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COMMENTARY

Essentials in the management of necrotizing soft-tissue infections

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Abstract

Aims Necrotizing soft-tissue infections (NSTI) are rare but severe diseases with rapid progression. Rates of mortality and morbidity are high and early diagnosis, immediate surgical intervention and antibiotic treatment are essential to improve prognosis. Thus, our commentary emphasizes important information in the management of NSTI.
Methods We describe the essentials in the management of necrotizing soft-tissue infections.
Results Six essentials were identified:

1. Necrotizing soft-tissue infections (NSTI) are primarily diagnosed clinically; pain out of proportion, rapid progression of skin infection and systemic signs should alert clinicians.
2. Early diagnosis can be rather delayed by several factors such as absence of fever, significant cutaneous manifestations, elevation of inflammatory parameters, systemic signs, and non-specific imaging tests.
3. NSTI can occur both in the elderly or patients with underlying diseases after major trauma (usually polymicrobial Gram-negative and Gram-positive pathogens) but also in healthy patients after minor trauma (often monomicrobial; most common among Gram-positive organisms: group A Streptococcus).
4. Immediate and radical debridement (incl. re-debridement after 24 h) remains the cornerstone of surgical therapy.
5. Empirical broad-spectrum antimicrobial treatment has to be administered shortly after admission. After isolation of the causative bacteria therapy should be tailored.
6. The value of adjunctive measures (hyperbaric oxygen therapy, intravenous immunoglobulines) is uncertain and their routine use cannot be recommended.

Summary Further efforts should be undertaken to increase the awareness for and the adherence to the essentials in the management of necrotizing soft-tissue infections.

Necrotizing soft-tissue infections are severe diseases with rapid progression. Classic manifestations include soft-tissue edema, erythema, severe pain, tenderness, fever and skin bullae or necrosis. Rates of mortality are estimated at around 23% and mild to severe functional limitations are reported for 30% of the patients [1, 2]. Due to the low incidence physicians rarely encounter this disease which bears the risk to fail early diagnosing. Therefore, the article aims to strengthen physicians' awareness for this severe infection as rapid treatment is essential to improve prognosis.

1. Necrotizing soft-tissue infections (NSTI) are primarily diagnosed clinically; pain out of proportion, rapid progression of skin infection and systemic signs should alert clinicians.

   Characteristic early manifestations of NSTI consist of soft-tissue edema, erythema pronounced pain, tenderness and fever progressing to skin bullae, necrosis and anesthesia in the later course [3]. Clinical findings were reviewed in a systematic literature search identifying swelling (present in 81% of NSTI cases), pain/tenderness (79%), erythema (71%), warmth (44%), bullae (26%), skin necrosis (24%) and crepitus (20%) as the most frequently encountered signs [4]. Fever was

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present in 40% of cases and hypotension in 21%. In a case–control study of Alayed et al. recent surgery, severe pain, hypotension, skin necrosis and bullae were helpful signs to discriminate NSTI from cellulitis [5].

2. Early diagnosis can be rather delayed by several factors such as absence of fever, significant cutaneous manifestations, elevation of inflammatory parameters, systemic signs and non-specific imaging tests.

   Pitfalls in early diagnosis of NSTI are diverse [6]: fever can be missing as analgesics are frequently administered; in the early course of disease of spontaneous deep infections characteristic cutaneous manifestations as necrosis may be missing [3]; in NSTI evolving after surgery, severe pain may be attributed to the intervention by mistake; fascial thickening and involvement of multiple compartments are sensitive findings on MRI, but non-specific findings occur [7]. The Laboratory Risk Indicator for Necrotizing) Fasciitis (LRINEC) score has been proposed as a diagnostic tool for distinguishing NSTI from other non-necrotizing skin and soft-tissue infections [8], but has not been implemented in most units due to several limitations (difficult external validation, poor sensitivity).

Most importantly, in uncertain cases with high clinical suspicion, an immediate surgical exploration is warranted to exclude or verify NSTI. Extensive noninvasive diagnostic procedures should not be initiated to avoid delay due to the time-consuming procedure [9].

3. NSTI can occur both in the elderly or patients with underlying diseases after major trauma (usually polymicrobial Gram-negative and Gram-positive pathogens) but also in healthy patients after minor trauma (often monomicrobial; most common among Gram-positive organisms: group A streptococcus).

   Different subtypes of NSTI exist and are determined mainly by the microbiological etiology (type I: polymicrobial; type II: monomicrobial). Type I is often seen in elderly or patients with underlying diseases with major traumata including surgeries whereas type II develops mostly in healthy patients after minor traumata. In type II NSTI group A streptococci followed by *S. aureus* are most commonly isolated. Further specific pathogen after minor trauma and water exposure are found (*Aeromonas hydrophila*: freshwater; *Vibrio vulnificus*: saltwater). Gas gangrene describes a clostridial myonecrosis which occurs spontaneously or after traumatic injury [10].
4. Immediate and radical debridement (incl. re-debridement after 24 h) remains the cornerstone of surgical therapy.

   Surgery plays a crucial role in NSTI management, both in diagnosis and treatment. Obtaining a frozen section biopsy in unproven NSTI has been proposed in earlier publications but has been abandoned meanwhile due to low accuracy. Therefore, in uncertain cases, early surgical exploration in the operating theatre is recommended in recent guidelines and reviews to prevent a delay in the diagnosis and treatment of NSTI. Moreover, surgical exploration offers the opportunity to obtain samples for culture and Gram's staining. Patients who underwent surgery within 6–12 h after admission had significant lower mortality rates than those who did not [11, 12].
5. An empirical broad-spectrum antimicrobial treatment has to be administered shortly after admission. After isolation of the causative bacteria therapy should be tailored.

   Empiric treatment should include antibiotics with activity against Gram-negative, Gram-positive and anaerobic organisms (e.g., piperacillin/tazobactam plus vancomycin; in cases of severe penicillin hypersensitivity: e.g., clindamycin with fluorochinolone). After isolation of the causative pathogen from blood culture or tissue therapy should be tailored (e.g., penicillin G for streptococci). The addition of a protein-synthesis inhibiting agents as clindamycin is recommended to reduce toxin-production, although evidence from randomized trials is lacking; nevertheless in vitro and in vivo mouse data demonstrate the positive effect of high dose clindamycin for group A streptococci [13–15].
6. The value of adjunctive measures (hyperbaric oxygen therapy, intravenous immunoglobulines) is uncertain and their routine use cannot be recommended.

   Hyperbaric oxygen therapy (HBOT) increases tissue oxygen tension in infected necrotic wounds and might potentiate antibiotic efficacy. Relevant studies to prove or refute the positive effect of HBOT are missing [16]. Polyspecific intravenous immunoglobulin (IVIG) has been proposed as adjunctive therapy in severe infectious diseases to neutralize bacterial toxins. There is only one randomized trial with intravenous immunoglobulins for NSTI published to date. It did not show any significant difference in self-reported physical functioning and mortality [17, 18]. Further studies are needed to evaluate if there is any value of adjunct IVIG in NSTI subgroups such as infections exclusively due to group A streptococci.

Compliance with ethical standards

Conflict of interest In the last 3 years NJ has received lecture fees from Gilead, Infectopharm and MSD and travel grants from Gilead, Basilea and Correvio. CE received honoraria for lectures and as consultant

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