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Review

Beta-lactam combination therapy for the treatment of *Staphylococcus aureus* and *Enterococcus* species bacteremia: A summary and appraisal of the evidence

Rachel Bartash*, Priya Nori

Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, USA

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ABSTRACT

Staphylococcal bacteremia and enterococcal bacteremia are prevalent in hospitalized or recently instrumented patients, and are associated with significant morbidity and mortality. They are often difficult to treat due to the pathogenicity of the organisms, poor response to antibiotics, and increasing development of multidrug resistance. Therefore, there has been increasing interest in combination therapy for the treatment of these infections. The aim of this review was to summarize and assess the evidence supporting combination beta-lactam therapy for both *Staphylococcus aureus* and *Enterococcus* species blood stream infections. Currently, there is promising in vitro data but little clinical evidence supporting combination beta-lactam therapy for this indication. Further clinical investigations are needed to elucidate the potential benefits of beta-lactam combination therapy over monotherapy for Gram-positive bacteremia, although combination therapy may be useful in refractory cases of bacteremia that do not respond to standard antibiotic therapy.

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Introduction

Staphylococcus aureus and *Enterococcus* species are responsible for approximately 30% of all nosocomial bloodstream infections, resulting in significant morbidity and mortality (Klein et al., 2007; Wisplinghoff et al., 2004). Due to the emergence of antimicrobial resistance as a result of antibiotic overuse, infections with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* species (VRE) pose significant treatment challenges, with studies showing increased treatment failure, relapse, and higher rates of mortality when compared to infections

* Corresponding author.
E-mail address: rbartash@montefiore.org (R. Bartash).

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caused by more susceptible organisms (Wisplinghoff et al., 2004; Yaw et al., 2014; Blot et al., 2002). In light of these poor outcomes, there is increasing interest in combination antibiotic therapy, especially for refractory infections. The available literature on combination beta-lactam therapy for staphylococcal and enterococcal bacteremia is reviewed herein.

Staphylococcus aureus

Staphylococcus aureus bacteremia is a frequently encountered nosocomial infection, comprising approximately 20% of all blood stream infections (Wisplinghoff et al., 2004). While both MSSA and MRSA are associated with significant mortality, outcomes from MRSA bacteremia are worse, with overall mortality as high as 25–50% (Wisplinghoff et al., 2004; Yaw et al., 2014). Drivers of poor outcomes from MRSA bacteremia are likely multifactorial, including differences in patient comorbidities, treatment regimens (Fätkenheuer and Kaasch, 2014), and timing of surgery, if surgical management is indicated. Antibiotic selection plays an important role in outcomes of *S. aureus* bacteremia, as higher rates of relapse and mortality are seen in patients with MSSA bacteremia treated with vancomycin compared to those treated with anti-staphylococcal beta-lactams (Kim et al., 2008; Stryjewski et al., 2007; Chang et al., 2003). Despite this, vancomycin remains the first-line therapy for MRSA bacteremia, as providers have significant experience with its usage and it is less expensive than alternative and newer agents.

Recently, newer agents, such as linezolid, ceftaroline, and daptomycin have been increasingly utilized for the treatment of MRSA infections. Linezolid, which became generically available in 2015, is an effective option for certain types of MRSA infection, such as skin and soft tissue infections and pneumonia, but due to its bacteriostatic properties, it is not considered first-line treatment for bloodstream infections and endocarditis (Liu et al., 2011). Similarly ceftaroline, a cephalosporin with anti-MRSA activity, is also approved for complicated skin and soft tissue infections and community-acquired pneumonia. While several case series (Polenakovik and Pleiman, 2013; Ho et al., 2012) and one case controlled trial (Arshad et al., 2017) regarding its use in bacteremia have been promising, to date there have been no large clinical trials to support the use in this setting. Daptomycin is the preferred agent for invasive MRSA infections with an elevated vancomycin minimum inhibitory concentration (MIC) >2 μg/ml, as studies have shown improved outcomes in this setting (Moore et al., 2012); however, rising daptomycin MICs have been observed on treatment, which may limit therapy (Marty et al., 2006). Although daptomycin is now generic, this medication is still often associated with a significantly greater cost (Fowler et al., 2006). In the authors' experience, use of daptomycin in outpatient parenteral antibiotic therapy for indications such as osteomyelitis or endocarditis is frequently cost-prohibitive, since extended antibiotic courses are not often covered by patient insurance.

Given the known disadvantages of vancomycin treatment, including the need for frequent monitoring of creatinine clearance and drug levels and suboptimal outcomes, and the limitations in other therapeutic options, there has been increasing interest in combination therapy for the treatment of MRSA bloodstream infections. While vancomycin in combination with aminoglycosides remains standard of care for patients with prosthetic valve endocarditis due to MRSA (Baddour et al., 2015), when used in native valve endocarditis and bacteremia there is an increased risk of renal impairment (Cosgrove et al., 2009), without clinical benefit (Drinkovic et al., 2003; Watanakunakorn and Baird, 1977). Based on these findings, this combination is no longer recommended in the absence of prosthetic material (Baddour et al., 2015).

Table 1
Summary of clinical studies on combination therapy for *Staphylococcus aureus* bacteremia[a].

	Author	Combination therapy regimen	Study design	Outcome	Potential clinical role
MSSA	Sakoulas et al. (Sakoulas et al., 2016)	Cefazolin + ertapenem	Single case study	Clearance of refractory bacteremia in a single case	Refractory MSSA bacteremia despite monotherapy and appropriate source control
	Moise et al. (Moise et al., 2013)	Daptomycin + beta-lactam	Multicenter, retrospective, observational study	8/8 patients successfully treated with combination therapy versus 12/16 patients treated without beta-lactams	Deep-seated infections, including endocarditis, joint/bone infections, and suspected endovascular sources
MRSA	Dilworth et al. (Dilworth et al., 2014)	Vancomycin + beta-lactam for at least 24 h	Retrospective cohort of 50 patients treated with combination therapy vs. 30 patients with monotherapy	Improved rate of microbiological clearance	Refractory MRSA bacteremia despite monotherapy with vancomycin Monitor for renal toxicity depending on beta-lactam used
	Davis et al. (Davis et al., 2016)	Vancomycin + flucloxacillin	Multicenter, randomized trial of 60 patients receiving vancomycin + flucloxacillin vs. vancomycin alone	Decreased duration of bacteremia by 1 day Potential for increased renal toxicity	Refractory MRSA bacteremia despite monotherapy with vancomycin Monitor for renal toxicity
	Gritsenko et al. (Gritsenko et al., 2017)	Ceftaroline + vancomycin	Case series of five patients	Clearance of refractory bacteremia in all patients	Refractory MRSA bacteremia despite monotherapy with vancomycin
	Dhand et al. (Dhand and Sakoulas, 2014)	Daptomycin + nafcillin or oxacillin	Case series of seven patients	Clearance of refractory bacteremia in all patients within 24–48 h of combination therapy	Refractory MRSA with high MIC to vancomycin despite monotherapy
	Sakoulas et al. (Sakoulas et al., 2014a)	Daptomycin + ceftaroline	Case series of 26 patients with staphylococcal bacteremia of which 22 patients had MRSA or VISA	23/26 resulted in clearance of bacteremia within 1–6 days	Refractory MRSA with high MIC to vancomycin, VISA, or VRSA despite monotherapy
	Moise et al. (Moise et al., 2013)	Daptomycin + beta-lactam	Multicenter, retrospective, observational study	18/22 patients successfully treated with combination therapy versus 27/34 patients treated without beta-lactams	Deep-seated infections, including endocarditis, joint/bone infections, and suspected endovascular sources

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*.

[a] Enterococcus not included given limited data available on specific combination regimens for isolated bacteremia in the absence of endocarditis.