Review article

Antimicrobial Resistance (AMR) and Newer Approaches to Combat against It

Akhiruzzaman[1], Asha DA[2], Chowdhury MAR[3]

Abstract

Antimicrobial resistance is a global health crisis and a threat to human and animal health, environmental safety, and economic stability. Indiscriminate use, overuse or misuse of antibiotics in human body, agriculture product and veterinary practices have boosted this condition and further worsened by the COVID-19 pandemic, where increase in irrational use of antibiotic was noticed. The main sufferer of this condition is low- and middle-income countries due to poor health infrastructure, poor regulation, and frequent practices of self-medication, particularly evident in regions such as South Asia. The present review discusses current scenario of antimicrobial resistance and recent strategies developed against it. These novel developments include bacteriophage therapy, bacteriocins, antimicrobial peptides and nanotechnology-based drug delivery approaches. Those emerging solutions offer some mechanisms like, targeted alternatives to conventional antibiotics, reducing the impact on beneficial microbiota and slowing resistance development. The One Health approach (household, animal and environmental health programs) play an integral part in the global restraint of AMR. Public awareness of proper use, antibiotic stewardship programs and enhanced surveillance will be essential to fostering responsible use of antibiotics and inhibiting the spread of AMR. A combined and multi-pronged response is needed to secure the efficacy of antimicrobial therapy for new generations.

Introduction

Antimicrobial resistance (AMR) is now considered one of the most serious health threats of the twenty first century and is a growing public health concern worldwide. The World Health Organization defines antimicrobial resistance as, "the ability of bacteria, viruses, fungi and parasites to develop resistance to the medications used to treat them". It means that standard treatments are no longer worked, resulting in prolonged illness, higher mortality rates and more expensive healthcare services.[1] Recently, AMR had escalated from a steady state to rise in a peak due to overuse and misuse of antibiotics in human medicine, agriculture product and veterinary practices. According to current estimates, if AMR continues without interventions, it may account for over 10 million deaths annually by the year 2050 which is more than the death from cancer.[2,3]

The use of antimicrobial therapy was increased to prevent the perceived risk of secondary bacterial infections among patients with COVID-19 which exacerbated the crisis of AMR. Studies report a significant surge in broad spectrum antibiotics, even when bacterial infections were absent, which accelerated the dissemination of drug-resistant pathogens.[4] In this aspect, the pandemic underlined the urgent need for more responsible antibiotic stewardship, while it also underlined the systemic challenges. The healthcare systems must balance immediate patient needs with long term public health outcomes.

The consequences of AMR are far-reaching, including impacts on not only clinical medicine but also on agriculture, environmental health and socio-economic stability. In low and middle income countries, the burden due to AMR is high because of an easy access to diagnostics and alternative treatments, leading to inappropriate use of antibiotics and dissemination of resistant strains.[5] Additionally, AMR increases the cost of healthcare as a result of extended hospitalization and further need for intensive care with more expensive and often toxic alternative drugs.[6] This situation is worsened by the lack of newly developed antimicrobial agents in the market due to preference of pharmaceutical companies who often prioritize more profitable areas than the noble outcomes.[7]

By acknowledging the current situation and the urgency

Author's Affiliation:

1. *Akhiruzzaman, Associate Professor, Department of Community Medicine and Public Health, TMSS Medical College, Bogura, Bangladesh
2. Dilara Ahmed Asha, MPH(Community Nutrition) Fellow, National Institute of Preventive and Social Medicine (NIPSOM), Mohakhali, Dhaka, Bangladesh
3. Md. Anup Rahman Chowdhury, Professor, Department of Pharmacology and Therapeutics, TMSS Medical College, Bogura, Bangladesh.

Address of Correspondence : *Dr. Akhiruzzaman, Associate Professor, Department of Community Medicine and Public Health, TMSS Medical College, Bogura. email: akhiruzzaman.88@gmail.com

of this problem, academicians and clinicians have been brainstorming new ways that confront AMR. A few newer approaches like bacteriophage therapies, bacteriocins, antimicrobial peptides along with optimization of antibiotic stewardship programs and research are running simultaneously. Recent studies have indeed looked promising with the application of phage therapy, a method using viruses that attack and kill bacteria that may prove highly targeted for antibiotic-resistant infections without harming beneficial microbiota.[8] Meanwhile, much interest has been focused on bacteriocins (small antimicrobial peptides produced by bacteria) due to their potential for selective inhibition of pathogenic bacteria, representing another effective alternative to classic antibiotics.[9]

Besides these biological approaches, the development of nanotechnology has also given rise to new ways of drug delivery and antimicrobial therapy. Nanoparticles help make existing antibiotics more effective by ensuring that the delivery is targeted and the dosage is lower, hence decreasing the chance of developing resistance.[10] Similarly, use of the CRISPR-Cas technology allows a new method of targeting resistant bacteria selectively by directly altering their genetic material, hence becoming one of the frontiers of precision medicine.[11]

Global health organizations and governments worldwide have identified a multi-sectoral approach is core concept to combat against microbial resistant. The WHO Global Action Plan on AMR emphasizes that the fight should interdisciplinary across human, animal and environmental health sectors (the so called One Health Approach).[12] It requires enhanced surveillance, better regulation of the use of antibiotics in agriculture and emphasis on sanitation and infection prevention measures across healthcare and agricultural settings.[13] Besides, awareness campaigns among the public to understand proper use of antibiotics and the risks of self-medication.[14]

Though AMR has many dimensions this paper will present the current scenario of the world and the recent advances in the fight against AMR from established approaches like antibiotic stewardship programs and infection prevention practices to newer approaches such as bacteriophage therapy, nanotechnology-based drug delivery and genetic interventions.

Current Scenario of AMR:

Bangladesh scenario

AMR is a critical and growing public health issue in Bangladesh, whose situation and prospects are further deteriorated by many factors, such as misuse of antibiotics, deficiency of regulatory controls and weaknesses in healthcare infrastructure. Hoque *et al.,* 2020 was reported that more than 70% of bacterial isolates from clinical infections were resistant to commonly used antibiotics, including Carbapenems, which are usually last-stage antibiotics in Bangladesh.[15] These are collectively caused by the high prevalence of self-medication practices, limited enforcement of prescription-only policies and substandard quality of antibiotics. Additionally, overcrowded urban areas along with poor sanitation facilities enhance the spread of AMR pathogens; this is particularly evident in hospitals and other healthcare facilities where healthcare associated infections are high contributors to AMR.[16]

Regional Scenario in Southeast Asia:

Southeast Asia is the most affected region in the world in terms of antimicrobial resistance. A report published by WHO's Regional office for Southeast Asia found many well-functioning antibiotics are recently resisted at alarming rates. Which is further worsened in some countries due to only poor regulatory systems and overuse or misuse of antibiotics.[17] Recently India, Pakistan and Nepal reported that drugs use for TB and malaria are repeatedly found resistance in their countries.[18] Notably, the colistin resistant *E. coli*, a superbug has been spreading rapidly in this region which is raising concern for the efficacy of last resort of antibiotics. Though, SEARO and its member countries are trying to strengthen AMR surveillance and develop national action plans but there are still a gap in enforcement of regulations and access to appropriate diagnostic services that help effectively to containment of AMR.[19]

Global Scenario:

Globally, the antimicrobial resistance has reached in such a level which is considered as a threats to public health, economic stability and the effectiveness of modern medicines. The WHO Global Antimicrobial Surveillance System report, 2021 showed a trend of increasing common infections caused by Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus. In Europe and America, the rates of healthcare associated infections (HAIs) are increased due to cross contamination and antibiotic overuse in hospital settings.[6] In developing countries, which are mainly located in Africa and Latin America found resource constraints, lack of diagnostics and use of low-quality antibiotics have contributed to the continued spread of AMR.[20]

Newer Approaches to Combat against AMR:

Researchers proposed and somewhere started to implement several approaches to combat against AMR. All those approaches are not possible to discuss in a single paper so, some new but applicable for Bangladesh are mentioned here in short.

1. Development of bacteriophage therapies

"Bacteriophage therapies" is one of the emergent strategies to fight against antimicrobial resistance. In this

approach viruses are used to kill the targeted bacteria. This approach has good results against multidrug-resistant pathogens as it can bypass the resistant mechanism of bacteria and work specifically on targeted bacteria without doing any harm the normal floras.[21,22] First of all a) the Bacteriophages recognize and bind to specific receptor on the bacterial cell surface. b) After attachment, it injects its DNA or RNA into the targeted bacterial cell. c) Replication of DNA/RNA inside the bacteria. d) When sufficient bacteriophage particles are assembled, it produces **endolysins** (enzymes) that break down the bacterial cell wall.[23]

2. Bacteriocins

Bacteriocins are peptides produced by some bacteria and a new promising approach in the fight against AMR. Bacteriocins kill or inhibit the growth of specific bacteria, including antibiotic-resistant strains. They disrupt the bacterial cell membrane or form pores and interfere with essential enzymes leading to cell death. It generally inhibit the growth of specific bacteria and only closely related bacterial strains, thus leaving the useful microbiota and minimizing the development of resistance among pathogens.[24] Studies showed the effectiveness of bacteriocins against multiple drugs resistant bacteria, thus making them useful under conditions where conventional antibiotics are not effective.[25] Due to their specificity of action and fewer side effects, bacteriocins therefore, raise a good prospect for alternative use to conventional antibiotics for new AMR solutions.[26]

3. Optimizing Antibiotic Stewardship Programs (ASP)

Antimicrobial stewardship programs represent key strategies for addressing the antimicrobial resistance challenge. ASPs are targeted to optimize appropriate use of antibiotics (make sure that the patients are receiving proper drug, dosage and duration) and reduce unnecessary or suboptimal antibiotic use. Well implemented ASPs in healthcare settings have been found effective to reduce the incidence of multidrug-resistant conditions, cut health care costs and improve patient outcomes. As this program involves microbiologists, pharmacists, clinicians and other healthcare providers, it in the monitoring of the pattern of antibiotic prescribing and trends in antibiotic resistance, as a means of ensuring responsible use of antibiotics.[27] Thus, the optimization of ASPs becomes critical to ensure a continuous effort towards sustaining efficacy in antibiotics and controlling the spread of resistant pathogens.

4. Potential of Antimicrobial Peptides

Antimicrobial peptides (AMPs) are naturally produced small molecules found within various organisms as a part of their innate immune systems. These peptides disrupt microbial membranes and interact with multiple cellular targets and kill the microbes.[28] Though many antibiotics also disrupt cell membrane, the uniqueness of the peptides are, a) They bind with targeted negatively charged phospholipids, which are found only in microorganisms and not in human cell. b) Their activities do not end after disrupting cell membrane only. These peptides enter the cell, blocking DNA & RNA replication and transcription and altering ribosomal functions.[29]

Due to variety of actions, these peptides have exhibited activity against multi-drug-resistant bacteria and may serve as promising candidates for novel therapy or as an adjunct to conventional treatments.[30] New approaches in AMP design and synthesis have lately reduced toxicity and augmented specificity, hence improving therapeutic utility.[31].

5. Advancing Nanotechnology or Nanobiotics

Nanoparticles (1 to 100 nanometer size) of different heavy metals and oxides like-silver, gold, zinc oxide etc. have been identified as potential antimicrobial agents due to their efficacy in causing microbial cell membrane damage and generating reactive oxygen species, interacting with the key functions of microbes.[10] Those particles are loaded with traditional antibiotics (Known as nanobiotics) to enhance the targeted delivery and controlled release of antibiotics at reduced dosages that can minimize side effects and subsequently the rate of resistance development.[32]

Some other approaches:

Along with the approaches discussed there are so many upcoming actions which will be more specific and effective to fight against the resistant microbes. The approaches are- CRISPR-Cas gene editing technology, Anti-Biofilm strategies, Bacterial communication inhibition (Quorum Sensing Inhibitors), Anti-resistance adjuvants, Microbiome engineering etc.

Conclusion:

It is assumed that the next pandemic which may disrupt the worldwide health system will be associated with anti-microbial drug resistance. Antimicrobial resistance affects not only public health but also indirectly impacts national economic stability. As mentioned in the discussion of this review, the situation regarding AMR is not the same in all regions. Bangladesh and other Southeast Asian countries are at highest risk due to the over prescription and overuse of antibiotics, poor health infrastructure and weak regulatory mechanisms. At the global level, the emergence and spread of multidrug resistant pathogens have the potential threat to the effectiveness of existing antibiotic therapies. Novel and newer approaches that have emerged as promising options in this context to fight against AMR.

Fighting effectively against AMR is impossible without continued investment in research, collaboration across the nations and multidisciplinary actions. Basic requirements for strengthening surveillance systems, enhanced regulatory approaches, public awareness and access to health on equal terms are required so that the global burden of AMR could be decrease. All those actions can make the difference and ensure the safe and healthy tomorrow.

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