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Maximizing positive outcomes for patients with staphylococcal infections

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Abstract

Maximizing positive outcomes for serious Gram-positive infections, such as those caused by *Staphylococcus* species, requires an aggressive treatment approach. Although specific approaches will depend upon many factors, the underlying common strategy should recognize the positive contribution of minimizing complications and inpatient treatment duration and the efficient use of healthcare resources, while also focusing on rapid resolution of infection and safety and tolerability. To advance the standard of care for patients, we need to utilize therapies that enable such a range of factors to be improved. Treatment guidelines are useful to establish evidence-based standards of care, but they are updated infrequently and there is currently no pan-European consensus for the treatment of staphylococcal infections. With the benefit of the clinical experience that has been acquired for the most recently licensed antibiotics, together with an appreciation of the appropriate usage of older agents, there are good prospects for achieving positive outcomes earlier and in a greater range of patients with staphylococcal infections, and treatment guidelines should be updated regularly to reflect this.

Keywords: Bloodstream infections, daptomycin, Gram-positive infections, infective endocarditis, *Staphylococcus aureus*

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Introduction

Despite recent advances, Gram-positive infections remain a significant cause of morbidity and mortality among hospitalized patients and are the cause of various serious hospital-acquired and community-acquired infections [1]. In order to maximize positive outcomes for patients, aggressive treatment approaches against the opportunistic pathogens that are the major causative agents of these infections are required. Of particular note for its pathogenicity is *Staphylococcus aureus*, methicillin-resistant strains of which have become more prevalent in some countries and are associated with greater morbidity and mortality than wild-type strains [2].

The past decade has witnessed significant changes in the profiles of susceptibility of Gram-positive bacteria to vancomycin, a traditional treatment of choice for serious infections caused by methicillin-resistant *S. aureus* (MRSA). These include the emergence of vancomycin-resistant staphylococci and enterococci, as well as vancomycin-intermediate *S. aureus* and heteroresistant vancomycin-intermediate *S. aureus* [3,4]. Furthermore, several reports indicate that the MICs of vancomycin for susceptible strains have increased over time in some healthcare institutions [5–8], and that this has had a negative impact on the clinical outcomes for patients [9–11]. This changing epidemiology serves to emphasize the difficulty of ensuring that patients receive appropriate antibiotic therapy.

Specific treatment approaches to staphylococcal infections will depend upon many factors, including the species, strain and site of infection, as well as the presence of any co-morbid conditions. However, the underlying common strategy should recognize universal goals of treatment that include minimizing the risk of complications experienced during prolonged infection, minimizing time spent in hospital and optimizing the use of limited healthcare resources. Therefore, the ideal antibiotic will resolve infection rapidly and completely, and will have a good safety and tolerability profile and a convenient dosing regimen. Each of these key features will be discussed in further depth in this review.

Minimizing Complications in Staphylococcal Infections

If not treated effectively and rapidly, patients with Gram-positive infections are at risk of developing serious complications. In a recent surveillance programme in Scotland, hospital-acquired infections contributed to mortality in 13% of all deaths [12]. Surgical site infections (SSIs) are some of the most frequent nosocomial Gram-positive infections, with incidence rates of up to 18%, even after clean surgery [13]. *S. aureus* continues to be a major cause of SSIs, being responsible for nearly 45% of orthopaedic-related SSIs in the UK between 2004 and 2007, with 62% of these being caused by MRSA [14]. A review of 3254 deaths of patients in all specialties of surgical care in Scotland during 2006 found that in 7% of the deaths that followed surgery, infection had developed at the operation site, and that 4% of all patients had hospital-acquired MRSA at the time of death [12]. Therefore, it would appear that effective management of these infections continues to be a significant challenge.

New antibiotics are continuously being developed, particularly for staphylococcal infections resistant to semi-synthetic penicillins. In light of the increasing number of available antibiotic agents, continuous reappraisal of treatment options is necessary to ensure that patients benefit maximally from these pharmaceutical advances; antibiotic agents with alternative modes of action may warrant particular consideration. Daptomycin (Cubicin) is the first available agent from a new class of antibiotics, the cyclic lipopeptides. The efficacy of daptomycin for patients with complicated skin and soft tissue infections (cSSTIs) was compared with that of conventionally recommended antibiotics (penicillinase-resistant penicillins or vancomycin) [15]. Response rates were similar among treatment groups, across all baseline diagnoses, with overall success rates of 83.4% and 84.2% for the daptomycin and comparator groups, respectively [15].

Bloodstream infections (BSIs) constitute a potential complication of many peripheral infections, including SSIs, and represent a route by which these can give rise to numerous serious complications, which may be localized, such as infective endocarditis (IE), infections of bones, joints or implanted devices, myositis, epidural abscess or meningitis, or systemic, such as systemic inflammatory response syndrome [16,17]. For patients with BSIs, MRSA and time to culture positivity (a surrogate marker for the size of the inoculum) have been reported as independent predictors of death [18]. Thus, BSIs are justifiably considered to be a medical emergency, especially when *S. aureus* is the suspected pathogen.

For many years, semi-synthetic penicillins and vancomycin have been the pillars of treatment for *S. aureus* BSIs. For methicillin-sensitive *S. aureus* (MSSA), the greater efficacy of β-lactams relative to vancomycin is well documented, despite the susceptibility of MSSA to vancomycin *in vitro* [19–22]. For example, in a multicentre, prospective observational study of 505 consecutive patients with *S. aureus* bacteraemia (SAB), nafcillin proved superior to vancomycin for the treatment of MSSA. Furthermore, therapy with vancomycin was significantly associated with relapse of infection [19]. One of the key strengths of vancomycin has been in the treatment of MRSA infections, although data now support a more sophisticated approach to its choice than reliance on a positive susceptibility test. Recent reports suggest that the efficacy of vancomycin against MRSA strains with a vancomycin MIC of ≥1.5 mg/L may be compromised [11,23]. Therefore, although vancomycin remains an effective treatment for many Gram-positive infections, clinicians may need to consider alternatives when the methicillin status of a suspected *S. aureus* infection is uncertain or when susceptible MRSA strains with vancomycin MICs at the upper end of the susceptible range have been identified or are suspected on the basis of local epidemiology. Daptomycin, as an alternative to these standard therapies, has demonstrated efficacy in complicated and uncomplicated SABs as well as right-sided IE in a recent study, despite there being few relevant patients for this specific indication (Fig. 1) [24]. In this study, daptomycin was proven to be effective against both MSSA and MRSA, and as such, may theoretically be advantageous over currently licensed agents for the empirical treatment of Gram-positive infections.

Rapid Resolution of Infection

In order to maximize patient benefit, the optimal treatment regimen should ensure the prompt administration of an appropriate antibiotic agent. However, a survey of physicians

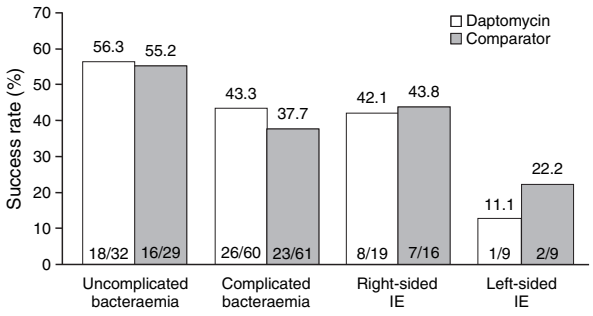

FIG. 1. Daptomycin success against *Staphylococcus aureus* bacteraemia and infective endocarditis (IE) in a phase III trial [24].