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# Antibiotic resistance in MRSA: Exploring alternative treatment options through linezolid and daptomycin

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## Abstract

Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections became difficult to cure as they expanded over the world. As, *Staphylococcus aureus* can cause a variety of illnesses in the body, MRSA infections, in particular, can be acquired in healthcare settings (HA-MRSA) and community settings (CA-MRSA). MRSA infections have been demonstrated to be resistant to penicillin, -lactam, and vancomycin, as well as other antimicrobials, restricting their treatment choices. Their susceptibility testing was examined using morphological, molecular, and new methodologies. Because it was resistant to numerous antibiotics, it was important to develop new agents for therapy; this article covers the current use of antibiotics, which include linezolid and daptomycin. This article discusses the mechanism of action, antibacterial activity, clinical perspectives, resistance, and side effects of the antibiotics: linezolid and daptomycin. Different antibiotics were tested in various parts of the world, and the results revealed that practically all antibiotics are resistant to MRSA infections, with linezolid and daptomycin in particular showing resistance at a very low ratio. As a result, linezolid and daptomycin are preferred for treatment; the following article also discusses their benefits and drawbacks for humans. Similarly, it focused on the developing threats to linezolid and daptomycin antibiotics. Combination therapy should be considered for the decrease of resistance to these antibiotics. The present paper seeks to provide a current and up-to-date review of antibiotic susceptibility testing for MRSA.

**Keywords:** MRSA infections, linezolid, daptomycin, antibiotic susceptibility testing, antibiotics resistance.

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## 1. INTRODUCTION

There are numerous varieties of gram-positive, cocci-shaped *Staphylococcus* species found in nature. Most commonly found bacterial species in Micrococcaceae family are *Staphylococcus aureus* which have relatively unique kind of properties i.e., they are catalase and coagulase positive bacteria, resistant to environment and disinfection agents, typical component of human flora[1], sometimes become opportunistic pathogen causing various diseases in humans (most notably toxic shock syndrome, food poisoning, and skin infections). *Staphylococcus aureus* is found to be the most common cause of hospital-acquired infections[2]. Biofilm development is a virulence factor in these species[3].

*Staphylococcus epidermidis* also come under the category of *Staphylococcus* species. *S. epidermidis* differs from *S. aureus* in that it is a coagulase-negative, facultative anaerobe, catalase-positive bacterial species [4]. Normal flora of these species is skin and mucous membrane[5]. They are also responsible for nosocomial infections and biofilm production like that of *S. aureus*[6]. Antibiotic susceptibility testing reveals that it is resistant to a wide range of antibiotics, including cefoxitin, moxalactam, norfloxacin, oxacillin, and others. Oxacillin was tested on IsoSensitest agar, whereas others were tested using the disc diffusion method. Tigecycline, vancomycin, and linezolid are still toxic to these species[7].

*Staphylococcus saprophyticus*, the third *Staphylococcus* species, is coagulase-negative and exhibits no haemolysis on blood agar. They cause Urinary Tract Infections (UTIs) in humans[8]. *S. saprophyticus* can be distinguished from *S. epidermidis* because it is resistant to the novobiocin antibiotic, whilst *S. epidermidis* is sensitive to it[9]. Antibiotic susceptibility testing reveals that these species are resistant to chloramphenicol, clindamycin, gentamicin, erythromycin, and a variety of other antibiotics. They are susceptible to a number of antibiotics, including linezolid, vancomycin, and nitrofurantoin[10].

Methicillin-Resistant *Staphylococcus aureus* (MRSA) are the most common pathogens and commensals that have emerged since the 1960s. *S. aureus* can cause endocarditis, bacteraemia, pneumonia, skin infections, and other health-care-related infections[11]. MRSA infections can be acquired in health-care settings (HA-MRSA) and community settings (CA-MRSA) [12]. Initially, such diseased patients were treated with penicillin antibiotics, but resistance developed within a year. It resulted in an increase in the incidence of such illnesses, which spread globally, although it is not a pandemic. Resistance developed in hospital-acquired MRSA (HA-MRSA) infections to antibiotics such as trimethoprim, clindamycin, and tetracycline after a while. Following, the administration of these antibiotics, vancomycin (commonly known as the last drug of choice) was administered but also became resistant to such infections. In recent times, Daptomycin and linezolid antibiotics are given to such patients. Daptomycin is particularly used to treat bacteraemia and endocarditis while linezolid treats pneumonia, whereas delafloxacin and omadacycline are used to treat skin and soft tissue infections. MRSA infections are still susceptible to the medications of antibiotics like daptomycin, linezolid, delafloxacin, and omadacycline. So, still these are the only antibiotics available to treat MRSA infections[11].

## 2. RESISTANT ANTIBIOTICS

There are various antibiotics that were tested against MRSA infections. Some are listed below:

### 2.1. Beta Lactams:

Penicillin is a well-known and natural antibiotic used initially to treat *Staphylococcus* infections. β-Lactams antibiotics were then tested, before administrating to the patients, through disk diffusion method in lab. Results shown that antibiotics can kill *S. aureus* in *in vitro* conditions in a time-dependent manner with negligible post-antibiotic effects. Through the use of molecular techniques on animal models, it was determined that if the serum level was checked for Minimum Inhibitory Concentration (MIC), and it exceeded 40-50% of the treatment interval, it would be best for the killing of *S. aureus* infections in animals. Graphs have been categorized against the MIC of *S. aureus* susceptibility, resulting in the goal of a β-lactam antibiotic dosing approach. This is best performed with short half-life penicillin like benzyl penicillin and flucloxacillin via continuous intravenous infusion, which is the most often utilized approach for the treatment of *S. aureus* infections[13].

The use of β-lactam medicines to combat MRSA infections was effective, but the inclusion of a gene that encodes PBP2a against MRSA infections was problematic since this gene helps *S. aureus* bacteria to grow and results in multiplication of bacteria. Aside from β-lactams, other antibiotics were employed to disturb the structure of cell wall: teichoic acid and cell membrane: micro domains, including statins, which developed a good response against *S. aureus* infections[14].

### 2.2. Vancomycin

Vancomycin antibiotic has a simple seven-membered short-chain structure with two sugars linked, vacosamine and glucose. It was isolated in pure form from the bacterium *Streptomyces orientalis*[15] in 1956.

Vancomycin has proven to be the most effective treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Nonetheless, the first vancomycin-resistant MRSA was discovered in a Japanese patient in 1996. A surgical wound infection developed that was resistant to long-term antibiotic treatment[16]. Vancomycin is commonly regarded to be just as effective as penicillinase-resistant beta-lactam antibiotics[17].

MICs of vancomycin against *S. aureus* were discovered through molecular testing against MRSA infections. The results showed that if the MIC range is 8-16mg/L, they are referred to as vancomycin-intermediate isolates, however if the MIC range is 32mg/L, they are referred to as vancomycin-resistant isolates. Vancomycin has a targeting agent that is the cell wall; it connects to the areas that aid in the creation of the cell wall, hence suppressing cell wall forming activity. It mostly binds to the cell wall's terminal D-alanyl-D-alanine site, inhibiting its synthesis. Vancomycin resistance is now thought to be induced possibly by the cell wall thickening[18].

As, linezolid is also becoming resistant against MRSA infections, so, new antibiotics are now developed, including linezolid, daptomycin, and tigecycline, which are being considered effective for the treatment of MRSA infections. Aside from these antibiotics, conventional glycopeptides such as dalbavancin, telavancin, and oritavancin are currently thought to be anti-MRSA agents. The current study will discuss the recently occurring clinical challenges and developing anti-MRSA medications[19].

## 3. EVALUATION OF NEW ANTIBIOTICS

Vancomycin, daptomycin, and linezolid are some of the current medicines that are under consideration for the treatment of Methicillin-Resistant *Staphylococcus aureus*. Linezolid is especially useful in the treatment of Hospital Acquired Pneumonia (HAP) [20].

### 3.1. Linezolid

Linezolid has shown *in vitro* to be a dominant antibiotic for treating infections such as MRSA and high-level penicillin-resistant *Streptococcus pneumoniae*, which evolved resistance by acquiring genes from *Enterococci* species[21]. Linezolid is regarded as the first accessible agent of a new class of antimicrobials known as Oxazolidinones, which was discovered in 1987[22].

#### 3.1.1. Mechanism of action

*Staphylococcus* species undergo transcription and translation processes. The translation process may take place when the 50S ribosomal subunit (which contains the 23S peptidyl transferase centre) attaches to the mRNA, where the 30S ribosomal subunit is already connected, to produce the 70S ribosomal subunit. In bacteria, ribosome binding is the first step in translation. Linezolid acts by binding to the 23S peptidyl transferase centre of 50S ribosomal subunit. This inhibits the binding of the 50S ribosomal subunit, 30S ribosomal subunit, mRNA, and tRNA to each other and, eventually, preventing the formation of complex. The translation process is hampered as a result of this inhibition[22]. Linezolid's mechanism of action differs from that of other protein synthesis inhibitors such as chloramphenicol, macrolides, and tetracycline because the former only interfere with the elongation process and not the initiation step. Linezolid is also unusual in its activity since it inhibits the development of *staphylococcal* and *streptococcal* virulence factors while remaining are specific in their action and not overlapping with pre-existing protein inhibitors[21]. Cross-resistance does not arise in its method of action, and linezolid is commercially available antibiotic[15].

#### 3.1.2. Antimicrobial activity

As, MRSA infections spread and became resistant to various antibiotics, the administration of linezolid has spread globally and has proven to be an effective antibiotic. Linezolid has broad antibiotic efficacy against a wide range of microorganisms, including *Chlamydia*, *mycoplasma*, *mycobacterium spp*., *Corynebacterium*, *Nocardia*, *Listeria*, *Bacteroides*, *Moraxella*, and others[22]. It is also effective against vancomycin-resistant *enterococci* (VRE), particularly *Enterococcus faecium*, penicillin-resistant *pneumococci*, gram negative anaerobes, and *mycobacteria*[15]. According to pharmacodynamics investigations, it possesses bacteriostatic effects against gram positive cocci and bactericidal properties against *staphylococci* and *streptococci*[21].

#### 3.1.3. Clinical Perspectives

In most of the cases, linezolid is administered orally to patients. It is used to treat skin and soft tissue inflammations, community-acquired pneumonia, nosocomial pneumonia, and bacteremia[22]. Pneumonia caused by *Staphylococcus* spp. can be healed by administering linezolid orally. It is also effective against the infections caused by Glycopeptide- Intermediate *Staphylococcus aureus* (GISA), methicillin-resistant coagulase-negative *staphylococci*, and Glycopeptide Resistant *Enterococci* (GRE) [15].

### 3.1.4. Resistance

As, linezolid is a synthetic medicine, no resistant genes obtained from natural sources are exposed. Resistance will only be developed if the target site had some site alterations. These point mutations typically originated as a result of naturally occurring modifications in the genetic material, rather than genetic cross-linkages. Resistance has occurred in several bacteria such as *Enterococci*, *Streptococcus pneumonieae*, and *Staphylococcus* aureus, however the frequencies of resistance are very low[21]. Resistance to this antibiotic was found using the disc diffusion method and the E-test, however in certain cases, molecular testing are required to identify resistance[23]. Possible factors of causing resistance include: previous usage of linezolid, solid organ transplant, immunosuppression, or any previous operation. While taking the dosage of linezolid, precautions should be made[21].

### 3.1.5. Adverse Effects

Linezolid accumulation may cause a variety of problems within the body, including myelosuppression, which occurs when mitochondrial respiration suffers due to a blockage in mitochondrial protein synthesis. When linezolid is taken for an extended period of time, it causes eyesight issues. Diarrhoea, headache, vomiting, nausea, sleeplessness, constipation, rashes, disorientation, and, most commonly, fever has been reported in such patients[22]. Furthermore, in these conditions, linezolid is a very effective treatment for treating MRSA infections, and only a small percentage of patients acquiring these infections have developed resistance to this antibiotic[15].

## 3.2. Daptomycin

Daptomycin belongs to the class of antibiotics known as lipopeptides, which have a peptide core and a lipid tail that imparts its specialised action. Daptomycin (DAP) is a frequently used antibiotic for killing Gram-positive bacteria. Currently, we are facing resistance problem in gram positive bacteria, such as methicillin resistance *Staphylococcus aureus*, and DAP is being used to combat this problem[24].

### 3.2.1. Antimicrobial activity

Daptomycin is a broad-spectrum antibiotic used to treat *S. aureus*, *streptococci*, and *enterococci* that are resistant to vancomycin, quinupristin-dalfopristin, and linezolid. It also works against vancomycin-resistant *Leuconostoc* spp. When it work with in collaboration with gentamicin to kill *staphylococci* and *enterococcus*[15].

### 3.2.2. Mechanism of action

They are structurally and functionally related to cationic antimicrobial peptides, which are the host's initial line of defence against bacterial infection. Daptomycin has a 13 amino acid cyclic polypeptide core. They also have 10 C-terminal residues that form a ring encompassed by an ester bond, as well as a 3-amino acid exocyclic acid chain with a terminal tryptophan.

The binding interaction of daptomycin with the target cell's membrane is a mystery, however it is presently thought that there may be contact with the bacterial membrane lipid phopsatidylglycerol (PG). It enters the cell membrane in a Ca2+-dependent manner, causing various modifications in the cell and the loss of some intracellular components such as k+, Mg2+, and ATP. The potency of antimicrobial drugs is the same as the concentration of free Ca2+ in human extracellular fluid, which is 1.2mM. The leakage of K+ ions causes membrane potential dissipation in both *S. aureus* and *Bacillus megaterium*. Bacterial cell death caused by daptomycin can occur for a variety of causes, including inhibition of peptidoglycan, lipo-teichoic acid production, and blocking of active amino acids[25].

### 3.1.3. Resistance of Daptomycin

Many mechanisms have been proposed to explain the non-susceptibility, including cell membrane depolarization, alterations in bacterial membrane fluidity, increased carotenoid pigment content, and cell membrane toxicity[26]. Disc diffusion studies demonstrated that all isolates were susceptible to daptomycin due to MHA that is allowed by two separate manufacturers (with the FDA-approved breakpoint of 16 mm). When using daptomycin to treat osteomyelitis, we recommend using the maximum tolerable dose and closely monitoring the patient to avoid relapse. We further recommend that clinical isolates of *S. aureus* be evaluated for daptomycin susceptibility with an FDA-cleared MIC device prior to initiating therapy and in cases of microbiologic failure[27]. Table 1 lists resistance pattern of MRSA to different antibiotics.

### 3.1.4. Toxicity and Adverse Effects

Daptomycin toxicity includes increased creatine phosphokinase and myopathy, both of will be resolve after the drug is discontinued. Weekly monitoring of creatine phosphokinase levels during daptomycin therapy is recommended during the treatment, if the increase is greater than or equal to 5 times the upper limit of normal. These side effects are more common when divided doses are used instead of once-daily dosing. Constipation and other gastrointestinal side effects have been observed as well[15].

Different antibiotic types were evaluated for their ability to treat MRSA infections, and the findings varied, indicating whether or not the particular antibiotic is susceptible to or resistant to a given population ratio.

**Table 1.** Antibiotic resistance in a given proportion of people[28]

| ANTIBIOTICS | RATIO OF PEOPLE (%) | RESISTANCE |
|---|---|---|
| Gentamicin | 100 | 36 |
| Rifampin | 27.78 | 10 |
| Oxacillin | 100 | 36 |
| Ciprofloxacin | 100 | 36 |
| Vancomycin | 0 | 0 |
| Clindamycin | 97.22 | 35 |
| Erythromycin | 100 | 36 |
| Daptomycin | 5.56 | 2 |
| Linezolid | 2.78 | 1 |
| Chloramphenicol | 41.67 | 15 |

## 4. CONCLUSIONS

To treat MRSA infections, which are now spreading worldwide, many antibiotics were utilized, including penicillin, -lactams, vancomycin, linezolid, and daptomycin. Most antibiotics are now resistant to MRSA infections, with daptomycin and linezolid being particularly resistant at a lower ratio. Vancomycin is ineffective against *enterococci* and most *staphylococci*, however linezolid is increasingly used to treat vancomycin-resistant gramme-positive bacteria. Daptomycin is also effective against vancomycin-resistant *Leuconostoc* spp., *staphylococci*, and *enterococci*. Furthermore, precautions should be taken to minimise antibiotic resistance, antibiotics should not be overdosed, and combination therapy, which are still insufficiently utilized, could be used to treat MRSA infections. These techniques may help to keep antibiotics from becoming resistant.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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