UDK 616-036.81:[579.61:612.017 **Review Paper**
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NEW ANTIMICROBIAL STRATEGIES IN THE TREATMENT OF INFECTIONS CAUSED BY MULTIDRUG-RESISTANT STRAINS OF GRAM-POSITIVE BACTERIA

***Gordana Zavišić*[1], *Slavica Ristić*[2], *Drina Janković*[3], *Branka Petković*[4]**
[1]Faculty of Pharmacy, Novi Sad, University Business Academy in Novi Sad, Heroja Pinkija 4, Novi Sad, Republic of Serbia
[2]Faculty of Medicine, University of Belgrade, Pasterova 2, Belgrade, Serbia
[3]Vinča Institute of Nuclear Sciences – National Institute of the Republic of Serbia, University of Belgrade, Mike Petrovića Alasa 12-14, Vinča, Belgrade, Serbia
[4]Institute for Biological Research "Siniša Stanković" – National Institute of the Republic of Serbia, University of Belgrade, Bulevar despota Stefana 142, Belgrade, Republic of Serbia

Abstract: *Infections caused by gram-positive, multidrug-resistant bacteria, especially streptococci, coagulase-positive staphylococci, and vancomycin-resistant enterococci, have been a major medical and economic problem for decades, leading to increased morbidity, mortality, and healthcare costs. Multidrug-resistant bacteria are often found in hospitals and long-term care facilities, infecting mainly people with a weakened immune system, such as patients on chronic hemodialysis and with post-operative wound infections, as well as solid organ transplant recipients. The World Health Organization categorizes these bacteria into critical, high, and medium priority groups depending on the urgency of developing new antibiotics. This review aims to summarize the latest findings on the research and development of new and necessary strategies to prevent the spread of antimicrobial resistance in gram-positive bacteria. A literature search on this topic over the last two decades was conducted in the PubMed, Scopus, and Google Scholar databases. As the number of newly developed and approved antibiotics decreases, great efforts are being made to find new antimicrobial strategies to treat infections caused by multidrug-resistant strains. These include (1) modulation of commercial antibiotics to enhance their effect, (2) development and application of specific monoclonal antibodies to neutralize bacteria, (3) blocking the production of virulence factors and inhibition of quorum sensing especially in biofilm, (4) modulation of the innate immune response by probiotics and fecal transplantation, (5) use of bacteriophages due to their pronounced ability to inhibit multidrug-resistant bacteria that cause wound infections, (6) combined use of bacteriophages and antibiotics, and (7) repurposing of non-antibiotic drugs. Despite the potential of the aforementioned antimicrobial strategies, the focus will continue to be on finding new strategies to more effectively address the challenge of antimicrobial resistance and improve public health.*

Key words: *multiresistance, gram-positive bacteria, antibiotics, alternative antimicrobial strategy, combined therapy*

Introduction

For the first time since 2015, the World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance (GLASS) has published global data on antimicrobial resistance (AMR) and antimicrobial consumption (AMC) in its annual reports [1]. The consequences of AMR are staggering. In 2019 alone, AMR was estimated to be responsible for around 1.3 million deaths worldwide, with this figure set to rise to 10 million per year by 2050 if nothing is done [2, 3].

Since the emergence of AMR is unavoidable, great efforts must be made to reduce its impact and prolong the effectiveness of the drugs. In addition to the development of new antimicrobial agents, a promising approach could be the research and development of new and alternative antimicrobial strategies: (1) modulation of commercial antibiotics to enhance their effect, (2) development and application of specific monoclonal antibodies to neutralize bacteria, (3) blocking the production of virulence factors and inhibition of quorum sensing especially in biofilm, (4) modulation of the innate immune response by probiotics and fecal transplantation, (5) use of bacteriophages due to their pronounced ability to inhibit multidrug-resistant (MDR) bacteria that cause wound infections, (6) combined use of bacteriophages and antibiotics, and (7) repurposing of non-antibiotic drugs [4] (Figure 1). In this review, the results of a literature search in the PubMed, Scopus, and Google Scholar databases over the last two decades on this topic are presented and discussed, with a focus on the treatment of MDR gram-positive bacteria.

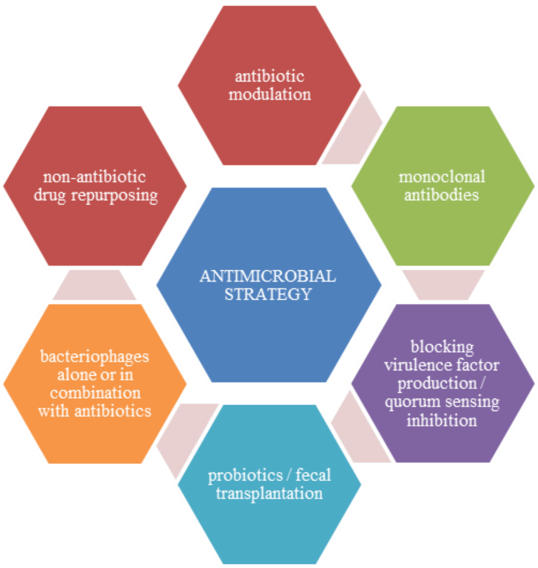

Figure 1. Alternative antimicrobial strategies

According to the WHO, Bacterial Priority Pathogen List is divided into three priority levels based on the urgent need for new antibiotics: **critical/Priority 1** (*Acinetobacter baumannii*, carbapenem-resistant; *Enterobacterales*, third-generation cephalosporinresistant; *Enterobacterales*, carbapenem-resistant; *Mycobacterium tuberculosis*, rifampicin-resistant), **high/Priority 2** (*Salmonella* Typhi, fluoroquinolone-resistant; *Shigella* spp., fluoroquinolone-resistant; *Enterococcus faecium*, vancomycin-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; Non-typhoidal *Salmonella*, fluoroquinolone-resistant; *Neisseria gonorrhoeae*, third-generation cephalosporin- and/or fluoroquinolone-resistant; *Staphylococcus aureus*, methicillin-resistant), and **medium/Priority 3** (Group A streptococci, macrolide-resistant; *Streptococcus pneumoniae*, macrolide-resistant; *Haemophilus influenzae*, ampicillin-resistant; Group B streptococci, penicillin-resistant) [5].

Some of the most common MDR gram-positive bacteria found in healthcare settings are methicillin-resistant *Staphylococcus aureus* (MRSA), known as the "superbug" [6], vancomycin-resistant *Enterococcus* spp., mainly *E. faecalis* and *E. faecium* [7], *Streptococcus pneumoniae* [8], *Clostridioides difficile* (formerly *Clostridium difficile*) [9], and *Mycobacterium tuberculosis* [10]. MDR bacteria are a serious threat to public health worldwide [11]. They possess resistance to antibiotics as a natural (innate, intrinsic), acquired or adaptive trait. **Natural resistance** refers to the inherent natural ability of bacteria due to the presence of inherent structural or functional characteristics, and includes both efflux pumps and reduced permeability. **Acquired resistance** is an evolutionary process in which resistance is acquired by horizontal gene transfer (e.g., transformation, transposition, and conjugation) of an exogenous new genetic material or chromosomal gene mutation, and is usually transmitted via a plasmid acquired by conjugation. **Adaptive resistance** is the acquisition of resistance over time due to high selection pressure from the increasing use and misuse of antibiotics, and includes high mutation rates, gene amplification, efflux pumps, biofilm formation, epigenetic inheritance, population structure, and heterogeneity. Because MDR bacteria are immune to the toxic effects of antibiotics, infections caused by MDR organisms result in poorer treatment outcomes for patients. MDR bacteria are not only associated with a high mortality rate, but also represent a significant financial burden for healthcare systems [12]. Therefore, the decline in newly discovered antibiotics and the increasing number of resistant bacteria have prompted the scientific community to seek alternatives to eliminate this threat to public health.

Modulation of commercial antibiotics to enhance their effect

Combination therapy, i.e., the use of two or more drugs, is a promising approach against resistant bacteria. Antibiotic adjuvants are compounds or agents that enhance the activity of antibiotics, either by potentiating their effects or by specifically influencing the mechanisms of antibiotic resistance [13]. Adjuvants such as efflux pump inhibitors, resistance-modifying agents, and compounds that disrupt bacterial biofilms act synergistically with antibiotics, contributing to increased antibacterial activity and overcoming resistance mechanisms. This could be achieved by (1) restoring the efficacy of existing antibiotics against resistant strains, (2) enhancing the activity of antibiotics through improved penetration into bacterial cells, increased stability or inhibition of efflux pumps that release antibiotics from bacterial cells, and/or (3) inhibiting the mechanisms that confer resistance so that pathogens become susceptible to the action of antibiotics. It has been shown that antimicrobial peptide-antibiotic combinations can also significantly increase the efficacy of antibiotic therapies [14]. The benefits of combining antimicrobial peptides with conventional antibiotics include increased membrane permeability, disruption of biofilms, direct potentiation of antibiotic efficacy, inhibition of resistance development, enhancement/modulation of immune response, reduction of inflammation, and improved tissue regeneration.

Development and application of specific monoclonal antibodies to neutralize bacteria

Monoclonal antibodies were initially developed for the treatment of inflammatory and neoplastic diseases, but they have been shown to have real therapeutic potential in the treatment of MDR bacterial infections [15-17]. Monoclonal antibodies are highly specific and directed against bacterial toxins, polysaccharides, and surface proteins. Some of the proposed mechanisms of action against these infectious diseases include neutralization of toxins, inhibition of virulence factors, complement-mediated killing activity, and opsonic phagocytosis. Many antibacterial monoclonal antibodies have been developed in recent years and several candidates have reached the preclinical or clinical development phase. Three are currently approved for clinical use: Raxibacumab and Obiltoxaximab against *Bacillus anthracis* infections and Bezlotoxumab against *C. difficile* infections.

Blocking the production of virulence factors and inhibition of *quorum sensing* especially in biofilm

Quorum sensing (QS) is a bacterial cell-to-cell communication system involved in sporulation, biofilm formation, antibiotic tolerance, drug resistance, conjugation, motility, and the production of virulence factors [18]. Many QS inhibitors have been developed to prevent or treat MDR bacterial infections. Polidocanol, a sclerosant indicated for the treatment of uncomplicated spider veins and reticular veins in the lower extremities, appears to be a promising option for the treatment of *E. faecalis* infections as it targets the fsr QS system and exhibits anti-biofilm activity [19]. 4-hydroxy-3-methoxybenzaldehyde, a naturally derived compound from vanilla beans, and theaflavins, a main bioactive component of black tea, were able to suppress exopolysaccharide and acid production, cell adherence, and biofilm formation by *S. mutans*, a primary causative agent of dental caries, in a dose-dependent manner without affecting cell growth [20, 21].

Modulation of the innate immune response by probiotics and fecal transplantation

The gut microbiota is an important reservoir for AMR organisms, and targeting it through diet, probiotics, bacteriophages, and fecal microbiota transplantation is a promising antibacterial strategy [22]. Probiotics are beneficial microorganisms that mainly belong to the genera *Lactobacillus* and *Bifidobacterium*. They positively impact gut health by influencing the composition and function of the gut microbiome [23] and have immunomodulatory properties that improve the host's immune system

[24]. Gut colonization with MDR bacteria is considered a strong risk factor for subsequent infections, especially in individuals with a weakened immune system, such as patients on chronic hemodialysis and with post-operative wound infections, as well as solid organ transplant recipients [25]. In these people, fecal microbiota transplantation, in which minimally processed fecal matter from a healthy donor is transferred into the gastrointestinal tract of a recipient to restore microbial diversity, is particularly successful in treating conditions such as *C. difficile* infection and other diseases related to gut microbiota dysbiosis, i.e., the imbalance caused by the dominance of certain taxa in the gut.

Use of bacteriophages due to their pronounced ability to inhibit MDR bacteria that cause wound infections

Bacteriophages are viruses that infect bacteria and multiply in them. They are an alternative or adjunct treatment to antibiotic therapy, as they can inhibit the formation of biofilms by MDR gram-positive bacteria such as *S. aureus* [26], *C. difficile* [27], and *E. faecalis* [28]. Bacteriophage therapy has the advantage over antibiotics that it has a high specificity for the target bacteria, can penetrate biofilms, and has a lower tendency to develop resistance [29]. It involves the application of a single phage or a cocktail/mixture of phages. For therapeutic applications, the lytic cycle of the phage is particularly important as it involves the direct destruction of bacterial cells.

Combined use of bacteriophages and antibiotics

Phage-antibiotic combination therapy is a promising strategy to reduce the antibiotic dose and the development of antibiotic resistance during treatment, and is therefore superior to phage and antibiotic treatment alone [30]. For example, combinations of *S. aureus* phage Sb-1 and antibiotics (vancomycin, daptomycin, ceftaroline, and cefazolin) showed the potential to control MRSA infections [31]. The combination of the staph phage vB_Sau_S90 and four antibiotics (fosfomycin, ciprofloxacin, oxacillin, and vancomycin) also showed efficacy against MRSA, especially when the antibiotics were administered after the phages [32]. This sequence of treatments initially led to phage-induced degradation of the biofilm and further antibiotic-induced suppression of bacterial growth, which contributed to better biofilm penetration and improved bactericidal efficacy.

Repurposing of non-antibiotic drugs

Drug repositioning or the use of already approved non-antibiotic drugs in the treatment of MDR infections is a promising and attractive strategy, as the costs, development time, and risks associated with clinical trials are low compared to traditional drug discovery [33]. For example, the antirheumatic drug auranofin, the non-steroidal anti-inflammatory drug ibuprofen, and the antiparasitic drug niclosamide are effective against *S. aureus* [34-36], the anticancer drug mitoxantrone is effective against vancomycin-resistant *E. faecalis* [37], the anticancer drug carmofur is effective against *S. pneumoniae* [38], and the antipsychotic drug thioridazine is effective against *C. difficile* [39].

Conclusion

The increase in MDR pathogens poses a major challenge for the treatment of infectious diseases. To overcome this problem as far as possible, new strategies are being explored to improve the efficacy of antibiotics and provide a valuable addition to current antimicrobial strategies. Although each of the newly proposed strategies has some advantages, it is expected that in the future two or more antimicrobial approaches will be used simultaneously and/or sequentially to combat MDR infections.

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NOVE ANTIMIKROBNE STRATEGIJE U LIJEČENjU INFEKCIJA UZROKOVANIH MULTIREZISTENTNIM SOJEVIMA GRAM-POZITIVNIH BAKTERIJA

***Gordana Zavišić*[1], *Slavica Ristić*[2], *Drina Janković*[3], *Branka Petković*[4]**
[1]Farmaceutski fakultet, Novi Sad, Univerzitet Privredna akademija u Novom Sadu, Heroja Pinkija 4, Novi Sad, Republika Srbija
[2]Medicinski fakultet, Univerzitet u Beogradu, Pasterova 2, Beograd, Srbija;
[3]Institut za nuklearne nauke "Vinča" – Institut od nacionalnog značaja za Republiku Srbiju, Univerzitet u Beogradu, Mike Petrovića Alasa 12-14, Vinča, Beograd, Republika Srbija
[4]Institut za biološka istraživanja "Siniša Stanković" – Institut od nacionalnog značaja za Republiku Srbiju, Univerzitet u Beogradu, Bulevar despota Stefana 142, Beograd, Republika Srbija

Sažetak. *Infekcije uzrokovane gram-pozitivnim, multirezistentnim bakterijama, posebno streptokokama, koagulaza pozitivnim stafilokokama i vankomicin rezistentnim enterokokama su decenijama veliki medicinski i ekonomski problem, što je dovelo do povećanog morbiditeta, mortaliteta i troškova zdravstvene zaštite. Multirezistentne bakterije su često prisutne u bolnicama i ustanovama za dugotrajnu njegu, inficirajući uglavnom osobe sa oslabljenim imunološkim sistemom, kao što su pacijenti na hroničnoj hemodijalizi i sa postoperativnim infekcijama rana, kao i primaoci transplantata solidnih organa. Svjetska zdravstvena organizacija kategoriše ove bakterije u grupu kritičnog, visokog i srednjeg prioriteta u zavisnosti od hitnosti razvoja novih antibiotika. Ovaj pregled ima za cilj da sumira najnovije nalaze o istraživanju i razvoju novih i neophodnih strategija za sprječavanje širenja antimikrobne rezistencije kod gram-pozitivnih bakterija. Pretraživanje literature o ovoj temi u posljednje dvije decenije obavljeno je u bazama podataka PubMed, Scopus i Google Scholar. Kako se broj novorazvijenih i odobrenih antibiotika smanjuje, ulažu se veliki napori u pronalaženju novih antimikrobnih strategija za liječenje infekcija uzrokovanih multirezistentnim sojevima. Ovo uključuje (1) modifikaciju komercijalnih antibiotika da bi se pojačao njihov efekat, (2) razvoj i primjenu specifičnih monoklonskih antitela za neutralizaciju bakterija, (3) blokiranje proizvodnje faktora virulencije i inhibiciju quorum sensing, posebno u biofilmu, (4) modulaciju urođenog imunološkog odgovora probioticima i fekalnom transplantacijom, (5) upotrebu bakteriofaga zbog izražene sposobnosti inhibicije multirezistentnih bakterija koje izazivaju infekcije rana, (6) kombinovanu primjenu bakteriofaga i antibiotika i (7) prenamjenu lijekova koji ne pripadaju antibioticima. Uprkos potencijalu navedenih antimikrobnih strategija, fokus će i dalje biti na pronalaženju novih strategija za efikasnije rješavanje izazova antimikrobne rezistencije i poboljšanje javnog zdravlja.*

Ključne riječi*: multirezistencija, gram-pozitivne bakterije, antibiotici, alternativna antimikrobna strategija, kombinovana terapija*