Methicillin-resistant *Staphylococcus aureus* infections: role of daptomycin/β-lactams combination

*Methicillin-resistant Staphylococcus aureus* (MRSA) is at present the most commonly identified antibiotic-resistant pathogen in many parts of the world [1, 2]. Methicillin was introduced in 1959 to treat infections caused by penicillin-resistant *S. aureus*. In 1961 there were reports from the UK of *S. aureus* isolates that had acquired resistance to methicillin, and apart from a period during the early 1970s, the incidence of this resistance has steadily increased [3]. Hospital-acquired MRSA strains are no longer limited to hospitals, but have now spread to other healthcare settings such as long-term care facilities [4]. As with other multi-resistant infections, MRSA infections are associated with high costs and extended hospital stay [5, 6]. On this point, Engemann et al. observed that patients with surgical site infections (SSIs) due to MRSA had a greater 90-day mortality rate than patients infected with methicillin-susceptible *S. aureus* (MSSA) (OR 3.4, 95%CI 1.5-7.2). Patients infected with MRSA had a greater duration of hospitalization after infection (median additional days=5; p<0.001), although this was not significant on multivariate analysis (p=0.11). Median hospital charges were US$ 29,455 for control subjects, US$ 52,791 for patients with MSSA SSIs, and US$ 92,363 for patients with MRSA SSIs (p<0.001 for all group comparisons). Patients with MRSA SSIs had a 1.19-fold increase in hospital charges (p=0.03) and had mean attributable excess charges of US$ 13,901 per SSI compared with patients who had MSSA SSIs [7]. In another study, Kopp et al. showed that patients with MRSA infections had a trend toward longer hospital length of stay (15.5 vs. 11 days; p=0.05) and longer antibiotic-related hospital length of stay (10 vs. 7 days; p=0.003). The median hospital cost associated with treatment of patients with MRSA infections was higher compared with patients with MSSA infections [8]. Cosgrove found that both the median length of hospitalization after *S. aureus* bacteraemia for patients who survived and the median hospital charges after *S. aureus* bacteraemia were significantly increased in MRSA patients. After multivariable analysis, compared with MSSA bacteraemia, MRSA bacteraemia remained associated with increased length of hospitalization (1.29-fold; p=0.016) and hospital charges (1.36-fold; p=0.017). MRSA bacteraemia had a median attributable length of stay of 2 days and a median attributable hospital charge of US$ 6916 [9]. There is some evidence suggesting that MRSA infection increases morbidity, risk of mortality, and costs [10, 11]. Cosgrove et al. performed a meta-analysis to summarize the impact of methicillin resistance on mortality in *S. aureus* bacteraemia. The authors described 31 studies on a total of 3963 patients with *S. aureus* bacteraemia. Analysis showed a significant increase in mortal-
ity associated with MRSA bacteraemia (OR 1.93, 95% CI 1.54-2.42; p <0.001) [12]. Similar findings were observed in patients affected by infective endocarditis, nosocomial pneumonia, intra-abdominal infections, skin and soft-tissue infections including diabetic foot infections, central nervous system infection, and bone and joint infections [13-22].

**ROLE OF GLYCOPEPTIDES IN THE TREATMENT OF MRSA INFECTIONS**

There is great controversy over the current utility of the backbone antibiotics, i.e., glycopeptides, for the treatment of MRSA infections. The poor pharmacokinetic/pharmacodynamic parameters, with poor tissue distribution, slow cidal activity and high protein binding predict poor patient outcome even without the advent of resistant strains. These facts may explain the higher mortality of MRSA infections and the poorer outcome even of MSSA infections when treated with vancomycin. Moreover, there is a growing body of evidence indicating that the glycopeptides minimum inhibitory concentration (MIC) has a real impact on patient outcome [23]. Sakoulas et al. found a statistically significant relationship between treatment success with vancomycin and decreases in both vancomycin MICs (≤0.5 μg/mL vs. 1.0-2.0 μg/mL; p=0.02) and degree of killing (reduction in log_{10} CFU/mL) by vancomycin over 72 h of incubation in vitro (p=0.03). For MRSA isolates with vancomycin MICs ≤0.5 μg/mL, vancomycin was 55.6% successful in the treatment of bacteraemia, whereas vancomycin was only 9.5% effective in cases in which vancomycin MICs for MRSA were 1-2 μg/mL [24]. In another study comparing infections caused by MRSA with a vancomycin MIC of >2 μg/mL with infections due to MRSA with a MIC of ≤2 μg/mL, response was significantly lower (62% vs. 85%; p=0.02) and infection-related mortality was higher (24% vs. 10%) in the high MIC group. In addition, a high MIC for vancomycin was an independent predictor of poor response in multivariate analysis of these MRSA infections [25]. Soriano et al. showed a significantly higher mortality for this disease when vancomycin was used empirically and the vancomycin MIC was 2 μg/mL [26]. In patients with bacteraemia, Lodise et al. showed that vancomycin MICs of >1.5 μg/mL had a 2.4-fold increase in failure compared to patients with MICs of <1.0 μg/mL (p=0.049). In the Poisson regression analysis, a vancomycin MIC of >1.5 μg/mL was independently associated with failure (adjusted risk ratio 2.6, 95% CI 1.3-5.4; p=0.01) [27]. A Consensus of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists suggested that in severe bacterial infections caused by *S. aureus*, a total trough serum vancomycin concentration of 15-20 μg/mL should be achieved. These recommendations are based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes. Trough serum vancomycin concentrations in that range should achieve an area under the curve (AUC)/MIC ratio of ≥400 in most patients if the MIC is ≤1 μg/mL. In order to achieve rapid attainment of this target concentration for seriously ill patients, a loading dose of 25-30 mg/kg can be considered. However, a targeted AUC/MIC of ≥400 is not achievable with conventional dosing methods if the vancomycin MIC is ≥2 μg/mL in a patient with normal renal function [28]. Therefore, alternative therapies should be considered. In the last years, newer antibiotics with activity against MRSA have been introduced: daptomycin, linezolid, tigecycline and more recently, ceftaroline, ceftobiprole, dalbavancin, oritavancin, and telavancin [29, 30].

**DAPTOMYCIN**

Daptomycin, a lipopeptide antibiotic, is highly bactericidal against the majority of Gram-positive human pathogens, including MRSA. Daptomycin also remains bactericidal (99.9% killing within 24 h) against stationary phase cultures of both MSSA and MRSA. Its mechanism of action involves insertion into and disruption of the Gram-positive plasma membrane without entering the cytoplasm of the cell. The mechanism involves a calcium-dependent binding of the lipophilic tail of daptomycin to the bacterial cell membrane. This results in potassium efflux, membrane depolarisation, cessation of macromolecular synthesis and cell death. Daptomycin has been approved for the treatment of bacteraemia and right-sided endocarditis due to *S. aureus* (including MRSA) and
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complicated skin and soft tissue infections [31]. It has excellent efficacy against stationary-phase staphylococci and it is being used in clinical practice to treat patients with bone and joint infections caused by Gram-positive pathogens, including MRSA [17, 21]. The once-daily administration makes it attractive for OPAT [32-34]. Daptomycin is successfully used for the treatment of severe (life-threatening) staphylococcal disease, although microbiological and clinical failure in treated patients has been documented. Moreover, selection of resistant strains has been reported during daptomycin-monotherapy. Several factors associated with loss of susceptibility are described, including high bacterial density and suboptimal drug concentration, particularly there are some concerns on standard dosage and monotherapy that can be inadequate [35, 36]. Thus, the use of high-dose daptomycin, alone or in combination, may be useful for difficult-to-treat Gram-positive infections [37].

DAPTOMYCIN PLUS β-LACTAMS COMBINATION

Several daptomycin-based combination therapy have been investigated in order to enhance clinical success rates and minimise the risk of development of resistance. Recently, several data showed that daptomycin plus β-lactams combination is a very intriguing treatment approach for patients with difficult-to-treat Gram-positive infections, including those cases due to MRSA. The use of this combination reduces the charge of the outer membrane, thus enhancing binding of daptomycin [37]. In a time-kill study, Rand et al. found that daptomycin-oxacillin combination had a synergistic activity against 18 MRSA strains. Daptomycin was tested at concentrations of 2, 1, 0.5, 0.25, 0.125, and 0.0625 μg/mL alone or in combination with oxacillin at a fixed concentration of 32 μg/mL. At 24 hours, the daptomycin-oxacillin combination with daptomycin at one-half the MIC showed bactericidal activity against all 18 strains, and the combination with one-fourth the daptomycin MIC showed bactericidal activity against 9 out of 18 strains [38]. In an experimental endocarditis model, a seesaw effect has been demonstrated between daptomycin and oxacillin, whereby the development of daptomycin-resistance in vitro was accompanied by increased oxacillin susceptibility in MRSA in a mecA-independent manner [39]. Dhand et al. treated 7 cases of MRSA bacteremia that were refractory to a number of vancomycin-based and daptomycin-based regimens. In all patients, the addition of high-dose antistaphylococcal β-lactams (nafcillin or oxacillin) to high-dose daptomycin (8-10 mg/kg/day) resulted in rapid bacteremia clearance. Moreover, the authors showed that this combination enhanced daptomycin bactericidal activity, increased membrane daptomycin binding, and decreased in the positive surface charge induced by antistaphylococcal β-lactams against daptomycin nonsusceptible MRSA [40]. In an experimental foreign-body infection due to MRSA, Garrigós et al. found that the overall effect of the addition of cloxacillin to daptomycin was a significantly greater cure rate against adhered bacteria than that for daptomycin alone [41]. Furthermore, in another experimental study, Mehta et al. observed that daptomycin/β-lactam combination showed a synergistic effect against daptomycin-resistant MRSA strains. Moreover, this combination seems to be able to delay in vitro the emergence of daptomycin-resistant strains [42]. Similarly, in the CORE (Cubicin Outcomes Registry and Experience) study, Moise et al. observed that the overall treatment efficacy was slightly enhanced with the addition of a β-lactam (87% vs. 78%; p=0.336), but this trend was most pronounced for bacteremia associated with endocarditis or bone and joint infection or bacteremia from an unknown source (90% vs. 57%; p=0.061) [43]. Finally, recent studies have shown a synergistic activity of daptomycin/ceftaroline and daptomycin/ceftobiprole combinations against strains of S. aureus with various resistance phenotypes [44-48].

CONCLUSIONS

Over the last decade, MRSA strains have emerged as serious pathogens in both nosocomial and community setting. Glycopeptides are the backbone antibiotics for the treatment of MRSA infections. However, several reports have highlighted the limitations of vancomycin, and its role in the management of serious infections is now being reconsidered. Daptomycin is successfully used for the treatment of severe staphylococcal infec-
tions, although microbiological and clinical failure in treated patients has been documented. Although there are very few clinical data to advise clinical practice, daptomycin plus β-lactams combination is a very intriguing treatment approach for patients with MRSA infections. Well-designed prospective studies are needed to provide more convincing evidence to fully assess the value of these newer combination regimens. 

**Keywords**: daptomycin, combination therapy, MRSA.

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**REFERENCES**

[1] Ippolito G., Leone S., Lauria F.N., Nicastri E., Wenzel R.P. Methicillin-resistant *Staphylococcus aureus* (MRSA) associated infection has become a worrisome issue worldwide. Glycopeptides are the backbone antibiotics for the treatment of MRSA infections. However, several reports have highlighted the limitations of vancomycin. Daptomycin is successfully used for the treatment of serious MRSA infections, however selection of resistant strains has been reported during daptomycin-monotherapy. This review will briefly discuss the available data on daptomycin/β-lactam combination therapies for the treatment of MRSA infections.


