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Review Article

Emerging Antibiotic Resistance in Gram-Positive Bacteria, with Focus on *Staphylococcus Aureus, Enterococcus Spp.,* and *Streptococcus Pneumoniae*

Olumakinde Charles Omiyale[1,*], Favour Onaskohare Okunbi[2], Confidence Damian Oparah[3], Victor Nduka Eluwa[4], Rosemary Modupeoluwa Awolade[5], Precious Ifechukwuni Ikuni[6], Muhammad Bello Demola[7], Christianah Oluwatosin Agboola[8], Temitope Oluwapelumi Babalola[9], Abdul-Hanan Saani Inusah[10], Abigail Daniel Agbo[11], Onyekachi Uchenna Uchejuru[12], Benjamen Minasu Oke[13], Stanley Augustine Ugbobuaku[14]

[1]Department of Pharmacology, Toxicology and Therapeutics, College of Medicine, University of Lagos, 101014, Nigeria

[2]Department of Microbiology, Faculty of Biological Sciences, Mountain Top University, 110106, Nigeria

[3]Department of Internal Medicine, National Hospital Abuja, Abuja, 900103, Nigeria

[4]Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of Portharcourt, 500272, Nigeria

[5]Department of Anatomy, Faculty of Basic Medical Science, Ladoke Akintola University Ogbomoso, 210274, Nigeria

[6]Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Delta State University, 330105, Nigeria

[7]Department of Biomedical Engineering, School of Engineering, University of University of Strathclyde, G1 1XQ, UK

[8]Department of Microbiology, Faculty of Sciences, Adekunle Ajasin University, 342111, Nigeria

[9]Department of Microbiology, Faculty of Life Sciences, University of Ilorin, 1515, Nigeria

[10]Department of Medicine, University of Development Studies, NT-0272-1946, Ghana

[11]Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of Jos. 930105, Nigeria

[12]Department of Public Health. Faculty of Health Science. Imo State University. 460281, Nigeria

[13]Department of Microbiology. School of Biological Sciences. Lagos State Polytechnic. 104233, Nigeria

[14]Department of Pharmacy. Niger Delta University. Amassoma. 560103, Nigeria

*Corresponding Author E-mail: 199096019@live.unilag.edu.ng

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Abstract

Antibiotic resistance is becoming more prevalent, which presents as an urgent risk to world-wide well-being, necessitating an urgent exploration of its mechanisms, implications, and potential mitigation strategies. This review provides an overview of the growing antibiotic resistance phenomenon within the realm of gram-positive bacteria, with a specific focus on three major pathogens: *Staphylococcus aureus, Enterococcus spp., and Streptococcus pneumoniae*. These pathogens, once susceptible to conventional antibiotics, have displayed remarkable adaptability to develop resistance, rendering standard treatment regimens ineffective. This review outlines the objectives of understanding the mechanisms underlying the emergence of resistance, deciphering the clinical impact of resistance development, and highlighting the potential interventions to mitigate the crisis. This review also highlights a comprehensive exploration of the interaction between these pathogens and the selective pressure of antibiotics, horizontal gene transfer, and genetic mutations are central themes elucidated in this study. The clinical implications of these emerging resistance mechanisms, including treatment failure, increased morbidity, and mortality, emphasize the urgency of addressing this escalating concern.

Furthermore, this review underscores the importance of alternative strategies, such as combination therapies, synergistic approaches, and the revival of older antibiotics, in combating gram-positive bacterial resistance. The study aims to provide insights into the novel strategies that hold promise for the treatment of gram-positive bacterial infections that are resistant to antibiotics.

The review aims to contribute to the global efforts in curbing the antibiotic resistance crisis.

Keywords: Antibiotic resistance, Antimicrobial drug resistance, Gram-positive bacteria, *Enterococcus species*, *Staphylococcus aureus*, *Streptococcus pneumoniae*.

Introduction

Resistance to antimicrobials continues to be a serious worldwide health issue, threatening the efficacy of one of modern medicine's greatest achievements-antibiotics [1]. The rise of resistance not only compromises our ability to treat infections effectively, but also heightens the risk of healthcare setbacks reminiscent of the pre-antibiotic era. The particular concern is the increasing prevalence of Gram stain test-positive bacteria that exhibit antimicrobial resistance, a class of microorganisms that includes some of the most notorious human pathogens [1]. The mechanisms of this resistance are shaped by a plethora of genetic determinants and biochemical processes. This includes changes to target locations, overexpression of pump genes that facilitate material outflow, and decreased permeation of the cell wall of microbes, as well as the enzymatic breakdown of antibiotics [2].

In the case of *Staphylococcus aureus*, the emergence of methicillin-resistant strains (MRSA) and their subsequent evolution into multidrug-resistant and extensively drug-resistant forms highlights the adaptability of gram-positive pathogens in countering antibiotic pressure [3].

Staphylococcus Aureus

Staphylococcus aureus, an adaptable human disease-causing agent, exemplifies the alarming escalation of gram-positive bacteria's antibiotic resistance. *Staphylococcus aureus* that is methicillin-resistant once dominated discussions, but the emergence of multi drug resistant (MDR), extreme drug resistant (XDR), and methicillin resistant *staphylococcus aureus* (MRSA) strains underscores the rapid acquisition and dissemination of resistance determinants [4]. Horizontal gene transfer's (HGT) function in the spread of resistant mutations further amplifies the challenge of treating *S. aureus* infections [5].

Enterococcus spp.

Enterococcus spp., including *Enterococcus faecalis* and *Enterococcus faecium*, have emerged as emblematic symbols of antibiotic resistance. Vancomycin-resistant *Enterococcus* (VRE) prevalence has increased, revealing the clinical hurdles posed by gram-positive pathogens leading to reduced drugs choices in treatment options [6]. The concurrent evolution of linezolid resistance poses additional therapeutic challenges, necessitating an understanding of the genetic underpinnings driving such resistance phenotypes [7].

Streptococcus Pneumoniae

Streptococcus pneumoniae, one of the main culprits in bacterial pneumonitis is difficult to treat since it comes in various drug-resistant forms (MDRSP). The phenomenon of serotype replacement has complicated vaccine strategies, underlining the need for a comprehensive approach to combat emerging resistance [8]. The intricate relationship between genetic diversity, serotype distribution, and antibiotic resistance further elucidates the complexity of the *pneumococcal* landscape.

Factors Fueling the Rise of Resistance

The ascent of antimicrobial resistance in gram-positive bacteria is intertwined with multifaceted factors. Inadequate infection control practices, unwarranted antibiotic prescription, and nosocomial transmission have accelerated resistance dissemination. Antimicrobial stewardship programs have become essential tools for addressing these issues and preserving the effectiveness of antibiotics [9].

Aims

Within this context, this review aims to examine the rising incidence of antimicrobial resistance in bacterial isolates with gram-positive genes, with a particular focus on well-known pathogens including *Staphylococcus aureus*, *Enterococcus species*, and *Streptococcus pneumoniae*. Understanding the mechanics of how antibiotic resistance is changing and developing is crucial for developing measures to stop its spread, hence this topic must be thoroughly explored.

The Covered Knowledge Gap

The primary knowledge gap filled by this review lies in its in-depth exploration of the interaction between gram-positive bacteria and the selective pressure of antibiotics. The research explores important concepts such as horizontal gene transfer (HGT) and genetic alterations, which are crucial to comprehend the development of antibiotic resistance in these bacteria using very recent literature (2018-2023). (1) Thorough investigation of the relationship between gram-positive

bacteria and the specific influence of antibiotics.
(2) Explanation of fundamental concepts such as horizontal gene transfer (HGT) and genetic mutations.
(3) Thorough examination of the ability of gram-positive bacteria to adapt and evolve mechanisms to withstand antibiotics.

Novelty

The originality and novelty of this review stems from its focus on alternate approaches to address the issue of gram-positive bacterial resistance. Significantly, it emphasizes the significance of using combination medicines, synergistic methods, and the reintroduction of earlier antibiotics as viable interventions. The discovery of these innovative approaches greatly enhances the field, offering valuable perspectives on potential paths for addressing antibiotic-resistant gram-positive bacterial infections.

This review makes a substantial contribution to the worldwide efforts to address the antibiotic resistance dilemma by addressing a critical lack of knowledge. Studying newly developing mechanisms of resistance and finding different approaches helps us comprehend the resistance of gram-positive bacteria better. This knowledge serves as a basis for future research and interventions in the crucial field of antimicrobial resistance.
(1) Focus on alternative approaches to address the issue of resistance in gram-positive bacteria.
(2) Emphasizing the significance of utilizing combination medicines, synergistic methods, and the resurgence of previously used antibiotics as viable solutions.
(3) Identification of potential strategies for the treatment of antibiotic-resistant gram-positive bacterial infections.
(4) Comprehensive analysis of the changing resistance profiles of prominent pathogens, such as methicillin-resistant *Staphylococcus aureus*, multidrug-resistant strains, and Vancomycin-resistant *Enterococcus* (VRE).
(5) This review discusses the difficulties caused by the development of resistance to linezolid in *Enterococcus spp.* and the complications involved in treating different drug-resistant strains of *Streptococcus pneumoniae*.
(6) Investigation of the contributing causes driving the increase in resistance, specifically examining substandard infection control procedures, unnecessary antibiotic prescribing, and transmission within healthcare settings.
(7) The incorporation of antimicrobial stewardship programs as vital instruments for tackling problems and safeguarding the efficacy of antibiotics.

Methodology

The methodology adopted for this analysis incorporates a thorough literature search that focuses on the growing issue of gram-positive bacteria gaining antimicrobial resistance. To guarantee that the most current developments in the area are included, the study particularly used quality peer-reviewed paper from a period of less than five years; from mid-2018 to mid-2023. The databases searched for relevant articles were PubMed, Scopus, Web of science, and Google Scholar for articles connected to the topic at hand. The keywords were "Antibiotic Resistance", "Antibiotic Resistance in Gram-Positive Bacteria", "Antibiotic Resistance in *Staphylococcus aureus*", "Antibiotic Resistance in *Enterococcus spp*.", and "Antibiotic Resistance in *Streptococcus pneumoniae*".

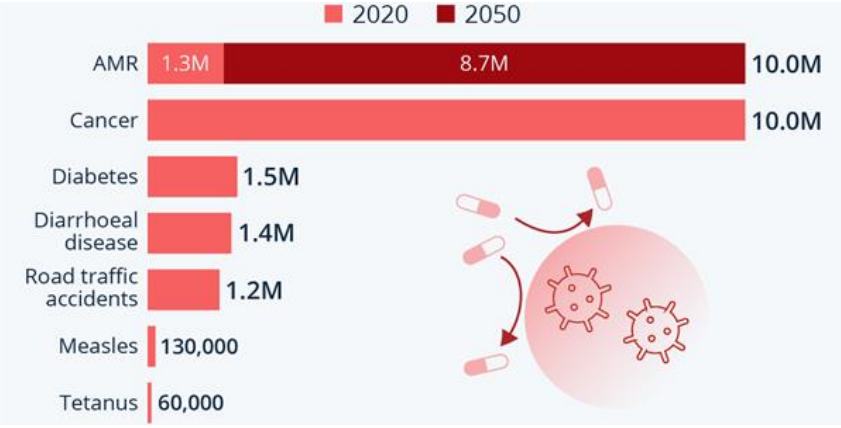

Figure 1 An illustration depicting predicted mortality from antimicrobial resistant infections versus today's common causes of deaths (Adapted from [9])

Gram-Positive Bacteria: Mechanisms of Antimicrobial Resistance

Typical Resistant Mechanisms

Gram-positive bacteria have evolved an arsenal of processes that mitigate bactericidal effects. This encompass enzymatic inactivation, target site modification, efflux pumps, and alterations in cell membrane permeability. These mechanisms, while shared among various bacterial species, reveal the adaptable nature of gram-positive bacteria in their bid to resist antibiotic pressure [2,10].

Specific Resistance Mechanisms in Prominent Pathogens

Staphylococcus Aureus

The resistance mechanisms exhibited by *Staphylococcus aureus* are emblematic of the swift evolution gram-positive bacteria have been discovered. Species of *Staphylococcus aureus* (MRSA) resilient to methicillin, characterized by acquiring the mecA gene, elude the activity of β-lactam antibiotics through altered penicillin-binding proteins [11]. The emergence of Panton-Valentine leukocidin (PVL)-positive MRSA strains further exacerbates clinical challenges, demanding a multifaceted approach to tackle their aggressiveness and resilience [12].

Enterococcus spp.

Enterococcus spp. have emerged as formidable foes in healthcare settings due to their innate and acquired resistance traits. Vancomycin-resistant *Enterococcus* (VRE) strains exhibit altered target sites through modifications in peptidoglycan precursors, impeding vancomycin binding [13]. Across *enterococcal species,* the spread of vancomycin genes susceptible to resistance underscores the complex network of horizontal gene transfer driving resistance dissemination [7].

Streptococcus Pneumoniae

The primary culprit of infections of the respiratory systems, *Streptococcus pneumoniae*, traverses the antibiotic blockade via different resistance pathways. Lactam antibiotic resistance results from changes in penicillin-binding proteins, whereas efflux pumps and target site gene alterations cause resistance to macrolides and fluoroquinolones [9]. Serotype-specific variation and the emergence of non-vaccine serotypes further complicate *pneumococcal* resistance patterns [10].

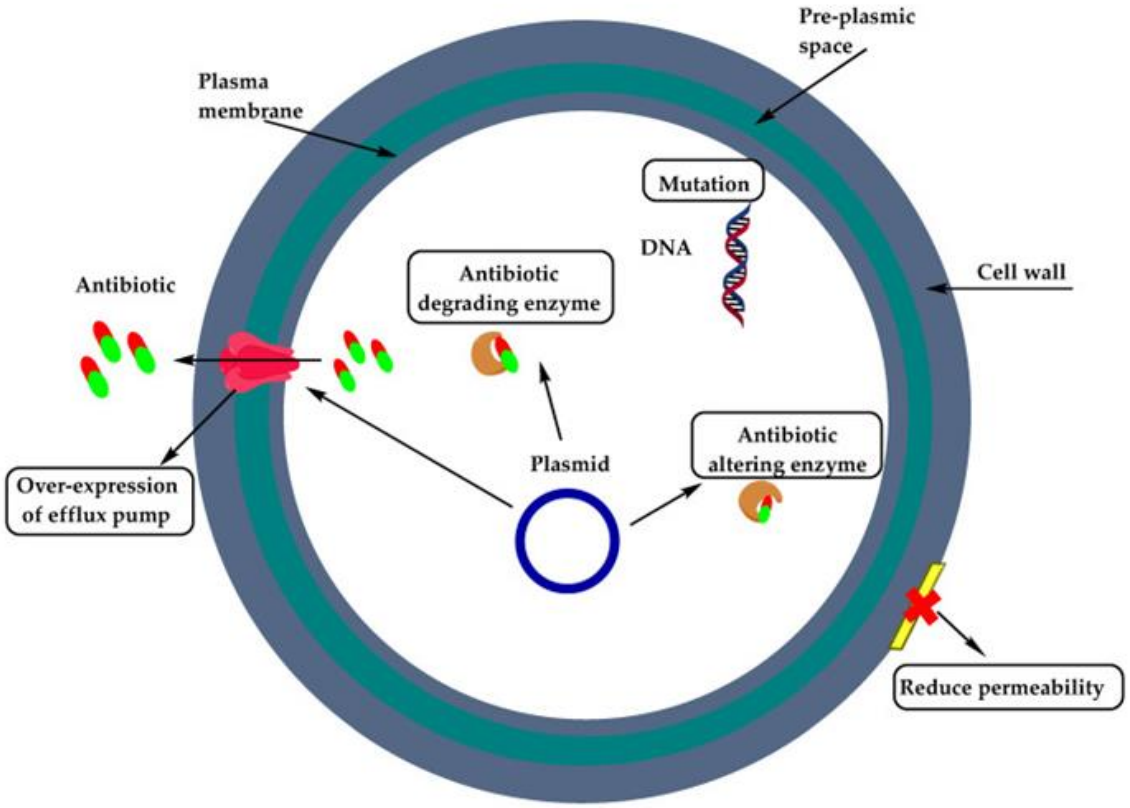

Figure 2 Illustration showing specific resistance mechanisms in prominent pathogens (Adapted from [10])

Rapid Evolution and Acquisition of Resistance Genes

The genetic plasticity of gram-positive bacteria is exemplified by the rapid acquisition and dissemination of resistance genes. Mobile genetic elements (MGE), plasmids, and transposons, which promote horizontal gene transfer (HGT), help spread resistance-related traits quickly [14]. This is made more difficult by the joint localization of resistant gene loci on mobile genetic components, which results in a reservoir of flexible resistance potential [15].

Implications and Future Perspectives

The gram-positive bacteria's convergent antibiotic resistance mechanisms have serious clinical consequences. The dwindling pool of effective antibiotics necessitates innovative therapeutic approaches and stringent antimicrobial stewardship practices. Combination therapies, exploiting vulnerabilities in resistance pathways, and repurposing existing drugs hold promise in mitigating resistance-associated morbidity [16].

Staphylococcus Aureus

The clinical importance of the adaptive and versatile gram-positive bacteria *Staphylococcus aureus* has long been acknowledged. But the advent of methicillin-resistant *Staphylococcus aureus* (MRSA) has thrust this disease to the forefront of worries about antibiotic resistance. The implications of MRSA extend beyond its intrinsic β-lactam antimicrobial resistance, as it underscores the broader challenge of antibiotic resistance within the gram-positive bacterial landscape [3].

Clinical Significance of MRSA: A Global Threat

MRSA has transformed from a niche concern to a global threat, manifesting in a wide range of healthcare and community-associated infections. This has brought about unprecedented clinical challenge posed by MRSA and its impact on patient outcomes, healthcare costs, and infection control strategies. Recent epidemiological data underscores the dynamic nature of MRSA, with varying rates of prevalence across different regions and healthcare settings [3,17].

MRSA Strains Which Are Substantially Resistant To Multiple Drugs

The evolution of MRSA strains beyond methicillin resistance has escalated the complexity of antibiotic resistance management. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) MRSA variants have emerged, often carrying resistance determinants against a spectrum of antibiotics. The recent developments in MRSA's resistance profile and increasing challenge of managing health issues brought on by these species cannot be over emphasized [17]. A study by Pajojesh *et al.* (2022) examined the correlation between the development of biofilm and the ability to resist antibiotics in strains of *Staphylococcus aureus* found in untreated cow milk in Shahrekord, Iran. The study utilized a total of 90 samples and using spectrophotometry and PCR techniques to detect and measure biofilm formation. The findings indicated a modest rate of recovery at 38.9%, with a significant proportion of isolates (65.7%) demonstrating high biofilm production. The antibiotic susceptibility tests indicated a concerning level of resistance to beta-lactam antibiotics, specifically penicillin, ampicillin, and oxacillin. The antibiotic resistance gene that was most frequently found was blaZ, with a prevalence of 71.4%. It was followed by mecA and Aac-D, which had a prevalence of 42.9 [19].

Mobile Genetic Elements and Horizontal Gene Transfer: Their Functions

The expansion of MRSA's antibiotic resistance repertoire is facilitated by the remarkable adaptability conferred by horizontal gene transfer (HGT) and mobile genetic elements (MGEs). Genetic elements like plasmids, transposons, and integrons enable the transfer of resistance genes between bacterial species, contributing to the spread of antimicrobial resistance [5]. HGT and MGEs have enabled MRSA to acquire resistance determinants against a range of antibiotics, amplifying the clinical impact of this pathogen.

S. Aureus Acquiring MGEs

1. Integration of plasmids or plasmid components into the DNA of an organism.
2. Plasmids can exist as autonomous circular DNA molecules.
3. There are plasmids designed specifically for inducing suicide in cells.
4. Transference of a transposon or an insertion sequence between plasmid and genomic DNA.
5. The transference of a transposon or an insertion sequence from one plasmid to another inside the same cell.
6. The process of transferring a transposon or an insertion sequence from the genomic DNA to another plasmid.

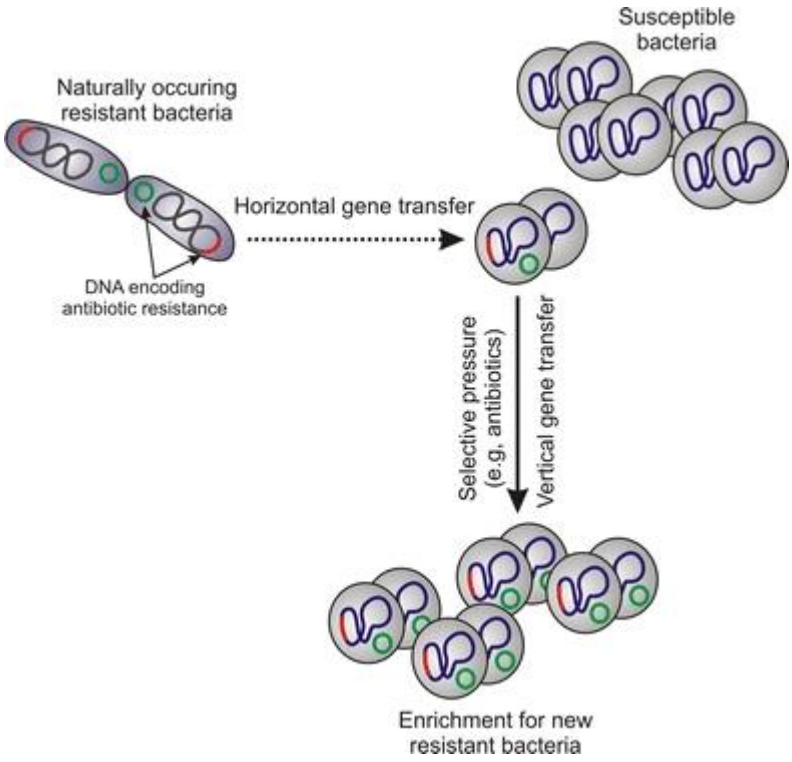

Figure 3 Mobile genetic elements (MGEs) are DNA fragments that contain genetic information for virulence and resistance traits, as well as enzymes that aid in their transfer and incorporation into the DNA of new host organisms. They exhibit intracellular and intercellular mobility and are transmitted between cells by lateral or horizontal gene transfer (HGT). Mobilizable genetic elements (MGEs) encompass several types of DNA sequences, such as Jubeh ion sequences, transposons, phages, plasmids, pathogenicity islands, and chromosome cassettes (Adapted from [20])

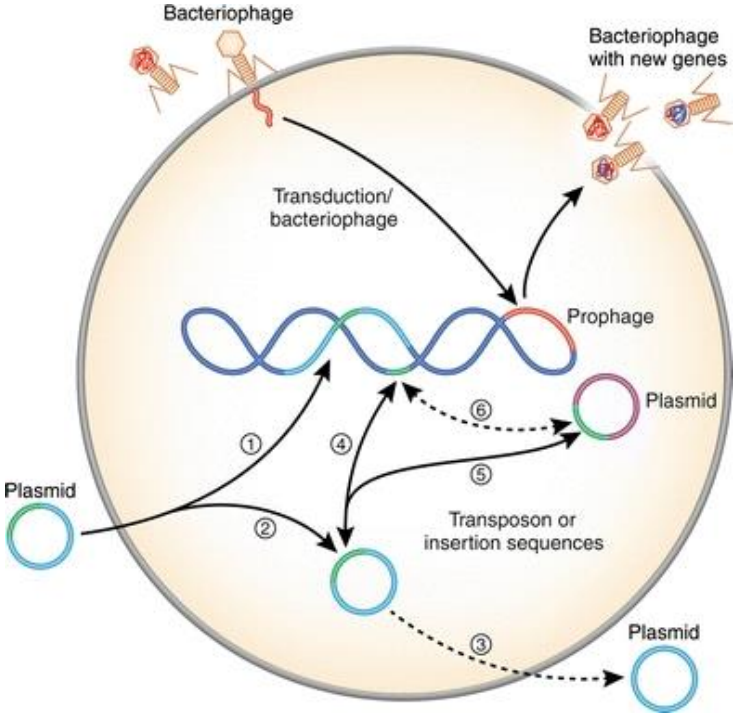

Figure 4 Illustrating how *S. aureus* acquire MGEs (Adapted from [20])

Emerging Mechanisms and Resistance Mechanisms

In addition to HGT and MGEs, some other mechanisms that underlie MRSA's multidrug resistance phenotype are the role of efflux pumps, alterations in drug target sites, and intrinsic mechanisms of antibiotic resistance. This forms a comprehensive picture of the strategies employed by MRSA to neutralize antibiotic efficacy [19].

Future Prospects and Challenges

The MRSA epidemic underscores the critical need for innovative strategies to combat antibiotic resistance. This section discusses ongoing research efforts to develop novel antibiotics and therapeutic approaches targeting MRSA's vulnerabilities. The advent of precision medicine, phage therapy, and combination therapy is explored as potential avenues to address the evolving challenge posed by MRSA [21].

The exploration of *Staphylococcus aureus*'s journey from methicillin resistance to multidrug resistance provides a glimpse into the broader challenges of antibiotic resistance in gram-positive bacteria. MRSA's adaptability and dissemination capacity highlight the urgency of a multifaceted approach that encompasses surveillance, infection control, antimicrobial stewardship, and novel therapeutic interventions [22]. By addressing the complexities of MRSA resistance, we gain insights into the overarching battle against antibiotic resistance and the imperative to preserve the potency of our antimicrobial arsenal.

Enterococcus spp.

Enterococcus spp., encompassing species such as *Enterococcus faecalis* and *Enterococcus faecium* have surfaced as emblematic representatives of the gram-positive bacteria's antibiotic resistance problem. An in-depth exploration of their antibiotic resistance patterns unravels the complex mechanisms underlying their adaptive response to therapeutic pressure [23].

Vancomycin-Resistant Enterococcus (VRE) Prevalence and Evolution

The escalating prevalence of vancomycin-resistant *Enterococcus* (VRE) has garnered significant attention [24]. New research has shed light on the global dissemination of VRE, emphasizing its ability to exploit diverse ecological niches, including healthcare settings, animal reservoirs, and the environment [25]. Investigating the genetic determinants driving vancomycin resistance, such as the VanA and VanB operons, elucidates the resistance mechanisms and the evolving selective pressures that facilitate the propagation of VRE [26].

Linezolid-Resistant Enterococcus: Treatment Implications and Mechanism

The emergence of linezolid-resistant *Enterococcus* poses a formidable challenge to treatment regimens. Delving into recent findings provides insight into the genetic events driving the development of linezolid resistance [27]. The cfr gene, responsible for phenotypic resistance, often presents on mobile genetic elements, facilitating its horizontal transfer. This underscores the potential for rapid dissemination and necessitates vigilant surveillance of this emerging resistance trait [28].

Biofilm Formation and Genetic Plasticity in Antibiotic Resistance

A comprehensive understanding of antibiotic resistance in *Enterococcus spp*. mandates the examination of biofilm formation and genetic plasticity. Recent

research underscores the critical role of biofilms in fostering resistance through impeding antibiotic penetration and providing a protective niche for persister cells. Investigating the genes and regulatory networks governing biofilm formation, such as fsrB and esp, unravels the intertwined connection between biofilm-related characteristics and antibiotic resistance [29]. A study by Dai *et al.* (2021) studied the analysis of antibiotic-induced drug resistance of *salmonella enteritidis* and its biofilm formation mechanism. The findings indicated a strong correlation between the sp, ebpA, ge1E, and fsrB genes and the development of *salmonella enteritensis* biofilm. The Qs-fsr system can modulate the expression of esp, ebpA, and gelE genes, leading to a decrease in the expression of esp and ebpA, and an increase in the expression of gelE [30].

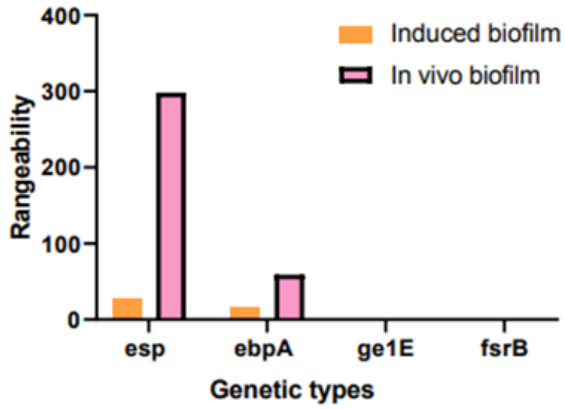

Figure 5 Comparative analysis of gene expression changes between biofilm and generated biofilm in an *in vivo* setting (Adapted from [30])

Moreover, the exploration of genetic plasticity mechanisms, including horizontal gene transfer, mobile genetic elements, and antimicrobial resistance islands, provides insights into the rapid adaptation and dissemination of resistance determinants within *Enterococcus* populations [23].

Potential Strategies to Combat Enterococcus Spp. Resistance

Recent advancements in our understanding of *Enterococcus spp.* resistance mechanisms offer avenues for the development of novel therapeutic strategies. Exploring the potential of combination therapies that target both intrinsic and acquired resistance mechanisms may enhance treatment efficacy. In addition, elucidating the interplay between host-pathogen interactions and resistance mechanisms paves the way for immunomodulatory approaches that complement traditional antibiotic treatments [31].

Streptococcus Pneumoniae

A Gram-positive bacterium called *Streptococcus pneumoniae* causes various infections, from minor respiratory disorders to fatal invasive diseases. The prevalence of *pneumococcal* infections has dramatically decreased due to vaccinations that target specific serotypes; the relentless evolution of antibiotic resistance threatens to undermine these gains. Recent findings shed light on the escalating prevalence of multidrug-resistant *Streptococcus pneumoniae* (MDRSP) strains, marking a critical juncture in the fight against bacterial infections [8,30].

Genetic Diversity and Serotype Distribution

The genetic diversity of *Streptococcus pneumoniae* plays a pivotal role in its adaptability and resistance acquisition. High-throughput sequencing technologies have revealed the complex landscape of genetic variations among *pneumococcal* strains, underpinning their ability to evade host immune responses and acquire resistance determinants [31]. Serotype distribution, driven by capsular polysaccharides, has exhibited fluctuations in response to vaccination campaigns, with non-vaccine serotypes rapidly emerging to fill ecological niches [32].

Antibiotic Resistance Profiles

The antibiotic resistance profile of *Streptococcus pneumoniae* is characterized by the interaction between resistance determinants and antimicrobial agents. *β*-lactams, macrolides, fluoroquinolones, and other classes of antibiotics encounter resistance through mechanisms such as altered target sites, efflux pumps, and horizontal gene transfer. Recent investigations have elucidated the molecular basis of resistance, uncovering novel mutations and genetic elements contributing to antibiotic insensitivity [33].

Emergence of MDRSP Strains

A serious threat to the public's health is posed by the rise of resistance of *Streptococcus pneumoniae* pathogens (MDRSP) strain to multiple types of antibiotics. Numerous studies from various geographical areas have found rising prevalence of MDRSP, which includes resistance to several different antibiotic classes. The modification of commensal flora and other pneumococcal strains to gain resistance genes and transduction has expedited the progression toward multidrug resistance [34].

Serotype Replacement and Vaccine Implications

Vaccination campaigns targeting select serotypes have successfully reduced the burden of *Streptococcus pneumoniae* infections [35]. However, the phenomenon of serotype replacement poses a considerable challenge. Non-vaccine serotypes, equipped with resistance determinants, are poised to exploit the ecological void left by their vaccine-targeted counterparts. The complex interplay between serotype distribution, genetic diversity, and antibiotic resistance necessitates a holistic approach to vaccine design and implementation [36].

Therapeutic Challenges and Future Prospects

The escalation of antibiotic resistance in *Streptococcus pneumoniae* has amplified therapeutic challenges. The limited arsenal of effective antibiotics, coupled with the increasing prevalence of MDRSP strains, underscores the urgency of innovative approaches. Advances in genome editing technologies, the repurposing of existing drugs, and the creation of innovative treatments that tackle the causes of resistance offer glimpses of hope in the fight against *pneumococcal* infections [37].

One Health Approach and Surveillance

A unified health strategy is essential to tackle the increasing strength of antimicrobial resistance in Streptococcus pneumoniae. incorporating environmental concerns, the wellness of animals, and human wellness, is crucial to mitigate the dissemination of resistant

strains. Robust surveillance systems, encompassing genomic analysis and epidemiological data, are pivotal in monitoring resistance trends, guiding treatment strategies, and informing vaccine development [38].

Antibiotic resistance is becoming more common, and *Streptococcus pneumoniae* underscores the urgency of comprehending and addressing this formidable challenge. The interplay between genetic diversity, serotype distribution, and antibiotic resistance underscores the complexity of the *pneumococcal* landscape. With vaccines serving as powerful tools and innovative therapeutic strategies on the horizon, collaborative efforts and research endeavors are pivotal to navigate the evolving terrain protect the effectiveness of antimicrobials in treating these Gram-positive bacteria in the face of drug resistance [39].

Factors Contributing To Emerging Resistance

Resistance to antimicrobial drugs by gram-positive bacteria is a complex phenomenon that is influenced by a number of different factors. These elements work together to amplify and spread resistance genes, making it more difficult to treat infections brought on by *Staphylococcus aureus*, *Enterococcus* species, and *Streptococcus pneumoniae* [9]. It is essential to have a thorough grasp of these contributing components to develop successful mitigation methods for the resistance propagation.

Inadequate Infection Control Practices

In healthcare settings, suboptimal infection control practices have been implicated in the transmission of drug-resistant pathogens. Recent studies underscore the critical role of environmental reservoirs and contaminated surfaces in facilitating the persistence and spread of resistant strains. Improved hospital hygiene protocols, stringent hand hygiene, and the implementation of barrier precautions have been identified as crucial interventions to curtail the dissemination of resistant gram-positive bacteria [40].

Unwarranted Antibiotic Prescription

Antibiotic resistance has been considerably aided by the excessive and harmful use of antimicrobial agents in both medical and farming contexts. Recent investigations have highlighted the excessive prescription of broad-spectrum antibiotics, even in the absence of confirmed bacterial infections. This unwarranted usage not only fosters the selection of resistant strains, but also disrupts the commensal microbiota, facilitating the colonization and subsequent dissemination of resistant pathogens [40].

Nosocomial Transmission

Healthcare-associated infections continue to be a predominant source of resistant gram-positive bacteria. Recent genomic studies have elucidated the complex dynamics of nosocomial transmission, revealing the part mobile genetic elements play in enabling the transfer of resistance genes between bacterial strains. Enhanced genomic surveillance has allowed for the tracing of transmission routes and identification of high-risk reservoirs within healthcare facilities [28].

Antimicrobial Pressure in Livestock

Antibiotic resistance notably that found in gram-positive bacteria has been linked to the application of antibiotics in animal production. The passing down of strains of resistance from agriculture-

related organisms to people via personal interaction, ingestion of contaminated food items and exposure to environmental contaminants is highlighted by recent study. The effects of this reservoir on public health highlight how urgent it is to use antibiotics wisely in agriculture and to switch to alternate methods of managing cattle [18].

Immunocompromised Population

Immunocompromised individuals, including those undergoing chemotherapy, organ transplantation, or suffering from immunosuppressive conditions, are particularly vulnerable to infections caused by resistant gram-positive bacteria. Recent studies have revealed the heightened risk of treatment failure in this population, necessitating tailored therapeutic approaches, increased vigilance, and the implementation of infection control measures to safeguard their health [39].

Global Travel and Migration

Modern global travel and migration patterns have facilitated the spread of antibiotic-resistant strains across geographical boundaries. Recent molecular epidemiological investigations have illuminated the role of international travel in disseminating resistant gram-positive bacteria. The identification of these strains in diverse geographic locations underscores the necessity of international collaboration to curb resistance transmission [39].

Summary and Implications

The complex relationship of these factors contributes to the alarming rise of antibiotic resistance in gram-positive bacteria. Recent findings underscore the urgency of a multidimensional approach that combines infection control measures, antimicrobial stewardship, innovative therapeutic strategies, and international cooperation. Addressing these factors comprehensively is essential to effectively mitigate the further dissemination of resistant gram-positive pathogens and ensure the continued efficacy of antibiotics in treating infections caused by these formidable adversaries.

Challenges and Future Directions

The escalating antibiotic resistance in gram-positive bacteria presents a formidable challenge that demands a multifaceted response. Recent research has illuminated the urgency of addressing this crisis through a comprehensive approach. The following section discusses the complexity of the challenges faced and potential future directions:

Evolving Resistance Mechanisms

The relentless pace at which antibiotic resistance mechanisms evolve poses a pressing challenge [40]. Recent studies have unveiled novel mechanisms underlying resistance in gram-positive bacteria, such as the emergence of plasmid-encoded drain pumps that confer to resistance to certain class of antimicrobial agents [2]. Comprehensive genomic studies are shedding light on the genetic mutations and horizontal gene transfer events that drive resistance. Understanding these mechanisms is essential to develop targeted interventions [18].

Clinical Implications

Resistance to antimicrobial agents and drugs in gram-positive microbes has a significant and expanding therapeutic impact. Infections that are resistant to treatment are linked to extended hospital admissions, higher medical bills, and

higher death rates. Recent epidemiological studies underscore the rapid dissemination of resistant strains within healthcare settings and communities. The emergence of hypervirulent strains that combine antibiotic resistance with enhanced virulence further exacerbates the clinical challenge [35].

Antibiotic Development Dilemma

A stark reality in combating antibiotic resistance is the scarcity of new antibiotic agents entering the market. While research has identified potential drug candidates, challenges in drug discovery, development, and regulatory approvals have hindered progress. Recent advances in exploring non-traditional antimicrobial approaches, such as the repurposing of existing drugs and the discovery of novel compounds from natural sources, offer hope for revitalizing the antibiotic pipeline [40].

The role of Genomics and Big Data

The advent of high-throughput genomics and data analytics has transformed our ability to comprehend how antibiotic resistance is determined by the interplay of genes and genetics. Recent efforts in whole-genome sequencing of resistant strains have revealed a treasure trove of information on resistance genes, mobile genetic elements, and genetic adaptations. Integrating these insights with computational approaches is aiding the prediction of resistance trends, contributing to informed clinical decision-making [32].

One Health Strategy

Antibiotic resistance affects more than only the wellness of people. Therefore, the One Health concept has gained popularity. Recent multifaceted studies have brought attention to the relationship between the health of people, animals, and the natural surroundings and the resistance propagation. Surveillance studies have uncovered shared resistance genes between pathogens of human and animal origin, emphasizing the need for collaborative efforts [38].

Antimicrobial Stewardship and Policy Implementation

Antimicrobial stewardship programs, designed to optimize antibiotic use, have gained prominence as a crucial tool against resistance. Recent studies have demonstrated the impact of such programs in reducing antibiotic consumption, curbing resistance rates, and improving patient outcomes. The implementation of robust policies, including guidelines for appropriate antibiotic usage and infection prevention measures, remains a critical step in mitigating resistance emergence [38].

Harnessing Technological Innovations

In the quest to address antibiotic resistance, technological innovations offer promising avenues. Recent breakthroughs in synthetic biology, clustered regularly interspaced short palindromic repeats (CRISPR)-based gene editing, and nanotechnology are being harnessed to design innovative antimicrobial strategies. Engineered bacteriophages, nanoparticles, and gene therapy approaches hold potential to selectively target resistant pathogens and mitigate their impact [18].

International Collaboration and Surveillance Networks

Addressing antibiotic resistance necessitates global collaboration and knowledge sharing. Recent initiatives have established international

surveillance networks to monitor resistance trends and disseminate data. Collaborations between research institutions, pharmaceutical companies, and public health agencies are fostering the development of a coordinated response to the challenge of gram-positive antibiotic resistance [32].

Precision Medicine

The fight against resistance to medications may be aided by recent developments in genetic sequencing and tailored therapy. In this age of personalized healthcare, it is possible to customize treatment plans depending on the characteristics of particular patients, bacterial gene variants, and resistance trends. Recent studies highlight the potential of genotypic-guided therapy, enabling the selection of the most effective antibiotics and minimizing the risk of treatment failure [35].

Conclusion

The alarming rise in antibiotic resistance among gram-positive bacteria, particularly in major pathogens like *Staphylococcus aureus, Enterococcus spp., and Streptococcus pneumoniae*, has become into a significant issue for world health. The multifaceted nature of this challenge, as discussed throughout this review, highlights the need for comprehensive strategies to mitigate the impact of emerging resistance.

Recent research has illuminated the evolution of resistance mechanisms, the clinical ramifications, and the potential for dire consequences if left unchecked. The exploration of innovative treatment approaches, leveraging genomics, and embracing a One Health perspective, underscores the complexity of this issue. From genomic insights to technological innovations, international collaborations to public engagement, a concerted effort is necessary to combat this formidable threat.

The urgency of this issue is evident as we witness the dwindling effectiveness of once-potent antibiotics against gram-positive infections. It is imperative to leverage the lessons learned from the recent findings to inform policy decisions, clinical practices, and future research directions. By adopting a holistic and proactive approach that integrates the efforts of researchers, healthcare practitioners, policymakers, and the public, we can effectively navigate the challenging terrain of emerging antibiotic resistance in gram-positive bacteria.

ORCID

Olumakinde Charles Omiyale
https://orcid.org/0000-0002-4951-3881
Favour Onaskohare Okunbi
https://orcid.org/0009-0004-2950-4699
Confidence Damian Oparah
https://orcid.org/0009-0003-1265-9718
Victor Nduka Eluwa
https://orcid.org/0000-0001-9215-9534
Rosemary Modupeoluwa Awolade
https://orcid.org/0000-0001-9215-9534
Precious Ifechukwuni Ikuni
https://orcid.org/0009-0002-7789-2185
Muhammad Bello Demola
https://orcid.org/0009-0002-5275-0180
Christianah Oluwatosin Agboola
https://orcid.org/0009-0007-4744-2235
Temitope Oluwapelumi Babalola
https://orcid.org/0009-0004-1727-446X
Abdul-Hanan Saani Inusah
https://orcid.org/0009-0007-4483-2473
Abigail Daniel Agbo
https://orcid.org/0009-0000-5244-148X
Onyekachi Uchenna Uchejuru
https://orcid.org/0009-0000-8667-4652
Benjamin Minasu Oke
https://orcid.org/0009-0001-9379-6997
Stanley Augustine Ugbobuaku
https://orcid.org/0009-0006-9048-365X

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