Daptomycin in Combination With Other Antibiotics for the Treatment of Complicated Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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ABSTRACT

Purpose: Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as one of the most important nosocomial pathogens. Resistance to antibiotic therapy has been known to emerge especially in clinically complex scenarios, resulting in challenges in determining optimal treatment of serious MRSA. Daptomycin, in combination with other antibiotics, has been successfully used in the treatment of these infections, with the aims of resulting in reducing the prevention of antimicrobial resistance and increased killing compared with daptomycin monotherapy.

Methods: This article reviews all the published studies that used daptomycin combination therapy for the treatment of bacteremia and associated complicated infections caused by gram-positive organisms, including MRSA. We discuss the rationale of combination antibiotics and the mechanisms that enhance the activity of daptomycin, with special focus on the role of β-lactam antibiotics.

Findings: There are limited clinical data on the use of daptomycin in combination with other antibiotics. Most of this use was as successful salvage therapy in the setting of failing primary, secondary, or tertiary therapy and/or relapsing infection. Synergy between β-lactams and daptomycin is associated with several characteristics, including increased daptomycin binding and β-lactam–mediated potentiation of innate immunity, but the precise molecular mechanism is unknown.

Implications: Use of daptomycin in combination with other antibiotics, especially β-lactams, offers a promising treatment option for complicated MRSA bacteremia in which emergence of resistance during treatment may be anticipated. Because it is currently not possible to differentiate complicated from uncomplicated bacteremia at the time of presentation, combination therapy may be considered as first-line therapy, with de-escalation to monotherapy in uncomplicated cases and cases with stable pharmacologic and surgical source control. (*Clin Ther*. 2014;36:1303–1316)

Key words: daptomycin, β-lactams, combination therapy, MRSA, *Staphylococcus aureus*, synergy.

INTRODUCTION

This article reviews all the published studies that used daptomycin combination therapy for the treatment of bacteremia and associated complicated infections caused by gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). We discuss the rationale of combination antibiotics and the mechanisms that enhance the activity of daptomycin, with special focus on the role of β-lactam antibiotics.

RESULTS

Daptomycin

Daptomycin, a fermentation product of *Streptomyces roseosporus,* is a cyclic lipopeptide antibiotic with potent bactericidal activity against most gram-positive organisms. It is approved for the treatment of complicated skin and skin structure infections and *S aureus* bacteremia, including those with right-sided infective

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endocarditis, caused by methicillin-susceptible *S aureus* and MRSA.[1] It has a unique structure among currently available antibiotics and a novel mechanism of action involving insertion of the lipophilic daptomycin tail into the bacterial cell membrane in a calcium-dependent manner, causing a potassium ion efflux and rapid membrane depolarization. This action is followed by arrest of DNA, RNA, and protein synthesis, resulting in bacterial cell death.[2]

In a simulated endocardial vegetation model, daptomycin remained bactericidal (99.9% kill within 24 hours) against stationary phase cultures of both methicillin-susceptible *S aureus* and MRSA present at high density (10^9 CFU).[3] Daptomycin demonstrates concentration-dependent activity, a half-life of 8 hours, a prolonged postantibiotic effect (PAE) up to 6.8 hours, and linear pharmacokinetics with minimal drug accumulation.[4] Daptomycin is primarily renally excreted, with the majority of the drug remaining intact in the urine. Because of daptomycin's unique mechanism of action and because it is not metabolized by cytochrome P-450 or other hepatic enzymes, it has minimal drug interactions.[5,6]

Based on its concentration-dependent activity, linear pharmacokinetics, and favorable safety profile, daptomycin has been used and studied at higher-than-indicated doses. Infectious Diseases Society of America guidelines from 2011 suggest using high-dose daptomycin (10 mg/kg/d), if the isolate is susceptible, in combination with another agent (eg, gentamicin 1 mg/kg IV every 8 hours, rifampin 600 mg PO/IV daily, or 300–450 mg PO/IV BID, linezolid 600 mg PO/IV BID, trimethoprim/sulfamethoxazole 5 mg/kg IV BID, or a β-lactam antibiotic) in the management of persistent MRSA bacteremia and vancomycin treatment failures in adult patients (B-III indication).[7]

Overall rates of resistance of daptomycin in staphylococci and enterococci remain rare. However, there are numerous reports of emergence of resistance during treatment with daptomycin in settings of at least one of the following factors: (1) high inoculum infections; (2) endovascular infections; (3) infections of biomedical devices with prolonged retention; (4) bone and joint infections; (5) hemodialysis patients; and (6) lower than recommended doses of daptomycin monotherapy.[8] Mechanisms of daptomycin resistance are still being elucidated and remain diverse. Daptomycin-resistant *S aureus* is usually caused by modification of the cell membrane. Resistant isolates often exhibit progressive accumulation of single nucleotide polymorphisms in the multipeptide resistance factor gene (*mprF*) and the *yycFG* components of the *yycFGHI* operon. Both of these loci are involved in key cell membrane events. *mprF* is responsible for the synthesis and outer cell membrane translocation of positively charged lysyl-phosphatidylglycerol. The resultant phenotype readout is increased in the relative positive surface charge and is associated with decreased daptomycin binding. It has also been demonstrated that the *VraSR* 2-component regulatory system contributes to *mprF*-mediated decreased susceptibility to daptomycin.[9] Other cell membrane mechanisms associated with daptomycin resistance in *S aureus* isolates are altered cell membrane order, increased cell membrane pigment production, resistance to depolarization and/or permeabilization, and reduced cell membrane peptidoglycan content. Modifications of the cell wall (including enhanced expression of *dlt* operon and progressive cell wall thickening) also contribute to daptomycin resistance.[10]

The mechanism of daptomycin resistance in enterococci may be associated with various gene mutations, increased septum formation, and alterations in membrane charge and phospholipid content. Whole-genome analysis suggests that mutations in several genes may play a role in the development of daptomycin resistance in enterococci. These include: (1) a 3-component regulatory system (designated *liaFSR*) that orchestrates the cell envelope response to antibiotics; (2) genes encoding proteins involved in phospholipid metabolism, including glycerophosphoryl diester phosphodiesterase (*gdpD*) and cardiolipin synthase (*cls*); and (3) a putative histidine kinase gene *yycG*, a member of the *YycFG* system that is involved in cell envelope homeostasis and daptomycin resistance in other gram-positive cocci. Nevertheless, none of the aforementioned gene mutations alone is sufficient to confer clinical levels of daptomycin resistance.[11]

Furthermore, analysis of an isolated cave microbiome, in low G+C gram-positive bacteria, revealed a novel mechanism of daptomycin resistance that involved inactivation by hydrolytic cleavage of the ester bond between the threonine and kynurenine residues, resulting in ring-opening inactivation.[12]

Rationale of Combination Antibiotics

Combinations of antibiotics are used to take advantage of the agents' different mechanisms of action and toxicity profiles. Common indications for combination antibiotic therapy is broad-spectrum empiric treatment of life-threatening infections,

treatment of polymicrobial infections, minimization of drug toxicity by using relatively low doses of ≥2 drugs with additive efficacies but independent toxicities, prevention of emergence of antibiotic resistance to a single agent, and exploitation of the possibility of synergistic inhibitory or bactericidal activities. Antibiotic synergy refers to a net increased antimicrobial effect resulting from the interaction of ≥2 drugs that is greater than the sum of their independent contributions.[13,14]

Various mechanisms of this synergistic activity have been proposed. A cell wall–active agent with aminoglycoside proves synergistic activity, with increased intracellular uptake of aminoglycosides leading to enhanced killing and bactericidal activity in certain gram-positive organisms.[15] In addition, inactivating enzyme inhibitors (eg, a combination of a β-lactam agent plus β-lactamase inhibitors) are another possible mechanism of this synergistic activity. Other examples include combinations of drugs acting at proximate steps of a metabolic pathway (eg, trimethoprim/sulfamethoxazole rendering the combination drug bactericidal and less prone to resistance) and combinations of drugs acting at various levels of peptidoglycan synthesis (eg, β-lactams, fosfomycin, glycopeptides, and lipopeptides).[16] Synergy in PAE is another possible mechanism. Synergistic PAEs have been observed classically in combinations of β-lactams with aminoglycosides and by addition of rifampin to other classes of drugs. Prolongation of PAE may provide higher protection against organism regrowth in situations when one or both antibiotics become subtherapeutic during the dosing interval.[17] Disadvantages of combination therapy includes the possibility of antagonism, increased risk of adverse effects, risk of emergence of other resistant organisms, *Clostridium difficile* infection, and increased cost of therapy. Short-course, low-dose gentamicin combined with vancomycin for MRSA bacteremia and native valve endocarditis and in combination with other β-lactams may be associated with an increased risk of nephrotoxicity.[18,19]

Based on the National Healthcare Safety Network data, in 2009–2010, *S aureus* remained the most common cause of health care–associated infection, with MRSA accounting for >50% of the clinical *S aureus* isolates recovered in US hospitals.[20] Infection with MRSA is associated with increased morbidity, requirement for a longer duration of antibiotic therapy, higher health care costs, prolonged hospitalization, and an increased risk of death.[21] *S aureus* bacteremia is associated with a poor outcome and a high rate of secondary infections such as infective endocarditis, septic arthritis, and osteomyelitis.[22] Vancomycin has been the cornerstone of treatment of patients with serious MRSA infections for 5 decades. Consequently, vancomycin use has been increasing since the mid-1980s, resulting in the emergence of MRSA with reduced susceptibility to vancomycin. *S aureus* strains with reduced susceptibility can be divided into 3 categories; vancomycin-resistant strains (MIC, ≥16 μg/mL); vancomycin-intermediate strains (VISA; MIC, ≥4 μg/mL); and heterogeneous VISA, which have MIC <4 μg/mL but subpopulations that grow at higher MICs.

Within the populations of *S aureus* that are considered to be susceptible, a changing pattern of vancomycin MICs has been observed in some centers, demonstrating an overall population drift in the clinical isolates of *S aureus* toward reduced vancomycin susceptibility. This phenomenon of "vancomycin MIC creep" varies considerably around the world and may not be uniformly applicable in all health care settings.[23] Infections caused by MRSA with higher vancomycin MICs are seen in patients with recent exposure to vancomycin within 1 month of the current infection, recent hospitalization, surgery within the last 6 months, and those with bloodstream infections before admission in intensive care units. In the treatment of MRSA bloodstream infections with vancomycin, higher vancomycin MIC values (≥1.5 μg/mL), regardless of MIC testing method and infection source, are predictive of treatment failure and associated with higher mortality.[24] These data highlighting such poor outcomes in patients with serious MRSA infections (including bacteremia) suggest that in many of these instances, the treatment strategy of vancomycin specifically, and monotherapy in general, seems to be failing. Evidence is mounting that serious MRSA infections such as bacteremia may require combination antibiotic therapy for optimal management, improving antibiotic durability and slowing the rate of emergence of resistance.[25–29]

Although new antimicrobial drugs (eg, linezolid, daptomycin, tigecycline, telavancin, ceftaroline) have been developed, none has been shown to be consistently superior to vancomycin for the treatment of

MRSA infections.[30–32] This finding is likely due to the fact that most of the randomized clinical trials comparing the newer antibiotics with vancomycin are restricted to relatively "low-risk" clinical situations because of the use stringent exclusionary criteria.

The optimal treatment of complicated MRSA infections thus remains a challenge. Physicians and pharmacists are meeting these challenges in a variety of ways, including: (1) the adoption of rapid molecular tests to quickly differentiate MRSA from β-lactam– susceptible strains and, therefore, convert patients with the latter more rapidly to superior β-lactam therapy; (2) optimization of antibiotic doses targeting higher trough levels for vancomycin and higher daptomycin levels for breakthrough MRSA infections and serious vancomycin-resistant enterococci infections; (3) switching early-on to alternative agents for MRSA infections when vancomycin MIC is 2 mg/L; and (4) using combination antibiotic therapy.

The combination of high-dose daptomycin with a second antibiotic has been used to treat refractory *S aureus* bacteremia because: (1) vancomycin first-line therapy has been shown to elicit changes that confer cross-resistance to daptomycin[33]; (2) in vivo persistence under selection pressure from innate cationic host defense peptides also independently select for reduced susceptibility to daptomycin[34]; and (3) organisms that establish endovascular infections such as endocarditis that frequently are the cause of persistent bacteremia demonstrate a fitness advantage of intrinsic resistance to cationic host defense peptides, with resulting increased heteroresistance to daptomycin.[25,35–38]

Combination of Antibiotics With Daptomycin: Clinical Data

In vitro data of interactions between daptomycin and other antibiotics have been reviewed extensively in other publications.[25,39,40] There are limited clinical data on the use of daptomycin in combination with other antibiotics. Most of this use has occurred in the setting of failing therapy and/or relapsing infection and "difficult to treat" infections. Characteristics of the antibiotics that were used in these studies, their mechanism of action, mechanism of resistance, and possible mechanisms of interactions with daptomycin are summarized in Table I.[41–56]

Table II[23,57–75] summarizes the clinical data regarding the use of daptomycin in combination with other antibiotics for the treatment of complicated bacteremia and other associated invasive infections caused by resistant gram-positive organisms. In these studies, daptomycin was used in combination with β-lactams, rifampin, trimethoprim-sulfamethoxazole, fosfomycin, tigecycline, and linezolid. Because most of the available clinical and in vitro data are for the combination therapy of daptomycin with various β-lactam agents, further discussion will focus primarily on this combination.

Daptomycin and β-Lactam Combination Therapy

Daptomycin and β-lactam combinations have been used successfully and increasingly as salvage treatment for refractory or relapsing infections caused by resistant gram-positive organisms (Table II). In addition to the "see-saw" effect,[76] the improved outcomes are based on:

- Synergy: β-lactam exposure increases the net surface negative charge on the bacterial cell wall leading to increased binding of the positively charged daptomycin Ca2+ complex, resulting in synergy and enhanced killing of resistant gram-positive organisms.[23,42,58]
- β-lactam–mediated increased killing by various cationic host defense peptides (HDPs): Increased resistance to vancomycin and daptomycin is associated with concomitant resistant to various HDPs that are produced by platelets, leukocytes, and keratinocytes.[35] Antistaphylococcal β-lactams sensitize MRSA for augmented clearance by innate immune effectors such as HDP and phagocytes and therefore augment the synergistic activity between these antistaphylococcal β-lactams and daptomycin.[23,42,77]
- Prevention of emergence of resistance: β-lactams when used along with daptomycin prevent the emergence of resistance to daptomycin in clinical MRSA isolates and in enterococci.[48,49,59,78]

Unique Role of Ceftaroline

Unlike other β-lactams, ceftaroline has activity against MRSA, heterogeneous VISA, VISA, vancomycin-resistant strains, and daptomycin-nonsusceptible *S aureus*, which is mediated by binding to PBP2a with 128 times greater affinity than any other clinically available β-lactam.[79] Because PBP2a on the cell surface decreases with reduced glycopeptide and lipopeptide susceptibility, the enhanced activity of daptomycin mediated by

Table I. Characteristics of antibiotics used as combination therapy with daptomycin (DAP).

Drug	Mechanism of Action	Mechanism of Resistance	Interaction With DAP
β-lactams	β-lactams act as substrate analogs for the PBPs. They bind irreversibly to the PBPs' active site, leading to termination of peptidoglycan cross-linking causing disruption of cell wall leading to cell lysis and death[41] Antistaphylococcal β-lactams also sensitize MRSA for augmented clearance by innate immune effectors as phagocytes and cationic host defense peptides from keratinocytes, neutrophils, and platelets[23,42] β-lactams may inhibit surface expression of fibronectin binding protein gene, thereby diminishing endovascular and osteoarticular virulence[43]	Staphylococci: Mutations in PBPs: PBP2a, PBP2', resulting in decreased affinity to all β-lactams[41] Expression of *blaZ* gene: degradation of penicillins[44] Enterococci: High levels of resistance involves expression of PBP5-R, alterations in the PBP5 protein around the active site, increased expression of PBP5, and utilization of a β-lactam–insensitive transpeptidase for cell wall synthesis[45]	See-saw effect: Increased susceptibility of antistaphylococcal β-lactam antibiotics with reduced susceptibility to glycopeptides and lipopeptides[46]. This is possibly mediated by reduction of PBP4 and PBP2a with a relative increase in PBP2[47] Synergy: β-lactam exposure increases the net surface negative charge on the bacterial cell wall leading to increased binding of the positively charged DAP Ca2+ complex, which results in synergy and enhanced killing. β-lactam exposure leads to host defense peptide–mediated innate immune response against MRSA, resulting in additional synergy between them and DAP or vancomycin[23,42] Combination of DAP and a β-lactam delays or prevents the selection of DAP-resistant variants in vitro[48,49]
Rifampin	Rifampin acts by interacting specifically with bacterial RNA polymerase encoded by the gene *rpoB*[50]	Mutations in *rpoB*, the gene that encodes the β subunit of RNA polymerase, are responsible for rifampin resistance.[51] Because of the rapid development of resistance, it should not be used as monotherapy but may be used in combination with another active antibiotic in selected scenarios	In vitro synergy has been show with various antibiotics, including DAP. In the presence of DAP, a striking reduction in the rifampicin MIC was seen in 11 of 15 (73.3%) VRE that were resistant to rifampicin[52]
TMP/SMT	The 2 components, TMP and SMT, work sequentially to inhibit enzyme systems involved in the bacterial synthesis of tetrahydrofolic acid. Reduced availability of tetrahydrofolic acid inhibits thymidine synthesis and,	Overproduction of para-aminobenzoic acid causes resistance to sulfonamides. Amino acid substitutions in both enzymes (dihydropteroate synthase and tetrahydrofolate reductase).	In vitro synergy has been show with various antibiotics, including DAP

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Table I. (continued).

Drug	Mechanism of Action	Mechanism of Resistance	Interaction With DAP
	subsequently, DNA synthesis. The combination (TMP/SMT) has a broader spectrum of antimicrobial activity, is more rapidly bactericidal, and is less susceptible to the development of resistance than either of the component drugs[53]	Exogenous thymidine as produced by some staphylococci also renders TMP/SMT inactive because it bypasses the double biosynthetic blockade[54]	
Fosfomycin	Targets the bacterial mucopeptide synthesis by inhibiting phosphoenolpyruvate transferase, which is involved in peptidoglycan synthesis. This results in a broad-spectrum bactericidal effect[55]	In gram-positive organisms, resistance may be mediated by fosfomycin resistance proteins (FosA, FosB, or FoX) that chemically modify and inactivate the drug[55]	In vitro synergy has been show with various antibiotics, including DAP.[56] Similar to other cell wall active agents such as β-lactams, fosfomycin may also lead to increased DAP binding by altering the charge of the outer membrane.

PBP = penicillin-binding proteins; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = *vancomycin-resistant enterococci*; TMP/SMT = trimethoprim/sulfamethoxazole.

ceftaroline is likely a result of synergistic activity as well. Ceftaroline has been used in combination with daptomycin to eradicate resistant *S aureus* and enterococcal infections and offers an attractive and potent therapeutic option for the treatment of resistant gram-positive infections.[59,62,77,80]

Is the Synergistic Activity of All β-Lactams With Daptomycin the Same?

While nafcilln and oxacillin enhance daptomycin and killing of MRSA, b-lactam antibiotics with penicillin-binding protein-1 (PBP1) binding demonstrate enhance the activity of daptomycin compared to those with relatively less PBP1 binding (cefoxitin, and cefaclor).[81] The mechanism for this specificity is unknown. However, given that PBP1 is a critical component of cell divisome formation that may be a compensatory response to daptomycin membrane insertion for initiation of surface repair, PBP1 inhibition or interference by β-lactam antibiotics that bind it may result in cell death with fewer daptomycin molecules inserted per cell (G.S., unpublished observations).[82]

CONCLUSIONS

A severe limitation in the treatment of *S aureus* bacteremia is that it takes several days for "complicated" versus "uncomplicated" situations to be determined.[83] In the meantime, however, under current first-line monotherapy treatment approaches frequently used with vancomycin, complicated infections are exacerbated by selection of drug resistance and consequent treatment failure. Currently, there is no way to risk-stratify the complicated versus uncomplicated cases early-on, although some research points to potential use of biomarkers to predict treatment failure and patient death. In light of the positive data that are emerging with combination therapy, particularly with daptomycin plus β-lactams in MRSA bacteremia, it may be reasonable to initiate combination therapy for 3 to 5 days and then de-escalate treatment based on clinical and microbiologic responses. Although much remains to be determined, including questions such as which β-lactam to use in the early empiric approach and the role of vancomycin in combination therapy schemes, the current data indicating such poor outcomes in MRSA bacteremia suggest that an alternative approach is required. There is insufficient clinical data using the combination of daptomycin with other antibiotics such as fosfomycin,

Table II. Summary of clinical studies with daptomycin (DAP) combination therapy for disseminated infections.

Study	Antibiotic	Infection	Outcome	Comments
Antibiotic combination of DAP + β-lactam agent				
Arias et al,[57] 2007	DAP 8 mg/kg/d Ampicillin 16 gm/d Gentamicin 1 mg/kg q 12 × 6 weeks	*Enterococcus faecium* (VRE) MV endocarditis Relapsing bacteremia	Cure at 6-month follow-up	DAP heteroresistance noted DAP MIC, 2–4; ampicillin MIC, 16–34
Dhand and Sakoulas,[23] 2011	Daptomycin (high dose) + nafcillin/oxacillin	Series of 7 patients with noncatheter-associated persistent MRSA bacteremia	Rapid clearance of bacteremia after addition of β-lactam	Initial cure in 7 of 7 patients, with a delayed relapse in 2 of the 7 patients. One isolate developed DAP nonsusceptibility. In vitro studies showed enhanced DAP bactericidal activity, increased membrane DAP binding, and decreases in positive surface charge induced by ASBLs against DAP nonsusceptible MRSA
Sakoulas et al,[58] 2011	DAP 12 mg/kg/dose Ampicillin 1 g q 6	*E faecium* (VRE) DAP MIC 1 Ampicillin MIC, >128	Rapid clearance of persistent bacteremia	Addition of ampicillin to DAP in vitro enhanced DAP activity and binding, changed the antibiotic profile from static to bactericidal, showed slow reduction in net positive surface charge, and made VRE more susceptible to killing by innate immune response mediated by cationic host defense peptides
Rose et al,[59] 2012	DAP 10 mg/kg/dose Ceftaroline 200 mg q 12	*S aureus* (MRSA, DNSA, VISA) HD catheter–related bacteremia, right-sided endocarditis, septic arthritis	Clearance of bacteremia	Ceftaroline restored DAP sensitivity in vivo. Improved DAP susceptibility in vitro in presence of oxacillin and ceftaroline. Rapid and sustained bactericidal activity Combination prevented emergence of DAP resistance in vitro. In DNSA, higher dose of DAP is required to optimize cell membrane damage
Sierra-Hoffman et al,[60] 2012	DAP 6 mg/kg q 48 Ampicillin 1 g q 6 × 6 weeks	*E faecalis* MV endocarditis	Cure at 12-month follow-up	DAP MIC, <4; ampicillin sensitive Overall efficacy of DAP was slightly enhanced (not statistically significant) with the addition of β-lactams. This benefit was most pronounced in bacteremia associated with endocarditis, osteoarticular infection, and bacteremia of unknown source. Combination therapy was well tolerated.
Moise et al,[61] 2013	Daptomycin with and without β-lactam	CORE data 2005–2009 106 patients with *S aureus* bacteremia		Addition of rifampin or gentamicin or vancomycin to DAP did not result in any significant change in outcome
Sakoulas et al,[62] 2013	DAP 8 mg/kg/dose Ceftaroline 600 mg q 8	*E faecalis* Aortic valve endocarditis High-level gentamicin resistance	Clearance of bacteremia Cure after 4 week of therapy and AVR	In vitro: 4-fold decrease in DAP MIC with addition of ampicillin or ceftaroline and synergy between DAP and ceftaroline. Enhancement of cathelicidin peptide activity and DAP binding in presence of ceftaroline

(continued)

Table II. (continued).

Study	Antibiotic	Infection	Outcome	Comments
Antibiotic combination of DAP + rifampin				
Stevens and Edmond,[63] 2005	DAP 8 mg/kg/dose Rifampin 300 mg q 8 h Gentamicin after HD 11 weeks	*E faecium* (VRE) Prosthetic MV endocarditis DAP MIC, 4	No microbiologic reoccurrence after 4 weeks of completion	In vitro synergy noted between DAP/rifampin/gentamicin
Ahmad and Rojtman,[64] 2010	DAP 6 mg/kg/dose Rifampin 300 mg q12 h 6 weeks	Persistent MRSA bacteremia DAP MIC increased to 2 while on DAP therapy	Rapid clearance of bacteremia after adding rifampin. Cure at 4-month follow-up	No in vitro synergy was noted
Lee et al,[65] 2008	DAP 6 mg/kg/dose Rifampin 6 weeks	MRSA Bacteremia, Likely AV graft infection, Septic brain emboli, meningitis	Cure	MRSA DAP MIC, 1 Leukocytoclastic vasculitis with vancomycin. Rifampin added for CNS disease
Jugun et al,[66] 2013	DAP 8 mg/kg/dose Rifampin 600 mg q 24 h	Gram-positive osteoarticular infections, N = 16 (staphylococcal, n = 15, streptococcal, n = 1)	Successful outcomes at >1-year follow-up	Median duration of treatment was 21 days (range, 10–122 days). Combination therapy well tolerated. Prosthetic device removal in 5 of 16, device exchange in 4 of 16, and device retention in 4 of 16
Rose et al,[67] 2013	DAP 4–8 mg/kg/dose Rifampin 300–600 mg/d	MRSA (n = 12) Osteoarticular (N = 9) HD catheter infection (1) Prosthetic valve endocarditis (1)	Cure in 9 of 12 patients	Checkerboard synergy was seen in 9 of 12 patients and was predictive of therapeutic success. Failure seen in prosthetic joint infection and deep abscess
Antibiotic combination of DAP + TMP/SMT				
Avery et al,[68] 2012	DAP 10 mg/kg/dose TMP/SMT IV to oral	DNSA, VISA 1. Bacteremia with vertebral osteomyelitis 2. Bacteremia, TV endocarditis, osteomyelitis	1. Cure 2. Clearance of persistent bacteremia	Suppression with oral TMP/SMT; course complicated by reversible myopathy and renal failure. In vitro combination showed sustained bactericidal activity at 36 to 48 hours
DiCarlo et al,[69] 2013	DAP 8 mg/kg/dose TMP/SMT 15 mg/kg/d	MRSA bacteremia MV endocarditis Intracranial hemorrhage	Cure	6 weeks of oral TMP/SMT after 6 weeks of combination IV therapy VAN MIC, 2
Antibiotic combination of DAP + fosfomycin				
Miro et al,[70] 2012	DAP 10 mg/kg/d FOS 2 g q 6 h	3 cases of left-sided endocarditis (MRSA, n = 2; MSSA, n = 1)	Alive at >6-month follow-up	In vitro activity of combination against (7 MSSA, 5 MRSA, 2 GISA) isolates showed synergy in 79% of isolates and bactericidal activity in 57% of isolates. Combination therapy was well tolerated
Chen et al,[71] 2011	DAP 12 mg/kg/d FOS 6 g q 6 h	MRSA/DNSA bacteremia, AICD infection, endocarditis, osteomyelitis	Cure	Delayed surgical removal of pacing wire. Eight weeks of intravenous therapy. Combination well tolerated. In vitro additive effect.
Teng et al,[72] 2012	DAP 12 mg/kg/d FOS 6 g q 6 h	MSSA, VT-MRSA Bacteremia, MV endocarditis, osteomyelitis	Cure	Combination well tolerated

(continued)

Table II. (continued).

Study	Antibiotic	Infection	Outcome	Comments
Antibiotic combination of DAP + tigecycline				
Jenkins,[73] 2007	DAP 6 mg/kg/dose Tigecycline 50 mg q 12 h × 70 d	*E faecium* (VRE) MV endocarditis DAP MIC, 4	Cure at 16-week follow-up	
Schutt and Bohm,[74] 2009	DAP 8 mg/kg/dose Tigecycline 50 mg q 12 h	*E faecium* (VRE) Bacteremia Possible TV endocarditis with pulmonary septic emboli	Rapid clearance of refractory bacteremia	Resistant to vancomycin, linezolid. DAP MIC, 3–4
Antibiotic combination of DAP + linezolid + rifampin				
Kelesidis et al,[75] 2011	DAP × 6 weeks Linezolid 600 mg q 12 h Rifampin 300 mg q 12 h	MRSA prosthetic device infection, bacteremia, meningitis, osteomyelitis	Cure after removal of shunt and combination antibiotics	In vitro analysis found that combination of linezolid with DAP produced indifference in checkerboard analysis and antagonism in time-kill assays. The addition of rifampin to the combination linezolid + DAP resulted in synergy in the time-kill assays when tested at 0.5 times the MICs for each drug and achieved 99.9% killing significantly quicker than the other combinations

VRE = vancomycin-resistant enterococci; MV = mitral valve; MRSA = methicillin- resistant *Staphylococcus aureus*; ASBL = antistaphylococal β-lactam; DNSA = DAP nonsusceptible *S aureus;* VISA = vancomycin-intermediate *S aureus;* HD = hemodialysis; CORE = Cubicin Outcomes Registry and Experience; AVR = aortic valve replacement; AV = arteriovenous; CNS = central nervous system; TMP/SXT = trimethoprim/sulfamethoxazole; FOS = fosfomycin; TV = tricuspid valve; MSSA = methicillin-susceptible *Staphylococcus aureus*; GISA = glycopeptide-intermediate Staphylococcus aureus; AICD = automated implantable cardioverter-defibrillator; VT = vancomycin tolerant.

linezolid, tigecycline, gentamicin, and trimethoprim-sulfamethoxazole in the treatment of MRSA bacteremia; further clinical studies are required to assess their efficacy and long-term tolerability. Early consultation with infectious diseases has increasingly been shown to improve mortality and other outcomes in *S aureus* bacteremia.[84,85] The early use of combination therapy for treatment of MRSA bacteremia, especially in clinical settings in which emergence of resistance during treatment is known to occur, may be an additional benefit that infectious diseases clinicians can offer to these patients with the goal of improving outcomes.

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CONFLICTS OF INTEREST

Dr. Dhand is a member of a speaker's bureau and has received speaking honoraria from Cubist Pharmaceuticals; he is also a consultant for Astellas and Theravance. Dr. Sakoulas is a member of a speaker's bureau and has received speaking honoraria from Cubist, Forest, Astellas, and Pfizer Pharmaceuticals; he has also received grant support and consulting fees from Cubist Pharmaceuticals.

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