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Review article

# Optimizing antibiotic therapy of bacteremia and endocarditis due to staphylococci and enterococci: New insights and evidence from the literature

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ABSTRACT

Gram-positive cocci are a well-recognised major cause of nosocomial infection worldwide. Bloodstream infections due to methicillin-resistant *Staphylococcus aureus*, methicillin-resistant coagulase-negative staphylococci, and multi-drug resistant enterococci are a cause of concern for physicians due to their related morbidity and mortality rates. Aim of this article is to review the current state of knowledge regarding the management of BSI caused by staphylococci and enterococci, including infective endocarditis, and to identify those factors that may help physicians to manage these infections appropriately. Moreover, we discuss the importance of an appropriate use of antimicrobial drugs, taking in consideration the *in vitro* activity, clinical efficacy data, pharmacokinetic/pharmacodynamic parameters, and potential side effects.



## 1. Introduction

Over the last four decades bloodstream infections (BSI) due to Gram-positive cocci have become widespread in hospitals around the world, and nowadays are among the most common causes of bacterial nosocomial infection [1,2]. Among Gram-positive microrganisms, staphylococci and enterococci are the leading causes of severe clinical syndromes like bacteremia or infective endocarditis (IE), and account for significant morbidity and mortality rates. The treatment of these infections is complicated by the spread of multidrug resistant (MDR) strains for which a limited number of antibiotics is available.

In the past, acquisition of MDR pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) was generally considered to be restricted to the nosocomial setting. However, in the last decade the epidemiology of Gram-positive infections has partially changed [3,4], as consequence of the increasing number of outpatients with extensive health care contact, and an increasing prevalence of infections caused by MDR Gram-positive strains have been registered in patients living in the community both in United States and Europe [5,6]; these infections have been named health-care associated (HCA) and are a cause for concern among physicians [7].

The purpose of this article is to review the current state of knowledge regarding bacteremia and IE due to Gram-positive cocci, and to identify the therapeutic factors that may help physicians to manage these infections appropriately.

## 2. *Staphylococcus aureus* and coagulase-negative staphylococci

*S. aureus* and coagulase-negative staphylococci (CoNS) are the most common Gram-positive pathogens responsible for all cases BSI and IE [1,2,8–10]. MRSA is currently recognized as a major problem in hospitals throughout the world, causing a various spectrum of clinical diseases, ranging from benign superficial skin infections to severe life-threatening conditions, such as bacteremia, IE, pneumonia, abscesses, and soft or bone-tissue infections [11]. The epidemiology of MRSA is now changing, and this pathogen, considered a "pure" nosocomial pathogen until the past few years, is nowadays isolated with increasing frequency at hospital

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admission and in the emergency department [12]. The community spread of MRSA strains arise from two different patient populations: first, patients with HCA strains that have been acquired during an exposure to a healthcare setting (e.g. patients receiving intravenous therapy, wound care, or specialized nursing care at home, attending a hospital or hemodialysis clinic or receiving intravenous chemotherapy, or residing in a nursing home or long-term care facility), and, second, patients with "true" community-acquired (CA) strains, with few or no risk factors, including athletes, prisoners, and healthy children [13]. These infections have been mostly associated with staphylococcal strains bearing the SCC*mec* type IV element and the Panton-Valentine leukocidin (PVL) genes, and these strains are more frequently susceptible to a variety of non-beta-lactam antibiotics, although macrolide resistance is variable [14].

Methicillin-resistant CoNS have been long considered as common contaminants in clinical specimens, but these organisms can be agents of clinically significant infections, especially in patients with prosthetic devices. The use of prosthetic devices is a "fertile ground" for development of severe infections due to CoNS, since these strains possess determinants that facilitate survival on skin surfaces, biofilm formation, adhesion to tissue and prosthetic surfaces, and components involved in immune evasion [15]. *Staphylococcus epidermidis* accounts for more than 75 percent of coagulase-negative staphylococci in clinical specimens, while other clinically significant species include *Staphylococcus haemolyticus*, *Staphylococcus saprophyticus* and *Staphylococcus lugdunensis*. Until recently, the glycopeptide antibiotics were effective options for the treatment of infections caused by methicillin-resistant staphylococci. However, a number of strains with reduced susceptibility or outright resistance to glycopeptides have now been reported, and evidence of a significant relationship between higher vancomycin minimum inhibitory concentrations (MICs) and treatment failure has led to calls for alternative therapies [7,16–18]. The principles for an optimal management of BSI caused by *S. aureus* and CoNS infections are more detailed discussed.

### 2.1. Treatment of Staphylococcus aureus bacteremia (SAB) and endocarditis

*S. aureus* invasive infections are traditionally associated with significant morbidity and mortality rates [5,19], and has been calculated that hospitalized patients with *S. aureus* infections have five times the risk of in-hospital mortality compared with in-patients without this infection [20]. Among patients with *S. aureus* bacteremia (SAB), metastatic infection and relapse are common [21,22], especially in non-neutropenic patients [10]. In Table 1 are reported the characteristics of the main antibiotics used in the treatment of SAB.

Two meta-analyses evaluating the impact of methicillin resistance on patient outcome has clearly demonstrated that MRSA is associated with significantly higher mortality rate than MSSA [23,24]. Compared to patients with MSSA infection, those with MRSA bacteremia are at higher risk to receive a delayed appropriate treatment, and to develop secondary complications such as metastatic abscesses, septic shock and death. In our experience, patients who developed secondary complications of SAB received an appropriate antibiotic treatment after a mean of 2.46 days, compared to patients who did not develop complications who received the adequate antibiotic treatment after a mean of 1.15 days ($p = 0.03$). At multivariate analysis, delay to adequate antibiotic therapy and septic shock resulted the sole factors associated with a complicated outcome [21].

Vancomycin has been long recommended as the treatment of choice for MRSA isolates [25] with the vancomycin susceptible breakpoints set by the Clinical and Laboratory Standards Institute (CLSI). These breakpoints were lowered in 2006 from an MIC of 4 μg/ml to an MIC of 2 μg/ml following reports of increased mortality associated with infections caused by *S. aureus* with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]/heterogeneous VISA [hVISA]) [26]. SAB caused by MRSA strains with vancomycin MIC > 0.5 μg/ml have been associated with treatment failure [27], and with mutations of regulatory staphylococcal genes [28]. Further studies clearly demonstrated that mortality associated with MRSA bacteremia is significantly higher when the empirical antibiotic is inappropriate and when vancomycin is empirically used for treatment of infection with strains with a vancomycin MIC > 1 μg/mL [16]. There are a lot of potential explanation for the association of elevated MICs and poor clinical outcome in patients receiving vancomycin. First of all, vancomycin, despite the susceptibility profile, is not an "ideal" antibiotic, since it has limited tissue penetration, is slowly bactericidal [29], and is suboptimal against MSSA [30,31]. Moreover elevations in vancomycin MICs may influence pharmacokinetic targets and studies have suggested that when MIC values are greater than 1 μg/ml, achievement of area under the concentration–time curve (AUC)/MIC target levels >400 would be unlikely [32,33]. When treating cases of MRSA bacteremia with a vancomycin MIC of 2 μg/mL using a dose of vancomycin of 15 mg/kg/12 h we would have trough concentrations and AUC/MIC ratio around 10 mg/L and 200, respectively [34], which is clearly under the ideal threshold of clinical efficacy; in these cases we would increase the vancomycin dose to achieve trough concentrations of 15–20 mg/L or more with increased risk of nephrotoxicity. Third, elevations in vancomycin MIC appear to be associated with alterations in *S. aureus* cellular functions such as cell wall changes and transcriptional alterations that may modulate virulence and microbiologic fitness. For example, Holmes et al. observed that elevations in vancomycin MIC appeared to be associated with unfavorable outcomes even in patients infected with MSSA who were treated exclusively with semisynthetic penicillins [35]. In support of this, Cervera et al. found that patients with IE by an MSSA strain treated with cloxacillin having a vancomycin MIC ≥ 1.5 μg/mL had 3-fold higher mortality (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.2–8.2) than controls after adjustment for age, year of diagnosis, septic complications, and nonseptic complicated endocarditis [36]. To confirm all these observations, three different meta-analyses found a correlation between higher vancomycin MICs and poor clinical outcome [37–39].

However, questions remain regarding whether or not these breakpoints should be lowered further, thus limiting the role of vancomycin in the treatment of MRSA bacteremia, and this controversy is in part maintained by the publication of a recent meta-analysis which did not find statistically significant differences in the risk of death when comparing patients with *S aureus* exhibiting high-vancomycin MIC (≥1.5 μg/ml) to those with low-vancomycin MIC (<1.5 μg/ml) [40]. Contrary to the previous 3 meta-analyses published which evaluated outcomes in patients with staphylococcal infections from various sites including skin and soft tissue, urinary tract, lungs, abdomen, and bloodstream [38–40], the latter one prospectively included only patients with SAB [41]. However, outcomes of patients with SAB are also related to various clinical confounding factors such as source control (eg, removal of infected vascular catheters, drainage of abscesses) and underlying diseases, which may bias the results of these studies. Thus, although a definite conclusion cannot be reached, vancomycin should be considered a second-choice drug in patients with infecting MRSA strains having MIC > 1 μg/ml.