Increasing Threats of Gram-negative Bacteria in the Era of Antimicrobial Resistance and Strategies to Combat

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Abstract

The health of populations and economies faces substantial detriment because of the increasing risk from Gram-negative bacteria during the antimicrobial resistance era. The bacteria feature an outer membrane as their signature structure which confers increased resistance to environmental threats as well as antibiotic substances and biological immune reactions. Healthcare treatment failures along with higher disease occurrence together with rising healthcare costs have emerged due to antibiotic misuse and multiple treatments. Overutilization combined with mis prescription of antibiotics along with agricultural usage and deficient education systems and weak surveillance systems are the main factors responsible for this issue. The solution requires proactive development of new vaccines together with antibiotics and adjuvants while establishing nutritional measures for strengthening immunity. Extensive antimicrobial resistance management demands the implementation of national action plans and nutritional interventions under the umbrella of one health initiatives.

Keywords: Gram-negative, Resistance, Antibiotics, Strategies, Bacteria

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Introduction

The health of populations and economies faces substantial detriment because of the increasing risk from Gram-negative bacteria during the antimicrobial resistance era (Jean et al., 2022). The bacteria feature an outer membrane as their signature structure which confers increased resistance to environmental threats as well as antibiotic substances and biological immune reactions (Salam et al., 2023). Healthcare treatment failures along with higher disease occurrence together with rising healthcare costs have emerged due to antibiotic misuse and multiple treatments (Furuyama & Sircili, 2021). Overutilization combined with mis prescription of antibiotics along with agricultural usage and deficient education systems and weak surveillance systems are the main factors responsible for this issue (Bisht et al., 2024). The solution requires proactive development of new vaccines together with antibiotics and adjuvants while establishing nutritional measures for strengthening immunity (Cantón et al., 2021; Jain et al., 2021). Some of the most important gram-negative resistant bacteria are *Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Klebsiella* spp., *Shigella* spp., *Enterobacter* spp., *Salmonella, Hemophilus influenza, Campylobacter* and *Escherichia coli* (Nourbakhsh et al., 2024). Enterobacteriaceae family are the most frequent reason of urinary tract infections, blood-stream infections, hospital associated pneumonia (Kumar et al., 2025). AMR is recognized as one of the top 3 critical global health risks by the WHO (Qureshi et al., 2023).

Antibiotics are powerful medicines that have enhanced treatment outcomes of bacterial infections (Lee et al., 2021). They are considered one of the most significant medical discoveries of the 20th century (Zhu et al., 2022). They are widely used in both human and animal care and play a crucial role in many regions, particularly in developing and underdeveloped. Antibiotics have been instrumental in driving socioeconomic progress by improving healthcare, reducing mortality rates, and increasing livestock productivity (Baudoin et al., 2021). Unfortunately, the improper and misuse of antibiotics worsened the problem of bacterial resistance, leading to ineffective treatments, increased disease prevalence, and escalating healthcare expenses (Muteeb et al., 2023). The growing presence of antimicrobial resistance in environmental, animal, and human domains heightens the risk of human infection by antimicrobial-resistant bacteria (Swarthout et al., 2022). There are multiple factors that are contributing to this problem such as overutilization, mis prescription, antibiotics use in agriculture, less education and knowledge on their use, overpopulation, hospital-acquired infections and poor surveillance system (Manyi-Loh et al., 2018).

Antibiotic use can disrupt the balance of the gut microbiota, favoring the growth and proliferation of resistant bacteria because of guts abundant nutrients and optimal temperature (Dahiya & Nigam, 2023). The exchange of genetic material between bacteria in the gut can spread antibiotic resistance genes (Broaders et al., 2013). A complex gut microbiota can harbor a pool of antibiotic resistance genes and resistant microorganisms (Zhang et al., 2013). Antimicrobial resistance occurs when germs like bacteria, viruses, and fungi become strong enough to survive despite medicines meant to kill them and Infections caused by antimicrobial-resistant organisms are harder to treat, cause severe illness and even death (Okeke et al., 2024).

There is a great need for some advanced research, alternative and beneficial strategies which help to solve this emerging issue (Dwivedi et al., 2022). Development of new vaccines, antibiotics, use of adjuvants, nanoparticles and improve immunity by nutrition are the best ways considered for cutting this prominent issue (Ahmad et al., 2024; Qurashi et al., 2024). However, botanical compounds are under study as an alternative strategy to combat antimicrobial resistance (Abbas et al., 2025). We must focus on educational programs, public health campaigns and information pamphlets for patients to highlight the risks of antibiotic misuse and adverse effects (Hunter & Owen, 2025).

Antibiotic-resistant Bacteria: Diffusion, Settlement, and Prevention Strategies

ARB (Antibiotic-Resistant Bacteria) transfers ARGs (antibiotic resistance genes) to other bacteria, making them resistant to antibiotics (Wang et al., 2023). These bacteria after entering the body move towards the gut using flagella or other motility structures (Halte et al., 2025). They move toward some specific location through the guidance of chemical attractions using flagellar movement (Xu et al., 2024). Chemical attraction means they locate nutrient-rich environments and migrate towards favorable conditions (Mohite et al., 2024). Next step is to adhere and start colonization at the specific site for infection development (Doohan et al., 2021). They attach to the gut lining using adhesions, which are some specific proteins, to facilitate attachment. Bacteria penetrate the lining of the gut using various virulence factors (secreted by them and called as type IV secretion system), overcome the natural defense system of gut and settle down there by colonization. Here are some expected plans to overcome their settlement and resistance, which can be helpful in solving this issue. We can first interfere with the flagella to avoid bacteria movement and for this we can use chemical inhibitors or manipulate the genes with involvement in flagella synthesis. We can also do coatings of surface that inhibit flagellar movement by creating an unfavorable environment for bacterial attachment. One of the critical steps is the bacterial adhesion and can be stopped by anti-adhesion vaccines, adhesion inhibitors, competitive inhibitors and antibiotics which can block adhesion to host cells. Next target the Type VI Secretion System of Gram-negative bacteria whose main component is T6SS gene (W. Li et al., 2022). Genetic manipulation to attenuate virulence and colonization capacity by targeting T6SS genes (Asgari et al., 2024). Phage therapy which targets T6SS-positive bacteria and prevents colonization and immunotherapy (Karnwal et al., 2025). All the above steps can prove very beneficial.

Sources of Antibiotic Resistance Development

Antibiotics are used in the agriculture field for disease control and to promote growth (Elnahal et al., 2022). Their use is contaminating soil, water, and air, which leads to the development of antibiotic-resistant bacteria in ecosystem and wildlife (Singh et al., 2024). This contamination spread resistance to humans through the food chain and is a cause of food-borne illnesses (Samtiya et al., 2022). There is a lack of knowledge about the consequences of antibiotic use in agriculture among the farmers, consumers and veterinarians (Dankar et al., 2022).

In hospitals contaminated surfaces, objects, and inhalation of aerosols holding pathogenic bacteria and antibiotic resistance genes can spread infections (Jabłońska-Trypuć et al., 2022). Overprescription and inadequate dosing in hospitals is a main factor which contributes to this issue (Lagarde & Blaauw, 2023). Extensive antibiotic use in veterinary farming and intensive animal farming can select for resistant bacteria (Jeżak & Kozajda, 2022).

Waste water from urban cities, agricultural lands and industrial waste can carry pollutants, which contain ARG and ARB (Anand et al., 2021). Plants which are treating wastewater can be a source of antibiotic resistance genes (ARG) and antibiotic-resistant bacteria (ARB) in the environment (S. Li et al., 2022). Treated wastewater contains ARG, which can persist even after treatment processes (Nguyen et al., 2021). This water then released into the water bodies and spread resistance issues widely. The processing plant produces aerosols containing ARG and ARB. By irrigation with this treated wastewater contaminates soil and crops and directly affects the consumers of those crops, including humans and animals. Recreational activities in contaminated water bodies and eating seafood are also sources of resistance emergence (Stec et al., 2022).

Challenges and Contributing Factors to Global Antibiotic Resistance

Overutilization and misapplication of antibiotics, resulting in emerging resistance (Fatima et al., 2023). Inadequate surveillance and regulation of antibiotic use in certain areas is one of the reasons for antimicrobial resistance. Wealthy countries have better access to antibiotics than poor countries, which causes more deaths and illnesses, faster spread of antibiotic resistance and heavier economic burdens on poor countries (Adekoya et al., 2021). Increased resistance leads to more medical expenses due to ineffective treatments and extended inpatient care. The factors due to which all this is happening are the availability of antibiotics without a medical prescription and not enough awareness about using antibiotics correctly. There is limited understanding of antibiotics' utilization and management among healthcare professionals and patients (Ashiru-Oredope et al., 2021).

Economic pressures are a main reason for influencing a doctor's selection of antibiotics and prescription and results in impaired performance of existing antibiotics (Christensen et al., 2022). The severity and cases of resistance are increasing day by day because of the continued emergence and spread of multidrug-resistant pathogens and lack of money for new antibiotic research (Alara & Alara, 2024). Inadequate collaboration between healthcare stakeholders and barriers to policy implementation because of politics and economics hinders progress in combating resistance (Shabangu et al., 2023). Lack of standardized data collection and reporting protocols, especially in low-income areas, and unwillingness to share data among countries due to privacy and national jurisdiction trigger this common resistance issue. Insufficient public awareness regarding antibiotic use and resistance, and doctors do not teach them enough, which contributes to rising cases of resistance (Virhia et al., 2023). These are all the factors and challenges which the whole world is facing right now and there is a great need to develop some alternatives and strategies to overcome this issue.

Strategies and Solution to Combat Antibiotic Resistance

Antimicrobial resistance is the most raised issue, and we immediately need to solve it. To fight these issues, we need to improve the use of antibiotics by monitoring them responsibly and improve the surveillance system (Godman et al., 2021). Professionals must have the latest information related to antibiotics and their prescribing practices. Antibiotics should never be used unnecessarily (Llor et al., 2022). We must get help from social media, posters, and other materials to make people aware and arrange training sessions for the professionals as well. One of the basic requirements in the current situation is the boosting of funds for research purposes and for the development of new solutions and antibiotics (Muteeb et al., 2023).

There is a great need to explore alternative approaches which provide new ways to combat antibiotic resistance. These innovations include phage therapy means use of viruses which target and kill resistant bacteria, use of immune therapy to boost immune system and use of chains of amino acids called antimicrobial peptides that disrupt bacterial cell membranes and kill the bacteria. Use of nanoparticles and combination of antibiotics can be a beneficial strategy (Saeed et al., 2025). Metals like silver, copper, ruthenium, gallium and bismuth etc. are considered good metallic antimicrobial agents (Evans & Kavanagh, 2021).

National Action Plans is an effective strategy on control of antimicrobial resistance with long-term viability (Willemsen et al., 2022). Six critical components of this plan include strengthening governance, prioritizing activities, operational plan cost, resource mobilization, implementing prioritized activities and then analyzing and monitoring all. One Health Action Plan to develop coordination between human and veterinary healthcare sectors is an effective approach to solve the recent issues (Muqadas et al., 2023).

Nutrition is the main point to be considered preventing the body from infections and to enhance immunity (Muqadas et al., 2024). High-fiber and low-fat diet support gut wellness and can help sustain a balanced microbiome which helps prevent antibiotic resistance (Hills Jr et al., 2022). Plant-derived compounds like polyphenols found in common dietary items, flavonoids and phenolic compounds have been associated with numerous health benefits. They have anti-inflammatory, antioxidant and anticancer properties. They promote beneficial gut bacteria and reduce harmful gut bacteria. Omega-3 fatty acids, calcium, vitamins A and D help maintain the health and functionality of the gut barrier. So different food ingredients are effective against various antibiotic-resistant bacteria (Friedman, 2015).

Conclusion

Bacteria are constantly evolving to resist antibiotics, either through mutations or by sharing resistance genes. Antibiotic-resistant strains is a global health emergency and now recognized as the highest health danger in the 21st century. There is a great need to share knowledge, best practices, and resources across borders to combat the global spread of antibiotic resistance. Countries and organizations must work together quickly to address antibiotic resistance and ensure a healthier future for generations to come. To combat AMR, we must focus on critical actions like tracking antibiotic use and enforcing regulations, reducing over-the-counter antibiotics and antibiotics in food animals, improving access to quality medicines, vaccines, and diagnostics. Further scientific research and advancements are essential to fight or eradicate the resistance issue.

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