

# Combination Antibiotic Treatment of Serious Methicillin-Resistant *Staphylococcus aureus* Infections

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## Abstract

Outcomes from methicillin-resistant *Staphylococcus aureus* (MRSA) infections are relatively poor, at least in part due to the limitations of vancomycin (the current standard treatment for MRSA). Combination antibiotic treatment for MRSA infections is an attractive alternative as it could address most of vancomycin's shortcomings, including poor tissue penetration, slow bacterial killing, and emerging resistance in some strains of MRSA. However, the theoretical promise of combination therapy for MRSA infections has not been borne out in most in vitro and animal studies. Multiple combinations have been tested and have been either antagonistic, indifferent, or have had conflicting findings in various studies. This includes combinations of two primarily active agents (such as vancomycin plus daptomycin or linezolid), or the addition of gentamicin or rifampin to either vancomycin or daptomycin. However, hope on this front has come from an unexpected quarter. Although MRSA is by definition inherently resistant to nearly all  $\beta$ -lactam antibiotics, this class of drugs has consistently shown evidence of synergy with either daptomycin or vancomycin in over 25 separate in vitro studies, and a limited number of animal and human observational studies. However, there are currently insufficient data to recommend  $\beta$ -lactam combination therapy in routine clinical use. Results of current and planned randomized controlled trials of this strategy are awaited.

## Keywords

- ▶ methicillin-resistant *Staphylococcus aureus*
- ▶ combination antibiotic therapy
- ▶ vancomycin
- ▶ daptomycin

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common antibiotic-resistant human pathogen, with an estimated 1,650 cases of blood stream infection and 500 deaths annually in Australia,<sup>1</sup> 11,000 deaths annually in the United States,<sup>2</sup> and an annual excess cost to Europe's health care system of €380m.<sup>3</sup> MRSA bacteremia has a mortality of 20 to 30%, exceeding that of methicillin-sensitive *S. aureus* (MSSA) at least in part due to the shortcomings of vanco-

mycin, the standard therapy for MRSA bacteremia. Vancomycin still remains the principal agent of choice in the treatment of MRSA.<sup>4</sup> However, multiple shortcomings of glycopeptide monotherapy have been recognized and include poor tissue penetration, slow bactericidal effect, and emergence of resistance during therapy. Combination therapy may theoretically overcome some of these deficiencies.

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Consequently, when exploring therapeutic combinations, the addition of a second agent is usually directed to address one or more of the above vancomycin deficiencies: to broaden the spectrum of activity (to include resistant isolates such as heteroresistant vancomycin intermediate *S. aureus* [hVISA]) and increase the bacteriocidal activity of vancomycin through synergy. Other potential benefits of adding antibiotics include enhancing treatment by providing better tissue or biofilm penetration and reducing toxin production especially in toxin-mediated infections. The alternative to combination therapy is to find a better agent than vancomycin. Several agents with useful activity against MRSA have reached the market in recent years, including daptomycin, linezolid, tigecycline, and quinupristin/dalfopristin. However, none of these agents has been shown to be superior to vancomycin, with clinical trials showing daptomycin is noninferior for *S. aureus* bacteremia (SAB) and endocarditis<sup>5</sup> and linezolid noninferior for *S. aureus* catheter-related blood stream infection,<sup>6</sup> and although linezolid achieved improved clinical cure for MRSA pneumonia, it did not result in reduced mortality.<sup>7</sup> Hence, combination therapy is an attractive possibility for improving outcomes from severe MRSA infections.

Most data on combination therapy come from in vitro experiments. These have three possible outcomes: synergy (increased bacteriocidal activity in excess of the additive actions of the two drugs), antagonism, and indifference. The most common in vitro methods used to measure synergy (in increasing order of complexity) are agar diffusion, checkerboard testing, time-kill curves, and simulated pharmacodynamic (PD) models. Agar diffusion methods use combinations of antibiotics either as antibiotic discs or Etest strips (Biomerieux, Paris, France; paper strips of graduated antibiotic concentration), allowing them to diffuse through the agar, and qualitatively examines bacterial growth in different zones of the agar. For example, two Etest strips (one for each antibiotic) can be placed at right angles on the agar plate, and bacterial growth examined near the intersection (where the combination concentration is highest) compared with the outer quadrants. Checkerboard testing uses multiple different dilutions of antibiotic combinations set out on an agar plate as a grid, ranging from below to above the minimum inhibitory concentration (MIC) for each agent. This allows a quantitative estimate of synergy and results are reported as a fractional inhibitory concentration (FIC). An FIC of  $\leq 0.5$  indicates synergy,  $\geq 2.0$  antagonism, and an FIC between these values indicates indifference. Time-kill methodology is dynamic rather than examining synergy at a single time point and thus is more likely to correlate with clinical use. Bacteria are cultured in liquid media in the presence of various concentrations of either single or combination antibiotics, and the speed of bacterial killing is quantified over time. In time-kill studies, synergy is defined as a reduction in  $\geq 2$  log colony forming units (cfu) of bacteria/mL compared with the cfu/mL of the most potent single drug. Finally, in vitro pharmacokinetic (PK)/PD models attempt to simulate antibiotic dosing within a human or animal host. An example is the fibrin clot model, where an ex vivo human blood clot is seeded with bacteria and exposed to dynamic concentrations of antibiotic, simulating a usual dosing interval.

## Combinations of Two Primarily Active Agents

### Vancomycin and Linezolid

Linezolid is an oxazolidinone, a new class of antibiotic with a mechanism of action directed at the early steps of protein synthesis. Its introduction into clinical medicine heralded the first new antibiotic with activity against MRSA since the introduction of vancomycin.

Linezolid and vancomycin combination therapy are reported to demonstrate indifference using checkerboard assays,<sup>8</sup> but synergy with time-kill assays.<sup>9</sup> Other studies, using similar methodology, were unable to demonstrate synergy but observed antagonism<sup>10,11</sup> or indifference.<sup>12</sup> Subsequent animal data have similarly been conflicting with an experimental rabbit endocarditis model,<sup>13</sup> observing some effect with the addition of linezolid, while a rat MSSA osteomyelitis model<sup>14</sup> showed indifference with no additional sterilization or cure rates compared with vancomycin alone. The inconsistency of these results suggests that there are a variety of mechanisms involved in determining antibiotic interactions, which may include the infecting bacterial strain, infection site, and host responses. Thus, this combination should be used with caution as the described antagonism may lead to suboptimal outcomes.

Nevertheless, this combination is still considered in toxin-mediated infections, as subinhibitory concentrations of linezolid inhibit *S. aureus* toxin production.<sup>15,16</sup> This modulation of virulence factors through reduced pathogen toxin synthesis may theoretically attenuate disease and influence outcomes. This hypothesis has not been shown in vivo to be effective, with no animal model data available. Although a single case report has been published showing the effectiveness of linezolid in the treatment of MSSA toxic shock syndrome,<sup>17</sup> no comparative data of the combination of linezolid with vancomycin in toxin-mediated clinical syndromes has been published.

### Vancomycin and Daptomycin

Daptomycin is a lipopeptide, which acts on the cell membrane through a complex process resulting in cell membrane depolarization and permeabilization, ion leakage, and ultimately cell death.<sup>18</sup> There is a paucity of in vitro and in vivo data for this combination due to concerns about the relationship between reduced vancomycin susceptibility and daptomycin nonsusceptibility.<sup>19</sup> This cross-resistance was first documented in vitro when a collection of VISA isolates underwent susceptibility testing and 80% were found to be daptomycin nonsusceptible, despite these isolates not having been exposed to daptomycin.<sup>20</sup> This association was later confirmed by serial passage studies, with all *S. aureus* isolates developing daptomycin nonsusceptibility in the presence of vancomycin.<sup>21</sup> Subsequently, several clinical cases have described the same phenomenon.<sup>22</sup> Although the precise mechanism remains unclear, experts speculate that increased cell wall thickness, as occurs in VISA, may also prevent daptomycin penetration to its site of action.<sup>23,24</sup>

Nevertheless, Tsuji and Rybak performed Etest synergy testing and time-kill experiments on one vancomycin heteroresistant and one vancomycin intermediate clinical *S. aureus* isolate. There was moderate agreement between the two methodologies with vancomycin/daptomycin combination showing either indifference or an additive effect (but not synergy).<sup>25</sup> This combination, albeit with the addition of rifampin, has been used in one published report of two cases. Both patients had orthopedic infections that relapsed after initial vancomycin/rifampin therapy and were cured with several weeks of triple therapy.<sup>26</sup> As both patients also underwent surgical debridement and prosthesis removal, the effectiveness of daptomycin/vancomycin remains unknown, but based on the above concerns, this combination is unlikely to be successful in most cases.

### Vancomycin and Tetracyclines including Tigecycline

hVISA was first isolated in Japan in the 1990s.<sup>27</sup> Given the lack of treatment options against hVISA, combination therapy was studied. Time-kill experiments using the Mu3 strain, the first recognized hVISA isolate, revealed antagonism when using minocycline/vancomycin in combination. The authors went on to examine possible bacterial changes that may result in this antagonism and found that cell wall thickening did not play a major role.

Tigecycline is a semisynthetic derivative of minocycline and is the first glycylycine antibiotic licensed for clinical use.<sup>28</sup> It offered great promise as a new agent with a broad spectrum of activity against gram-negative and -positive bacteria, including multiresistant organisms. However, postmarketing experience has resulted in more selective indications, as it is associated with increased mortality when used in certain clinical settings.<sup>29</sup> Nevertheless, given its spectrum of activity, using it in combination with vancomycin remains an attractive option. Mercier et al performed time-kill studies and found vancomycin and tigecycline to be indifferent when used with four MRSA (three of which were VISA) isolates.<sup>30</sup> Petersen et al obtained similar results using checkerboard and time-kill experiments on 10 *S. aureus* isolates.<sup>31</sup> There have been few experimental animal studies evaluating tigecycline combinations.<sup>28</sup> A rabbit osteomyelitis model found no difference between combination therapy compared with vancomycin or tigecycline monotherapy.<sup>32</sup> Similarly, no difference was observed in bactericidal activity in a biofilm model for this combination.<sup>33</sup>

The main conclusion from the available data is that there is no benefit with tetracycline and vancomycin combinations. Unless tigecycline is required for a coexistent multiresistant gram-negative infection, combination with vancomycin is not recommended for the treatment of MRSA infections.

### Daptomycin and Tigecycline

Time-kill and Etest experiments demonstrated an indifferent effect when using this combination.<sup>25</sup> These results are in contrast to a subsequent study, which showed this combination to be synergistic based on time-kill studies and checkerboard titration assays using 10 *S. aureus* isolates.<sup>34</sup> To corroborate their results, the authors went on to perform an animal surgical site infection model. Tigecycline/daptomycin still showed synergy.<sup>34</sup>

No clinical data are available. The role of tigecycline is likely to be limited as discussed previously and thus further studies are unlikely to occur with this combination.

### Daptomycin and Linezolid

The impact of biofilm-associated infection remains significant especially in light of the aging population and increased joint replacements undertaken. Linezolid/daptomycin combination was studied by Parra-Ruiz et al in their validated in vitro PK/PD biofilm formation model.<sup>35</sup> This study observed that linezolid/daptomycin combination therapy showed better efficacy than either agent alone and confirmed the results of one previous study using a simulated endocardial vegetation model.<sup>36</sup> Although a single published case report showed clinical benefit, this occurred in the setting of triple therapy with daptomycin, linezolid, and rifampin.<sup>37</sup> Thus, the benefit of this combination is unclear especially as checkerboard and time-kill experiments showed antagonism.

### Vancomycin and Quinupristin–Dalfopristin

Quinupristin–dalfopristin is an injectable streptogramin antibiotic with in vitro activity against MRSA. The combination of quinupristin–dalfopristin with vancomycin has resulted in mixed results<sup>38</sup> with studies demonstrating both antagonism<sup>39</sup> and synergy.<sup>40–43</sup> There remain very limited published clinical data to guide the use of this combination.<sup>44,45</sup> Given that quinupristin–dalfopristin is not recommended for MRSA bacteremia due to reports of treatment failures and emergent resistance, and there are no published original studies since 2002 on the combination of quinupristin–dalfopristin with vancomycin, it is unlikely to be further advanced as a clinical treatment option.

### β-Lactam Combination Therapy

Empirical therapy for SAB often includes both vancomycin and antistaphylococcal penicillin such as nafcillin. This is not only because incorrect initial empiric therapy for MRSA bacteremia is associated with a twofold increase in mortality<sup>46</sup> but also because vancomycin monotherapy for MSSA infections is associated with higher rates of hospitalization,<sup>47</sup> treatment failure,<sup>48</sup> and mortality<sup>49,50</sup> compared with β-lactam therapy (e.g., with nafcillin or ceftazolin). Given the increasing prevalence of community-acquired MRSA infection,<sup>51–53</sup> β-lactam combination therapy is often used in patients with positive blood cultures where the Gram stain shows clustered gram-positive cocci for the first 24 to 48 hours of therapy, but before identification and susceptibility profile of the organism has been determined. Hence a potentially synergistic combination is unwittingly being increasingly used in the subset that turn out to have MRSA infection. Considering the very definition of MRSA is that it is resistant to antistaphylococcal penicillins, it is counter-intuitive to hypothesize that β-lactams might have any benefit when added to standard therapy for MRSA infections. However, unexpected synergy between β-lactams and both vancomycin and daptomycin has been found to occur in vitro, initially only in VISA and hVISA strains, and then more broadly in MRSA.

## Vancomycin/ $\beta$ -Lactam Combinations

### In Vitro Studies

At least 16 in vitro studies have explored synergy between vancomycin and  $\beta$ -lactams against MRSA isolates,<sup>54-69</sup> all but one of which found evidence of synergy in some or all of the tested strains (**Table 1**). These studies varied in their methodology (checkerboard synergy testing or time-kill curves), types of strains tested (MRSA vs. hVISA vs. VISA) and the  $\beta$ -lactams used, but a consistent finding across nearly all the studies was synergistic bacterial killing in *most* but not *all* strains tested. There are no consistent characteristics in these reports in the strains where synergy was not demonstrated. However, there was a general tendency across these studies (and *within* some studies<sup>56,66</sup>) to an increasing degree of synergy with increasing vancomycin MICs. The one study that did not demonstrate synergy did not actually include any MRSA isolates. In this study, Joukhadar et al tested 10 clinical isolates of methicillin sensitive *S. aureus* and found evidence of neither synergy nor antagonism in any strain, both using fixed drug concentrations, and in a dynamic model simulating clinical dosing.<sup>62</sup>

### Animal Studies

The few studies that have assessed combinations of vancomycin with  $\beta$ -lactams in animal models have all found evidence of synergy.<sup>56,61,65</sup> Climo et al found faster sterilization of infection with vancomycin plus nafcillin in MRSA rabbit endocarditis and renal abscess models.<sup>56</sup> Ribes et al tested various combinations of linezolid, vancomycin, and imipenem in a murine peritonitis VISA model using time-kill curves, and found faster bacterial killing with vancomycin plus imipenem compared with vancomycin alone, in both strains tested.<sup>61</sup> Finally, Fernandez et al investigated the anti-MRSA cephalosporin ceftobiprole against an MRSA and a VISA strain in a rat endocarditis model. They found good activity of ceftobiprole against both strains in terms of sterilizing vegetations and preventing mortality; the combination of vancomycin plus ceftobiprole led to faster killing on time-kill curves, but similar rates of mortality and of sterilization of vegetations compared with ceftobiprole alone.<sup>65</sup>

### Human Studies

There are currently no published prospective controlled trials of vancomycin/ $\beta$ -lactam combination therapy in patients with MRSA bacteremia, but one observational study has recently been published.<sup>67</sup> In this single-center retrospective cohort study, Dilworth et al described the outcomes of 50 patients with MRSA bacteremia who received combination therapy with vancomycin and at least 24 hours of  $\beta$ -lactam (at their clinicians' discretion), and compared them with 30 patients treated at the same hospital, during the same time period with vancomycin alone. They found a higher rate of microbiological eradication in the combination therapy group (96 vs. 80%,  $p = 0.02$ ), which persisted on a multivariate model attempting to control for potential confounders (adjusted odds ratio for achieving microbiological eradication in the combination group = 11.24,  $p = 0.01$ ).

## Daptomycin/ $\beta$ -Lactam Combinations

### In Vitro Studies

At least 10 in vitro studies have examined the combination of daptomycin with various  $\beta$ -lactams against MRSA and VISA strains (**Table 2**).<sup>25,70-79</sup> The findings of these studies are remarkably similar to the vancomycin/ $\beta$ -lactam synergy articles cited earlier: synergy for most but not all strains tested, and an increasing degree of synergy with increasing MICs to both vancomycin and daptomycin. No studies have found evidence of antagonism with this combination.

### Animal Studies

A recently published animal study mirrored the findings of the in vitro studies. Garrigós et al used a rat tissue cage model of MRSA infection to study the combination of daptomycin with cloxacillin, and found superior cure rates with the combination than with daptomycin alone.<sup>80</sup>

### Human Studies

As for the vancomycin/ $\beta$ -lactam combination, there are no clinical trials of daptomycin with  $\beta$ -lactams either published or in trials registries. However, limited observational data suggest this combination may be effective, particularly MRSA with poor response to daptomycin. In a case series of seven patients with persistent MRSA bacteremia for more than 1 week despite high-dose daptomycin, all cleared their bacteremia within 48 hours once nafcillin or oxacillin was added to their therapy.<sup>81</sup> In a second case series of 22 patients with persistent MRSA bacteremia despite daptomycin for a median of 10 days, the addition of ceftaroline led to clearance of bacteremia in all cases, in a median of 2 days.<sup>82</sup>

### Summary

Although the studies on  $\beta$ -lactam combination therapy are heterogeneous, there are some consistent findings (with either vancomycin or daptomycin as the companion agent): adding a  $\beta$ -lactam leads to synergistic bacterial killing in the majority of strains tested and in all animal models tested. The most consistent data come from more resistant strains and from antistaphylococcal penicillins or ceftaroline rather than other  $\beta$ -lactams.  $\beta$ -lactam combination therapy (with either vancomycin or daptomycin) is not recommended in Infectious Diseases Society of America (IDSA) or other guidelines at this stage, but the emerging data are intriguing, and at least one phase 2b randomized controlled trial (RCT) of this strategy is underway (Australia and New Zealand Clinical Trials Registry number ACTRN12610000940077). A key question that emerges from these data is: what is the mechanism of the observed synergy? The mechanisms have not been entirely elucidated, but are becoming clearer over time. Increasing vancomycin resistance in *S. aureus* is paradoxically associated with decreasing MICs to oxacillin, and this so-called "see-saw effect"<sup>68,83</sup> is at least in part due to alteration of the *MecA* gene in some strains of VISA and vancomycin resistant *Staphylococcus aureus* (VRSA),<sup>84,85</sup> and possibly to other structural changes in penicillin-binding proteins.  $\beta$ -lactams have been shown to enhance binding of daptomycin to the bacterial cell wall.<sup>79</sup> Finally, Sakoulas et al recently

**Table 1** In-vitro and animal studies investigating synergy between vancomycin and beta-lactams against MRSA

Author (y)	Setting	Organism	Base antibiotic(s)	Beta-lactam(s)	Finding	Comments
Seibert et al (1992) <sup>54</sup>	In vitro	MRSA	Vancomycin	Cefiprome Cefoperazone Ceftazidime	Synergy with cefiprome/Vancomycin and cefoperazone/Vancomycin but not ceftazidime/Vancomycin	Synergy with "most" MRSA strains
Palmer and Rybak (1997) <sup>55</sup>	In vitro	MRSA	Vancomycin	Pip-Tazo Imipenem Nafcillin	Synergy with Vancomycin/Imipenem and Vancomycin/Nafcillin, for hVISA but not VISA	Time-kill studies in infected fibrin clots
Climo et al (1999) <sup>56</sup>	In vitro Rabbit endocarditis model Rabbit renal abscess model	MRSA MRCNS	Vancomycin	Oxacillin Ceftriaxone Ceftazidime Amoxy-clav	In vitro synergy for all combinations In vivo only nafcillin tested—synergy for sterilizing vegetations and renal abscesses	Synergy was proportional to Vancomycin MIC
Lozniewski et al (2001) <sup>57</sup>	In vitro	MSSA MRSA	Vancomycin	Cefepime	Synergy in 3/10 MRSA by checkerboard, and 3/3 and 2/3 MRSA by time-kill assays	
Domaracki et al (2000) <sup>58</sup>	In vitro	MRSA MRCNS	Vancomycin	Oxacillin	Synergy in 14/21 strains	Sub-MIC concentrations of Vancomycin
Drago et al (2007) <sup>59</sup>	In vitro	MRSA	Vancomycin Teicoplanin	Cefotaxime Cefepime Imipenem Pip-Tazo	Vancomycin + Cefotaxime synergistic in 43/50 strains	
Kobayashi (2005) <sup>60</sup>	In vitro	MRSA	Vancomycin Teicoplanin	Various carbapenems	Synergy in 25/27 of MRSA strains with Vancomycin, 20/27 with Teico	
Ribes et al (2010) <sup>61</sup>	In vitro Murine peritonitis model	hVISA VISA	Vancomycin Linezolid	Imipenem	Linezolid plus imipenem most effective Combo in vivo	Linezolid plus Vancomycin antagonistic
Joukhadar et al (2010) <sup>62</sup>	In vitro	MSSA	Vancomycin	Oxacillin	Indifference	Note not MRSA
Silva et al (2011) <sup>63</sup>	In vitro	MRSA MRCNS	Vancomycin	Imipenem	Synergy in 21/22 strains	
Hagihara et al (2012) <sup>64</sup>	In vitro	MRSA hVISA VISA	Vancomycin	Cefazolin	Synergy for all strains	In vitro PK/PD model
Fernandez (2012) <sup>65</sup>	Rat endocarditis model	MRSA VISA	Vancomycin	Ceftobiprole	Synergy for Vancomycin + ceftobiprole	
Leonard (2012) <sup>66</sup>	In vitro	hVISA MRSA MSSA	Vancomycin	Nafcillin	23/25 h VISA strains synergy. Also against MRSA and MSSA, but least effect against MSSA	5 strains had PK/PD simulations—also demonstrated synergy

(Continued)

Table 1 (Continued)

Author (y)	Setting	Organism	Base antibiotic(s)	Beta-lactam(s)	Finding	Comments
Werth et al (2013) <sup>68</sup>	In vitro PK-PD model	hVISA Daptomycin R VISA	Daptomycin Vancomycin	Ceftaroline	Daptomycin + ceftaroline synergistic against both strains; Vancomycin plus ceftaroline only against the daptomycin S strain	
Werth et al (2013) <sup>69</sup>	In vitro	VISA hVISA	Vancomycin	Ceftaroline Oxacillin	Vancomycin/Oxa synergy in 3/5 VISA. Vancomycin/ceftaroline in 5/5 VISA	Inverse correlation between Vancomycin and $\beta$ -lactam susceptibility
Dilworth et al (2014) <sup>67</sup>	In vitro	MRSA VISA	Vancomycin	Pip-Tazo Oxacillin	Synergy in all strains for both oxa and Pip-Tazo	

Abbreviations: (h)VISA, (heteroresistant) vancomycin intermediate *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase negative *Staphylococcus*; Pip-Tazo, piperacillin-tazobactam; PK-PD, pharmacokinetic/pharmacodynamic.

reported exciting data derived from ex vivo study of human blood which adds another potential advantage for the use of  $\beta$ -lactams for MRSA—they lead to increased activity of innate host defense peptides such as cathelicidin LL-37,<sup>86</sup> which in turn allows more efficient bacterial killing.

## Other Combination Therapy

### Rifampin

#### Vancomycin/Rifampin

Rifampin is attractive as an adjunctive agent as it is bactericidal,<sup>87</sup> has activity against cells in stationary growth phase,<sup>88</sup> and is better able to penetrate cells,<sup>89,90</sup> tissues, and biofilms<sup>91,92</sup> than vancomycin.<sup>93,94</sup> However, most in vitro studies demonstrate either antagonism or indifference for the combination of rifampin with vancomycin.<sup>25,87,95–102</sup> There is some in vitro evidence of synergy in the presence of biofilm production<sup>33,103</sup> and in animal models of osteomyelitis<sup>96,104</sup> or foreign body infections.<sup>101,105,106</sup> Bayer and Lam found in a rabbit MRSA endocarditis model that the combination of vancomycin and rifampin improved valvular sterilization and overall cure.<sup>107</sup> However, these findings have not been replicated in other animal endocarditis models.<sup>108,109</sup> A systematic review of in vitro and animal experiments specifically addressing the benefit of adding rifampin to other antibiotics for *S. aureus* infections concluded that the effect of rifampin therapy was often inconsistent and method dependent.<sup>92</sup>

Clinical studies to date have not provided evidence in support of the combination of vancomycin with rifampin for severe MRSA infections. Levine et al randomized 42 patients with MRSA endocarditis to vancomycin or vancomycin plus rifampin.<sup>110</sup> The median duration of bacteremia was longer in the combination arm (9 vs. 7 days) and rates of treatment failure were similar. Similarly, Riedel et al determined in a retrospective cohort of 84 patients with *S. aureus* native valve infective endocarditis (IE) that the addition of rifampin was associated with longer duration of bacteremia and increased mortality compared with controls.<sup>111</sup> There was also a higher incidence of hepatotoxicity and significant drug–drug interactions for patients receiving rifampin.<sup>112</sup> Jung et al conducted a RCT in patients with MRSA nosocomial pneumonia.<sup>112</sup> Clinical cure at day 14 was achieved in 54% (22 of 41) of patients in the vancomycin plus rifampin arm compared with 31% (13 of 42) in the vancomycin alone arm ( $p = 0.047$ ). Although these data are promising, the study was unblinded and single center, and vancomycin dosing (1 g q12h) was lower than current recommendations. Based on the Levine et al<sup>110</sup> and Riedel et al<sup>111</sup> studies, the IDSA MRSA treatment guidelines recommend *against* the addition of rifampin to vancomycin for MRSA bacteremia or native valve IE (level A-I; good evidence, at least one properly RCT).<sup>4</sup>

Nonetheless, Thwaites et al have cogently argued that equipoise exists for the addition of rifampin to standard therapy for SAB and a RCT comparing standard therapy to standard therapy plus adjunctive rifampin for SAB in the United Kingdom is currently being conducted (the adjunctive rifampin to reduce early mortality from *Staphylococcus*

**Table 2** In-vitro and animal studies investigating synergy between daptomycin and beta-lactams against MRSA

Author (y)	Setting	Organism	Base antibiotic(s)	β-lactam(s)	Finding	Comments
Silva et al (1988) <sup>71</sup>	In vitro	MRSA Enterococci Peptococci	Daptomycin	Aztreonam Ceftriaxone	Synergy against all MRSA strains tested	Time-kill curves
Rand and Houck (2004) <sup>72</sup>	In vitro	MRSA (18 strains)	Daptomycin	Oxacillin Amp-Sul Tic-Clav Pip-Tazo	All combinations synergistic	Sub-MICs of daptomycin
Snydman et al (2005) <sup>70</sup>	In vitro	MRSA MSSA VRE	Daptomycin	Oxacillin Ceftriaxone Cefepime Imipenem	Indifference of all combinations for MSSA Synergy in 7/10 MRSA isolates	
Cilli et al (2006) <sup>74</sup>	In vitro	VRE MRSA MRSE	Daptomycin	Amp-Sul Tic-Clav Pip-Tazo	Synergy in > 70% of MRSA strains	
Tsuji and Rybak (2006) <sup>25</sup>	In vitro	hVISA (2 strains)	Daptomycin Vancomycin	Ampicillin-Sulbactam	Synergy with Vancomycin/AS but indifference with daptomycin/AS	Etest and time kill
Mehta et al (2012) <sup>73</sup>	In vitro	MRSA (Dap S and Dap R)	Daptomycin	Nafcillin Cefotaxime Amoxy-Clav Imipenem	Synergy with all blac combinations, esp oxacillin	
Garrigós et al (2012) <sup>80</sup>	Animal model	MRSA	Daptomycin	Cloxacillin	Combo better cure rates, but only mildly. Daptomycin-Rif was better	Rat tissue cage model (foreign body infection)
Rose et al (2012) <sup>77</sup>	Case report In vitro PK/PD model	DNS MRSA	Daptomycin	Ceftaroline	Synergy	
Werth et al (2013) <sup>69</sup>	In vitro	hVISA DNS hVISA	Daptomycin Vancomycin	Ceftaroline	Combination synergistic for both strains with daptomycin, for one strain with Vancomycin	Time-kill curves
Leonard and Rolek (2013) <sup>76</sup>	In vitro	VISA	Daptomycin	Nafcillin	Synergy in 11/20	Increasing synergy with increasing daptomycin MIC
Werth et al (2014) <sup>78</sup>	In vitro PK-PD model	hVISA Daptomycin R VISA	Daptomycin Vancomycin	Ceftaroline	Daptomycin + ceftaroline synergistic against both strains; Vancomycin plus ceftaroline only against the daptomycin S strain	
Barber et al (2014) <sup>75</sup>	In vitro	MRSA (20 isolates)	Daptomycin	Ceftobiprole	Dapto plus ceftobiprole synergistic in all isolates	Time-kill curves

Abbreviations: (h)VISA, (heteroresistant) vancomycin intermediate *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase negative *Staphylococcus*; Pip-Tazo, piperacillin-tazobactam; PK-PD, pharmacokinetic/pharmacodynamic; DNS, Daptomycin non susceptible.

aureus bacteraemia [ARREST] study).<sup>113</sup> In a review of four previously published RCTs,<sup>110,112,114,115</sup> Thwaites et al determined that adjunctive rifampin for serious staphylococcal infections was associated with a reduction in infection-related deaths by 55% ( $p = 0.02$ ).<sup>113</sup> Notably, two of these studies principally focused on MSSA infections treated with oxacillin,<sup>114,115</sup> and the combined findings in this systematic review probably do not apply to MRSA and vancomycin therapy. In the ARREST trial, MRSA bacteremia is not a prespecified subgroup. Thus, despite this being the largest planned RCT for SAB to date, the study may be underpowered to make specific conclusions regarding the MRSA subgroup, particularly as reductions in numbers of MRSA bacteremia in the United Kingdom may result in MRSA bacteremia being a minority of infections.<sup>116</sup>

There is stronger but still inconclusive evidence for the use of adjunctive rifampin for prosthetic joint infections (PJIs), where biofilm assumes a critical importance. For example, Peel et al<sup>117</sup> and Aboltins et al<sup>118</sup> have reported on successful outcomes with debridement and retention of carefully selected patients with PJI prescribed prolonged courses of rifampin and fusidic acid. However, these studies suffer from their retrospective and observational nature, a limited number of patients with MRSA ( $n = 39$ ), and notably MRSA infection (compared with coagulase negative staphylococci) remained an independent risk factor for treatment failure.<sup>117</sup> The combination of a fluoroquinolone with rifampin has also been demonstrated to be effective in treating selected PJIs with a debridement and retention approach in both a small RCT<sup>119</sup> and several retrospective cohort studies.<sup>120–122</sup> However, the RCT reported by Zimmerli et al<sup>119</sup> only included 15 PJI patients, included a relatively ineffective control arm (ciprofloxacin monotherapy), and when reanalyzed by intention to treat found no significant difference between the rifampicin and nonrifampicin containing arms. Somewhat controversially,<sup>123</sup> based largely on this single RCT, the 2013 IDSA guidelines recommend that rifampin be added to initial parenteral therapy for MRSA PJI, followed by prolonged combination oral therapy with rifampin with a companion agent such as a fluoroquinolone.<sup>124</sup>

### Daptomycin/Rifampin

In vitro and animal studies demonstrate an overall pattern of either antagonism or indifference with the addition of rifampin to daptomycin. For example, in an in vitro IE model, the combination of daptomycin with either rifampin or gentamicin antagonized or delayed the bactericidal activity of daptomycin alone.<sup>125</sup> Similarly, in time-kill experiments and a rabbit endocarditis model, the combination of daptomycin and either rifampin or gentamicin demonstrated no enhancement of the effectiveness of daptomycin against MRSA compared with daptomycin alone.<sup>126</sup> There are currently only case reports or small case series of clinical studies involving the combination of daptomycin and rifampin.<sup>127–129</sup>

### Gentamicin

#### Vancomycin/Gentamicin

Several studies have demonstrated a consistent in vitro synergism between aminoglycosides and vancomycin.<sup>130,131</sup>

However, clinical studies do not support the addition of an aminoglycoside to vancomycin. In a retrospective evaluation of 87 patients with persistent SAB, 48 of whom had MRSA infection, those treated with an aminoglycoside had lower incidence of recurrence within 6 months, but there was no significant association with mortality or other outcomes.<sup>132</sup> In analyzing data from the daptomycin registrational RCT,<sup>5</sup> Cosgrove et al found that 27/122 (22%) of patients who received initial low-dose gentamicin therapy (in combination with either nafcillin or vancomycin) experienced a clinically significant decline in renal function, compared with 8/100 (8%) of those who did not receive gentamicin.<sup>133</sup> Based on these clinical studies, the IDSA recommends that gentamicin should not be added to vancomycin for the treatment of MRSA bacteremia or native valve endocarditis.<sup>4</sup>

### Daptomycin/Gentamicin

The combination of daptomycin with gentamicin has been tested in vitro with varying results; synergy has been demonstrated in some studies,<sup>70,134–136</sup> but not in others.<sup>25,125,126,137–140</sup> Unfortunately, a RCT comparing daptomycin to daptomycin combined with gentamicin was terminated early after recruiting only 24 patients (Clinical trials NCT00638157). Thus, the combination of daptomycin with gentamicin cannot be recommended at this stage.

### Other Combinations

Daptomycin-nonsusceptible *S. aureus* (DNS) not infrequently emerges during daptomycin therapy.<sup>5,141</sup> Among agents tested in combination with daptomycin, trimethoprim-sulfamethoxazole has shown promise in a PK/PD model for the treatment of DNS.<sup>36,142</sup> Although clinical experience is currently limited<sup>143,144</sup> for DNS infections that are refractory to standard treatment, the combination with trimethoprim-sulfamethoxazole should be considered.

In vitro studies have determined that subinhibitory concentrations of clindamycin, linezolid, and rifampin can block production of toxins such as Pantone-Valentine leukocidin and  $\alpha$ -toxin by *S. aureus*.<sup>145–147</sup> Clinical experience of the use of these agents in severe toxin-mediated staphylococcal infections (e.g., toxic shock syndrome or necrotizing pneumonia) is limited.<sup>148</sup> Two retrospective studies suggest that there may be a clinical benefit for suppression of toxins in such cases.<sup>149,150</sup> Treatment guidelines from the United Kingdom and France recommend that antitoxin therapy be instituted where toxin-mediated staphylococcal disease is suspected or apparent<sup>151,152</sup> and in the absence of robust evidence for the treatment of these life-threatening infections, these recommendations are clearly sensible.

Studies of combination therapy for MRSA involving novel antibiotics are also beginning to emerge. In a small number of clinical MRSA isolates tested in vitro (five VISA and five hVISA), oritavancin (a novel lipoglycopeptide antibiotic) appears to be synergistic when used in combination with either gentamicin, linezolid or rifampin,<sup>153</sup> as does telavancin (a second novel lipoglycopeptide antibiotic), when used with gentamicin, ceftriaxone, rifampin, or meropenem.<sup>154</sup> Since only these two drugs became Food and Drug



Administration approved in 2014, and are not approved for treatment of MRSA bacteremia, clinical experience is limited and the implications of these in vitro studies are unclear at this stage. Despite its lack of activity as a single agent against MRSA, fosfomycin appears to be synergistic with linezolid against clinical MRSA isolates in an in vitro model<sup>155</sup> mirroring the  $\beta$ -lactam concept, where a seemingly inactive agent makes an important contribution when combined with an active agent.

## Conclusion

Because of the limitations of vancomycin, the standard therapy for serious MRSA infections, many combinations of antibiotics have been tested, primarily in in vitro models. Unfortunately, studies of the majority of these combinations have reported mixed or negative data. However, several  $\beta$ -lactam antibiotics have consistently been shown to be synergistic for the majority of MRSA strains (including hVISA and daptomycin nonsusceptible strains), when combined with either vancomycin or daptomycin. Although these combinations appear promising, limited clinical data are available, and clinical trials are only just beginning to be performed. Currently, there is insufficient evidence to recommend any combination therapy for serious MRSA infections in actual patient care.

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