Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/45/20240620

The mechanism of MRSA drug tolerance and the comparison between vancomycin and daptomycin in the treatment of MRSA infections

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Abstract. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a superbug that is resistant to multiple antibiotics commonly used in medication and has caused severe infections in humans for hundreds of years. This review examines the MRSA drug resistance mechanism and compares the efficacies between two antibiotics, daptomycin and vancomycin, in treating MRSA infections. The resistance mechanism of MRSA alters the structure of inactivating the antibiotics. Therefore, the MRSA resistance to daptomycin and vancomycin is analyzed to show how MRSA reacts to different antibiotics preferred in therapy. Moreover, the efficacies of two antimicrobial drugs were analyzed by the research and data from journals and magazines. Combined with rifampin, two antibiotics show more potent efficacies with fewer doses, and could be an alternative therapy to conventional individual antibiotics only.

Keywords: MRSA, resistance, vancomycin, daptomycin, efficacy

1. Introduction

MRSA, a type of Gram-positive staphylococcal bacterium, is responsible for various infections in animals. The application of antibiotics is a common approach to eliminate pathogens either in vivo or in vitro. However, S. aureus has developed a robust resistance to many commonly used medical antibiotics. This bacterial superbug can rapidly acquire resistance to multiple antibiotics due to shifts in antibiotic target, enzymatic inactivation of drugs, reduced susceptibility to existing antimicrobial compounds, and decreased drug responsiveness[1].

To address the challenge of widespread drug resistance, vancomycin, a glycopeptide antibiotic, has been widely used to treat severe MRSA infections. Unfortunately, the overuse of vancomycin has led to the emergence of vancomycin tolerance and resistance, necessitating new treatment strategies against MRSA and other staphylococcal bacteria[2].

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This review aims to elucidate the fundamental mechanisms behind MRSA adaptation to antibiotic resistance while also conducting an analysis and comparison of the effectiveness of vancomycin and daptomycin against MRSA. Additionally, we will explore the potential of designing new antibiotics to combat MRSA based on existing drugs used in MRSA treatment to mitigate antibiotic resistance.

2. The adaptation of MRSA resistance to antibiotics in the fundamental mechanism

Methicillin-resistant Staphylococcus aureus (MRSA) is a Staphylococcus aureus, specifically Methicillin-resistant Staphylococcus aureus (MRSA), initially appeared as a significant infectious concern during the latter part of the 1960s, coinciding with the bacterium acquisition of resistance against methicillin, a synthetic variant of penicillin [3]. Staphylococci bacteria, including Methicillin-resistant Staphylococcus aureus (MRSA), typically inhabit the skin of individuals in good health without causing significant harm. However, these microorganisms are adept at capitalizing on any available opportunity to infiltrate wounds, nasal passages, or mucous membranes, leading to the prompt development of infections that may pose a severe risk to life [4].

The pathogenicity of Staphylococcus aureus is characterized by a high degree of complexity since individual cells could possess genes encoding a wide range of virulence factors that are either present on the cell surface or secreted. The expression of these factors is regulated by several mechanisms. Moreover, it is worth noting that antibiotic-resistance genes could be horizontally transferred at a significant rate. Consequently, this phenomenon leads to the rapid emergence of antibiotic-resistant strains that exhibit resistance to a wide range of routinely prescribed antibiotics [5, 6].

The comprehension of genetic markers that contribute to virulence, host adaptability, resistance, and selection within different clones is crucial for understanding their effectiveness and finding prospective targets for future therapeutics.

The utilization of various molecular techniques, such as spa typing, multilocus sequence typing (MLST), whole-genome sequencing, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), and microarrays, has facilitated the examination of MRSA strain genomes. These tools have provided valuable insights into the ongoing evolution of the population structure in response to environmental selective pressures [7, 8]. The primary objective of the research is to identify the molecular processes that underlie the success of both hospital-acquired methicillin-resistant Staphylococcus aureus (HA-MRSA) and community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA). These mechanisms are often responsible for the occurrence of significant epidemic outbreaks. Although the fundamental structure of each lineage remains relatively unchanged, approximately 15-20% of the genome is composed of mobile genetic profiles [9].

Clones that have achieved success in the realm of cloning, such as HA-MRSA, CA-MRSA, and LA-MRSA, exhibit diverse profiles of mobile genetic elements (MGEs). However, specific genes within these MGEs are frequently shown to be closely linked with distinct epidemiological patterns or ecological habitats. Mobile genetic elements (MGEs) often include genetic information about well-documented virulence and resistance genes, which possess the ability to undergo horizontal gene transfer (HGT). These genetic elements have the capability to modify the observable characteristics of the recipient bacteria, enabling it to adjust and thrive in novel ecological habitats [10].

Mobile genetic elements (MGEs) are significant in facilitating the ability of Staphylococcus aureus (S. aureus) to adapt to the selective pressures imposed by the human host. These elements contribute to the flexibility and adaptability of the genome. The elements encompassed within this category consist of bacteriophages, plasmids, S. aureus pathogenicity islands (SaPIs), transposons, and staphylococcal chromosomal cassettes (SCCs) [11, 12].

3. Antibiotic resistance of staphylococcus aureus (S. Aureus) against vancomycin

As a semisynthetic derivative of penicillin, methicillin was developed to treat the severe infections that *Staphylococcus aureus* could lead to sepsis or death. However, *S. aureus* has developed methicillin resistance over time due to a mutation in chromosome-encoded penicillin-binding protein. Among

DOI: 10.54254/2753-8818/45/20240620

various other antibiotics that have been utilized and prescribed to withstand *S. aureus*, vancomycin showed effectiveness in the early stage but showed signs of resistance afterwards.

As a class of glycopeptide antibiotics, vancomycin has high effectiveness on gram-positive infections, targeting groups of bacteria with a single membrane. The main principle of vancomycin acting on S. aureus is to interrupt the proper cell wall synthesis, specifically in the propagation method. While the peptidoglycan cell wall structure needs to be enlarged, vancomycin can enable hydrogen bond formation interactions. In addition, this interaction could prevent the incorporation of growing peptidoglycan chain and transpeptidation action, eventually leading to cell wall decomposition causing lysis of bacteria [13].

In a clinical trial conducted in China, 35 out of 140 MRSA patients were treated with vancomycin [14], in which 27 cases demonstrated successful clinical effectiveness. In comparison, three patients died due to MRSA infection [14]. However, in 2002, the first VRSA strain was recovered in Michigan, USA; then, in the same year, there was a discovery and isolation of the second VRSA strain in Pennsylvania, USA [15]. Correspondingly, 14 cases in the USA, 16 cases in India, 11 cases in Iran, 9 cases in Pakistan, 1 case in Brazil, and 1 case in Portugal have been reported in a total of 52 patients, to carry van genes[15]. The presence of VRSA could arise due to mainly a combination of genetic mutations and horizontal gene transfer mechanisms.

On one hand, selective pressure from which the living environment of bacteria triggers genetic mutation is a common phenomenon of natural selection. *Staphylococcus aureus*, in similarity to other bacteria as well, has genetic material that can mutate over time. Mutations can occur in the genes that are responsible for producing the target site of vancomycin action, which is the cell wall. These mutations can alter the structure of the cell wall, making it less susceptible to the effects of vancomycin. This allows the bacteria to survive and multiply in the presence of the antibiotic. Hospitals and other healthcare settings can be breeding grounds for antibiotic-resistant bacteria. These environments often have a higher density of patients, many of whom are on antibiotics. The overuse and misuse of antibiotics, including vancomycin, creates selective pressure on *S. aureus*. Bacteria that are already resistant or have acquired resistance mechanisms, especially in the case of MRSA into VRSA, have a survival advantage in the presence of antibiotics. The remaining resistant ones among the susceptible bacteria killed by vancomycin lead to a predominance of resistant strains.

On the other hand, bacteria may acquire resistance genes not only by itself, but also obtained from other bacteria through horizontal gene transfer, especially significant in the case of vancomycin resistance. Some bacteria, such as Enterococcus species, naturally carry resistance genes for vancomycin. If Staphylococcus aureus encounters these bacteria, it can potentially acquire these resistance genes through mechanisms like conjugation, transformation, or transduction. This can lead to the development of vancomycin resistance in *Staphylococcus aureus*.

To address the development of antibiotic resistance, including resistance to vancomycin, it is essential to practice responsible antibiotic use, improve infection control measures, and develop new treatment strategies. This helps slow down the emergence and spread of resistant bacteria and preserves the effectiveness of our existing antibiotics.

4. The MRSA drug resistance to daptomycin

Antibiotics can be used as treatment, but they also trigger the development of drug resistance. When an antibiotic existence is forcing the bacteria to adapt, it will accelerate the antimicrobial resistance. For survival, bacteria will make some defense strategies against antibiotics and antifungals, which is the drug resistance Mechanism. In addition, DNA will give information to bacteria, and then the bacteria will produce the specific protein. This decides the defense mechanism of the bacteria because the bacteria and fungi can have genes with multiple drug resistance.

Daptomycin is a cyclic lipopeptide antibiotic with broad-spectrum gram-positive activity, including methicillin-resistant *Staphylococcus aureus* (MRSA) [16]. Daptomycin was a standard antibiotic to cure MRSA, and it was defined as a therapeutic method that can be used with vancomycin to treat MRSA. According to the data published since 2007, Early initiation of daptomycin is beneficial in patients with MRSA bacteremia, and data from two matched retrospective cohort studies found that initiation of

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daptomycin within 72 hours of MRSA bacteremia significantly reduced 30-day mortality. Furthermore, the information from the Iowa City VA health system had research findings that when patients switch to taking Daptomycin within they take three days of vancomycin, it can significantly reduce the probability of death within 30 days. Daptomycin's structure and functions are related to the Cationic antimicrobial peptides that are made by the congenital immune system.

In Staphylococcus aureus, one of the genes that are always linked with the development of DAP-R is mprF. It codes for a bifunctional enzyme for various peptide resistance factors, catalytic lysinization of PG, and replacement of L-PG from the inner lobule to the outer lobule of CM. The positive charge of L-PG seems to be the main donor to the transformation of the surface charge, and it assists in repelling the daptomycin antibiotic molecules from the surface [17]. In an in vitro passage experiment, *Staphylococcus aureus* was revealed to rising sublethal concentrations of daptomycin, and the change in MprF was one of the first genetic variations found in DAP-R derivatives in at least 12 different loci where many mprF mutations have been described [17].

Calcium ions can convert daptomycin into an active conformation making it more amphiphilic. This can help strengthen the interaction of ionized daptomycin with negatively charged phospholipids. When daptomycin closes to the cell membrane of bacteria, the lipophilic end will then be inserted into the fatty acid chain of the phospholipid molecule of the cell membrane. Then binds irreversibly to the bacterial cell membrane with a non-covalent bond., which will cause it depolarization and potassium ions will leak away [17]. The synthesis of the macromolecules will then stop and cause the cell to die.

In an *in vitro* experiment from Hebrew University, patients were treated with methicillin-resistant Staph aureus. During the whole process, research workers collected blood samples from the patient so they could test the antibiotics one by one [18]. Doctors started with vancomycin as one of the treatments, but MRSA quickly resisted. When MRSA becomes resistant to vancomycin, doctors add rifampicin to treatment. After eight days, doctors replaced vancomycin with daptomycin. Even with the combination treatment, the patient still had a mutation in the polymerase gene rpoB. It was found that all isolates resistant to vancomycin were also highly resistant to daptomycin. In this experiment, the researchers found that the efficiency of daptomycin was much lower after the combination of daptomycin, and the speed of killing bacteria was relatively reduced. This also proves that MRSA is slowly developing resistance to daptomycin when combined with drugs. The researchers obtained the same result when they tested other bacteria. The researchers therefore concluded that while combining drugs, MRSA can become resistant to antibiotics that are still effective [18].

5. The efficacy of vancomycin in MRSA

Vancomycin is a tricyclic glycopeptide antibiotic produced by *Streptococcus orientalis*. It is extensively used in medical treatment to prevent severe infections caused by Gram-positive bacteria, especially to treat MRSA (methicillin-resistant Staphylococcus aureus). Vancomycin can inhibit the biosynthesis of cell walls by blocking the formation of peptidoglycan, leading to bacterial death. Thus, it is bactericidal for reproductive bacteria.

The Antimicrobial efficacy of Vancomycin depends on when the concentration of Vancomycin in serum is higher than the minimal inhibitory (MIC). When the concentration of Vancomycin reaches about four or five times that of MIC, the efficacy is highest [19]. Plus, Vancomycin is an unusually complex tricyclic glycopeptide antibiotic that weighs 1,500 daltons. It was hardly absorbed by the gastrointestinal tract. Therefore, it is intravenously administered. For adults, each intravenous dose should be 1g. After a 1-to 2-hour injection, the concentration of plasma will be 15 to 30 ug/ml for 1 hour. It is eliminated by renal excretion, and only 5% go through the process of metabolism. About 90% of the appointed dose is excreted by glomerular filtration [20]. Besides, Vancomycin hydrochloride is sold in the market in the form of diluted sterile power. Guidelines recommend the dilution of around 2.5 to 5.0 mg/mL. The usual dose for adults is 30mg/kg/day fractional in 2 or 3 doses. For patients who have impaired renal function, they should pay more attention before taking the medicine. Therapeutic monitoring, dosage individualization, building up ideal doses and evaluating the renal function are significant steps to guarantee safety and effectiveness before starting the treatment with Vancomycin.

DOI: 10.54254/2753-8818/45/20240620

Apart from that, Vancomycin is not the first consideration not only because of the adverse effects like hypotension, phlebitis, nephrotoxicity, ototoxicity and hypersensitivity reactions but also another vital concern on Peripheral IV complications [21]. However, there are still arguments about the reasonable use of Vancomycin on international guidelines and safety. As a result, the articles suggest that the lack of doses and spending too much time on therapy lead to the toxic levels rising and worse the side effects.

6. The comparison of daptomycin and vancomycin efficacy in MRSA

As mentioned before, daptomycin is a negatively charged cyclic lipopeptide discovered by researchers at an American pharmaceutical company from a soil sample from Turkey in the late 1980s. Daptomycin, an antibiotic generated by a Gram-positive bacterium, *Streptomyces roseosporus*[22], the first accepted lipopeptide antibiotic, shows compelling bactericidal ability against a variety of Gram-positive bacteria. It was found effective in treating diseases caused by MRSA as well[23-25]. Due to the multiple functions of the bacterial membrane, it targets and the synthesis inhibition of DNA, RNA, and proteins, it became an ideal choice for killing bacteria resistant to other antibiotics. Especially daptomycin has a distinguished efficacy in the treatment of MRSA infections. Therapies with vancomycin were commonly found with severe concerns over the decades due to lagged sterilization efficacy, difficulty in cure, restricted penetration ability, adverse safety conditions, and growing risks of failure [26]. Daptomycin is an alternative antibiotic for conventional treatment in multiple bacterial infections, although vancomycin is still considered the main force against MRSA.

Based on the studies of treating patients with certain antibiotics presented by Moise, P.A. et al., using daptomycin has only half of the failure rate of vancomycin at the end of treatment (EOT) (11% and 24%); significantly lower rates of acute kidney injury (9% in daptomycin and 23% in vancomycin); and recovery rate of vulnerable patients suffering from bacteremia (94% in daptomycin vs 56% in vancomycin) [27]. Daptomycin has a lower risk and a higher cure rate superior to vancomycin. According to their analysis, the most typical EOT failure reasons may attribute to clinical or microbiological mistakes and accidents during therapy.

According to another experiment presented by Appleman and Citron, the MIC for vancomycin was kept stable at 2 μg/mL for MRSA, but the MIC for daptomycin was only 1.1 μg/mL. In 29 years of study until 2010, daptomycin had robust bacteriostatic and bactericidal ability against MRSA. However, more strains tolerant to vancomycin were found in recent experimental reports [28].

Daptomycin combined with rifampin is commonly used in the treatment of MRSA infections. Different from applying daptomycin alone, co-administration of daptomycin and rifampin together has an outstanding efficacy in inhibition of MRSA. In John, A.K.'s studies, the MRSA strain population dropped 0.3 $\log_{10}$ CFU/ml with daptomycin alone, however, accompanied with rifampin, a decline of greater than 6 $\log_{10}$ CFU/ml in the counts was detected [29]. In overview, daptomycin combined with rifampin is a relatively ideal therapy for inhibiting MRSA, except for immunocompromised patients. It could also minimize the development of antibiotic resistance [30]. In future treatment, co-administration of daptomycin and rifampin together may apply more extensively in clinical trials and practical medication.

7. Conclusion

This review has discussed the adaptation of the MRSA resistance mechanism to antibiotics and how MRSA resists vancomycin and daptomycin, respectively. Besides, the efficacy of two antibiotics on MRSA is evaluated and compared, obtaining the conclusion that daptomycin has a more potent efficacy in inhibiting MRSA and a lower risk of causing injuries to tissues compared to vancomycin. It was also found that rifampin and daptomycin as coadministration have remarkable efficacy in treating MRSA and lead to minimum resistance. Further clinical experiment is required to test the appropriateness of these two drugs to apply to global medication. With the development of the pharmaceutical industry, new forms of antibiotics can be produced efficiently and inexpensively, resulting in MRSA infections being away from worldwide public health.

DOI: 10.54254/2753-8818/45/20240620

Acknowledgments

Chun Xu, Yuming Li, Yan Pan, Yanzi Li, and Yanning Zhang contributed equally to this work and should be considered co-first authors.

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