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EDITORIAL

Therapeutic targets in necrotizing soft tissue infections

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Necrotizing soft tissue infections (NSTIs) are rare and life-threatening bacterial infections characterized by an extensive necrosis of skin and subcutaneous tissues. Necrotizing fasciitis (necrosis of fascial planes), however, is less objective as a separate entity and it is possibly better to lump all severe soft tissue infections into the overall label of NSTIs, as the treatment of all is similar (antibiotics, early extensive surgery and supportive care are the mainstay of all NSTIs; see later).

NSTIs can affect any part of the body but the extremities—particularly of lower limbs—are most commonly involved. In most cases, the infection is polymicrobial, involving gram-positive cocci, *Enterobacteriaceae*, non-fermenting bacilli as well as anaerobic bacteria [1, 2]. In some instances, however, NSTIs are monomicrobial with group A streptococcus (GAS) and *Staphylococcus aureus* being the most frequently isolated pathogens [3]. In the early phase, management of NSTIs relies on broad-spectrum antibiotic therapy, rapid surgical debridement of all infected tissues and, when present, treatment of associated organ failures in the intensive care unit, following general sepsis and septic shock recommendations [4]. No specific guidelines have been proposed regarding early resuscitation strategies in patients with NSTIs; as recently suggested by a panel of experts, strategies to use more restrictive fluid resuscitation methods may be preferred [5]. Source control may require several surgical debridements, and amputation may be necessary in up to 15% of cases [6]. A coordinated multidisciplinary approach is required (Fig. 1). Yet, the mortality of NSTIs remains high, with 20–50% of patients dying during the early phase [1, 2, 7]. In this context, practice guidelines for the management of skin and soft tissue infections have been established by the Infectious Diseases Society of America (IDSA) in 2005 and updated in 2014 with a systematic weighting of the strength of the recommendations and quality of evidence [8]. For instance, a strong recommendation with a low level of evidence has been made against the use of hyperbaric oxygen therapy in patients with NSTIs. In fact, most recommendations have been made with a low level of evidence because of the lack of randomized controlled studies available in this field. Consequently, regarding the research agenda on NSTIs, the IDSA guidelines strongly advocate the development of clinical trials, particularly aimed at assessing treatments targeting staphylococcal and streptococcal NSTIs. These subtypes of NSTIs may indeed present with the classical toxic shock syndrome, for which clindamycin should be combined with penicillin in order to suppress streptococcal/staphylococcal toxins as well as cytokine production [9]. In this setting, the efficacy of intravenous immunoglobulins (IVIG) remains debated [10]. Several observational studies have indeed reported conflicting results [11–14] and one small randomized controlled trial [15] was prematurely terminated because of slow patient recruitment after including 21 patients (10 in the IVIG group and 11 in the placebo group). This study demonstrated a significant reduction in the SOFA score at days 2 and 3 in patients of the IVIG group as compared to others, as well as a significant increase in plasma neutralizing activity against superantigens. Notably, as a result of the discrepancy of the available data, the IDSA guidelines provided no recommendation regarding whether IVIG should be administered to patients having NSTIs and called for studies addressing this question.

In this context, Madsen et al. have performed the INSTINCT trial [16]—a blinded randomized placebo-controlled study recently published in *Intensive Care Medicine*—in which they evaluated the effect of IVIG on patient-reported quality of life, as assessed by the physical

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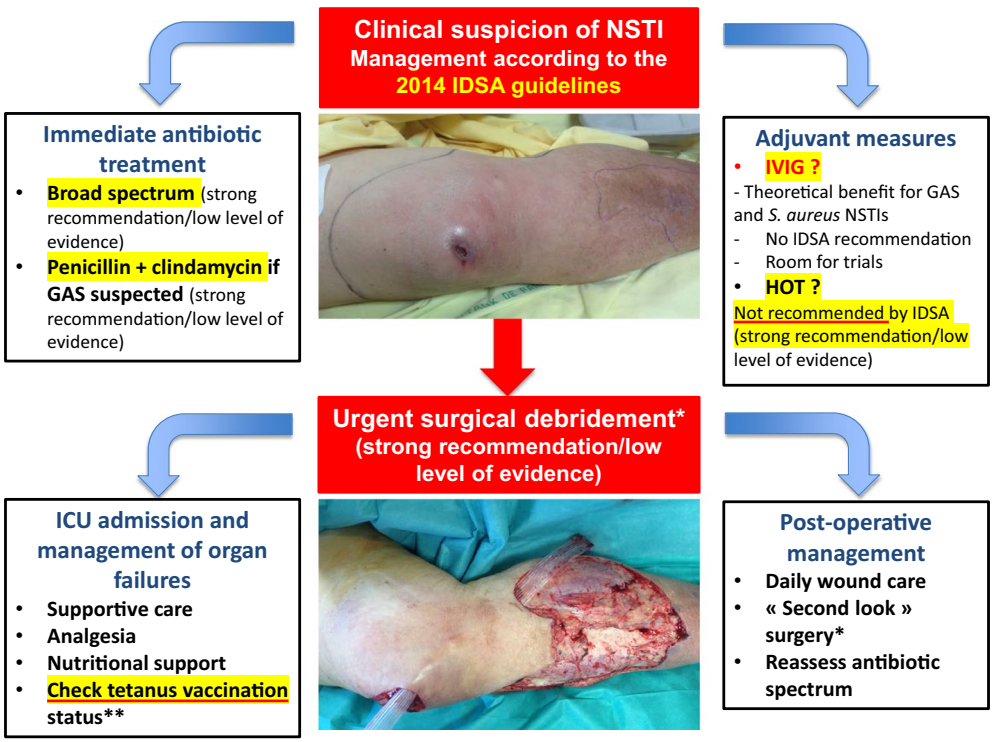

Fig. 1 Main steps and principles of early phase management of necrotizing soft tissue infections (NSTIs). Recommendations are provided according to the Infectious Diseases Society of America (IDSA) practice guidelines for the diagnosis and management of skin and soft tissue infections [8] (the strength of the recommendations and the quality of evidence are shown between parentheses). Other aspects of management in the intensive care unit and principles of postoperative care presented here do not come from the IDSA guidelines. *Surgical debridement should be performed as soon as possible and repeated daily until the surgeon finds no further need for debridement. Amputation may be required on a case-by-case basis. **Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years (strong recommendation/low level of evidence [8]). *IVIG* intravenous immunoglobulins, *GAS* group A streptococcus, *HOT* hyperbaric oxygen therapy, *IDSA* Infectious Diseases Society of America

component score of the SF-36 questionnaire measured 6 months after randomization, in patients admitted in the ICU for NSTIs. In all, 100 patients with NSTIs were randomized to receive IVIG (one daily 25-g infusion for three consecutive days) or an equivalent volume of 0.9% saline. The main result of the study is that in the intention-to-treat analysis, which included 87 patients, the physical component score was not significantly different in patients receiving IVIG (36 [0–43]) than in those who received saline (31 [0–47]; $p = 0.81$), a score of 0 being attributed to patients who had died. Secondary analyses in the per protocol population, in predefined subgroups, including that of patients with head/neck/extremities NSTIs in whom a higher rate of gram-positive cocci NSTIs had been anticipated, as well as other post hoc analyses, all yielded consistent results. Although the study was negative—in a context where 28-day mortality was very low (12% in both groups, for a median SAPS II of 42), possibly because patients where managed in an institution where the case volume of NSTIs is uniquely high, allowing for a rapid multidisciplinary management—the authors certainly have to be congratulated for performing one of the rare high standard randomized controlled trials in NSTIs. Also, the choice of using a composite outcome measure, merging a patient-related outcome (i.e., physical component score of the SF-36 questionnaire) and death, was particularly relevant to NSTIs, as these are usually characterized both by a high in-ICU mortality [1, 2, 7] and by serious long-term sequelae and related disability in survivors [6].

This study has, however, a number of limitations that deserve to be highlighted. First, the study appears to be underpowered, not only because 13 of 100 included patients did not complete the primary outcome measure, thereby leaving only 87 patients to be included in the intention-to-treat analysis, but also because of the limited number of patients eventually documented with GAS ($n = 13$) or *S. aureus* ($n = 3$) NSTIs. It is these bacterial species in which IVIG would be expected to provide a clinical benefit and the numbers in the study were lower than anticipated and hence certainly not large enough to allow for a significant difference between both groups to

be observed; not to mention the fact that these microorganisms were not evenly distributed between the IVIG and the placebo groups. Second, in view of IVIG being a standard of therapy within their hospital, patients could be included in the study provided they had not received more than one dose of IVIG prior to randomization. This resulted in 40% of patients in the placebo arm (vs 16% in the interventional arm) receiving IVIG before inclusion, thereby reducing the contrast between both arms and potentially blunting any beneficial effect related to IVIG. Third, the dose of IVIG administered (25 g daily for 3 days) was lower than in previous studies (for instance, 1 g/kg of body weight on day 1 and 0.5 g/kg on days 2 and 3 in the study by Darenberg et al. [15]), and was thus possibly suboptimal.

Nevertheless, in spite of these limitations, the study by Madsen et al. [16] provides valuable data and represents a big step forward in an evidence-based approach of NSTIs. The negative results of this study compel us to further explore whether there is any benefit of IVIG in patients in whom there is a high suspicion of streptococcal/staphylococcal infections. Further studies aiming at identifying factors associated with these microorganisms are required before embarking on large trials targeting these subtypes of NSTIs. Until such time, this study should be enough to put a damper on the use of IVIG.

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Compliance with ethical standards

Conflicts of interest
The authors have no conflict of interest to disclose.

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