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REVIEW ARTICLE

Growing Menace of Antimicrobial Resistance and Combating Strategies: Underlying Myths and Realities

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ABSTRACT

Unlimited and unethically usage of antibiotics has accelerated the global spread of antibiotic-resistant microorganisms. Therefore, the emergence of antibiotic resistance has jeopardized the effectiveness of antibiotics, which have previously saved millions of lives by treating bacterial infections. This correspondence article highlights the growing emergence of antimicrobial resistance and immediate efforts needed to mitigate the menace of drug resistance. However, despite several offered solutions, the AMR continues to be a complex and global health concern, seeking an urgent solution for societal benefits. There is a need for global actions across veterinary practice, human medicine, and the agriculture sector to minimize the inappropriate use of antimicrobials. Furthermore, the development of new combination approaches coupled advanced delivery system is required to combat AMR effectively.

Keywords: *Antimicrobial resistance, Antibiotic, Multi-drug resistance, Therapeutics.*

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INTRODUCTION

Antimicrobials include antibacterial, antivirals, antifungals, and antiparasitic components that are used to treat and prevent infections in humans and animals. In the last few decades, the unlimited and unethically usage of antibiotics has accelerated the global spread of antibiotic-resistant microorganisms. Therefore, the emergence of antibiotic resistance jeopardizes the effectiveness of antibiotics, which have previously saved millions of lives by treating bacterial infections [1]. The global emergence of antimicrobial resistance (AMR) in pathogenic bacteria is associated with rising mortality and morbidity. Besides this, a surge in multi-drug-resistant (MDR) strains in both Gram-positive (Gram +ve) and gram-negative (Gram -ve) bacteria has rendered most conventional antibiotics ineffective against infections [2]. Another important aspect of antimicrobial resistance is due to lack of early identification of causative bacterial pathogens, especially in the case of bacteraemia and other serious infection that has led to the inappropriate administration of broad-spectrum antibiotics. The non-judicious usage of broad-spectrum antibiotics has broadened the emergence of AMR and untreatable hospital-acquired infections [3]. AMR is regarded as one of the most serious threats to humans in this century. The first surveillance report by World Health Organization (WHO) in 2014 showed the extent of this menace in many parts of the world. Research published in the Lancet predicted that AMR was responsible for 4.95 million deaths in 2019, including 1.27 million deaths owing to bacterial AMR. The report estimated a higher mortality rate owing

to AMR in western sub-Saharan Africa i.e. 27·3 deaths per 100 000 individuals, whereas the lowest rate was estimated for Australia i.e., 6·5 deaths per 100 000 individuals. In 2019, lower respiratory infections were responsible for over 1.5 million resistance-related fatalities, making them the most worrying infectious syndrome [2,3]. Furthermore, globally, at least 700 000 people die annually because of drug-resistant infections, and if the necessary AMR-combat measures are not taken, the number may rise to 10 million by 2050 [4]. Hence, it is a key concern since most recent medicines and treatments are inconceivable without the use of effective antimicrobials. Antibiotic resistance bacteria are rising continuously, even though there are resistant bacteria for all known antibiotics and only very few new agents are in pipeline for development to avoid global health tragedies. Moreover, the rise in antibiotic resistance jeopardizes the effective treatment and prevention of infections at surgical sites, organ transplants, chemotherapy, and surgeries. Further spread of antibiotic-resistant genes between different bacterial species in an environment led to the development of multi-drug resistant bacteria [5]. Also, the pandemics such as Covid-19 have been reported to further exacerbate antimicrobial resistance. A study in the United States identified that 72% of covid-19 positive patients were given broad-spectrum antibiotics even if they were not clinically required [6]. Therefore, such emerging diseases can also contribute to the rise of bacterial resistance where we are lacking antimicrobials in the development pipelines. Hence along with deciphering the origin of antibiotic resistance and its mechanism, new antimicrobial strategies or approaches and therapeutic interventions are required (Fig. 1).

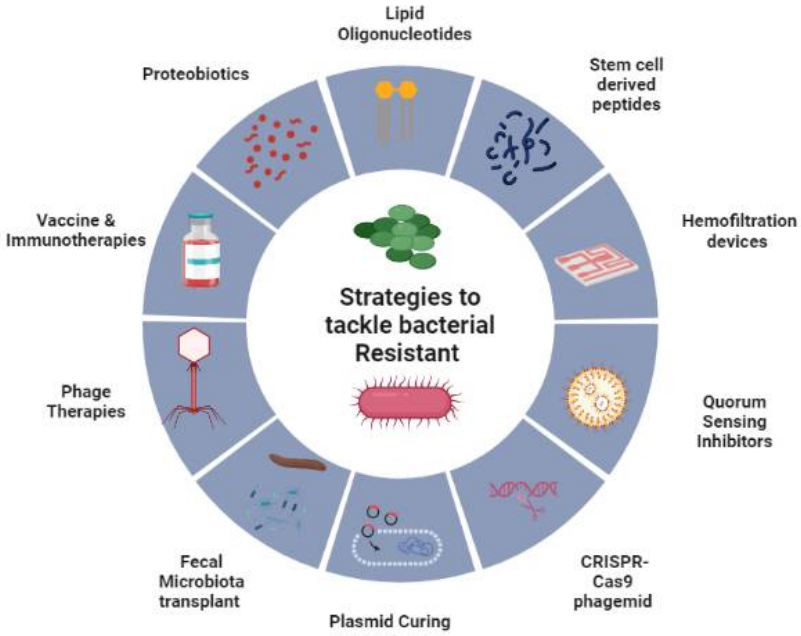

Figure 1: Futuristic approaches to tackle antimicrobial resistance.

PARADIGM SHIFT TOWARDS BETTER THERAPEUTICS

Phage therapy is widely tested as a therapeutic alternative to treat bacterial infections. Presently, this technique is gaining attention as phages are pervasive, harmless, host-specific, and can be taken orally alongside food. Phage therapy has been developed for AMR pathogens like *P. aeruginosa* and *Staphylococcus aureus* [7]. The rate of successfully treating life-threatening diseases using phage therapy is increasing. One such example includes a 68-year-old patient infected with MDR *Acinetobacter baumannii* as well as having a condition of diabetes and necrotizing pancreatitis. Despite several antibiotic regimens, the patient's health deteriorated over time (4-month period). However, the administration of bacteriophages having lytic activity against *A. baumanniii* (isolated from the patient) resulted in the clearance of MDR *A. baumanniii* as well as a return to healthy state [8].

Vaccination Strategies

Vaccination has helped humanity tackle numerous diseases and may be employed for years with relatively lower risk of resistance development than antibiotics. Vaccine administration lowers the chances of undergoing antimicrobial drug treatment upon pathogen exposure, thereby reducing the selection of AMR variants. Over the past 40 years, several vaccines have been licensed, and new vaccines are also being developed against a wide range of AMR bacteria. A vaccine against a particular pathogen

decreases the incidence of pathogen resistance and antibiotic use. By the time vaccines were introduced against *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, and *Neisseria meningitidis* (meningococcus) resistance has already become a problem, but vaccines have lowered or almost eliminated the problem of resistance in these pathogens [9]. Globally, the veterinary and agriculture sector accounts for 50% of antibiotic consumption which has been listed as a key driver in resistance emergence. However, recent studies have shown that vaccination of food-producing animals significantly reduced antibiotic usage and AMR emergence risk. Vaccines can reduce AMR emergence if the majority of the residents who are susceptible to infection get vaccinated, especially in nations where AMR bacteria are endemic. Miserably, vaccines are not yet available against most of the key AMR pathogens. However, several candidate vaccines including vaccines for *S. aureus* and *Clostridioides difficile* infection prevention, vaccines for Gram -ve bacterial infection prevention, and pneumococcal conjugate vaccines with extended serotype coverage are under development, which not only holds promises to combat life-threatening infections, but also curbs the antibiotic use, hence prevent AMR [10].

Other than vaccines, therapeutic monoclonal antibodies (mAbs) can be an alternative option to combat emerging contagious diseases and AMR pathogens. After binding to virulence factors such as polysaccharides, effector proteins, adhesions, or toxins that are expressed by pathogenic bacteria, mAbs act by three different mechanisms i.e., target activity inhibition, promotion of complement-mediated cellular lysis, and enabling bacterial opsonophagocytosis by effector phagocytic cells [7]. Several mAbs are under different stages of development against AMR pathogens. For example, the most advanced is a combination of two mAbs targeting toxin A and B of *C. difficile* [11] and a bispecific mAbs targeting the virulence factor (exopolysaccharide) of *P. aeruginosa* [12].

Faecal Microbiota Transplant

Faecal microbiota transplant (FMT) is a therapeutic approach of transferring human faecal matter from a healthy donor to a recipient to treat disease associated with microbiome imbalance (Figure 1). Recently, the US Food and Drug Administration (FDA) licensed Rebyota (which contains a variety of bacteria from a healthy human donor) for the treatment of recurrent *C. difficile* infections where conventional antibiotics are ineffective. During the process, the complete microbiome of donor organism is transferred to recipient, either orally through a capsule or by colonoscopy. Post-treatment, a 70.6% success rate was noted after 6 weeks by the approval committee in preventing recurrent *C. difficile* infection compared to 57.7% for placebo recipients [13]. This improvement is modest but significant. Other candidates (oral) such as from Seres Therapeutics (SER-109) and Finch Therapeutics (CP101) are also seeking approval for the prevention of recurring *C. difficile* infection [13].

Proteobiotics

Proteobiotics are the metabolites from probiotics. These compounds are known to interrupt bacteria cell-to-cell communication. Proteobiotics act as anti-virulent and thus downregulate the virulence genes in both Gram +ve and Gram -ve bacteria. Since this therapeutic strategy does not directly kills the pathogen, thus there is less possibility for antibiotic resistance development (Figure 1). Furthermore, the host's microbiota remains unaffected, and selection pressure gets reduced to circumvent the evolution of resistance against anti-virulence therapy. At present, one approved proteobiotics product namely Nuvio derived from *Lactobacillus acidophilus* is being used in the treatment of piglets with enteric colibacillosis and showing significant positive outcomes.

Antimicrobial Peptides

Nowadays, antimicrobial peptides have been developed as a unique class of antimicrobial chemicals. These are small molecules of host defence present in a variety of species, including humans, and are considered crucial components of innate immunity. It has been discovered that they exhibit an immune response against microorganisms such as bacterial and fungal pathogens. Although their action mechanism is not fully understood. Several investigations have demonstrated the antibacterial properties of mesenchymal stem cells (MSCs). These cells release soluble proteins such as interleukin-10 (IL-10), LL37, tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2), beta-defensin, and IL-6 that have a protective effect [14]. MSCs have recently been employed as a novel therapeutic intervention for the treatment of inflammatory bacterial diseases. *In-vitro* studies have demonstrated the effectiveness of MSC peptides against *E. coli*, *S. aureus*, and even MDR *Mycobacterium tuberculosis* and *A. baumannii* [15,16]. Thus, more clinical investigations are necessary to show their efficacy for human usage.

Antisense Therapy

Oligonucleotide treatment, namely antisense therapy, is an important approach developed in recent years for combating bacterial resistance (Figure 1). In this technique, oligonucleotides are coupled with mRNA and inhibit the expression of bacterial genes responsible for AMR, like beta-lactamases. Despite their

enormous promise, the cellular uptake of oligonucleotides by bacterial cells is essential step for their bioactivity, as targeted mRNA against bacterial genes is located inside the cells [17]. Recent investigation has shown that lipid-oligonucleotide conjugates increase their uptake by bacterial cells [18].

CRISPR/Cas9 System

Recently, the discovery of the CRISPR/Cas9 system enables the development of gene-specific antimicrobials that may be less likely to promote AMR than traditional antibiotics (Figure 1). CRISPR's self-targeting technology has been developed in recent years to target pathogenic bacteria. The main challenge associated with this technology is its delivery to target microorganisms with sufficient efficiency and specificity to achieve clinically significant effectiveness. Therefore, phages have gained attention for their ability to deliver plasmids and phagemids harbouring CRISPR/Cas9 to antibiotic-resistant bacteria in target populations. A study demonstrated that the temperate phage delivering this system successfully controlled resistant *E. coli* and *S. aureus* [19]. Meanwhile, another study revealed the delivery of antimicrobials to numerous gut pathogens by using tail-engineered phage P2 [20]. Yet, this technique still faces obstacles, including the inefficiency of phage-based delivery methods. Because of the enormous potential of CRISPR/Cas9-based antimicrobials, it is necessary to create a novel delivery mechanism for their administration.

CONCLUSION

Despite several offered solutions, the AMR continues to be a complex and global health concern, seeking an urgent solution for societal benefits. There is a need for global actions across veterinary practice, human medicine, and the agriculture sector to minimize the inappropriate use of antimicrobials. Furthermore, the development of new combination approaches coupled advanced delivery system is required to combat AMR effectively.

ETHICAL APPROVAL

Not applicable.

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DATA AVAILABILITY STATEMENT

Data will be made available upon request.

DECLARATION OF COMPETING INTEREST

None

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