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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A B S T R A C T

Gram-positive cocci are a well-recognized 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.

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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 microorganisms, 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 multi-drug 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
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 SCCmec 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 (e.g. 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.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Bacterial effect and mechanism of action</th>
<th>Route of administration and dosing recommendations</th>
<th>Dosage adjustment for renal and hepatic impairment</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>“Slow” bactericidal activity concentration independent; cell wall inhibition</td>
<td>IV: 500 mg q6 h or 1000 mg q12 h; high-dose therapy (15–20 mg/kg total body weight q8 to 12 h) currently recommended when MIC values are 1 μg/mL</td>
<td>Renal: Dosing adjustments are necessary; dosing nomograms and monitoring trough serum vancomycin concentration recommended Hepatic: no adjustment needed</td>
<td>Nephrotoxicity; man syndrome; neutropenia; thrombocytopenia</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Bactericidal (concentration-dependent); membrane depolarization (Ca ++ dependent)</td>
<td>IV: cSSSI: 4 mg/kg (total body weight) q24 h; S. aureus bacteremia: 6 mg/kg (total body weight) q24 h; possible higher doses (8 to 10 mg/kg) for bacteremia/infective endocarditis</td>
<td>Renal: For CrCl &lt;30 mL/min, every 48h</td>
<td>CPK elevation; myopathy: peripheral neuropathy; case reports of rhabdomyolysis and eosinophilic pneumonia</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Inhibition of bacterial cell wall synthesis by binding to the D-Ala-D-Ala terminus of the peptidoglycan in the growing cell wall Disruption of bacterial membranes by depolarization</td>
<td>IV: 10 mg/kg q24 h</td>
<td>Renal: CrCl 30–50 mL/min: 7.5 mg/kg IV q24 hr CrCl 10–29 mL/min: 10 mg/kg IV q48 hr Hepatic: No specific recommendations</td>
<td>Renal toxicity, interference with coagulation testing</td>
</tr>
<tr>
<td>Quinupristin-dalfopristin*</td>
<td>Dalfopristin binds to the 23S portion of the 50S ribosomal subunit, and changes the conformation of it, enhancing the binding of quinupristin Quinupristin binds to a nearby site on the 50S ribosomal subunit and prevents elongation of the polypeptide</td>
<td>IV: 7.5 mg/kg every 8–12 h</td>
<td>Renal: No change Hepatic: No specific recommendations</td>
<td>Arthralgias Myalgias Nausea, diarrhea or vomiting Rash or itching Headache Phlebitis Hyperbilirubinemia</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Bacteriostatic; protein Synthesis inhibition (23S RNA at 50S ribosomal subunit)</td>
<td>IV or PO: 600 mg q12 h</td>
<td>Renal: None Hepatic: No specific recommendations</td>
<td>Thrombocytopenia and anemia; peripheral and optic neuropathy; lactic acidosis; serotonin syndrome</td>
</tr>
</tbody>
</table>

Legend. IV: intravenous; PO: per os; MIC: minimum inhibitory concentration; cSSSI: complicated skin and skin structure infection; CrCl: creatinine clearance; CPK: creatine phosphokinase.

* For the administration of this antibiotic a central venous catheter is necessary.
Teicoplanin is characterized by a prolonged terminal half-life of 83–168 h, is less toxic than vancomycin and can be given both intravenously and intramuscularly. However, this antibiotic resulted clearly less efficacious than antistaphylococcal penicillins and vancomycin in cases of intravascular staphylococcal infections [41,42]. Additionally, many reports have demonstrated the emergence of staphylococcal species, especially S. haemolyticus, expressing heteroresistance or full resistance to teicoplanin [43].

During the last years new drugs active against MRSA have been introduced. Daptomycin, a cyclic lipopeptide with bactericidal activity against MRSA, has been shown to be very efficacious in trials of complicated skin and soft tissue infections [44], and in a randomized trial was compared with vancomycin for patients with SAB; daptomycin was not inferior to standard therapy (success rate, 44.2% [53/120] vs 41.7% [48/115]; absolute difference, 2.4% [95% CI –10.2% to 15.1%]), in which standard therapy consisted of vancomycin (for MRSA bacteremia or for patients allergic to penicillin) or an anti-staphylococcal penicillin (for MSSA bacteremia), each in combination with low-dose, short-course gentamicin [45]. Daptomycin may be considered as a first-line therapy in intravascular infection caused by VISA strains, but should not be used for the treatment of pneumonia because its activity is inhibited by pulmonary surfactants. Compared to glycopeptides, daptomycin shows good clinical activity against MRSA and enhanced MRSA killing by cathelicidin LL-37 and neutrophils [56]. Table 2 summarizes the potential combinations of daptomycin plus other antibiotics for the treatment of methicillin-resistant staphylococcal BSI or IE.

Telavancin is a bactericidal lipoglycopeptide antibiotic that is active against a range of clinically relevant Gram-positive pathogens including MRSA. In experimental animal models of sepsis telavancin was shown to be more effective than vancomycin, and in clinically evaluable patients enrolled in a pilot study of uncomplicated SAB, cure rates were 88% for telavancin and 89% for vancomycin therapy [57]. Further clinical experiences includes bacteremic patients with catheter-associated infections, HAP, osteomyelitis, and endovascular infections, which showed comparable clinical cure rates between telavancin and vancomycin, although the findings were based on very small sample sizes [58]. Nephrotoxicity warnings caution in its use, especially among patients at high risk for development of renal dysfunction, and additional clinical experience is needed to fully assess the effectiveness and safety of telavancin in patients with SAB.

Linezolid is a bacteriostatic agent available in oral and intravenous formulation that possesses high tissue penetration, but it does not ensure prolonged concentrations in the blood, a critical factor for the treatment of intravascular infection. For these instances, it should be considered as a second-line therapy for patients with MRSA BSI, while it may be considered as adjuvant therapy in patients with MRSA SAB or IE and central nervous system (CNS) involvement. As matter of fact, linezolid achieves remarkably high concentrations in the cerebrospinal fluid (CSF) [59], and, in our experience, it was successfully used for the treatment of disseminated cerebritis due to MRSA in a patient with IE unresponsive to vancomycin therapy [60]. However, at time a prolonged use of this agent is not advisable because of haematotoxicity and neurotoxicity problems. Of importance, pharmacokinetic parameters of linezolid in critically ill patients with primary bacteremia may be affected and suboptimal serum concentrations may be achieved, with risk of therapeutic failure and development of resistance. However, linezolid was associated with outcomes that were not inferior to those of vancomycin in patients with secondary SAB [61].

During last years new antibiotics active against methicillin-resistant staphylococci have been studied for clinical use. Many of these are familiar derivatives of antibiotic classes currently used to treat MRSA (eg, glycopeptides, oxazolidinones, cephalosporins, activity against MRSA, including strains with reduced susceptibility to glycopeptides and lipopeptides [55]. Daptomycin plus ceftaroline was used in 26 cases of persisting staphylococcal bacteremia (20 MRSA, 2 VISA, 2 MSSA, 2 methicillin-resistant S. epidermidis); after daptomycin plus ceftaroline was started, the median time to bacteremia clearance was 2 days (range, 1–6 days) with recovery of patients, and in vitro studies showed ceftaroline synergy against MRSA and enhanced MRSA killing by cathelicidin LL-37 and neutrophils [56]. Table 2 summarizes the potential combinations of daptomycin plus other antibiotics for the treatment of methicillin-resistant staphylococcal BSI or IE.

<table>
<thead>
<tr>
<th>Primary bacteremia</th>
<th>Daptomycin</th>
<th>Oxacillin</th>
<th>Amoxicillin/clavulanate</th>
<th>Cefotaxime</th>
<th>Imipenem/neopenem</th>
<th>Cefaroline-fosamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/prosthetic joint infection</td>
<td>Daptomycin</td>
<td>Rifampin</td>
<td>[11,25]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related</td>
<td>Daptomycin</td>
<td>Rifampin</td>
<td>[11,25,103]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td>Daptomycin or vancomycin</td>
<td>Rifampin ± gentamicin</td>
<td>[11,25,103]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Combination of daptomycin plus partners drugs in different clinical conditions.
tetracyclines, see Table 3), and may have significant antibacterial and pharmacologic benefits compared to MRSA agents currently used. For example, tedizolid is a novel oxazolidinone that has completed a phase 2 study in ABSSSIs, has reported findings from a phase 3 trial, and has recently completed enrollment for a second phase 3 trial for acute bacterial skin and skin structure infections (ABSSSIs). Results from the first phase 3 trial confirm non inferior response (compared to linezolid) at 48–72 h after the start of therapy and when the outcome from 6 days of tedizolid is compared to 10 days of linezolid (see results in this supplement). Tedizolid differs from linezolid by having in vivo bactericidal activity, activity against linezolid resistant strains associated with the cfr gene, once-daily dosing, a shorter duration of therapy for treating ABSSSIs, and a lower incidence of gastrointestinal and myelosuppressive adverse events [62]. Ceftriaxone is a novel cephalosporin that binds tightly to the penicillin-binding proteins (PBPs), including those responsible for β-lactam resistance in staphylococci (PBPla), which demonstrates potent activity against gram-positive pathogens including MRSA together with activity against gram-negative pathogens commonly associated with pneumonia [63]. Compared to dalbavancin, daptomycin, linezolid, and tigecycline cephalosporin has shown good activity against MRSA blood isolates [64]. Dalbavancin and oritavancin are currently completing phase 3 clinical trials for the treatment of ABSSSIs caused by MRSA. The new FDA draft guidance for ABSSSI includes a new primary endpoint of clinical response at 48–72 h after initiating antimicrobial therapy, with endpoint criteria outlined by the Biomarkers Consortium of the Foundation for the National Institutes of Health [65], that will likely reshape the conduct and outcomes of future product development.

Although in the past authors recommended to treat SAB was with 4–6 weeks of intravenous antibiotics [66], investigators have tried to identify a subgroup of patients who can safely be treated with shorter durations of therapy. A prerequisite for shorter therapy is the ability to prospectively differentiate patients with uncomplicated SAB (defined as infection in which (1) IE has been excluded, (2) no implanted prostheses are present, (3) follow-up blood cultures drawn 2–4 days after the initial set are sterile, (4) the patient defervesces within 72 h of initiation of effective antibiotic therapy, and (5) no evidence of metastatic infection is present on examination [26] from patients with complicated SAB, for whom longer treatment is necessary. In patients with uncomplicated SAB, the recommended treatment duration is at least 14 days of intravenous antibiotics from time of first negative blood culture. However, one prospective study reported high relapse rates in patients meeting the guideline definition of uncomplicated SAB who were treated for less than 2 weeks [67]. Thus this recommendation should be taken with caution and the decision should be individualized on the basis of the clinical features of the patients. A cost-effectiveness analysis showed that transesophageal echoangiography (TEE) was a useful method to identify patients with intravascular catheter–associated SAB for whom short-course therapy may be adequate. A multicenter randomized trial of treatment duration in staphylococcal bacteremia is under way [68].

Table 3

<table>
<thead>
<tr>
<th>Antibiotic agent</th>
<th>Lipoglycopeptidem</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbavancin</td>
<td>Lipoglycopeptidem</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Lipoglycopeptidem</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>Oxazolidinone</td>
<td>Oral and intravenous</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Lipoglycopeptidem</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Cephalosporin</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>

remaining patients an antibiotic course ranging from 4 to 6 weeks of intravenous therapy is recommended.

Table 4 reports the recommendations for the first choices of therapy in patients with MRSA bacteremia. Table 5 summarizes therapeutic recommendations in patients with MRSA, CoNS, and enterococci IE. Finally, in Table 6 are reported indications and timing of surgery in left-sided native valve IE.

2.2. Coagulase-negative staphylococci bacteremia and endocarditis

CoNS account for approximately one-third of bloodstream isolates in ICUs, making these organisms the most common cause of nosocomial BSI. Among patients with blood cultures positive for CoNS, approximately 12–25 percent have clinically significant BSI. The distinction between contamination and true infection is important for clinical management. Microbiologic factors include growth in culture within 48 h, growth in both aerobic and anaerobic bottles, and multiple cultures (two or more blood culture sets) positive for the same organism with identical antibigrams.

Much of the work on the bacteremia due to CoNS derives from the observation that most infections occur in the setting of prosthetic devices. Following attachment of the organism to the foreign material, CoNS produce an extracellular polysaccharide matrix, which encases the bacteria, called "biofilm". Biofilm acts as a barrier to antibiotic penetration and interfere with host defenses, including T lymphocyte activation, opsonization, polymorphonuclear leukocyte migration, and macrophage function [69]. Resistance to metillin and semisynthetic penicillins has been observed in more than 80 percent of CoNS isolates [70].

The agent of choice for empiric treatment of infections due to CoNS is vancomycin, while in the setting of infection due to CoNS that is known to be metillin susceptible, the preferred agent is nafcillin or oxacillin.

Additional agents with potential activity against CoNS include daptomycin, linezolid, telavancin, ceftaroline, quinupristin-dalfopristin, tedizolid, and dalbavancin.

A worrisome trend in reduced susceptibility to glycopeptides has been observed in CoNS, especially in such species like S. haemolyticus [71]. A reduced susceptibility is more frequent for teicoplanin due to the presence of hetero-resistant populations in the context of bacterial inoculum [43,72]. For these reasons, teicoplanin is not a drug of choice for patients with CoNS bacteremia or endocarditis, and vancomycin should be preferred. A further option is represented by daptomycin, which possess a strong activity against staphylococcal biofilm [73], and is more effective than vancomycin for the treatment of experimental foreign-body and systemic infections by biofilm-producing metillin-resistant S. epidermidis [74]. Daptomycin has been also used in CoNS infections caused by linezolid-resistant strains [75].

Table 4

<table>
<thead>
<tr>
<th>Primary bacteremia</th>
<th>Vancomycin</th>
<th>Daptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary bacteremia</td>
<td>1. SST1</td>
<td>1. Daptomycin</td>
</tr>
<tr>
<td>2. Pneumonia</td>
<td>2. Vancomycin or linezolid</td>
<td>2. Daptomycin or teicoplanin or vancomycin</td>
</tr>
<tr>
<td>3. Bone</td>
<td>3. Daptomycin or teicoplanin or vancomycin</td>
<td>3. Daptomycin or teicoplanin or vancomycin</td>
</tr>
</tbody>
</table>

Legend. MRSA: methillin-resistant Staphylococcus aureus; MIC: minimum inhibitory concentration; SSTI: skin soft tissue infection.
Legend. IE: infective endocarditis; HF: heart failure; MDR: multidrug-resistant.

Since the introduction of linezolid in the clinical practice several mechanisms of linezolid-resistance (LNR) have been described, with mutations in the V domain of the 23S rRNA recognized as the major mechanism of resistance, and recently cfr mediated resistance mechanism is becoming predominant. Recently we reported an important risk factor for the selection of LIN-R strains. This suggests that both antibiotic selection pressure and cross transmission play a role in the local emergence and spread of the resistant clones, and the need for strict observance of infection control measures to prevent catheter-related infections in ICU [76].

Ceftraroline alone or in combination with daptomycin, may be used as salvage therapy for persistent CoNS bacteremia, although experience is primarily with S. aureus and not with CoNS [77,78]. Other agents with potential efficacy include teicoplanin, clindamycin, and trimethoprim-sulfamethoxazole. Gentamicin is rapidly bactericidal for CoNS, but its clinical utility is limited by resistance (60–70 percent of isolates in some studies) [79]. More than 90 percent of CoNS isolates remain susceptible to rifampin, although this drug must be used in combination with another antibiotic since resistance develops rapidly with rifampin monotherapy. Fluoroquinolones and macrolides may not be an appropriate choice for treatment of CoNS infections for the rapid emergence of resistant strains after few days of therapy.

### Table 5
Antibiotic treatment of infective endocarditis caused by staphylococci and enterococci.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antibiotic regimen</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible staphylococcal IE on native valve</td>
<td>Oxacillin plus gentamicin (3–5 days)</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td>Methicillin-resistant staphylococcal IE on native valve</td>
<td>Vancomycin plus gentamicin (3–5 days)</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td>Methicillin-susceptible staphylococcal IE on prosthetic valve</td>
<td>Oxacillin plus gentamicin (two weeks) plus rifampin</td>
<td>≥6 weeks</td>
</tr>
<tr>
<td>Methicillin-resistant IE staphylococcal infections on prosthetic valve</td>
<td>Vancomycin or daptomycin plus gentamicin (two weeks) plus rifampin</td>
<td>≥6 weeks</td>
</tr>
<tr>
<td>Enterococcus spp β-lactams susceptible strain, not high-level aminoglycoside resistance</td>
<td>Ampicillin/amoxicillin plus gentamicin or Ampicillin plus ceftriaxone</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td>Enterococcus spp, high-level aminoglycoside resistance</td>
<td>Ampicillin plus ceftriaxone</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Enterococcus spp, β-lactams resistance</td>
<td>Vancomycin plus gentamicin</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Enterococcus spp, multiresistant to aminoglycosides, β-lactams, and/or vancomycin</td>
<td>Linezolid or Quinupristin-dalfopristin Daptomycin plus ampicillin Imipenem plus ampicillin Ceftriaxone plus ampicillin</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

Legend. IE: Infective Endocarditis.

- **a** Recent studies have restrained directed therapy of aminoglycosides to situations in which there are no appropriate alternatives [104].
- **b** If patients have renal impairment or as primary therapy [84].
- **c** Ceftriaxone should be used at dosage of 2 g every 12 h [84].

### Table 6
Indications for surgery in left-sided native valve and prosthetic valve infective endocarditis.

<table>
<thead>
<tr>
<th>Heart failure</th>
<th>NVE PVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic or mitralic IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock</td>
<td>x x</td>
</tr>
<tr>
<td>Aortico or mitralic IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock</td>
<td>x x</td>
</tr>
<tr>
<td>Aortic or mitralic IE with severe acute regurgitation or valve obstruction and persisting HF or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)</td>
<td>x x</td>
</tr>
<tr>
<td>Aortic or mitralic IE with severe regurgitation and no HF</td>
<td>x</td>
</tr>
<tr>
<td>Severe dehiscence without HF</td>
<td>x</td>
</tr>
<tr>
<td>Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)</td>
<td>x x</td>
</tr>
<tr>
<td>Persisting fever and positive blood cultures &gt;7–10 days</td>
<td>x x</td>
</tr>
<tr>
<td>Infection caused by fungi or MDR organism</td>
<td>x x</td>
</tr>
<tr>
<td>Infection caused by staphylococci and gram-negative bacteria</td>
<td>x</td>
</tr>
<tr>
<td>Prevention of embolism</td>
<td>x x</td>
</tr>
<tr>
<td>Aortic or mitralic IE with large vegetation (&gt;10 mm) following one or more embolic episodes despite appropriate antibiotic therapy</td>
<td>x x</td>
</tr>
<tr>
<td>Aortic or mitralic IE with large vegetation (&gt;10 mm) and other predictors of complicated course (HF, persistent infection, abscess)</td>
<td>x x</td>
</tr>
<tr>
<td>Isolated very large vegetation (15 mm)</td>
<td>x x</td>
</tr>
</tbody>
</table>

Legend. IE: infective endocarditis; HF: heart failure; MDR: multidrug-resistant.

### 3. Enterococcal bacteraemia and endocarditis

A progressive increase in enterococcal bacteraemia has been described over the last three decades [80], and it is of special interest owing to its severity and therapeutic difficulties due to an increasing rate of antimicrobial resistance. Risk factors for enterococcal bacteraemia may be divided into two types, endogenous and exogenous: endogenous risk factors are those associated with underlying diseases, including liver cirrhosis, intestinal cancer, neutropenia and organ transplantation; exogenous risks factors include the presence of indwelling devices such as intravascular catheter, urinary catheter and nasogastric tube and the prior use of antibiotics, especially cephalosporins and imipenem [81]. Enterococcus faecalis is the leading species causing BSI or IE, and accounts for about the 65–70% of the cases while Enterococcus faecium for about the 25%. In USA approximately 12% of the hospital-acquired infections are Enterococcus species.
Enterococci are relatively resistant to the killing effects of cell wall–active agents (penicillin, ampicillin, and vancomycin) and are impermeable to aminoglycosides. Therefore, a combination regimen of two agents, a cell wall–active agent with a synergistically active aminoglycoside is required for optimal cure rates of invasive infections, such as BSI or IE. Combination of ampicillin plus gentamicin has been long considered the regimen of choice, but during last two decades further combinations have been tested. Combination of ampicillin and ceftriaxone may saturate low-molecular-weight penicillin-binding proteins (PBPs) 2, 3, 4 and 5, producing the bactericidal synergistic effect [82,83]. Since enterococcal endocarditis appears generally in older patients, and age is associated with a higher risk of nephrotoxicity, less toxic regimens like ampicillin plus ceftriaxone may be preferred. Important data were recently published about the role of ampicillin and ceftriaxone combination in the treatment of *E. faecalis* infective endocarditis (EIE). In an observational, nonrandomized, comparative multicenter cohort study, the ampicillin-ceftriaxone combination was as effective as ampicillin plus gentamicin for treating *E. faecalis* infective endocarditis [84]. Although patients treated with ampicillin-ceftriaxone combination were in poorer general condition before acquiring the infection than patients treated with ampicillin plus gentamicin, there were no differences in mortality between the treatment groups; moreover, ampicillin-ceftriaxone combination was effective in both high-level aminoglycoside resistance and non-high-level aminoglycoside resistance EFIE.

Colonization and clinical infection with vancomycin-resistant enterococci (VRE) were first described in Europe in the 1980s [85] and soon thereafter in the United States [86]. The presence of VRE in Europe was related to the use of glycopeptides such as avoparcin as a food additive for growth promotion in animals for more than 20 years, a practice that was subsequently banned by the European Union. Multiple epidemics of VRE infection have been described in diverse hospital settings (eg, medical and surgical intensive care units, and medical and pediatric wards) and, like methicillin-resistant *S. aureus*, VRE is endemic in many large hospitals. The vast majority of VRE isolates are *E. faecalis*, and data from the NHSN suggest that vancomycin resistance is present in the 80 percent of *E. faecium* isolates and 6.9 percent of *E. faecalis* isolated reported in 2006 and 2007 [87].

VRE infections have been associated with adverse outcomes. The magnitude of this effect was illustrated in a meta-analysis of nine studies of 1614 enterococcal bloodstream infections, 42 percent of which were due to VRE [88]. The mortality rate was significantly higher in patients with VRE compared with vancomycin-susceptible enterococcal isolates (summary odds ratio 2.5, 95% CI 1.9–3.4); however, it is difficult to ascertain the exact role of VRE infection in determine death because these organisms frequently colonize or infect very compromised patients with severe underlying diseases. It is recommended an antimicrobial therapy in patients with at least two or more positive blood cultures associated, or a single positive blood culture accompanied by signs of sepsis. Daptomycin and linezolid are feasible options in cases of VRE infections. A recent meta-analysis shows that linezolid treatment for VRE bacteremia was associated with a lower mortality than daptomycin treatment [89].

4. **Pharmacokinetic/pharmacodynamic (PK/PD) considerations in the management of gram-positive bacteremia and endocarditis**

Critically ill patients with BSI have several dysfunctions related to the septic syndrome which, together with drug interactions and other therapeutic interventions (e.g., haemodynamically active drugs and continuous renal replacement therapies), may affect drug pharmacokinetics [90]. Variations in the extracellular fluid content and/or in renal or liver function are the most relevant and frequent pathophysiological mechanisms possibly affecting drug disposition in critically ill patients; hydrophilic antimicrobials (e.g. β-lactams, aminoglycosides and glycopeptides) and renally excreted, moderately lipophilic, antimicrobials (e.g. ciprofloxacin, gatifloxacina and levofloxacin) have to be considered at high risk of presenting substantial daily fluctuations in plasma concentration during.

Hydrophilic antimicrobials exhibit a volume of distribution (Vd) limited by the extracellular space, and their plasma and interstitial concentrations may drop dramatically because of substantial fluid extravasation to the interstitial space, known as third spacing. Abundant intravenous fluid therapies, total parenteral nutrition, pleural effusion, mediastinitis, peritoneal exudates and ascites, by causing an increase in the extracellular compartment fluid, may lead to a significant increase in Vd; moreover, hypoalbuminemia, a common condition in critically ill patients, may also contribute to fluid extravasation and antimicrobial dilution by reducing plasma oncotic pressure, whereas the increase in the free fraction of drugs may increase their Vd. In surgical patients, indwelling drainages may represent a pathway of antimicrobial loss and contribute to lower antimicrobial levels. In ICU setting the use of haemodynamically active drugs (e.g. dopamine, norepinephrine) can modify renal blood flow and thereby glomerular filtration, tubular secretion rates and renal clearance. Under these circumstances higher dosages for most hydrophilic antimicrobials (either aminoglycosides or β-lactams) should therefore be considered to ensure therapeutic concentrations are maintained, and therapeutic drug monitoring (TDM) may be of great value in the clinical conditions described above.

Pharmacokinetics of vancomycin shows broad variability in critically ill patients due to a significant change in both clearance and the Vd [91]. Higher doses of vancomycin seem to be necessary in critical patients, even when the pathogens have MIC values typical of susceptible microorganisms, and TDM is strongly recommended. According to a PK/PD analysis, vancomycin standard dosages lead to a 33% risk of not achieving the recommended AUC0–24/MIC breakpoint for *S. aureus* in ICU patients, possibly leading to an unfavourable clinical outcome [92]. The results of Monte Carlo simulation revealed that doses of 3000 mg or even 4000 mg daily may be necessary to reach the highest probability of efficacy when susceptible *S. aureus* strains are involved critically ill patients, and similar results were found for other staphylococcal isolates [93]. Regarding glycopeptide-intermediate *S. aureus* (GISA) strains, doses as high as 5000 mg/day would be necessary [93]. With the aim of improving the results of vancomycin therapy, a variety of strategies such as higher doses, combination therapy and continuous infusion have been proposed. Continuous infusion might make treatment monitoring and adjustment easier and cheaper because vancomycin concentrations in serum are less variable and more sustained [94]. In a prospective multicentre randomised trial comparing critically ill patients with severe methicillin-resistant staphylococcal infections, continuous infusion of vancomycin resulted in therapeutic concentrations being achieved more quickly, less AUC variability between patients, fewer samples required to monitor treatment, and reduced 10-day antibiotic cost; clinical efficacy and safety were comparable to the intermittent infusion schedule [95]. Di Filippo et al. observed more favourable clinical outcomes in patients with continuous infusion of vancomycin in terms of improved organ function and leucocyte response, but overall disease evolution was not altered [96], probably because the study sample was too small (N = 25). The evidence suggests a strict monitoring of vancomycin serum concentrations in critically ill patients and the preference for continuous infusion at least in strains fully susceptible (MIC < 1 μg/ml).
As regards to daptomycin, Safdar et al. demonstrated that both the AUC/MIC<sub>0–24</sub> ratio and the C<sub>max</sub>/MIC ratio were strong predictors of in vivo efficacy [97,98] of the drug. Using an in vitro pharmacodynamic model with simulated endocardial vegetations Cha et al. compared daptomycin at 6 and 8 mg/kg/day versus vancomycin at 1 g every 12 h against MRSA, methicillin-resistant-<i>Staphylococcus epidermidis</i>, GISA and glycopeptide-intermediate <i>S. epidermidis</i>, and VRE [99]. Both daptomycin regimens achieved greater killing (more than 99.9% kill by 8 h) and greater bacterial reduction than vancomycin against all tested isolates at 24, 48 and 72 h. A further clinical experience showed that patients with MRSA BSI and severe sepsis or septic shock may experience a significant reduction of daptomycin serum levels, leading to lower exposure and poor clinical outcome [100]. The underexposure of daptomycin was related to an increased clearance of the drug, and was independent from weight and from the dosage used since it was detected also in patients receiving 8 mg/kg/day. Monte Carlo simulations showed that a fixed dosage of 750 mg/day might be the best choice to optimize the drug exposure and to minimize side effects in septic patients [101]. A simple method to calculate daptomycin AUC may also be used to adjust dosages in the clinical practice [102]. These findings suggest that higher daptomycin doses are likely necessary at the onset of therapy in critically ill patients, and that future interventional randomized studies are needed to clarify the best daptomycin dosing.

TDM and PK/PD correlations should be encouraged in all patients with BSI or IE receiving antibiotic therapy, and may result in a better clinical outcome and a reduction in antibiotic resistance and economic costs.

5. Conclusions

During the last decades important changes in the epidemiology of infections due to Gram-positive cocci have occurred, and MRSA, methicillin-resistant CoNS, and MDR enterococci have emerged as a major cause of nosocomial infection. The optimisation of antimicrobial therapy in patients with BSI is mandatory, especially in patients with sepsis or septic shock that have several dysfunctions related to the septic syndrome, which may affect drug pharmacokinetic parameter. PK/PD relationships are the major determinants of the in vivo efficacy of antimicrobial agents and allow optimisation of the dosage regimen to improve the outcome and reduce the selection of resistant mutants.

A correct choice of empirical antibiotic therapy and the development of new drugs with good activity against MDR Gram-positive cocci appear the most useful tools to reduce the morbidity and mortality associated with these infections.

Conflict of interest

No conflict of interest.

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