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Clinical approach

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Current approach to skin and soft tissue infections. Thinking about continuity of care

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ABSTRACT

Skin and soft tissue infections are a common reason for patients seeking inpatient and outpatient medical care. Surgery is an essential part of managing in many episodes. Careful evaluation of antibiotic therapy could help clinicians in early identification to patients with treatment failure and to consider an alternative approach or a new surgical revision in "focus control". With the arrival of new drugs, there is a need to refine the appropriate drug's decision-making. Drugs with a long half-life (long-acting lipoglycopeptides such as dalbavancin or oritavancin), which allows weekly administration (or even greater), can reduce hospital admission and length of stay with fewer healthcare resources through outpatient management (home hospitalization or day hospitals). New anionic fluoroquinolones (e.g. delafloxacin), highly active in an acidic medium and with the possibility of switch from the intravenous to the oral route, will also make it possible to achieve these new healthcare goals and promote continuity of care. Therefore, management should rely on a collaborative multidisciplinary group with experience in this infectious syndrome.

KEYWORDS: Skin and soft tissue infections, cellulitis, source control of infection, antimicrobial therapy, new and long-acting antibiotics.

INTRODUCTION: CLINICAL AND EPIDEMIOLOGICAL IMPACT

Skin and soft tissue infections (SSTI) are a common reason for patients seeking inpatient and outpatient medical care with more than 14 million outpatient visits a year [1], and almost 900.000 inpatient admissions in the United States [2]. Between 2005 and 2010, approximately 4.8 SSTIs requiring medical attention occurred per 100 person-years annually among those aged 64 years and younger [3]. Although this number has remained relatively stable, the high incidence of SSTI, if properly treated, has enormous potential to reduce disease morbidity and health care utilization. Cellulitis is one of the most common forms of clinical presentation of SSTIs affecting the dermis and subcutaneous tissue. There has been a rise in cellulitis incidence and associated costs over the past few decades [1,4]. From 1998 to 2013, cellulitis hospitalizations doubled (approximately 650.000 cases), and costs increased by nearly 120% to more than $3.7 billion annually in the USA [5]. Cellulitis contributed 0.04% of the total global disease burden in 2013 [6]. In 2019, the global incidence and rate of disability-adjusted life years for cellulitis were 54.84 million and 6.96 per 1.000 person-years, respectively.

SSTI accounts, by some estimates, for 3-30% of all hospital visits to the emergency departments (ED) [7,8] and is one of the five entities with the greatest variability in clinical decisions [9]. An estimated 12-40% [10,11] of SSTI seen in the ED are later admitted to the hospital, and 0.7% to intensive care unit [12]. Sepsis occurs in 4-8% of all patients who suffer from complicated skin and soft tissue infections (cSSTI), in which signs or symptoms related to sepsis may occur [13]. Severe SSTIs with sepsis are relatively frequent, and they are responsible for about 10% of all cases of septic shock [14]. Following pneumonia (55–60%) and abdominal infections (25%), cSSTI are the third most frequent cause of severe sepsis or septic shock [15]. Necrotizing soft tissue infections (NSTI) are almost always complicated by severe sepsis or septic shock [16].

SSTI comprehend a wide spectrum of conditions ranging from superficial skin abscesses that may be safely managed as an outpatient basis to dramatic presentations with extensive necrosis of underlying structures and sepsis-related organ failures resulting in major functional sequelae or death, such as necrotizing fasciitis (one of the main kinds of NSTI) [17]. Early initiation of adequate antimicrobial therapy is the essential

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Table 1 Main features and details associated with increased likelihood of NSTI

Clinical characteristics	Laboratory parameters
Rapid progression of cellulitis or fasciitis	Progressive hyperlactatemia
Cellulitis refractory to antimicrobial treatment	Renal failure (decreased creatinine clearance or glomerular filtrate abnormalities)
Pain out proportion to examination	Hyponatremia (serum sodium < 135 mmol/l)
Tenderness beyond area of erythema	Leukocytosis (white blood cell count > 15.000 cell/µl) or leukopenia (< 3.000 cell/µl)
Cutaneous anesthesia	Haemostasis disorders, prolonged clotting times
Bullae, hemorrhagic blisters	Elevated C-reactive protein together with probably very high procalcitonin values
Dusky appearance of skin	Rhabdomyolysis (creatine phosphokinase elevations and/or lactodehydrogenase)
Crepitus	Hyperglycemia or hypoglycemia (underlying diabetes mellitus decompensation)
Systemic toxicity	
Fever that does not respond to treatment, or unexplained hypothermia	

NSTI: necrotizing soft tissue infections (e.g. necrotizing fasciitis, myonecrosis, gas gangrene).

key to improve outcomes in patients with life-threatening SSTI, along with prompt surgical evaluation, source control with repeated debridement and removal of necrotic tissues when required, and resuscitation procedures, such as fluid administration, vasopressors infusion, intravenous immunoglobulin therapy in case of associated staphylococcal or streptococcal toxic shock syndrome (STSS), and other sepsis directed cares [18]. Severe SSTI –in particular necrotizing fasciitis and STSS– is often associated with aging and comorbidities, such as diabetes mellitus, chronic renal failure, arterial occlusive disease, intravenous drug abuse, morbid obesity, liver diseases and immunosuppression.

DEFINITIONS AND SPECTRUM OF PROGNOSTIC SEVERITY

SSTI, cSSTI, and NTSIs refer to the terminology and concept of the set of infections in this location that are seen by clinicians in the real world. Acute bacterial skin and skin structure infections (ABSSSI) are a common and heterogeneous group of diseases that ranges from superficial uncomplicated entities to life-threatening disease. According to the terminology introduced by the Food and Drug administration, ABSSSI include cellulitis, erysipelas, mayor skin abscess and wound infections [19]. The objective of this definition is to provide a regulation that makes it possible to homogenize the episodes of SSTIs and to compare the different antibiotic treatments (old and new), using agreed and pre-established parameters, and to make it easier for regulatory agencies to evaluate randomized clinical trials rigorously and accurately, in order to be able to position each new antimicrobial drug [20].

The cause of the SSTI is confirmed in about half of the patients, with current evidence suggesting the predominant role of *Staphylococcus aureus* including methicillin-resistant strains (MRSA) [21], *Streptococcus pyogenes* and other β-haemolytic streptococci; however, in some regions Gram-negative bacteria are increasingly reported as a cause of monomicrobial or polymicrobial infections, being involved up to 30% of the cases in some studies [22,23].

Severity of illness due to SSTI loosely correlates with depth of skin structure involvement, though there is no universally agreed upon severity scoring system. Severe SSTI include necrotizing fasciitis, STSS and myonecrosis/gas gangrene. In addition, patients having any SSTI meeting criteria for severe sepsis or septic shock or having a quick Sequential Organ Failure Assessment (SOFA) score at least 2 will be considered to have a severe SSTI [24]. NSTIs are frequently complicated by sepsis or septic shock and are the main example of severe SSTIs [25]. Several factors can make SSTI complicated or severe. Some of these factors are patient specific (e.g., immunosuppression), others have to do with local wound conditions (e.g., rapid progression) or treatment patterns (e.g., necessity for significant surgical intervention) [26]. NSTI are serious, life-threatening infections of the soft tissues. When tissue death appears, the infection is referred to as necrotizing. An NSTI is an infection that can start in one location and spread to large areas of the body within just a few hours [25]. NSTI can affect any part of the body, but most commonly occur on the arms and legs and, rarely, on the neck or face. One of the classic signs of NSTI is pain out of proportion to the examination, referring to the fact that the infected area might look normal and may not be too tender but the patient has severe pain (Table 1). The area directly over the affected tissues can look red or grayish or swollen or can have blisters; however, because the actual infection is located deeper in the soft tissues, the top part of the skin may look normal. Sometimes, bacteria can produce gas, which can lead to a crunchy sensation when the affected skin area is pressed. Unlike a focal infection of the skin, an NSTI is a systemic disease, which means that it may cause fever, changes in heart rate and blood pressure, and changes in level of alertness (Figure 1) [24,25]. Diagnosis is made based on the

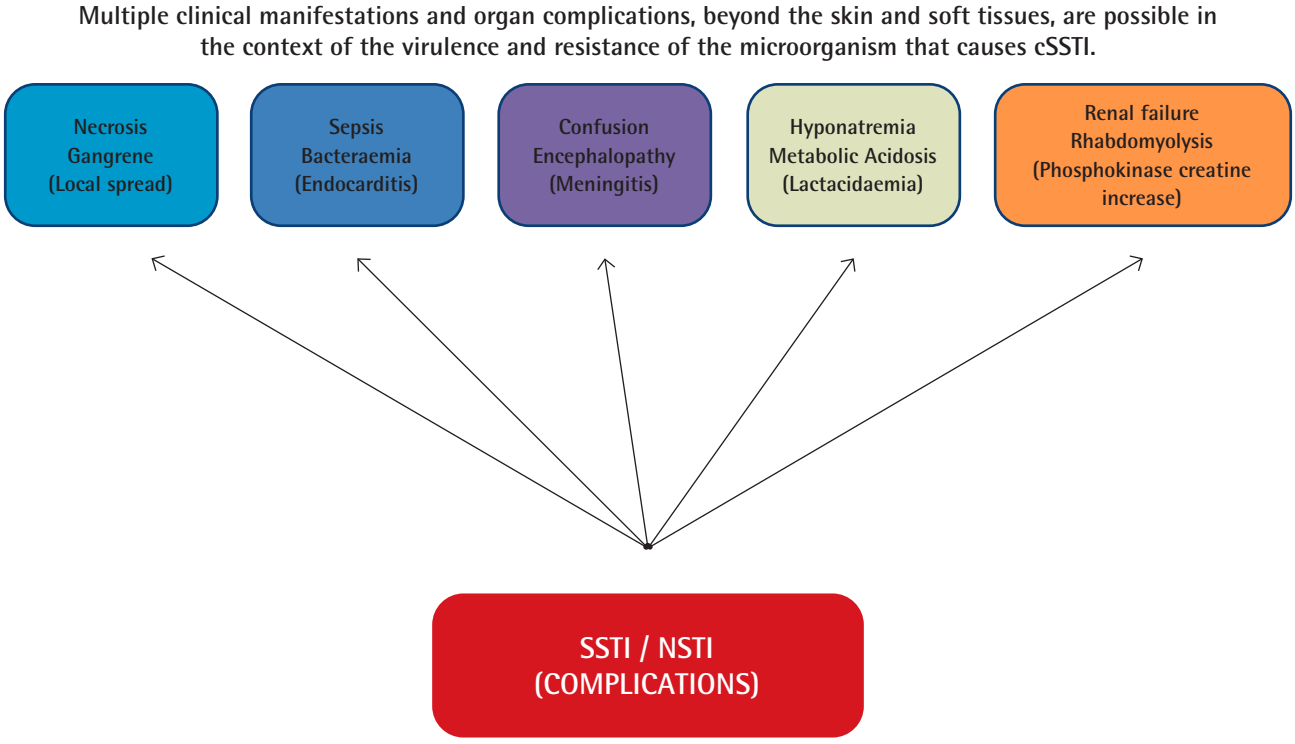

Figure 1 | **Complicated cellulitis and necrotizing fasciitis as local disease models with potential impact and serious systemic manifestations of sepsis and hematogenous dissemination**

SSTI: skin and soft tissue infections; cSSTI: complicated skin and soft tissue infections; NSTI: necrotizing soft tissue infections (e.g. necrotizing fasciitis, myonecrosis, gas gangrene).

patient's medical history, the physical examination, and the results of blood tests. If the diagnosis is not clear, an x-ray or computed tomography (CT) scan might help clarify the diagnosis. However, imaging is not recommended because it rarely establishes the diagnosis of an NSTI, and these tests delay the start of treatment [25,26].

In a recent prospective and observational study of 606 adult patients with cellulitis admitted to several Spanish hospitals, the factors associated with sepsis were: increased blood leukocytes and serum creatinine, blood culture drawn, modification of the initial antimicrobial regimen, and maximum length of cellulitis [27]. Regarding therapy, patients with sepsis associated to SSTI were related with poor treatment responses and more likely to undergo changes in the initial antimicrobial regimen, received more antimicrobials, received longer intravenous treatment, and underwent surgery more commonly than patients without sepsis with statistical significance [27,28].

For severe SSTI, intensive care, source control by means of early radical surgical debridement, and empirical broad-spectrum antimicrobials are required for the initial phase of illness and remain the cornerstones of therapy in NSTI. Owing to the rareness of NSTI, general clinical awareness is low and prompt diagnosis is often delayed. New diagnostic instruments (scoring systems, MRI) have either a low accuracy or are time consuming and cannot guide clinicians reliable currently. The choice of empirical agents depends on the type and location of SSTIs, place of onset (i.e. community acquired versus hospital-acquired), immune status, exposure history (animals, water, trauma), initial severity and whether the patient presents or not with specific risk factors (e.g. travel history) for multidrug-resistant bacteria (MDRB), with local epidemiology and prior antimicrobial use being among the main features to consider [29]. The value of adjunctive measures (intravenous immunoglobulin, hyperbaric oxygen therapy) is uncertain as well. Morbidity and mortality in NSTI remain high, ranging from 20 up to over 30% [26]. Further clinical research is necessary to shorten diagnostic pathways and to optimize surgical, antimicrobial, and adjunctive treatment.

NOVEL ASPECTS IN COMPREHENSIVE MANAGEMENT

In the modern comprehensive management of SSTI, sev-

Table 2 **Risk factors associated with methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTI)**

Risk Factors Associated with MRSA SSTI (including CA-MRSA)
Ethnicity (African Americans, Hispanic compared with Caucasian); recent travel (in Africa, Latin America or South East Asia)
Socioeconomic lower quintile, poor hygienic conditions, overcrowded housing, incarceration
Previous antibiotic therapy; recent (last three previous months)
History of MRSA: Previous colonization or *S. aureus* infection
Exposure: hospitalization in the previous 12 months, ICU admission, residence of long-term care facility, household contacts
Previous minor or major surgery
Intensive procedures and other instrumental techniques (e.g. image or radiological studies, central vascular catheters, implantable device)
Contact activities, such as daycare young children, contact sports activities, military service, contact with farm animals, insect bite injuries
Presence of underlying comorbidities: diabetes mellitus, peripheral vascular disease, cardiovascular disease, chronic wounds on extremities (often open), chronic renal disease, dialysis dependence, intravenous drug use,
Preexisting skin lesions (burns, eczematous dermatitis, etc.)
Purulent cellulitis
Hereditary (primary or congenital immunodeficiencies) or iatrogenic neutrophil disorder; immunosuppression

Methicillin-resistant *Staphylococcus aureus*: MRSA; skin and soft tissue infections: SSTI; Intensive care unit: UCI; Community-acquired methicillin-resistant *Staphylococcus aureus*: CA-MRSA.

eral guidelines for action must complement each other, mainly highlighting three: the so-called "focus control", the pharmacokinetic and pharmacodynamic optimization of antimicrobials and adjuvant measures.

The impact of surgical source control for severely ill patients with sepsis is underrepresented in clinical trials and the literature. Source control in cSSTI ranges from removal of central venous catheters or other device to radical debridement of extensive body areas. NSTIs serve as a model disease for the value of surgical measures in severe cSSTI [30]. Early diagnosis and timing of surgical intervention, the necessary extent of surgery and the assessment of adjunctive therapies (hyperbaric oxygenation, intravenous immunoglobulins) have been recently investigated [31]. The evidence for simple source control measures (i.e., wide opening and drainage of an abscess, limited debridement of infected tissue) remains low, but appears to be self-evident. Radical debridement of necrotic tissue (or even limb amputation) remains the standard of care for those patients with soft tissue sepsis because of NSTI. Specificities of NSTI with tissue necrosis and local ischemia resulting in hindered tissular diffusion are consistent with the need for urgent and aggressive surgical debridement of necrotic tissues. Surgical treatment should be performed within the first 12 h after admission. NSTI are a medical emergency. The key to treatment is emergency surgery to remove as much of the affected tissues as possible. This debridement may be extensive and disfiguring. Although a combination of antibiotics is used to help the body fight the infection, surgery is the only treatment proven to help. The risk of death with antibiotic treatment alone is very high, compared with 25% when antibiotics and emergency surgery are used together [25,26,30]. When present, treatment of associated organ failures in the intensive care unit is mandatory. Patients need to stay in the intensive care unit, may require a breathing tube, and usually need more than one operation for the infection to definitively be controlled. The incision in the skin is left open and packed with dressings. Treatment and recovery may take several weeks. Once the infection is definitively cured, patients might need plastic and reconstructive surgery in the areas that were affected. The value of other adjunctive measures (hyperbaric oxygen therapy, intravenous immunoglobulins) is uncertain [26,30,31]. Only an aggressive approach offers the possibility to save limbs (and life) of the affected patients [18,31].

Taking care of pharmacokinetic/pharmacodynamics (PK/PD) principles deriving from the most recent findings may help clinicians in maximizing treatment of SSTI with antimicrobials in every situation [32]. Recent studies suggest that distinguishing between bacteriostatic or bactericidal activity when choosing an antimicrobial for the treatment of severe SSTI could probably be clinically irrelevant. Conversely, what could help clinicians in maximizing the therapeutic efficacy of the various drugs in routine practice is taking care of some PK/PD parameters. Antibiotic therapy for NSTI patients faces several challenges and should achieve the best possible tissue diffusion with regards to impaired regional perfusion, tissue necrosis, and PK/PD alterations [33]. Concentration-dependent agents may exhibit more rapid bacterial killing than observed with time-dependent agents. Serum concentrations may not always adequately predict tissue exposure in patients with SSTIs, and measuring concentrations at the infection site is preferable. Hydrophilic antimicrobials showed generally lower penetration rates than the lipophilic

ones into the interstitial fluids of soft tissue and might require alternative dosing approaches in the presence of severe sepsis or septic shock. Features of septic shock from any cause (increased distribution volume, altered renal clearance, hypoalbuminemia, and reduced tissue perfusion) abound for optimizing delivery of hydrophilic and time-dependent drugs such as β-lactams by using high-loading doses and prolonged infusion with therapeutic drug monitoring [34]. Conversely, tissue penetration of lipophilic antimicrobials, molecules with higher tissue diffusion (e.g., clindamycin, linezolid and daptomycin), is less affected by the pathophysiological status and might be of interest in this setting. Estimation of the probability of target attainment at the infection site is of paramount importance in understanding whether or not the defined daily dosage of a specific antimicrobial may ensure optimal antimicrobial treatment in deep seated infections. Real-time therapeutic drug monitoring may be a very helpful tool for optimizing therapy of severe SSTIs.

Toxin production plays a key role in the pathogenesis of various SSTI caused by Gram-positive bacteria, mainly severe infections by *S. aureus*, *S. pyogenes* or *Clostridium. perfringens*. In standard clinical practice, combined antibiotic treatment is used to treat severe SSTI, whereby one of the drugs is usually a protein synthesis inhibitor antibiotic. These antibiotics given as adjuvant treatment may improve clinical outcomes and survival in patients with severe SSTI. This has been confirmed in *in vitro* studies, animal models, case reports and in clinical patient management. Although randomized clinical trials are lacking, in the light of several new drugs marketed for the treatment of these infections (oxazolidinones, lipoglycopeptides), the data available point to the greater efficacy of these options. Therefore, combination therapy (with β-lactam antibiotics), including an adjuvant protein synthesis inhibitor antibiotic for toxin suppression, should be used both in patients with severe SSTI and in those with moderate infection and risk factors for methicillin-resistant positive- or Panton-Valentine leukocidin positive-*S. aureus* infection [35].

ANTIMICROBIAL TREATMENT OPTIONS AND CONTINUITY OF CARE MANAGEMENT

The selection of initial antimicrobial therapy constitutes a growing challenge in hospitalized patients with cSSTI due to the wide spectrum of pathogens and resistance phenotypes of MDRB that may be encountered [29,36]. In this population, inadequate initial antimicrobial therapy has been associated with longer treatment duration, extended hospitalization, higher healthcare costs, more frequent subsequent readmissions, and an overall increase in the likelihood of death [37]. This issue, which applies to both community-acquired and healthcare associated SSTI, is even more critical in immunocompromised hosts, a subgroup in whom mycobacterial and fungal pathogens may also be implicated [38]. Microbiological documentation is pivotal in moderate-to-severe cases, both for ensuring timely treatment optimization and easing antimicrobial stewardship initiatives to limit unnecessary exposure to broad-spectrum drugs and their inherent adverse events. SSTI management guidelines do not include a clear recommendation on when and how to investigate the cause of SSTI [39]. It is not usually necessary to obtain microbiological samples in uncomplicated infections, except in cases of recurrences or for epidemiological control purposes. In the case of complicated infections, the samples are of two different types: those obtained from the affected area (surgical samples, punctures of abscesses or swabs) and systemic samples (i.e. blood cultures). The clinical condition also determines the type of samples to be obtained. In cases of systemic involvement, blood cultures are mandatory [40]. For immunocompromised patients, who may present atypical infections, detection of antigens, serologies or molecular biology techniques may be helpful. The rapid diagnosis is currently the goal to be pursued by implementing techniques such as matrix assisted laser desorption ionization-time of flight, commercial real-time PCR or the promising next-generation sequencing methods. Rapid diagnostic tools and clinical metagenomics are under evaluation for the management of SSTI and will hopefully help tailoring antimicrobial therapy in a close future in patients with risk factors for MDRB [29,41]. Identifying the optimal empirical antimicrobial regimen in patients with SSTI is increasingly challenging due to the rising prevalence of MDRB as the causative pathogens of these infections and (more generally) the growing population of individuals at-risk for MDRB-related condition.

The mainstem of empiric antibiotic treatment suggested in severe SSTI or in NSTI (and even at probable risk of MDRB) is a broad-spectrum β-lactam (e.g., piperacillin-tazobactam or combination of cephalosporins with new β-lactamase inhibitors) with additional aminoglycosides in case of septic shock33. Clindamycin or linezolid (antibiotics that inhibit protein synthesis) should be included in association in case of documented or suspected *S. pyogenes* infection (limb infection, features of STSS, absence of comorbidities, blunt trauma, absence of chronic skin lesions, homelessness, injectable drug use, non-steroidal anti-inflammatory drug use) or suspicion of MRSA. Coverage of resistant gram-negative bacilli by carbapenems should be used according to local ecology and individual risk factors (hospital acquired infection, β-lactam or quinolone exposure in the previous three months, history of extended spectrum beta-lactamase [ESBL] carrying, germ colonization/infection or travel to high ESBL endemic areas in the previous three months). Similarly, use of anti-MRSA drugs (rare and occasionally against enterococci) such as vancomycin, linezolid, tedizolid or daptomycin should be considered in case of local endemicity, residence in a long-stay care facility, chronic dialysis, permanent transcutaneous medical devices or prior MRSA infection/colonization. MRSA and *P. aeruginosa* represent the main pitfalls that predispose to inadequate initial therapy in community onset SSTI. In patients with hospital-acquired SSTI, MRSA (both hospital-associated and community associated lineages), multi-drug-resistant *P. aeruginosa* and *Acinetobacter baumannii*, ESBL-producing Enterobacterales and vancomycin-resistant enterococci are nowadays isolated on a regular basis, though the risk correlates closely with local epidemiology [29].

Table 3 **Potentially relevant factors to be balanced on a case-by-case basis for optimizing the use of antibiotics (either already available or future new-generation) in patients with SSTI at moderate or high risk of MRSA infection**

Antibiotic	Switch to oral therapy and early discharge	Useful if poor adherence factors to outpatient therapy (oral treatment at home)	Avoidance (no need) of hospitalization	Significant Drug interactions	Use in kidney dysfunction or renal failure	Coverage of GNB	Low risk of CDI	Use if Allergy to β-lactams
New anti-MRSA cephalosporins: Ceftaroline, Ceftobiprole	-	-	-	-	(+)*	+	-	-
Tedizolid	+	-	+	+	+	-	+	+
Long-acting lipoglycopeptides: Dalbavancin, Oritavancin	-	+	+	-	(+/-)*	-	+	+
Telavancin	-	-	-	-	-	-	+	+
Delafloxacin	+	-	+	(-)*	(+/-)*	+	-	+
Omadacycline	+	-	+	+	+	+	-	+

Skin and soft tissue infections (SSTI); methicillin-resistant *Staphylococcus aureus* (MRSA); *Clostridioides difficile* infection (CDI); Gram-negative bacilli (GNB). (+)*: Dosage adjustments adapted to creatinine clearance are necessary. (-)*: Less common and relevant than in older quinolones. (+/-)*: Still with little experience and few data.

There are now several active agents against MRSA and other gram-positive cocci that are FDA-approved for the treatment of SSTI [23], including tedizolid [42], ceftaroline, ceftobiprole [43], delafloxacin (an anionic fluoroquinolone) [44], new long half-life glycopeptides (dalbavancin, oritavancin) [45,46], telavancin and omadacycline (based on an aminomethylcycline) [47] [these last two not yet in Spain] [48]. Considering the similar efficacy that arose from direct comparisons in phase-3 randomized clinical trials to ABSSSI, in order to adopt the best approach for treating cSSTI on patient-tailored basis, the different safety profiles and formulations of the different available agents should be balanced by taking into account the specific features of each treated patient in terms of baseline comorbidities, related risk of toxicity, need for hospitalization, possibility of early discharge, and expected adherence to outpatient oral therapy. Ceftaroline, ceftobiprole, dalbavancin, oritavancin and telavancin are intravenous antibiotics offering excellent coverage for MRSA-SSTI and either expanded spectrum, longer half-life or better safety profile than older formulations. Delafloxacin, omadacycline and tedizolid are new oral antibiotics for treatment of SSTI with available intravenous formulations, making them potential step-down therapies. In turn, delafloxacin and omadacycline have expanded spectrum of coverage with activity against Gram-negative pathogens, making them attractive options for empiric treatment [49]. Older treatment options may be associated with toxicity and require frequent dosing; however, the current IDSA guidelines for MRSA infection and SSTI [17] as well as the recently published UK guidelines [50] on MRSA treatment only consider these drugs as alternative choices or do not mention them at all [48].

Current and future options for treating cSSTI focus on fluoroquinolones and long-acting lipoglycopeptide antibiotics. Clinical and pharmacological characteristics, advantages and limitations of the fourth-generation fluoroquinolone –delafloxacin-, and the semisynthetic long-acting lipoglycopeptide agents –dalbavancin and oritavancin- have been reviewed in detail in recent publications [44,45,46,48,49,51]. Delafloxacin is an anionic fluoroquinolone, active at acid pH (e.g. cystic fibrosis, abscesses or skin necrosis), with excellent penetration into biofilms, high potency against pneumococci, streptococci and staphylococci, as well as being active on MDRB strains and isolates resistant to levo/moxifloxacin. Its current approved indications are cSSTI, community-acquired pneumonia, and would allow sequential treatment from iv. to oral route [43,50]. Dalbavancin and oritavancin are characterized by the presence of an additional hydrophobic moiety, which determine their long half-lives (terminal half-life of 336 and 393 hours, respectively) but, most importantly, markedly improve their antimicrobial activity by increasing their membrane affinity and thus their concentration near the target [23,45,46,48,49,51]. Long-acting lipoglycopeptide antimicrobials represent another strategy for achieving ED. Their long half-lives allow treatment of SSTI with a single or weekly iv. dose, providing long-term iv. treatment without requiring continuous iv. access or inpatient stay. While they are approved by the FDA for SSTI / ABSSSI, their pharmacological properties suggest a potential role for the treatment of deep-seated and severe infections, such as bloodstream and bone and joint infections.

Both families of antibiotics could achieve: a) A reduction in hospital admissions; b) A shortening of the length of hospital stays; c) Easiness of early discharge; d) Maintenance of

high quality of care; and e) Adherence to antimicrobial stewardship.

So, for this reason, the use of these antimicrobials is particularly appealing when prolonged therapy, early discharge, suspicion of poor or non-adherence to oral therapy and avoidance of long-term intravascular catheter access are desirable or when multidrug-resistant bacteria are suspected. Other factors to be taken into account for influencing the choice when considering novel, approved agents for the treatment of cSSTI, especially in patients at high risk of MRSA infection (Table 2), are: acute kidney injury or chronic kidney disease, reduced platelet count or concomitant selective serotonin reuptake inhibitors, risk of *Clostridioides difficile* infection, no (more) need for hospitalization or facilitate switch to oral and early discharge possible (Table 3).

CONCLUSIONS

With the development of new drugs and the current evidence of their use, there is a need to refine the appropriate drug's decision-making. Drugs with a long half-life (long-acting lipoglycopeptides such as dalbavancin, oritavancin), which allows weekly administration (or even greater), can reduce hospital admission and length of stay with fewer healthcare resources through outpatient management (home hospitalization or day hospitals). New anionic fluoroquinolones (e.g. delafloxacin) that are highly active in an acidic medium and have a great capacity for tissue penetration, with a greater safety profile and the possibility of switch from the intravenous to the oral route, will also make it possible to achieve these new healthcare goals and promote continuity of care. Shorter courses of antibiotics are recommended based on the doctrine of "less is more", backed by scientific evidence.

Careful evaluation of antibiotic therapy after 48-72 h of initial therapy could help clinicians in early identification of patients with treatment failure and, therefore, consider an alternative approach or a new surgical or instrumental revision in "focus control". Surgery is an essential part of managing many SSTIs, but guidelines often do not include clear indications for either timing or surgical technique. Close monitoring of patients with multiple comorbidities, drug-drug interaction or adverse host factors are also necessary. In cSSTI or NSTI, PK/PD should be optimized by use of high-loading doses and prolonged infusions for molecules with time-dependent bactericidal activity such as β-lactams, and therapeutic drug monitoring should be used when available. The role of stewardship programs will continue to expand, but the positioning of oral antimicrobials in treating severe SSTI requiring hospitalization is unclear, as is the timing and manner of de-escalation of intravenous treatments.

Therefore, management should rely on a collaborative multidisciplinary group with experience in this infectious syndrome.

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