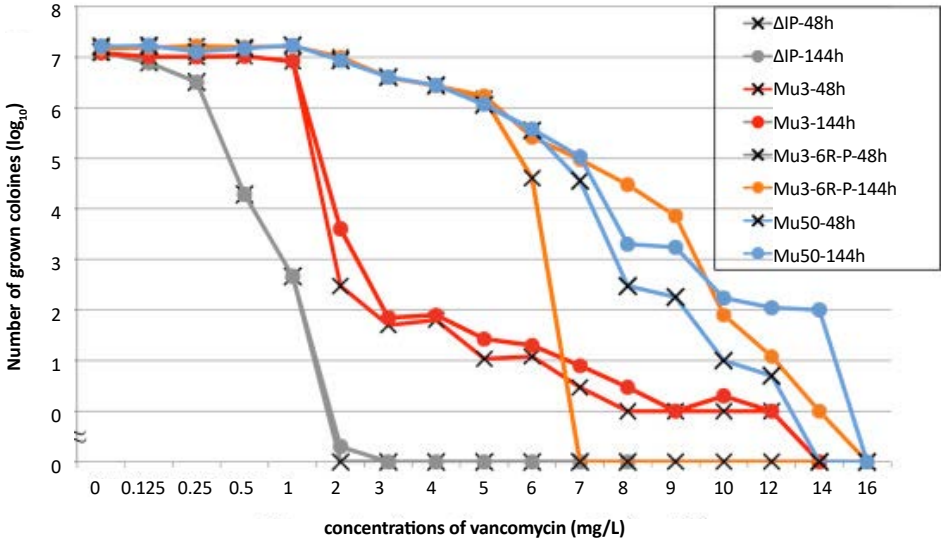

Figure 2. Growth analysis of *S. aureus*

Note: Bacteria were grown with different concentrations of vancomycin for different intervals of time, [×] Represent number of colonies counted after 48 h and 144 h incubation [10].

Multi-drug-resistance mechanism

Although multiple unique drugs have been introduced in the market today, patients are still infected by MDR pathogen noticeably and rapidly due to prolonged antibiotic exposure [32]. Generally, antimicrobial drugs act on microorganisms by hindering metabolic activity such as protein or nucleotide synthesis or combating the enzyme substrate forming the cell wall [33]. Microbes have developed different strategies to last the drug's action by counteracting the drug's efficacy. The four most important basic mechanisms due to which microbes develop resistance against antibiotics are alteration in the binding site, antibiotic efflux by efflux transporter, reduced uptake of antibiotics due to a mutation in porin genes, and destruction or inactivation of antibiotics by enzymes (Figure 3) [34].

Certain modification in metabolic pathways alters binding sites which highly express target enzymes, proceeding towards evading the target, t and producing other targets, and counteracting with protein synthesis [33]. Target modifications typically occur due to spontaneous mutations in the bacterial chromosomal genes. For example, mutations in RNA polymerase and DNA gyrase inflict sudden resistance towards rifamycin and quinolones. In certain cases, different types of genetic exchange (conjugation, transduction, or transformation) from another organism might take place to develop such kind of resistant characteristics. For example, acquiring the *mecA* genes provides methicillin resistance in *S. aureus* and the various *Van* genes responsible for the glycopeptide resistance in *enterococci* [35].

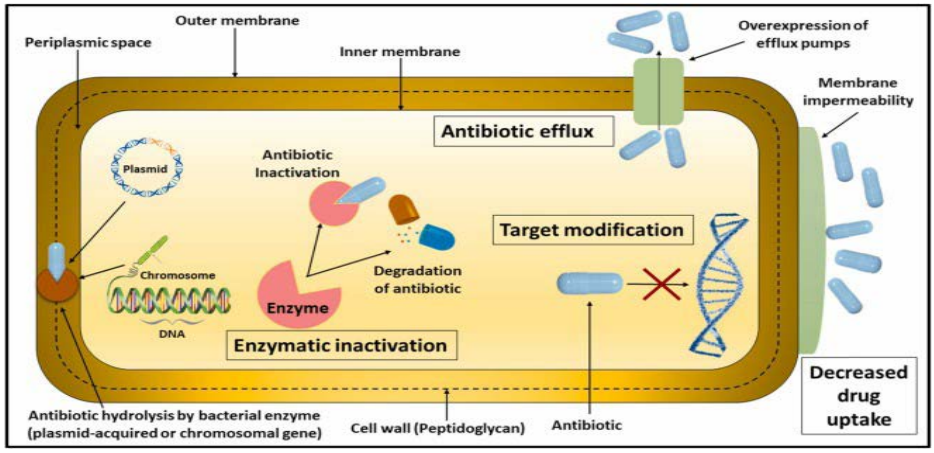

Figure 3. Diagrammatic presentation of multi-drug-resistance mechanism in bacteria

Why AMR crisis

The main reason for antimicrobial resistance is mutation due to genetic level variability. The mutation is considered the spontaneous change in an organism's genes which provides or helps to develop generally multi-drug resistance mechanisms in microbes [36]. Antimicrobial drugs are generally designed to adversely impact microbial growth and thus create a particular pressure over microbial colonies. Under antibiotic treatment, only those microbes which survive will predominate in the microbial community, and in this way, resistance is developed [37].

Presence of antimicrobial resistance in environmental sources

Human activities always contribute to the contamination of environmental sources and include the discharge of MDR strains in the environment. 'One health' term encompasses humans, animals, plants, and the environment; hence, collaborative efforts are necessary for the global action plans against AMR. With new resistance mechanisms leading to the formation of 'superbugs,' studying the environmental presence of such drug-resistant bacteria is important to stop the discharge or spread of MDR strains between people and from animals to people through animal foodstuffs or by other means and mitigate the risk associated with the emergence of more resistant bacteria [37].

Multi-drug resistance ended an evolutionary war

Over the last few years, medical scientists sounded the alarming situation about the next phase in public co-existence with microbes, predicting dark future advanced strains have rendered powerful antibiotics useless [38]. Recently, the United Nations projected that multi-drug resistant bacteria would force up to 24 million individuals into utmost poverty in the coming few decades and result in 10 million deaths yearly by 2050 unless new therapies are developed [39]. Scientists are particularly apprehensive regarding a wide group of bacteria circulating in hospitals. Not only blockbuster drugs like penicillin and tetracycline are dodged by bacteria but even the last crucial option of antibiotic, i.e. colistin. In the case of MDR infections, if it fails, there is no other antibiotic option than colistin [40].

Recently, a group of scientists stated their discovery of an element capable of outmaneuvering colistin's resistance. When they experimented on animals, colistin antibiotic was found to be more potent against the opportunistic microbe, i.e. *A. baumannii*. Few previous findings helped us to construct a new class of antibiotics to counteract those strains which respond to no other treatment [41]. Some species have acquired a new gene called *mcr-1* that evades colistin's toxicity, making these bacteria resistant to the drug. Colistin resistance spreads fast, partly because *mcr-1* sits on a plasmid, a ring of DNA that is not part of the bulk bacterial genome and can transfer easily from cell to cell. "It jumps from one bacterial strain to another, or from one patient's infection to another's" [42].

Contributing factors of the global AMR crisis

Because AMR is causing more deaths than cancers or accidental deaths, it has become a major concern for global health. WHO has also declared AMR one of the top 10 global health problems [22]. Therefore, studying the contributing factors of the global 'AMR crisis' becomes a requisite to reduce the global health burden of this issue.

Sources of AMR

Studying the sources of AMR is essential to plan and curb the spread and evolution of MDR bacteria. Some bacteria are commensal and become opportunistic pathogens when they shift from their usual sites in the body to another. The consumption of antibiotics in humans and animals results in the development of antibiotic resistance in both and moves from humans to animals and vice-versa through wastes, soil, and water resources during handling, processing of animals or animal-related foodstuffs, farming activities, and poor wastewater treatment or waste disposal methods. Sites like hospitals or pharmaceutical manufacturing industries, food, animal, agriculture production and processing places, and wastewater or waste disposal areas are hotspots of drug-resistant bacteria [42]. Antibiotic manufacturing industries discharge many antibiotics in natural environments; hence pharmaceutical manufacturing industries are hotspots for MDR bacteria. Hence, it is important to find the sources of antimicrobial agents in contact with bacteria in natural resources to avoid the development, evolution, and further transmission of MDR strains to humans and animals.

Clinical use

Monitoring AMR and misuse of antimicrobial agents

The first source of overuse at the clinical level is clinicians' often first-hand usage of the antimicrobials [43]. The practical inadequacies to rapidly diagnose infectious disease, its causative pathogen, and perhaps most importantly, its susceptibility to a particular antimicrobial therapy leads to more frequent and erratic use of antimicrobials [44]. Longer durations (often taking days or even weeks) are required to accurately diagnose infections and the status of their causative agents, with currently available multiple laboratory-based tests [45]. The negligence occurs while prescribing an antimicrobial therapy, mostly based on experience and local epidemiology rather than clinical thorough investigation or testing of pathogens and their antimicrobial sensitivity [46].

The serial application of antimicrobials is often driven by patient demand for an immediate resolution to their illness. This can take the form of belligerent patients demanding antimicrobials at one extreme and the other, overprescription by practitioners to appease patients and so garner repeat business [47]. By lessening the demand for the immediate application of antimicrobials in non-acute patients, appropriate diagnostics will be facilitated, so effective and proper prescription of antimicrobials will occur more frequently [45].

Established methodologies

Antimicrobials are commonly prescribed in a fixed regimen at a particular dose and rate and for a definite period. Typically, the period of regimens last for 5–7 days, and sometimes, if needed, might be extended to 14 days or even longer [48]. The fundamental assumption behind such extended regimes is that exposure to high dosages of antimicrobials over long periods will eradicate the infecting pathogen from the body [49]. However, recent studies indicated that relapse rates are not significantly higher in case of discontinuing the treatment regimen in patients as symptoms diminish, compared to those taking the full course of treatment [50].

Public behavior

Hoarding

The practice of unfinished prescribed courses of antimicrobial treatment might not immediately impact the patient's clinical outcome [51, 52]. However, when the balance of the course is "hoarded" against a perceived future need, the potential for misapplication of antimicrobial therapy to non-susceptible organisms is significantly increased [53].

Non-prescription purchase

At the global level, not everywhere there are controlled access to antimicrobials is maintained. In many countries, no concrete regulations are made for producing and selling antimicrobials for certain levels or sometimes completely unregulated. This causes the production of therapeutic materials with extremely variable quality to manage availability in large quantities and cheap manner for the public [54]. Before the advent of the Internet, such easy access to antimicrobials was confined to first-world countries, i.e. restricted to returning travelers. However, nowadays, online shopping has enabled widespread and easy access to even currently restricted antibiotics such as rifampicin and ciprofloxacin [55].

Socioeconomic issues

Socioeconomic factors also contribute to the AMR crisis across the world. Different issues like social inequities to access good healthcare facilities and medications, poor infrastructure or improper maintenance of infrastructure, poor hygiene and sanitation, corruption in government organizations, and poor policymaking to handle the AMR problem assist in increasing this crisis.

Strategies to overcome MDR

The consistency in the outcomes during research studies on different types of antibiotics and related experimental designs points out the extensive correlation between tolerance and the evolution of antibiotic resistance. Henceforth, the focus shifted to making substantial efforts to establish strategies to eradicate the development of persistence in microbial cells, which further leads to resistance evolution [56]. The financial and clinical burden on healthcare departments and patients is very challenging. According to the latest research in 2000, FDA approved four new classes of antibiotics, i.e. daptomycin, tigecycline, linezolid, and streptogramin. MRSA and VRE are resistant to the first three drugs. Currently, the problem is that bacteria are getting resistant much faster than the development of new drugs [23, 57]. So, to combat MDR in pathogens, the most common approaches are used, which involve drug repurposing and drug repositioning (viz. anti-inflammatory, anti-psychotics, anti-cancerous drugs, etc.), use of combinational therapies, and anti-virulence compounds, production of new

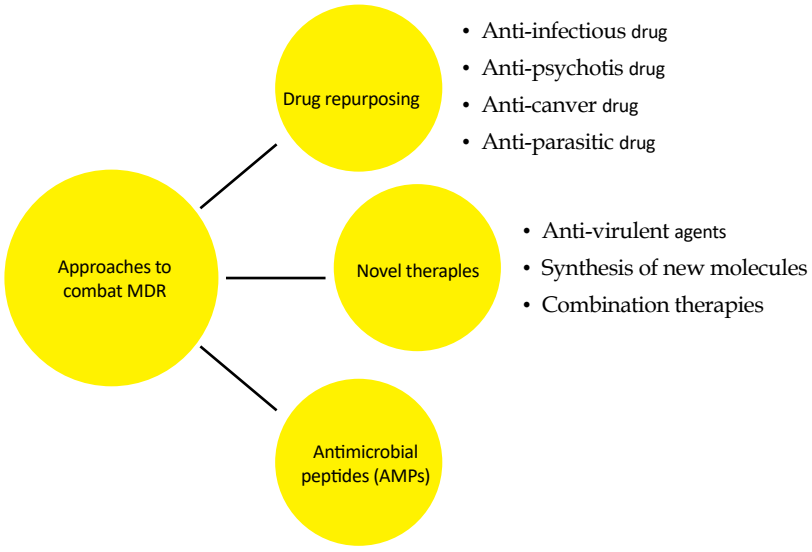

Figure 4. Anti-infectious strategies to encounter persistent and resistant microorganisms

inhibitory molecules, and antimicrobial peptides and all of these strategies will be further discussed in this review [58, 59] (Figure 4).

How to handle the crisis

Important healthcare bodies like WHO and CDC worldwide have widely acknowledged the problem of the emergence of the antimicrobial crisis and its importance to the future of the human race [60].

Promoting universal surveillance and awareness to curb the AMR problem

To observe the global burden of the AMR issue, WHO started Global Antimicrobial Resistance and Use Surveillance System in 2015 to avoid gaps in sharing knowledge and informing essential strategies. Along with that, WHO has also promoted World Antimicrobial Awareness Week since 2020. The information and data obtained from different countries and territories help make better policies to handle the global burden of AMR [22].

Avoiding contamination of antibiotic-resistant genes (ARGs) in environments

WHO has highlighted that maintaining proper hygiene and sanitation is essential to avoid the development of MDR microbes in the environment. Ecological connectivity assists in the transmission of drug resistance from nature to humans and animals. Good hygiene and sanitation conditions and control of environmental pollution driving factors, such as pesticides, the release of industrial, pharmaceuticals, and domestic and animal wastes in natural resources, help reduce the burden of ARGs in natural resources [22, 52].

Antimicrobial stewardship

Antimicrobial stewardship is a coordinated program that encourages properly planned use of antimicrobials to improve the effectiveness and outcomes of the treatment on patients, decrease the spread of infections, reduce the chances of development of MDR pathogens, avoid failure of the treatments, and minimize the length of hospital stay and costs. It promotes proper governance of the healthcare sectors and guides the health system to take responsibility for the health and wellness of the populations, nationally and globally.

Advanced technology to treat MDR and XDR

The eight new antibiotics' activity against ESBL (extended-spectrum β-lactamase) enzymes is effective against carbapenem-resistant Enterobacteria (KPC/producers). However, a few compounds are active against carbapenem-resistant *P. aeruginosa* and multi-drug resistant *A. baumannii* [61]. Unfortunately, a limited number of therapeutic alternatives are available for the latter. Such antibiotics are chiefly used to treat cUTI and cIAI [62]. These concerns endorsed major research efforts to discover alternative strategies to treat such drug-resistant bacterial infections.

Nanobiotechnology is an upcoming and rapidly developing field with potential human welfare applications [63]. An important advantage of nanotechnology is the development of reliable and environmentally friendly processes to synthesize nanoscale-size particles through biological systems [64]. With an urgent and critical need to design and engineer novel therapeutic alternatives for eradicating MDR and XDR bacteria, novels and burgeoning technologies, such as the production of metal nanoparticles, genetic engineering techniques, CRISPER-Cas9, synthetic biology approaches, peptide therapeutics, and combinatorial treatments, can help solve this crisis [65-67].

Non-antibiotic approach

Use of Immunotherapeutic and development of effective vaccines

Immunotherapeutic agents boost the immune system against certain infections. They can be a better option to fight against pathogens by promoting the impact of the internal immune system against bacterial pathogens. Monoclonal antibodies (mAbs) neutralize external virulence factors and clear bacterial infections. Hence mAbs provide alternate effective treatment strategies and avoid the risks of recurrent infections [68]. Vaccines provide immunity against disease-causing agents, using recombinant technologically developed vaccines against such bacterial pathogens. Vaccines help target and develop immunity against external bacterial proteins or toxins, can help reduce bacterial infections at primary and secondary levels, and help provide herd immunity in the population against that particular pathogen. Recently, such vaccines have been under development, and clinical trials are still going on, e.g. *M. tuberculosis* (phase II), *S. aureus* (phase II), and *Clostridium difficile* (phase III). Such vaccines can provide a better preventive strategy against bacterial infections than antibiotic therapy and reduce the threat of AMR development [69].

Use of natural substances

Plants synthesize different types of chemical compounds, which are called secondary metabolites. Medicinal herb extracts have proved their efficiency against pathogenic bacteria. These secondary metabolites from plants show antibacterial effects by restricting protein-protein interactions and also have immunomodulatory effects. Solvent extracts of certain herbal Aloe vera, Neem, Tulsi, Lemongrass, etc. had shown good antimicrobial effects against MDR pathogens [70]. Resperine, an indole alkaloid isolated from *Rauwolfia serpentine* (Indian snakeroot), showed potential efflux pump inhibitory activity against fluoroquinolone-resistant *Stenotrophomonas maltophilia* bacteria and also suppressed its antibiotic resistance abilities [71]. Allicin (diallyl thiosulfinate) from garlic showed antimicrobial activity against pathogens like *Streptococcus agalactiae, P. aeruginosa*, MRSA, and *Staphylococcus epidermidis* [69, 70]. Along with its use against MDR pathogens, the chemical complexity of these naturally present phytochemicals provides an edge over antibiotics. Such pathogenic bacteria cannot develop resistance mechanisms against chemically complex phytochemicals, unlike specifically targeting antibiotics.

Combinational therapy approach

Different resistance mechanisms aid in the survival and growth of microorganisms against various currently used antibacterial agents. Also, developing new antibacterial agents require lots of effort, time, and financial investment. A 'combinational therapy' involves the use of different therapeutics. Since other antimicrobial agents have different targets, this alternative treatment strategy helps to reduce microbial growth and assist the host's immune system [70]. In the case of polymyxin-sensitive and resistant opportunistic pathogen P. aeruginosa, a combination of two antibiotics, polymyxin, and amikacin, result in a synergistic effect on the important metabolisms in bacteria that are essential for its survival and growth [71]. Aminoglycoside antibiotics (AGAs) and b-lactam antibiotics exert synergistic antimicrobial effects by damaging bacterial cell walls by b-lactam antibiotics to ease the entry of AGAs and increase their killing process. So AGAs and β-lactam antibiotics combination is used to treat multi-drug resistance-related severe infections like acquired and ventilator-associated pneumonia and sepsis [71]. Natural plant extracts and antibiotics have also shown synergistic antimicrobial effects against multi-drug resistant bacteria. High-content catechin in *Camellia sinensis* (green tea) and gentamicin jointly exert strong antibacterial effects against multi-drug resistant *E. coli* and *S. aureus* by destroying cell membranes to cause bacterial cell death [72]. Triphala, combining three plant extracts and gentamicin, showed excellent synergistic antibacterial effects against MDR gram-negative bacilli. Such combinational therapies help eradicate drug-resistant pathogens from the body system and make it a more effective treatment strategy than monotherapy. Therefore, due to the effectiveness of this strategy, it is currently being used to cure severe infections caused by drug-resistant bacteria [72].

Upcoming clinical scenarios of MDR

The MDR gram-negative bacteria threaten critically serious patients facing multiple comorbidities [68]. According to recent research, MDROs are considered superbugs because they have very limited therapeutic options and will become more notorious if not properly treated. Some MDRs are treated with only one or two antibiotics which have adverse toxic side effects on the liver. Boucher et al. reported an ESKAPE pathogen in which he replaced K (*K. pneumonia*) with C (*Clostridium difficile*) [69, 70]. The suggested treatment guidelines while managing MDR gram-negative infections address overall epidemiological and clinical level scenarios rather than certain MDR gram-negative pathogens [71].

Resistance progression of AMPs

As the bacteria have developed resistance and continue to acquire more against conventional antibiotics is becoming a global health problem. AMPs have proposed a promising group of new antibiotics with less susceptibility to microbial resistance [72]. The variability in pharmacodynamics features and mode of action of AMPs compared to conventional antibiotics might be a probable reason for the resistance evolution. The AMP (Pt5-1c; phosvitin derivative) action, along with vancomycin, azithromycin, oxacillin, and streptomycin, is suggested for MDR pathogens, such as *K. pneumoniae*, *E. coli*, and *S. aureus* [73].

Conclusion and future roadmap

MDR and XDR have emerged as serious health problems showing no reduction in symptoms. Shortly, if the resistant strains are not closely detected and monitored through laboratory techniques, the world will suffer, but the poorest countries will be affected earlier and the most. Nowadays, society's main challenge is developing and designing advanced therapeutic strategies that will spearhead old clinically-associated MDR pathogen therapies. Recently introduced techniques such as nanotechnology and CRISPER/Cas9 should be followed to combat this resistance.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Conflict of interest

The author declared no conflict of interest.

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