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Review

Early clinical assessment of response to treatment of skin and soft-tissue infections: how can it help clinicians? Perspectives from Europe

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ABSTRACT

Skin and soft-tissue infections (SSTIs) are a common indication for antibiotic use in Europe and are associated with considerable morbidity. Treatment of SSTIs, occasionally complicated by infection with meticillin-resistant *Staphylococcus aureus*, can be resource intensive and lead to high healthcare costs. For patients treated in an inpatient setting, once the acute infection has been controlled, a patient may be discharged on suitable oral antibiotic therapy or outpatient parenteral antibiotic therapy. The recently confirmed efficacy of single-dose (e.g. oritavancin) and two-dose (e.g. dalbavancin) infusion therapies as well as tedizolid phosphate, a short-duration therapy available both for intravenous (i.v.) and oral use, for treating SSTIs has highlighted the need for clinicians to re-evaluate their current treatment paradigms. In addition, recent clinical trial data reporting a novel endpoint of early clinical response, defined as change in lesion size at 48–72 h, may be of value in determining which patients are most suitable for early de-escalation of therapy, including switch from i.v. to oral antibiotics, and subsequent early hospital discharge. The aim of this paper is to review the potential impact of assessing clinical response on clinical decision-making in the management of SSTIs in Europe, with a focus on emerging therapies.

1. Introduction

Skin and soft-tissue infections (SSTIs) encompass a wide spectrum of clinical presentations, depending on the anatomical site of infection [1]. They range in severity from mild superficial forms to severe life-threatening infections that penetrate the deep subcutaneous tissues and/or require hospitalisation [2]. A variety of acronyms and definitions are used to describe SSTIs, which can lead to confusion among clinicians, including prescribers [3]. For example, skin and skin-structure infection (SSSI) is a commonly used term that can be considered synonymous with SSTI [4]. The term complicated SSTI (cSSTI) is used to describe infections that are at the extreme end of the clinical spectrum; cSSTIs are often accompanied by some evidence of systemic sepsis [1]. The US Food and Drug Administration (FDA) has introduced the term acute bacterial skin and skin-structure infection (ABSSSI) to help delineate the types of skin infections that should be assessed in registration trials of new antibiotics [4]. ABSSSIs include cellulitis/erysipelas, wound infections and major cutaneous abscesses, but exclude infections resulting from animal or human bites, necrotizing fasciitis, diabetic foot infection and decubitus ulcer infection [4]. For clarity, the term SSTI will be used here to describe all types of skin infection except where specifically stated otherwise.

The aim of this article is to review how early assessment of the patient's response to treatment can help clinicians in Europe improve the patient journey, such as shortening the hospital length of stay (LOS) and optimising outpatient therapy, thereby addressing important antimicrobial stewardship goals. To achieve this aim, clinical trials of recently licensed antimicrobials for the treatment of SSTI (due both to susceptible and resistant strains of *Staphylococcus aureus*) will be considered.

1.1. Clinical burden and epidemiology

SSTIs are a common indication for antibiotic use in Europe and are associated with considerable morbidity [5]. Data from the European Centre for Disease Prevention and Control (ECDC) estimated that 4% of all healthcare-acquired infections (HAIs) reported between 2011 and 2012 were SSTIs, with surgical-site infections being the second most frequently reported HAI (19.6%) [5]. During 2008 and 2009 there were 82,113 cellulitis hospital admissions in England and

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Wales with a mean hospital LOS of 7.2 days, and an estimated £133 million (€170 million; US$209 million) of costs were due to direct inpatient bed stay [6].

In Europe, the most frequently isolated Gram-positive pathogens in SSTIs are *S. aureus* [including meticillin-resistant *S. aureus* (MRSA) and meticillin-susceptible *S. aureus* (MSSA)], followed by β-haemolytic streptococci [1,7,8]. In skin infections that have a more complex aetiology, such as those resulting from necrotizing fasciitis, diabetic foot infection and ecthyma gangrenosum, the range of pathogens is numerous and is dependent on the clinical setting [4,9].

The prevalence of MRSA varies greatly across Europe, with much higher frequencies seen in southern and southeastern countries [10]. Based on the European Antimicrobial Resistance Surveillance Network (ERAS-Net), the European population-weighted mean percentage for MRSA was 17.4% in 2014, ranging from 0.9% in the Netherlands to 56.0% in Romania [10].

1.2. Resource implications

Treatment of hospitalised patients with SSTI in Europe is resource intensive and is associated with prolonged hospital LOS and high healthcare costs [11,12]. The drivers of increased LOS are described in Table 1. Patients with MRSA-SSTI experience a longer LOS compared with patients with MSSA-SSTI, which can be further prolonged when the initial antibiotic treatment fails [12]. The acquisition cost of antibiotics represents a relatively small proportion of the overall cost of managing cSSTIs in hospitals. A 2009 study estimated that for linezolid-treated patients, the per-patient total treatment cost (comprising hospitalisation, antibiotic, inpatient tests and aftercare charges) was €7778 [14]. The cost of the antibiotic itself was €1595, representing ≈ 20% of the total. The same study demonstrated that vancomycin treatment was associated with a higher overall cost (€8777) despite the comparatively lower cost of this drug (€964; ≈ 11% of the total) [14].

For inpatients, once the acute infection has been controlled and there are no other reasons for continued hospitalisation, it should be possible to discharge patients on suitable oral antibiotic therapy or outpatient parenteral antibiotic therapy (OPAT) [15–17]. Treatment outside of the hospital setting is generally preferred by patients, is relatively low cost and is aligned with antimicrobial stewardship strategies [16,18]. Three new antibiotics (oritavancin, dalbavancin and tedizolid phosphate) could offer additional opportunities for early discharge of cSSTI patients [19–21], in keeping with antimicrobial stewardship initiatives. Oritavancin and dalbavancin offer, respectively, a single-dose or two-infusion dose of treatment, representing a novel paradigm for treating such infections [22,23]. Tedizolid phosphate offers both intravenous (i.v.) and oral treatment options for a 6-day treatment duration [24,25]. Phase 3 trials of tedizolid phosphate demonstrated that 6 days of therapy, which is a shorter duration than that recommended for most other antibiotics for this indication [26–29], was non-inferior to 10 days of therapy with linezolid [24,25], providing evidence-based reassurance for clinicians to consider shorter durations of treatment with this antibiotic.

Table 1
Drivers of increased length of stay for hospitalised patients with complicated skin and soft-tissue infections (cSSTIs) (adapted from Nathwani et al) [13].

- Increased length of intravenous (i.v.) therapy
- History of i.v. drug abuse
- High number of co-morbidities
- Patients with deep or extensive cellulitis (versus patients with a surgical site or post-traumatic wound infection)
- Infection in the torso or abdomen (versus upper extremity infection)
- Infection developed ≥4 days after admission
- Severe sepsis
- Surgery
- Late initiation of antibiotic treatment (≥3 days after the date of cSSTI diagnosis)
- Failed/inappropriate initial/empirical therapy
- No i.v.-to-oral antibiotic switch options and/or lack of corresponding protocol
- Not discharged from the hospital with outpatient parenteral antibiotics
- Cultural attitudes of physicians toward completion of i.v. course in hospital
- Healthcare system reimbursement policies
- Lack of awareness of treatment/administration options

2. Management of skin and soft-tissue infections

Management of SSTIs is dependent on the clinical presentation and the severity of the infection [2]. In general, a combination of surgical debridement or drainage and antibiotic treatment is used to treat the infection [1], although incision and drainage, without the need for antibiotics, is usually sufficient for treating simple abscesses or boils [30]. Determining the level of disease severity is an important first step in the clinical management of SSTIs in order to determine the type of care and empirical therapy [31]. Failure to do this can lead to inappropriate prescribing, with overtreatment of mild SSTIs and undertreatment of severe SSTIs having been reported previously [32,33]. For non-necrotizing SSTIs, including those caused by MSSA, commonly used antibiotics include penicillin G, cloxacillin, ceftriaxone and clindamycin [3]. The Infectious Diseases Society of America (IDSA) recommends early empirical therapy with an anti-MRSA agent for all hospitalised patients with SSTI [2]. These treatments are discussed below.

In Europe, where there are vast disparities in the prevalence of MRSA between countries [10], emphasis should be placed on understanding local epidemiology patterns for MRSA to ascertain the level of risk and the requirement for antibiotic therapy directed towards this pathogen [3]. Initial treatment of SSTIs is usually empirical because microbial culture results are generally not available for several days, and patients with SSTI benefit from rapid initiation of appropriate therapy [34]. The importance of early treatment for MRSA-SSTI was underscored by a recent retrospective study showing that patients who received therapy 1 day or 2 days after their date of diagnosis with cSSTI had a significantly shorter duration of i.v. therapy and hospital LOS than patients whose treatment was initiated ≥3 days after their date of cSSTI diagnosis [13].

The first-line antibiotic treatments recommended for MRSA-cSSTI in Europe are the glycopeptides vancomycin and teicoplanin. Additional antibiotics recommended by guidelines for cSSTI with proven or suspected MRSA involvement include linezolid, daptomycin and tigecycline (Table 2), with 7–14 days of therapy generally being recommended [35,36,38,40–43]. Several new antibiotics approved in Europe for the treatment of ABSSSIs (oritavancin, dalbavancin and tedizolid phosphate) [19–21] or cSSTI (ceftaroline) [44] are not yet discussed in European guidelines. The use of inappropriate initial antibiotic treatment can be associated with adverse clinical outcomes, increased morbidity and mortality, and increased hospital LOS or costs [41,45–48], highlighting the importance of establishing a microbiological diagnosis promptly.

3. Treatment patterns in Europe

The REACH study was a large, multicentre observational study that examined treatment patterns, healthcare resource utilisation and clinical outcomes for hospitalised patients with cSSTI ($n = 1995$) in 10 European countries from 2010 to 2011 [8,12,49]. This analysis revealed that of cSSTI patients managed with antibiotics, 60.3% received penicillin with or without a β-lactamase inhibitor, 5.2% received vancomycin, 4.4% received daptomycin and 1.9% received linezolid as their initial antibiotic treatment [8], whereas teicoplanin and tigecycline were less commonly used.

A survey conducted in 2014 among 350 respondents from European infection societies indicated that the preferred initial i.v.

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