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UNDERSTANDING THE DISEASE

Understanding necrotizing soft tissue infections in the intensive care unit

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Necrotizing soft tissue infections (NSTIs) are a rare group of severe and heterogenous infections. Distinguishing NSTIs from much more frequent non-necrotizing infections is a crucial step of initial management, as the former require not only medical treatment but also urgent surgical debridement of infected tissues [1]. Additional categorizations based on the microbiology or the anatomical extent of the disease have been proposed but are of little help to the clinician [2]. Only the topography (i.e., limb, abdomino-perineal, thoracic or head/neck localization) is immediately available and can modify early management. Approximately half of NSTI patients will develop organ failures and require intensive care unit (ICU) admission. Thus, intensivists must maintain high awareness for this rare condition, particularly in patients having a locally benign cutaneous presentation but with signs of systemic toxicity (i.e., sepsis/septic shock) and no other obvious source of infection. Initial misdiagnosis has been reported in about 50% of cases as presentation can be insidious, with no reliable biological or radiological diagnostic tool. Mortality ranges from 10 to 30% according to initial patient severity, and long-term health-related quality of life is deeply impacted in survivors, 15% of whom require limb amputations. A recent survey across European ICUs revealed great heterogeneity regarding both the expertise of practitioners (be it intensivists, surgeons or dermatologists) and the local management of patients [3]. For surveyed intensivists, the main factors contributing to surgical delay, one of the main modifiable prognostic factors, were misdiagnosis, a delayed surgical decision and logistical issues regarding operating room access. Suspecting the diagnosis must trigger the initiation of multiple urgent interventions and involve a multidisciplinary team coordinated by the managing physician (Fig. 1).

When to suspect a NSTI?

Any cutaneous infection showing any local or systemic sign of severity must be managed with a high index of suspicion for a necrotizing infection. Clinicians must be aware that the most frequent clinical features of NSTIs are also those of non-necrotizing infections (i.e., erythema, edema and pain), with prospective data showing that more specific signs of NSTIs, including bruising, bullae and crepitus, are present in only 51%, 27% and 14% of cases [4]. Thus, the diagnosis of NSTI must never be ruled out if these signs are lacking, particularly in patients presenting with sepsis/septic shock, failure to improve under antibiotic treatment or pain requiring opioids, out of proportion to physical findings or extending beyond the area of macroscopic cutaneous involvement [2].

How to make the diagnosis?

There is no perfectly reliable biological or radiological diagnostic tool, and the gold standard for diagnosis is surgical exploration revealing swollen, dull gray tissues with a thin, brownish exudate, with or without necrosis [5]. The LRINEC score, derived from standard serum parameters, has not performed convincingly to discriminate NSTI from non-necrotizing infections and cannot be recommended for this purpose [2, 6]. Other biomarkers may be elevated in patients with NSTI, including serum procalcitonin, creatine phosphokinase and lactate, but none of these have been shown to provide robust diagnostic yields. MRI has the best sensitivity amongst imaging modalities, and CT scan is useful for assessing source and extension of cervico-facial and abdomino-perineal

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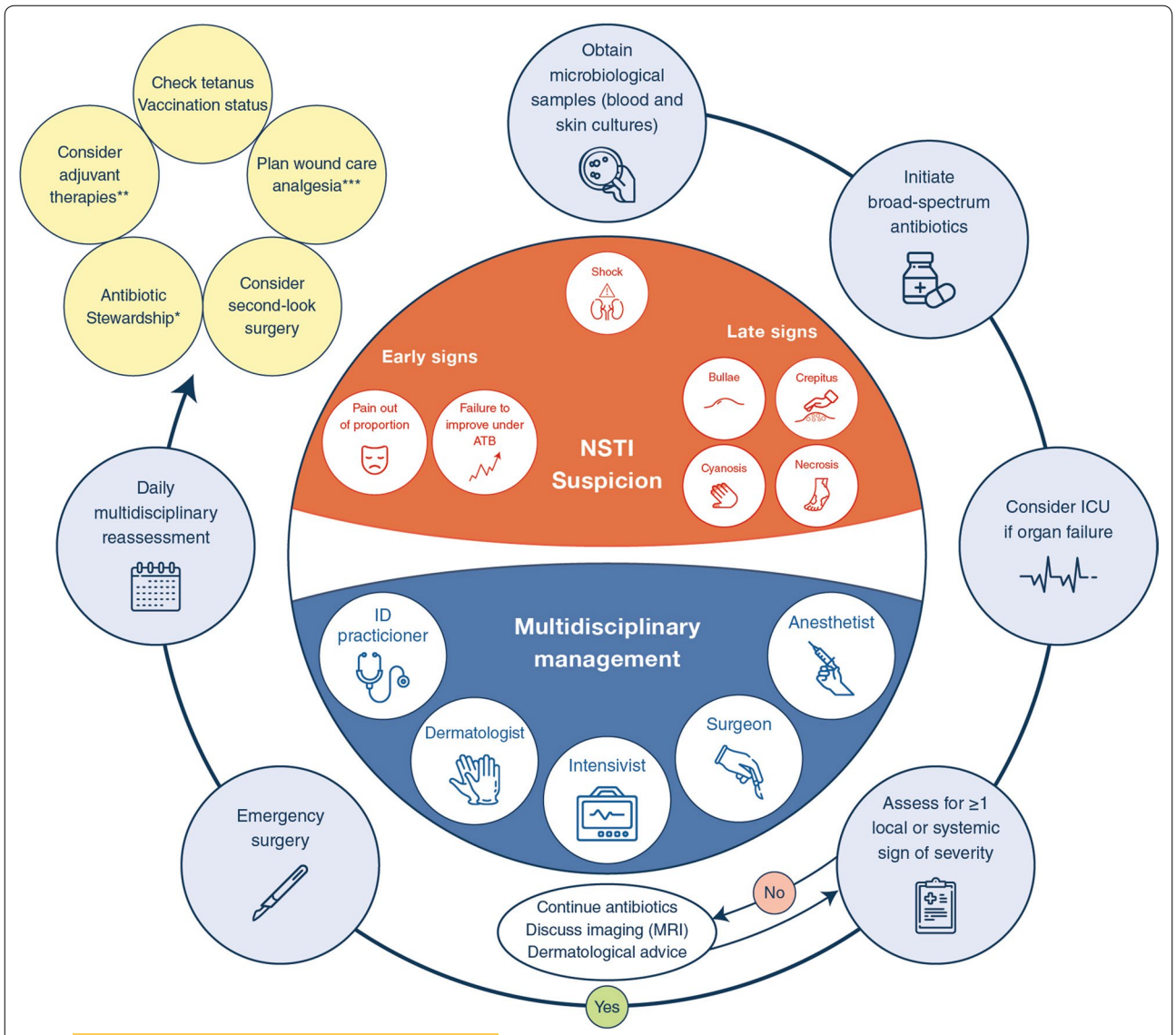

Fig. 1 Proposal of a multidisciplinary management algorithm for patients with necrotizing soft tissue infections. Figure representing the multiple and urgent interventions required during early management of necrotizing soft tissue infections. Once clinical suspicion is raised based on local and/or systemic signs of severity, the patient should be regularly and throughout management reassessed by a multidisciplinary team coordinated by the managing intensivist.

*Antibiotic stewardship consists in adapting spectrum to documentation in collaboration with microbiologists (mostly de-escalating), doses to plasma concentrations and duration to clinical evolution.

**Adjuvant therapies include intravenous polyvalent immunoglobulins in case of GAS infections and hyperbaric oxygen therapy in centers where the technique is available without delaying other aspects of managements.

***Including negative pressure wound therapy

infections to guide surgery. However, due to its poor sensitivity, imaging must never delay urgent surgical exploration, particularly in the most severe forms (i.e., patients with septic shock) [2, 5]. Although a negative surgical exploration rate of 20% has been reported, close surveillance of patients with normal intraoperative findings is essential, as 14% will eventually be diagnosed with NSTI upon re-exploration [7]. Associating visual exploration to simultaneous histological and microbiological examination of tissue samples could enhance diagnostic sensitivity [8]. Microbiological samples should include blood cultures, blister punctures or subcutaneous aspirations

and multiple per-operative samples with aerobic and anaerobic cultures.

The cornerstones of management

Broad-spectrum empiric intravenous antibiotics, urgent surgical debridement and supportive care are the cornerstones of NSTI management.

As NSTIs are frequently polymicrobial [4, 9, 10], first-line antibiotics should include a broad-spectrum beta-lactam active on both gram positive, gram negative and anaerobic species, such as piperacillin-tazobactam. Aminoglycosides may be associated in case of shock, and anti-MRSA drug adjunction, although routinely recommended by the 2014 Infectious Diseases Society of America (IDSA) guidelines [5], should likely be considered according to local ecology and individual risk factors. Because group A streptococcus infections (GAS) are frequent, particularly in limb and head/neck NSTIs, adjunctive clindamycin might be beneficial [5].

Time to surgery is one of the main modifiable prognostic factors, with a negative impact on mortality for surgery performed more than 14 h after ICU admission in a retrospective study of 106 patients [11]. Along with confirming the diagnosis and collecting samples for microbiological examination, surgery should consist in an aggressive and complete debridement of necrotic and infected tissues. This is considered performable by surgeons from any specialty. Yet, patient transfer to an expert center might be considered, as observational data suggest that patients managed in centers having a higher case volume have better outcomes than others [12], providing surgery is not unduly delayed [13]. Daily reassessment is warranted, often with a systematic second-look surgery performed at a maximum of 24 h after initial surgery, as progression of necrosis often requires multiple debridements [4].

Multidisciplinary management and adjuvant therapies

Standardizing multidisciplinary management, with designated referents in each specialty involved locally, could be associated with improved outcomes [2, 9, 10]. Daily multidisciplinary reassessment of patients will allow for evaluating the need for surgical debridement, adjusting antibiotic spectrum, and discussing adjuvant therapies (Fig. 1). There is a theoretical rationale for intravenous immunoglobulins in GAS infections, but the only randomized trial focusing on NSTIs could not find a benefit [14]. In the lack of robust evidence hyperbaric oxygen therapy should probably not delay other aspects of management [1, 2, 5].

Recent advances

Recent data suggests that the clinical heterogeneity of NSTIs reflects different underlying physiopathologies, with specific host–pathogen interactions [15].

The etiology of NSTIs differs, depending on the body part affected [4]. Limb infections are more likely to be monomicrobial, mainly GAS-associated, whereas infections of the head and neck or abdomen and ano-genital area are more often polymicrobial. The host response is characterized by expression of genes encoding inflammatory mediators in both polymicrobial and monomicrobial streptococcal infections. Nevertheless, genes encoding extracellular matrix components are more commonly expressed by the polymicrobial infectious microbiome. This consists of co-occurring bacteria forming an interconnected network, that facilitate colonization and tissue destruction, and different bacteria contribute to expression of specific virulence functionalities to a different extent. On the other hand, genes of the interferon pathway are prevalent in streptococcal NSTI, which are known for their ability to mediate a massive inflammatory response, and several streptococcal virulence factors have been identified as ways of evading the immune response through, for instance, complement inhibition [15]. This corresponds with GAS-associated NSTIs having higher rates of septic shock—but surprisingly lower odds ratios for death [4].

Host–pathogen interactions could offer new therapeutic targets. The peptide AB103 competes with superantigens, key actors of invasive GAS infections, for binding on the CD28 receptor on lymphocytes. No signs of harm were observed in a phase II trial, and results from a recent RCT are awaited [16].

Finally, faster techniques for microbiological diagnosis, including 16S rRNA gene sequencing and shotgun metagenomic sequencing [17], may in the future allow for faster targeted antibiotic treatment.

Conclusion

The growing understanding of NSTI pathophysiology could lead to therapeutic innovations in coming years. Yet, as of today, the focus of intensivists should be on optimizing the simple interventions most likely to impact outcome: First, a high index of suspicion should be maintained to avoid misdiagnosis and delays in treatment initiation; second, intensivist should coordinate multidisciplinary teams to anticipate and protocolize urgent management based on early surgical debridement and broad-spectrum antibiotics.

Abbreviations
ATB: Antibiotics; GAS: Group A streptococcus; ICU: Intensive care unit; ID: Infectious diseases; MRI: Magnetic resonance imaging; NSTI: Necrotizing soft-tissue infection.

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