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European perspective and update on the management of complicated skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* after more than 10 years of experience with linezolid

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Abstract

Complicated skin and soft tissue infections (cSSTIs) are a diverse group of infections, with a range of presentations and microbiological causes. Hospitalization is common for patients with a cSSTI, which is treated by drainage of the affected area and with antibiotics. Host factors such as co-morbidities, and microbial factors, in particular drug resistance, complicate the management of these infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cSSTI pathogen in Europe, and its involvement can be associated with poor patient outcomes. European guidelines recommend vancomycin, teicoplanin, linezolid, daptomycin, tigecycline or ceftaroline for treatment of MRSA cSSTIs. Of primary importance when treating cSSTIs is the agent's clinical efficacy against the causative pathogens, as well as its bioavailability in the skin and associated structures. Linezolid is well-suited for the treatment of MRSA cSSTIs; it achieves high penetration into skin and soft tissues with 100% oral bioavailability, and therefore enables an intravenous to oral switch and outpatient treatment. When eligible patients are offered oral therapy the associated length of hospital stay and overall costs can be reduced. Linezolid has demonstrated clinical efficacy and favourable outcomes in patients for the treatment of MRSA cSSTIs including the treatment of lower extremity infections. Furthermore, efficacy has been documented in key defined populations, such as individuals with renal impairment and the obese. The safety profile of linezolid is well-documented, making this antibacterial a viable choice for the treatment of MRSA cSSTIs.

Keywords: Clinical management, complicated skin and soft tissue infections, Europe, linezolid, methicillin-resistant *Staphylococcus aureus*, resource use

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Introduction

Bacterial skin and soft tissue infection (SSTI) is a common cause of morbidity and mortality in both the community and hospital settings. *Staphylococcus aureus* is the predominant cause of these infections [1] and methicillin-resistant *S. aureus* (MRSA) is an important contributory factor in the development of complicated SSTIs (cSSTIs). This review addresses the definition and aetiology of cSSTIs and evaluates recent advances in the field of managing this heterogeneous group of conditions. In particular, we explore the situation in Europe with regard to MRSA and its treatment with linezolid, which is indicated for cSSTIs that are caused by Gram-positive bacteria [2].

Definition of cSSTI

Invasion of the epidermis, dermis and subcutaneous tissue by bacteria leads to SSTIs, which can produce a variety of clinical presentations [1]. The severity of these infections is dependent

on a series of factors, and the clinical spectrum ranges from mild forms to more life-threatening variants [3]. Otherwise healthy individuals with severe infections can be affected by SSTIs, as can patients with major co-morbidities and relatively minor infections [1].

In many cases, the severity of the SSTI necessitates hospitalization [4]. When the infection penetrates to the deeper subcutaneous tissue and/or surgery is required, it is considered 'complicated' (cSSTI) [5]. Included within this category—which sits at the extreme end of the clinical spectrum—are major cutaneous abscess, cellulitis, erysipelas, infected decubitus ulcer, infected ischaemic ulcer, infected venous stasis ulcer, bite-related infection, wound infection, surgical-site infection and trauma infection [1,6]. Complicated SSTIs can threaten lives and limbs, and therefore require early recognition and prompt management. Aside from surgery and drainage of the affected tissue, treatment for cSSTIs is centred on appropriate antibiotic therapy [1].

Recognition of cSSTI

Numerous species of microorganisms colonize the skin, and when broken, the skin can be penetrated by a wide variety of bacteria [7]. Infection, which is distinct from colonization, develops when microbial pathogenicity overcomes the host's immunological defences [8]. Local, systemic and microbial factors interact in a dynamic process to complicate SSTIs, and clinical recognition of these risk factors is important (Table 1). These processes account for the heterogeneity of cSSTIs, as previously discussed [1,8–11].

In some cases, cSSTI can present as a septic illness in previously fit and healthy individuals who are not immunocompromised. These are typically caused by highly pathogenic strains of common organisms, for example *S. aureus* expressing Panton-Valentine leucocidin (PVL) or toxigenic strains of *Streptococcus pyogenes* [11]. Typically, these infections spread rapidly and are medical emergencies that require prompt clinical recognition (which in most cases is driven by the observation of raised inflammatory markers); urgent surgical debridement should be carried out, and high doses of antibiotics should also be administered.

TABLE 1. Recognizing complicated skin and soft tissue infections: local, systemic and microbial warning signs

Local [1,9]	Systemic [8]	Microbial [1,10,11]
Vascular insufficiency Depth of tissue penetration Involvement of contiguous structures Involvement of foreign bodies (e.g. prosthesis, grafts)	Alcoholism Chronic renal failure Cardiovascular disease Cirrhosis Diabetes mellitus Elderly age Human immunodeficiency virus infection Iatrogenic immunosuppression Malnutrition Neuropathy Nicotine addiction Obesity and sedentary lifestyle Peripheral vascular insufficiency Solid and haematological tumours	Antibacterial resistance Polymicrobial infection Toxin production (e.g. Panton–Valentine leukocidin)

Local warning signs for cSSTIs include vascular insufficiency, increased depth of infection into the surrounding tissues, spread toward contiguous structures and involvement of foreign bodies (e.g. prostheses, grafts) [1,9]. Peripheral vascular disease is also associated with an increased risk for cSSTI. It is a predictor of impaired wound healing and is independently associated with major leg wound complication after saphenous vein harvest for coronary artery bypass graft procedures [12]. Vascular insufficiency can severely limit drug penetration to the site of bacterial infection, potentially leading to inadequate drug concentrations, clinical and microbiological treatment failure and the development of antimicrobial resistance [13]. Peripheral vascular disease is further associated with impaired renal function, hypertension and diabetes, which are also independently associated with impaired wound healing [12,14,15].

A series of systemic host risk factors may also escalate the recognition of cSSTIs (Table 1). Factors such as more advanced age, alcoholism, chronic renal failure, cardiovascular disease, cirrhosis, diabetes mellitus, human immunodeficiency virus infection, immunosuppression, malnutrition, neuropathy, nicotine addiction, obesity, sedentary lifestyle, peripheral vascular insufficiency and solid and haematological tumours have all been shown to influence the course of disease [8]. The most common risk factors for cSSTIs are hospitalization within the past 6 months and antibiotic use within the past 30 days [5].

Most often, cSSTIs are due to monomicrobial infection caused by Gram-positive or Gram-negative bacteria; however, they can also be polymicrobial [1], with a mixture of Gram-positive and Gram-negative bacteria comprising nearly one-fifth of infections in a US study [10]. Polymicrobial infections occur most often where tissue vascular perfusion is compromised, such as during infection of ischaemic or venous ulcers and in patients previously treated with antibiotics [1]. When more than one species of bacteria is involved in cSSTI there can be a synergistic effect, which can increase the pathogenicity and present a further challenge for clinical management [16,17].

Another microbial factor to consider in the recognition of cSSTIs is toxin production. *Staphylococcus aureus*, for example, commonly colonizes the skin and nasal membranes; however, its genome contains numerous potential virulence factors, such as adhesins, exoenzymes and exotoxins, which can result in varying degrees of pathogenicity. Production of the PVL toxin,