When sepsis persists: a review of MRSA bacteraemia salvage therapy

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MRSA bacteraemia (MRSAB), including infective endocarditis, carries a high mortality rate, with up to 50% of patients failing initial therapy with vancomycin and requiring salvage therapy. Persistent MRSAB can be difficult to successfully eliminate, especially when source control is not possible due to an irremovable focus or the bacteraemia still persists despite surgical intervention. Although vancomycin and daptomycin are the only two antibiotics approved by the US FDA for the treatment of patients with MRSAB as monotherapy, the employment of novel strategies is required to effectively treat patients with persistent MRSAB and these may frequently involve combination drug therapy. Treatment strategies that are reviewed in this manuscript include vancomycin combined with a β-lactam, daptomycin-based therapy, ceftaroline-based therapy, linezolid-based therapy, quinupristin/dalfopristin, telavancin, trimethoprim/sulfamethoxazole-based therapy and fosfomycin-based therapy. We recommend that combination antibiotic therapy be considered for use in MRSAB salvage treatment.

Introduction
The IDSA 2011 MRSA guidelines recommend vancomycin or daptomycin, each approved by the US FDA for MRSAB, for first-line MRSAB therapy.1 Although definitions vary, treatment failure is encountered in up to 50% of cases.2 There are multiple reasons for treatment failure including poor source control, inadequate surgical debridement, host innate immunity deficiency and antibiotic pharmacodynamic factors. Irrespective of the reason, MRSAB treatment failure per se is linked to poorer outcomes, including a greater likelihood of metastatic infections and increased mortality.3,4 The IDSA guidelines recommend switching to an alternative agent rather than adding to a failing (defined as persistent bacteraemia at or around 7 days, but earlier if clinical deterioration is present) regimen.1 However, these patients represent a complex heterogeneous group with sparse data addressing how they should be optimally treated. The objective of this paper is, therefore, to review MRSAB treatment options for patients requiring salvage therapy.

Salvage therapy options
Vancomycin + β-lactam
In vitro studies have demonstrated synergistic activity between vancomycin and several β-lactams against S. aureus, including MRSA.5,6 This observed synergy extends to heterogeneous vancomycin-intermediate S. aureus (hVISA) and VISA isolates, with several studies observing reduced total vancomycin binding (but potentially greater target-specific binding) to the cell wall and reduced cell wall thickness following exposure to ceftriaxone and oxacillin or nafcillin, respectively.5,7,8

Vancomycin is synergistic with a variety of penicillinase-stable β-lactams in vitro. In a small number of VISA and hVISA strains, ceftriaxone appeared more reliably synergistic with vancomycin than did oxacillin.7 Further benefit from the addition of a β-lactam may accrue from the ability of these agents to potentiate cationic host defence peptides (HDPs).9

Since vancomycin is generally considered the first-line treatment option for most MRSA infections, published experience with the use of vancomycin alone or in combination with a β-lactam as salvage therapy is limited. Vancomycin combined with a β-lactam at or near the initiation of therapy, however, has been reported to yield improved results compared with vancomycin monotherapy. A retrospective study found that MRSAB microbiological eradication was achieved in 48/50 patients (96%) who received vancomycin with a β-lactam (piperacillin/tazobactam; 34/50) compared with 24/30...
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<th>Study identifier</th>
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<tr>
<td>Sakoulas et al.</td>
<td>case series</td>
<td>patients treated with ceftaroline + daptomycin for documented refractory staphylococcal bacteraemia</td>
<td>26 patients total, 20 patients with MRSA</td>
<td>not clearly defined</td>
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<tr>
<td>Dhand et al.</td>
<td>case series</td>
<td>patients treated with daptomycin + antistaphylococcal β-lactam for persistent MRSAB</td>
<td>7 patients</td>
<td>not clearly defined</td>
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<tr>
<td>Kullar et al.</td>
<td>retrospective cohort</td>
<td>patients, not on dialysis, with confirmed or suspected <em>S. aureus</em> and/or enterococcal infections at any site; who received daptomycin at ≥8 mg/kg/day (total body weight) for ≥72 h</td>
<td>250 patients, 126 patients with MRSA</td>
<td>not clearly defined</td>
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<tr>
<td>Kullar et al.</td>
<td>retrospective cohort</td>
<td>patients with IE with positive blood cultures for staphylococcal or enterococcal species; who received daptomycin at ≥8 mg/kg/day (total body weight) for ≥72 h</td>
<td>70 patients, 54/64 patients with organism isolated had MRSA</td>
<td>not clearly defined</td>
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<tr>
<td>Lai et al.</td>
<td>retrospective cohort</td>
<td>patients with serious infections who received daptomycin dosed at ≥6 mg/kg/day (total body weight) for ≥72 h</td>
<td>67 patients, 38 patients with MRSA</td>
<td>not clearly defined</td>
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<td>Moise et al.</td>
<td>retrospective cohort</td>
<td>patients from the Cubicin Outcomes Registry and Experience who received daptomycin at ≥8 mg/kg/day</td>
<td>94 patients, 19 patients with MRSA</td>
<td>not clearly defined</td>
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<tr>
<td>Casapao et al.</td>
<td>retrospective cohort</td>
<td>patients treated with ceftaroline for ≥72 h for Gram-positive infections</td>
<td>527 patients total, 127 patients with MRSA</td>
<td>not clearly defined</td>
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<td>Paladino et al.</td>
<td>case–control</td>
<td>cases: patients with MRSA treated with vancomycin (MIC 2–4 mg/L) initially who were then switched to ceftaroline or placed on ceftaroline empirically; controls: patients with MRSA treated with vancomycin (MIC 2–4 mg/L), who then continued on vancomycin or were placed on an alternative antibiotic active against MRSA (excluding ceftaroline)</td>
<td>16 patients as ceftaroline cases matched to 16 patients as vancomycin controls</td>
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<td>Polenakovik and Pleiman</td>
<td>case series</td>
<td>patients with MRSAB treated with ceftaroline</td>
<td>31 patients</td>
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<td>Tattevin et al.</td>
<td>case series</td>
<td>patients with IE who received ceftaroline as salvage therapy for &gt;48 h</td>
<td>8 patients, 5 patients with MRSA</td>
<td>not clearly defined</td>
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<td>Lin et al.</td>
<td>case series</td>
<td>patients with MRSAB and deep-seated MRSA infections treated with ceftaroline and who failed to clinically respond to vancomycin therapy</td>
<td>10 patients</td>
<td>not clearly defined</td>
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<tr>
<td>Moise et al.</td>
<td>prospective cohort</td>
<td>patients who received linezolid as part of a compassionate use programme with ≥1 of the following criteria: isolation of <em>S. aureus</em> with resistance or intermediate susceptibility to currently available antibiotics, including vancomycin; clinical intolerance of licensed antimicrobial agents conventionally used to treat patients with infections caused by <em>S. aureus</em>; inability to tolerate long-term intravenous treatment; and a documented failure to respond to initial therapy</td>
<td>40 patients with MRSA receiving linezolid as salvage therapy</td>
<td>failure of vancomycin treatment defined as if patient received vancomycin at appropriate dosages for ≥5 days, if specimens from the sites of infection continued to yield the same pathogens and if they exhibited ≥1 of the following: persistence of signs and/or symptoms of infection present at baseline; appearance of new signs and/or symptoms; or exacerbation of ≥1 sign or symptom present at baseline</td>
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<td>Howden et al.</td>
<td>case series</td>
<td>patients with serious infections due to <em>S. aureus</em> with reduced vancomycin susceptibility (hVISA)</td>
<td>25 patients, 21 patients treated with antibiotics (18/21 patients treated with linezolid-based therapy)</td>
<td>glycopeptide failure defined as a blood culture positive for <em>S. aureus</em> after ≥ 7 days of glycopeptide therapy or as a sterile site isolate positive for <em>S. aureus</em> after ≥ 21 days of glycopeptide therapy</td>
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<td>Jang et al.</td>
<td>retrospective cohort</td>
<td>patients with persistent <em>S. aureus</em> bacteraemia, defined as ≥ 7 days</td>
<td>41 patients total, 35 patients with MRSAB</td>
<td>persistent bacteraemia, defined as the isolation of <em>S. aureus</em> in blood cultures obtained from peripheral veins on ≥ 7 consecutive days despite appropriate antibiotic administration for ≥ 5 days</td>
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<tr>
<td>Park et al.</td>
<td>prospective cohort</td>
<td>patients with persistent MRSAB (≥ 7 days bacteraemia) treated with linezolid-based salvage therapy or glycopeptide-based therapy</td>
<td>90 patients, 52 patients treated with glycopeptide-based therapy and 38 patients treated with linezolid-based therapy</td>
<td>persistent bacteraemia, defined as isolation of <em>S. aureus</em> in blood cultures obtained from peripheral veins or central lines on ≥ 7 consecutive days despite appropriate antibiotic administration for ≥ 5 days</td>
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<tr>
<td>Sander et al.</td>
<td>prospective cohort</td>
<td>patients with methicillin-resistant staphylococci who did not respond to vancomycin therapy and were placed on quinupristin/dalfopristin for ≥ 7 days as part of a compassionate use programme</td>
<td>12 patients total, 7 patients with MRSAB</td>
<td>(i) signs and symptoms of infections persisted or worsened or (ii) staphylococci isolates persisted</td>
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<tr>
<td>Ruggero et al.</td>
<td>case series</td>
<td>patients with refractory MRSAB with or without IE treated with telavancin</td>
<td>14 patients</td>
<td>refractory MRSAB, defined as persistent, MRSA culture-positive bloodstream infection for &gt; 72 h on appropriate antimicrobial therapy with vancomycin with a trough ≥ 10 mg/L, appropriately dosed daptomycin or sequential therapy with both medications not clearly defined</td>
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<tr>
<td>Claeys et al.</td>
<td>case series</td>
<td>patients with deep-seated MRSA infections treated with daptomycin + trimethoprim/sulfamethoxazole</td>
<td>28 patients</td>
<td>bacteraemia ≥ 7 days or disease progression on therapeutic levels of initial drugs</td>
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<tr>
<td>Fabre et al.</td>
<td>case series</td>
<td>patients who received ceftaroline-based therapy for &gt; 3 days for MRSAB IE and who did not respond to initial therapy</td>
<td>29 patients, 23/29 patients ceftaroline + trimethoprim/sulfamethoxazole</td>
<td>not clearly defined</td>
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<tr>
<td>del Rio et al.</td>
<td>prospective cohort</td>
<td>patients treated with fosfomycin + imipenem with MRSAB, including IE, needing rescue therapy due to persistent bacteraemia or relapse with vancomycin or daptomycin</td>
<td>16 patients</td>
<td>persistent bacteraemia defined as positive MRSA blood cultures for 6 days despite appropriate antibiotic therapy relapse defined as positive MRSA blood cultures within 4 weeks after the end of therapy</td>
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<tr>
<td>Study identifier</td>
<td>Definition of clinical success</td>
<td>Clinical success (%)</td>
<td>Definition of microbiological eradication</td>
<td>Microbiological eradication (%)</td>
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<td>Sakoulas et al.</td>
<td>not defined</td>
<td>20/20 (100%)</td>
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<td>Dhand et al.</td>
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<td>Kullar et al.</td>
<td>included cure and improvement</td>
<td>209/250 (83.6%)</td>
<td>negative cultures at the end of high-dose daptomycin therapy</td>
<td>175/218 (80.3%)</td>
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<td>Kullar et al.</td>
<td>included cure and improvement</td>
<td>55/64 (85.9%) clinically evaluable patients</td>
<td>negative cultures at the end of high-dose daptomycin therapy</td>
<td>57/64 (89.1%)</td>
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<td>Lai et al.</td>
<td>resolution of the signs and symptoms of attributed infections during treatment with high-dose daptomycin</td>
<td>52/67 (77.6%)</td>
<td>eradication or presumed eradication of infecting pathogens at sites of infection</td>
<td>55/67 (82.1%)</td>
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<tr>
<td>Moise et al.</td>
<td>clinical signs and symptoms were resolved and/or no additional antibiotic therapy was necessary or infection cleared with a negative culture result reported at end of therapy</td>
<td>10/19 (52.6%)</td>
<td>not defined</td>
<td>not available</td>
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<tr>
<td>Casapao et al.</td>
<td>resolution of all signs and symptoms of infection without need for escalation of antimicrobials while on ceftaroline</td>
<td>of 129 clinically evaluable S. aureus bacteraemia cases, 101 (78.3%) success</td>
<td>eradication of infecting organism</td>
<td>of 120 microbiologically evaluable S. aureus bacteraemia cases, 109 (90.8%) success</td>
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<td>Definition of microbiological eradication</td>
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<tr>
<td>Paladino et al.</td>
<td>complete resolution of all symptoms and signs of infection or a return to patient’s baseline state</td>
<td>cases: 13/16 (81.3%); controls: 7/16 (43.8%)</td>
<td>MRSA eliminated from the initial infection site during or upon completion of therapy</td>
<td>cases: 16/16 (100%); controls: 14/16 (87.5%)</td>
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<tr>
<td>Polenakovik and Pleiman</td>
<td>resolution of signs and symptoms of infection at the end of ceftarolin therapy as documented by infectious diseases physician</td>
<td>23/31 (74.2%)</td>
<td>negative blood culture for MRSA after completion of ceftarolin therapy</td>
<td>20/31 (64.5%), not all patients had microbiological cure assessed</td>
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<tr>
<td>Tattevin et al.</td>
<td>not defined</td>
<td>3/5 (60%) MRSA</td>
<td>not defined</td>
<td>1/5 (20%) MRSA</td>
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<tr>
<td>Lin et al.</td>
<td>resolution of all signs and symptoms of infection or improvement such that no further antimicrobial therapy was needed</td>
<td>6/10 (60%)</td>
<td>negative cultures after antimicrobial therapy</td>
<td>7/10 (70%)</td>
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<tr>
<td>Moise et al.</td>
<td>resolution of the baseline clinical signs and/or symptoms of infection</td>
<td>clinically evaluable: 14/20 (70%); all-treated: 14/29 (48%)</td>
<td>documented or presumed eradication of the baseline pathogen</td>
<td>microbiologically evaluable: 13/19 (68.4%); all-treated: 13/20 (65%)</td>
</tr>
<tr>
<td>Howden et al.</td>
<td>no clinical or laboratory evidence of infection after the completion of antimicrobial therapy, with the patient alive at follow-up</td>
<td>16/21 (76.2%)</td>
<td>not defined</td>
<td>not stated</td>
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<tr>
<td>Jang et al.</td>
<td>salvage success defined as if agent used was not subsequently changed due to ineffectiveness and S. aureus-related death did not occur</td>
<td>vancomycin based: 9/19 (47.4%); linezolid based: 12/16 (75%)</td>
<td>early microbiological response was defined as conversion of positive blood culture results to negative within 72 h of antibiotic initiation</td>
<td>vancomycin based: 2/12 (16.7%); linezolid based: 12/16 (75%)</td>
</tr>
<tr>
<td>Park et al.</td>
<td>salvage success defined as if agent used was not subsequently changed due to ineffectiveness and S. aureus-related death did not occur</td>
<td>linezolid based: 28/38 (73.7%); glycopeptide based: 35/52 (67.3%)</td>
<td>early microbiological success defined as negative conversion of blood cultures within 72 h of the start of salvage therapy in which rifampicin or trimethoprim/sulfamethoxazole were added to glycopeptides or glycopeptides were switched to linezolid with/without carbapenem for glycopeptide-continued patients, early microbiological response defined as negative results for follow-up blood culture within 72 h after 10 days of persistent MRSAB cultures negative for staphylococci</td>
<td>glycopeptide based: 32/52 (61.5%); linezolid based: 17/38 (44.7%)</td>
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<tr>
<td>Sander et al.</td>
<td>signs and symptoms of infection improved or resolved</td>
<td>5/7 (71.4%)</td>
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<td>5/7 (71.4%)</td>
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</table>
patients (80%) \((P=0.021)\) who received vancomycin monotherapy; combination therapy was an independent predictor of microbiological success. However, combination therapy was initiated for the treatment of possible polymicrobial infections, not specifically for the treatment of MRSAB, and thus did not constitute salvage therapy.

Barber et al.\(^\text{11}\) presented a case of a haemodialysis patient with septic subclavian thrombophlebitis who failed treatment of relapsed MRSAB with high-dose daptomycin (12 mg/kg) plus ceftaroline (400 mg every 8 h), with the daptomycin MIC increasing from 0.5 to 2 mg/L. Vancomycin was subsequently substituted for daptomycin with continuation of ceftaroline and bacteraemic clearance within 24 h. Time–kill studies demonstrated that vancomycin combined with ceftaroline was more potent than daptomycin plus ceftaroline, leading to the authors’ conclusion that in the absence of heteroresistance to vancomycin, ceftaroline combined with vancomycin rather than daptomycin may be preferred.

Recently, results from an open-label, multicentre trial from Australia supported the use of a \(\beta\)-lactam with vancomycin for MRSAB, with 60 patients randomly assigned to receive vancomycin \((n=29)\) or vancomycin plus flucloxacillin \((n=31)\). The mean duration of bacteraemia was shorter in the combination versus standard therapy group (1.94 versus 3 days), with fewer patients having persistence at days 3 and 7 in the combination arm.\(^\text{12}\)

**Daptomycin + \(\beta\)-lactam**

*In vitro* analyses have shown that \(\beta\)-lactams impact the surface charge of MRSA, enhancing daptomycin binding and resulting in synergistic killing.\(^\text{13,14}\) \(\beta\)-Lactams with PBP-1 binding (e.g. meropenem, ampicillin, nafcillin, cefepime and piperacillin/tazobactam) appear to enhance daptomycin anti-MRSA activity the most.\(^\text{15}\) Combining a second antibiotic with daptomycin *in vitro* also slows the loss of susceptibility to daptomycin.

Sakoulas et al.\(^\text{18}\) reported the results of salvage therapy in persistent (median 10 days; range 3–23 days) *S. aureus* bacteraemia with daptomycin plus ceftaroline therapy in 26 patients. The most common source of bacteraemia was IE \((n=14; \text{left-sided, } 12 \text{ patients})\) with 22 infections due to MRSA. Of these, two were vancomycin intermediate while four isolates were daptomycin non-susceptible (DNS). Upon initiation of daptomycin plus ceftaroline, bacteraemia cleared in a median of 2 days (range 1–6 days). *In vitro* analysis showed ceftaroline offered a potential dual benefit not only by its favourable interaction with daptomycin, but also by sensitization of MRSA to the innate HDP cathelicidin LL37. A recent study by Barber et al.\(^\text{19}\) confirmed this synergistic activity in an *in vitro* biofilm model, revealing that this combination displayed therapeutic enhancement against MRSA biofilms.

Single case reports and a series of seven cases indicated similar success in MRSAB salvage therapy with daptomycin combined with a \(\beta\)-lactam.\(^\text{13,20,21}\)

**High-dose daptomycin**

Daptomycin is approved by the FDA for the treatment of *S. aureus* bacteraemia and right-sided IE at 6 mg/kg/day.\(^\text{2}\) Non-susceptibility may, however, emerge when daptomycin is administered at this dose, particularly when given after vancomycin treatment failure in cases of high inoculum infections, IE and device infections.\(^\text{22}\) Daptomycin heteroresistance may occur even in the absence of
administered antibiotics, possibly due to selective pressure exerted by cationic HDPs whose mechanism of action resembles that of daptomycin presumably by cationic HDPs providing the selective pressure. Consequently, the IDSA MRSAB treatment guidelines recommend daptomycin to be dosed at 10 mg/kg/day when used as monotherapy. Moreover, the recently published 2015 European Infective Endocarditis treatment guidelines recommend daptomycin to be dosed at ≥10 mg/kg/day and combined with a second antibiotic (a β-lactam or fosfomycin) to increase activity and avoid the development of resistance.

Kullar et al. reported the results of high-dose daptomycin therapy for complicated Gram-positive infections, with 184/250 patients receiving this agent as salvage therapy after vancomycin failure. MRSA was the most common pathogen isolated (57.8%) and 54.4% were bacteremic. Ninety-one patients (36.4%) received daptomycin at ≥10 mg/kg/day. Overall, 209/250 (83.6%) patients had clinical success and the organism was eradicated in 175/218 (80.3%). There was no significant correlation between daptomycin dose (mg/kg) and the highest observed creatine phosphokinase level while receiving therapy ($r_s=0.042, P=0.63$). Similar success and safety rates were found in a study conducted by the same group evaluating high-dose daptomycin in patients with IE.

Lai et al. evaluated the use of high-dose daptomycin in patients with serious Gram-positive infections, with 63/67 (94%) patients receiving high-dose daptomycin as salvage therapy. MRSA was isolated in 56.7% patients and 80.6% patients were bacteremic. The overall clinical and microbiological success rates were 77.6% and 82.1%, respectively. Although these and other retrospective studies have shown high-dose daptomycin to be safe and efficacious in MRSAB salvage therapy, a comparator trial between high- and standard-dose daptomycin in MRSAB treatment failure is warranted.

**Ceftaroline**

Ceftaroline is distinguished from other β-lactams by its uniquely high binding affinity for PBP-2a, thus conferring its activity against MRSA. There has been increasing off-label ceftaroline use for the treatment of MRSAB including IE, particularly for salvage therapy. In the largest retrospective evaluation of patients treated with ceftaroline, clinical success was reported in 101/129 (78.3%) patients with S. aureus (92.5% MRSA) bacteremia, 92% of whom had IE. These patients were part of a larger cohort of 527 ceftaroline recipients, 80% of whom initially received another antibiotic (most commonly vancomycin), with the most frequent reason for the switch being ‘disease progression’, accounting for the change in 48% of patients. Forty-one of 527 (7.8%) patients experienced an adverse event, with renal failure being the most common. Notably, 13/76 patients (17.1%) receiving an off-label dose experienced an adverse event. The interpretation of these results with regard to the efficacy of ceftaroline as salvage monotherapy is, however, problematic since the proportion of bacteremic patients who received a combination therapy with ceftaroline is uncertain and the number of patients still bacteremic at the time of switch is unknown.

Polenakovik and Pleiman evaluated ceftaroline use in 31 patients, 9 of whom had IE (mostly right-sided). The vancomycin MIC (via microbroth dilution) for all but 2 patients was 2 mg/L and this was the primary reason for an antibiotic switch in 14 patients. Only 10 patients had bacteremia persisting for >7 days during initial therapy with vancomycin or daptomycin while another 2 had recurrent infections—these 12 constituted the potential salvage group. Microbiological cure was documented in 20 patients (64.5%) with the true rate likely greater since not all had microbial tests of cure. Clinical success was achieved in 74.2%. In the three patients who had recurrent MRSA despite ceftaroline therapy, all were related to retained prosthetic material.

Overall, these clinical data and five recently published case reports support the use of ceftaroline as an option for MRSAB salvage therapy. In contrast to salvage therapy with daptomycin, there has been no observed association of prior vancomycin exposure and ceftaroline failure. Several patients in the studies mentioned above received doses higher than the FDA-approved dose (600 mg every 12 h) with increased rates of adverse effects. Further studies are warranted to determine the safety and added benefit of this higher total daily dose. Additionally, details of a completed prospective cohort study of ceftaroline (600 mg every 8 h) including patients with persistent MRSA are expected and may further refine ceftaroline recommendations, although its non-comparative nature may preclude definitive conclusions.

**Linezolid**

Although the bacteriostatic nature of linezolid is considered by many to preclude its use in IE, the IDSA guidelines mention linezolid as among the options for MRSAB salvage therapy. In a linezolid compassionate access programme, 40 patients with MRSA who had failed (n=11) or were intolerant (n=29) to vancomycin were given linezolid. Clinical success was achieved in 18/21 (83.7%) of bacteremic patients and in 3/4 patients with IE. Linezolid therapy was continued for a median of 28 days with an adverse event leading to discontinuation in 18.3% cases.

In a study of patients with confirmed hVISA bacteraemia, 19/25 patients (76%) failed empirical vancomycin therapy and 60% (15/25) had persistent bacteremia (7–32 days). Sources of bacteremia included IE and osteomyelitis, usually in the setting of a prosthetic device. Linezolid monotherapy was prescribed as the sole salvage agent in five cases, with subsequent microbiological clearance occurring in four patients. Of the remaining 10 episodes, 7 were treated with regimens that included linezolid alone as part of sequential therapy or in combination with other agents such as rifampicin. Overall effective therapy was observed in 8/12 cases (67%). Treatment success generally occurred in those patients who also underwent surgical intervention. Several patients experienced adverse events (32%) with a median duration of linezolid therapy of 41 days (7–78 days).

Jang et al. evaluated patients who required salvage therapy for S. aureus bacteraemia persistence. Of 377 patients with S. aureus bacteraemia, 41 cases (11%) were persistent despite administration of appropriate antibiotics. Thirty-five of the 41 persistent bacteremia patients had persistence due to MRSA, with further treatment details available for 28 patients. Salvage therapy consisted of either the addition of an aminoglycoside or rifampicin to vancomycin (n=12) or vancomycin substitution with linezolid (n=16) alone (n=7) or in combination with a carbapenem (n=9). The observed vancomycin dosing would, by current standards, be considered suboptimal with trough levels <15 mg/L in approximately half the patients. Nevertheless, linezolid substitution was significantly more effective, with MRSA clearance in 75% compared with 17% with vancomycin-based therapy continuation.
(P=0.006). Thrombocytopenia developed in 7/12 (58%) evaluable patients in the linezolid group, resulting in a switch back to vancomycin in these patients. Two of these seven patients had bacteraemia recurrence and were successfully treated with readministration of linezolid.

Park et al. undertook a prospective observational study, with propensity matching, evaluating salvage therapy in patients with persistent MRSA infections, where patients were continued on a vancomycin-based regimen or linezolid was substituted for vancomycin with or without a carbapenem. Of 377 MRSA episodes, 90 (24%) were persistent, and 38 (42%) were switched to linezolid monotherapy (n=19) or together with a carbapenem (n=19) after persistence of bacteraemia for a median of 16 days (range 10–24 days). Early microbiological response and treatment success was achieved in 17 (45%) and 28 (74%) patients, respectively. Linezolid-based patients had a significantly lower 30 day mortality compared with glycopeptide-based patients (11% versus 25%; P=0.008).

Several case reports have been published using linezolid successfully in persistent MRSA cases. These data suggest that linezolid may be a viable option in salvage therapy, at least in the absence of IE; however, due to the prolonged course of therapy bacteremic patients may require, clinicians should be cautious with linezolid’s reversible myelosuppressive effects and should closely monitor patients’ complete blood counts.

**Quinupristin/dalfopristin**

Quinupristin/dalfopristin was used as salvage therapy in 12 critically ill patients who had failed vancomycin therapy. Nine patients had MRSA infections, with seven being bacteraemic. Microbiological clearance was obtained in 77% (7/9) with all persistent bacteremia patients (n=4) clearing their bloodstream. Quinupristin/dalfopristin use is generally limited even in salvage settings due to the substantial rate of adverse events and need for a central venous catheter for administration. Furthermore, resistance to macrolides–lincomycines–streptogramins mediated by ribosomal methylation (e.g. erm) that is present in most healthcare-related MRSA strains involved in persistent bacteremia renders quinupristin/dalfopristin, a bacteriostatic antibiotic, an unfavourable property in bacteremia therapy, particularly in IE.

**Telavancin**

Although lipoglycopeptides, such as telavancin, act by inhibiting cell wall biosynthesis, they also rapidly depolarize the cell membrane leading to cell death. This additional mechanism of action results in greater in vitro bactericidal activity and increased potency compared with vancomycin. These agents also retain activity against hVISA, VISA and DNS isolates. Consequently, they may be effective options since DNS isolates may arise during vancomycin failure. In a recently published case series, 14 patients received telavancin as salvage therapy. Of the 14 patients, the median duration of bacteremia prior to receiving telavancin was 12 days (range 3–26 days). Eleven of the 14 had IE as their source of bacteremia with 6 patients switched to daptomycin prior to commencing telavancin monotherapy. Ten of 14 patients became blood culture negative in a median of 1 day (1–3 days) following the initiation of telavancin, but 6 patients died, each of whom had mitral valve IE. Further studies are warranted to define the optimal role of telavancin in the treatment of MRSAB and IE.

**Trimethoprim/sulfamethoxazole**

Trimethoprim/sulfamethoxazole is a bactericidal agent with in vitro activity against MRSA. Although no studies have evaluated trimethoprim/sulfamethoxazole for MRSA salvage therapy, a recent randomized controlled study of initial therapy has cast doubts about its utility used alone in this setting since greater bacteremic persistence was observed with trimethoprim/sulfamethoxazole monotherapy compared with vancomycin.

Recent studies have examined trimethoprim/sulfamethoxazole in combination with either daptomycin or ceftolozane. Trimethoprim/sulfamethoxazole plus daptomycin exhibits potent synergy in vitro. These in vitro findings have been supported in non-comparative clinical case reports and case series, offering this combination as a viable option in MRSA salvage therapy. A recent case series evaluated the clinical outcomes of patients with MRSA including IE that failed initial therapy and were switched to trimethoprim/sulfamethoxazole plus ceftolozane. Of 29 patients, 23 received the combination therapy, with the median duration of bacteremia being 9.5 days (IQR=7–15 days) before the switch and 3 days (IQR=2–5 days) after the switch. The most common source of infection was endovascular (65%), consisting of 15 cases with IE (4 right-sided, 11 left-sided). Microbiological success was achieved in 90%, with a success rate of only 31% (due in part to ~25% patients lost to follow-up).

The dose employed in trimethoprim/sulfamethoxazole combination studies is frequently 10–15 mg/kg/day (representing the dose of trimethoprim), in two to three divided doses. While showing some promise, trimethoprim/sulfamethoxazole use does warrant an element of caution due to potential haematological adverse effects, associated hyperkalaemia and the uncertainty surrounding dosing in renal insufficiency.

**Fosfomycin**

A multicentre trial was conducted in Spain consisting of 16 patients who were treated with 2 g of fosfomycin intravenously every 6 h plus 1 g of imipenem intravenously every 6 h as salvage treatment in MRSA. All patients cleared their blood within 72 h, with a clinical success rate of 69%, and the regimen was well tolerated. Fosfomycin may be increasingly relied upon as a component of combination salvage therapy for MRSA in countries where the parenteral formulation is available. Currently, intravenous fosfomycin is not available in the USA, with only oral fosfomycin being available. Provided very low oral bioavailability, with resulting peak serum concentrations of <10 mg/L, it is unlikely that oral fosfomycin will be useful as an MRSA salvage agent.

**Future directions and conclusions**

Before considering alternative antimicrobial options, clinicians should remember: (i) source control remains critical; (ii) administered antibiotics do not exert their effect in a vacuum but within a complex host; and (iii) there is inconsistency in the definition of first-line treatment failure to identify patients who may benefit most from salvage therapy.

Although various regimens have been suggested, the optimal therapeutic approach in a patient with MRSAB failing treatment remains unknown. Adding a second agent to an initial failing regimen (e.g. adding a β-lactam to vancomycin) has not been formally
evaluated. Switching from vancomycin to another antimicrobial such as daptomycin or ceftaroline may be beneficial, but the study designs make it difficult to reach an unequivocal conclusion. Various data suggest that the daptomycin dose in this salvage setting should be 10 mg/kg/day, but no clinical studies demonstrating greater benefit from this higher versus standard dose exist. Similarly, switching to either daptomycin or ceftaroline and adding a second antibiotic (e.g., a β-lactam) may also prove beneficial, but the data to date are insufficient to make this assessment. Despite these uncertainties, a reasonable approach to the patient failing vancomycin therapy is to switch to either daptomycin or ceftaroline (assuming in vitro susceptibility) and, if bacteraemia persists, to consider adding a β-lactam antibiotic.

These uncertainties dictate the direction of necessary future investigations. We recommend a consistent definition for what constitutes clinically relevant MRSA persistence on therapy and to utilize this definition in clinical therapeutic trials. Randomized clinical trials are warranted to compare the switch from vancomycin to either daptomycin or ceftaroline with, in the case of continued MRSA persistence, a further randomization to continue therapy or to add a β-lactam antibiotic.

Transparency declarations
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Disclaimer
The views expressed here by R. K. are her own and not necessarily those of Merck & Co, Inc.

References
chemotheraphy

Methicillin-resistant S. aureus (MRSA) infections are a significant public health concern due to the increasing resistance of Staphylococcus aureus to antibiotics such as methicillin. The use of host-defense cationic peptides and daptomycin coemerge in the treatment of complicated gram-positive infections: a large, multicenter, retrospective study. *Pharmacotherapy* 2011; 31: 527–36.


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Moise PA, Forrest A, Birmingham MC et al. The efficacy and safety of linezolid as treatment for Staphylococcus aureus infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J Antimicrob Chemother* 2002; 50: 1017–26.


