Necrotizing soft tissue infections: a review.


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ABSTRACT

Necrotizing soft tissue infections (NSTIs) constitute a rare condition, with morbidity and mortality rates that range between 25% and 76% according to the series. They may initially be confused with cellulitis, but progression is rapid and the outcome fatal in most cases. NSTIs are most common in patients with immunosuppression, diabetes mellitus, a history of splenectomy, drug use and advanced age but they may also occur in patients without relevant medical history. The outcome depends primarily on early diagnosis and treatment, and surgical debridement is at present the only modifiable prognostic factor. However, at early stages, correct diagnosis remains a challenge; currently there is no foolproof diagnostic method, and on many occasions a high suspicion of the entity is necessary.

KEYWORDS

Necrotizing soft tissue infection, necrotizing fasciitis, polymicrobials, debridement.

INTRODUCTION

NSTI is a rare condition that affects the soft tissues. Given its high mortality (ranging from 6% to 76%, depending on the series) it represents a surgical emergency [1-5].

Its main features are its rapid development, in most cases fulminant, and the difficulty of diagnosis, given the similarity of its signs and symptoms to less severe soft tissue infections. Due to the radical difference in prognosis and treatment of these infections, it is vital to distinguish between them, to establish a prompt diagnosis and to determine the strategy to follow. The superficial infections (those limited to the epidermis and dermis) include erysipelas, impetigo, folliculitis, furunculosis, ethyema, carbunculosis and cellulitis (although this last condition may also affect the superficial fascia). However, necrotizing fasciitis affects the superficial and deep fascia, subcutaneous fat, the neurovascular bundle, and on occasion the underlying muscle as well [1,2,4,6].
To add to the confusion, the condition has been given several different names. Until Wilson coined the term “necrotizing fasciitis” in 1952, the disease was referred to variously as malignant ulcer, gangrenous ulcer, putrid ulcer, phagedaena, gangrenous phagedaena, hospital gangrene, fulminating gangrene, necrotizing erysipelas, gangrenous erysipelas, crepitant cellulitis, gangrenous cellulitis, Meloney cellulitis, necrotizing synergistic cellulitis, hemolytic streptococcal gangrene, progressive bacterial synergistic gangrene, Fournier gangrene, necrotizing abscess, galloping gangrene, flesh-eating bacteria disease, and so on.

Nor is there a clear consensus on the limits of the involvement. While some authors define the condition as a necrosis of subcutaneous tissue and fascia, with occasional muscle involvement, others report that the muscle is relatively spared [1-4, 6]. This clinical entity is fulminant if treatment is delayed and is therefore a surgical emergency.

**PATHOPHYSIOLOGY, ETIOLOGY AND EPIDEMIOLOGY**

Necrotizing fasciitis is characterized by a microbial invasion causing local thrombosis and liquefactive necrosis (Fig. 1). The histology findings are varied, but all are related to the thrombosis. In the initial horizontal phase the edema and the inflammation infiltrate the fascia, the subcutaneous fat, and the reticular dermis, progressing to superficial fascial necrosis, fascia infiltration by polymorphonuclear leukocytes (though their presence varies and may even be minimal depending on the causative agent), thrombosis of the veins and arteries passing through the fascia, with a large-scale proliferation of the microorganism. At this time the patient presents intense local pain, swelling, redness, poorly defined margins, local heat, fever and increasing general malaise (Fig. 2).

The horizontal phase is followed by the vertical phase, characterized by ischemic necrosis of the skin and gangrene of the subcutaneous fat and dermis. There may also be areas of muscle necrosis. At this time, the formation of small blisters, initially containing serum, raises the suspicion of severe necrotizing fascitis. These blisters (though not always present) increase in size as the condition progresses, converge with each other, and with time contain serum and blood (Fig. 3). Fluctuation, crepitus and focal necrosis of the skin may also be observed resembling deep burns, with superficial serous-purulent exudate, and finally, after the necrosis of the subcutaneous nerves, hypoesthesia or local numbness (Fig. 4). With the release of toxins into the bloodstream the patient's general state may worsen, with signs and symptoms of septic shock. Distant septic emboli and formation of metastatic abscesses in the liver, kidneys, spleen, lungs, and heart have been described [1-4,9,10]. Depending on the patient and the virulence of the organism, evolution may be very fast, and may even result in a fatal outcome in 24-48 hours. Mortality is almost 100% if the patient is not treated promptly.

The infection can occur in any region of the body but is most common in the limbs, abdomen and perineum. Possible points of entry for the pathogen are burns, abrasions, bruises, ulcers, accidental punctures, intravenous or subcutaneous drug injection, insect bites, surgical or accidental incision, postoperative complications, skin infections, or dissemination via the blood. On occasion the point of entry is not found [2,4,10,11].

The Giuliano classification of causative organisms[12] differentiates between type I (polymicrobial), and type II. In type I, the infection is caused by non-group A Streptococcus species, either anaerobic or aerobic, and in type II by
Streptococcus pyogenes, either alone or in conjunction with staphylococcus. However, no significant differences have been found to date between types I and II in terms of clinical course, morbidity, or mortality [4]. The anatomic location of the condition may indicate the causative agent. In the abdomen and perineum, the cause tends to be polymicrobial, in the form of enteric pathogens (Giuliano type I), such as aerobic and anaerobic Gram-negative bacteria (E. coli, P. aeruginosa, Klebsiella sp, P. multocida, Bacteroides sp, Clostridium sp), Enterococcus, and less commonly Staphylococcus and Streptococcus. In the limbs, on the other hand, a single microbial species in the skinflora tends to be the cause, such as group A beta-hemolytic Streptococcus and Staphylococcus (Giulianotype II).

A third group has also been described, in which the microorganisms responsible are Gram-negative marine vibrios such as V. vulnificus, V. damsela, V. alginolyticus, V parahemolyticus [1-4,13-19].

Beres et al [22] found that the largest generator of different genotypes ingroup A Streptococcus (serotype M3) was the acquisition and loss of promoters (prophages). This molecular process contributes to the epidemic behavior of M3 invasive infections. But it has also been detected in the genome of S.
pyogenes M1T1, which is involved in invasive disease. This study suggest that phages can be shared by different M serotypes, and even by different bacterial species. Some host genetic factors also play an important role in determining the severity of group A streptococcal infections, altering the scale of the cytokine response to the pyrogenic exotoxins secreted by the streptococci. Group A streptococcal infections require the bacteria to penetrate areas of the body that are normally sterile sites. The activation of plasminogen and plasmin (or fibrinolysin) is involved in the invasion by S. pyogenes and other bacterial species. The evidence suggests that the group A streptococcus has multiple strategies for acquiring and activating human plasminogen and that the process depends on the plasminogen receptors and streptokinase alleles expressed by the bacterium. The studies by Berge, Pancholi and Lottenberg [23-25] identify two mechanisms in the binding of plasminogen receptors to streptococci: direct (mediated by three receptors: PAM or M53, alpha enolase or SEN, and GAPDH) and indirect, mediated by the formation of a trimolecular complex (plasminogen, streptokinase, fibrinogen). The interaction of streptokinase with plasminogen reflects the spread of several streptococcal species in mammalian hosts. The species-dependent nature of the plasminogen activation, and its importance in the virulence, is exemplified in immunoregulatory models of streptococcal infection. When the plasminogen is resistant to activation by streptokinase, it is also resistant to infection by S. pyogenes; in contrast, when the human plasminogen is present at the site of infection it increases the virulence of the group A streptococcus. Moreover, if streptokinase is placed in contact with human plasminogen-rich serum before being introduced into the mouse model, its virulence increases [26-30]. These studies confirm the key role played by the human plasminogen in the in vivo pathogenicity of group A streptococcus. Nevertheless, several issues remain unclear: for example, how plasminogen binds to the cell surface of S. pyogenes, how the acquired plasminogens are activated, and how this protease contributes to the spread of bacteria [31].

No gender predominance is observed in NSTI. Lamagni found a significant increase in cases between the ages of 30 and 45, and from 70 years onwards [32]. That study, which publishes the experience of hospitals in five European countries, also recorded a peak incidence in the spring time. Affected patients often present risk factors such as diabetes mellitus, immunosuppression, parenteral drug use, peripheral vascular disease, liver cirrhosis, splenectomy, alcoholism and malnutrition. However, necrotizing fasciitis has also been described in patients without any risk factors [3].

**DIAGNOSIS**

**History of present illness**

It is important to ask about the presence of punctures, burns, abrasions, bites, stings, subcutaneous or intravenous injection, lacerating or contused wounds, and so on. The history of recent surgery, traumatic manipulation of urinary and perianal structures, mouth infections, coital trauma or balan infections of the skin should also be considered. On occasion, no relevant data regarding penetrating traumas are forthcoming. Patients should be asked about characteristic symptoms, such as intense pain that is disproportionate to the physical findings, fever, malaise, anorexia, fatigue, functional impotence, neurological status, and limb sensitivity and mobility, which may be affected in advanced stages of NSTI. But if (as is quite possible) the patient is in an advanced state of illness and presents symptoms and signs of septic shock, it is even more difficult to obtain information and to decide on the clinical orientation.

**Complementary imaging tests**

X-ray can demonstrate the presence of gas in soft tissue, a highly predictive sign. However, the sensitivity of this test is less than 40%, so it is not very helpful for assessing soft tissue involvement (Fig. 5).

Computerized tomography (CT) is more sensitive for detecting gas in soft tissues and also reveals the extent of the infection. Because of its speed and ease of performance, CT is the most commonly used test to diagnose NSTI (Fig. 6).

![Fig. 6. Cross section study conducted by Computed Tomography, showing the presence of gas at the level of the anterior compartment of the right thigh.](image)
patient with damaged skin (blisters, skin necrosis, etc.) might report disproportionate pain on palpation and manipulation of the affected area; these features may preclude a full, accurate assessment of the entity [34,35].

MRI appears to be the most sensitive and specific test, providing information on specific anatomical limits of the inflammation of the fascia and muscles. The use of GD-DTPA allows detection of non-perfused necrotic tissue \[1,4,10,12,21\]. However, issues such as the difficulty of accessibility and the presence of contrast-induced renal toxicity in patients who already have impaired renal clearance mean that MRI screening is not routine in these patients.

Additional laboratory tests

In order to create a tool for assessing NSIT and quantifying the risk involved, Wong published the LRINEC scale in 2004 \[4\], which assigns scores for laboratory parameters such as glucose, leukocytes, creatinine, hemoglobin, C-reactive protein and sodium. The scale classifies patients into three groups depending on the risk: low, intermediate and high risk. According to the results, additional diagnostic tests will be performed, or if necessary the patient will be sent straight to surgery.

However, recent assessments of the LRINEC scale in hospitals in Europe have shown the scale to be unhelpful, because it classifies many patients with histologically confirmed NSTI as low-risk. The reason is that patients often arrive at hospital before the condition has fully evolved and do not present significantly altered biochemical and hematological parameters [36-39].

Leukocyte counts above 30,000, sodium below 135 mmol/l, BUN increase above 15 mg/dl, presence of high lactate when there is muscle necrosis, elevated CK, alterations in blood pH, and alterations in creatinine, glucose, sodium and hemoglobin are all characteristic findings, but unfortunately they are not always present.

Invasive tests

Frozen section biopsy (FSB) and the "finger test" [20] are also used. FSB comprises a biopsy and examination of a frozen section. In the "finger test", proposed by Stamenkovic and Lew, a small incision is made of the affected area under local anesthetic and the fascia is palpated with the index finger: the test is positive if there is little or no bleeding, if the tissue offers little resistance to dissection, and if "dish water pus" is observed. In both explorations the skin incision must be made in a non-sterile environment; in addition, the area to be manipulated is not always suitable for local anesthesia. The need for an urgent biopsy (at night, for example) is another inconvenience to consider, as well as the subjective assessment of easy dissection by the finger[40].

TREATMENT

1. General therapeutic measures

In this case, the main objective is to restore an adequate supply of oxygen and of substrates to the tissues. Intravascular volume depletion is common in patients with sepsis, so the administration of intravenous fluids is important to ensure adequate organ perfusion. In patients with underlying heart or kidney disease, central venous pressure must be kept between 10 and 12 cm H2O. Diuresis must be maintained above 30-35 ml/h and the use of diuretics may be necessary. Circulatory status can be evaluated by clinical parameters such as neurological status and skin perfusion, although whenever possible by determination of oxygen supply and consumption. Assisted ventilation is indicated in cases of hypoxemia or hypercapnia, respiratory muscle failure, or significant deterioration of neurological status. Bicarbonate is administered in the case of metabolic acidosis. If signs of disseminated intravascular coagulation appear, fresh plasma and platelets are administered. However, the bottom line is to treat the underlying infection. The presence or development of complications such as nosocomial infections, deep vein thrombosis, continuity solutions skin ulcers and stress should all be monitored.

2. Use of Hyperbaric Oxygen Therapy (HBOT)

Hyperbaric therapy (HBOT) has been used to treat NSTI. Its effectiveness has proved difficult to assess: all the analyses carried out to date have been retrospective and no significant evidence is available from prospective randomized studies. The treatment protocols vary in terms of the number and frequency of sessions and the sample sizes are small, meaning that statistically significant comparisons between groups in terms of mortality and morbidity cannot be obtained. The use of HBOT in very ill patients also introduces a bias. The study by Eltorai in a series of seven patients with Fournier's gangrene favors HBOT, with a mortality of 0% when combining HBOT and surgical debridement (although there are errors in the duration of the study and the relationship between debridement and HBOT) [41]. Gozal [42] reports a mortality rate of 12.5% when combining HBOT, antibiotics and surgical debridement (there were no controls in the study). Riseman reports a 66% reduction in mortality in controls compared to a 33% reduction in those treated with HBOT, and a decrease in the number of debridements (3.3 with HBOT vs. 1.2 without) [43]. Conversely, Tehrani’s results (of eight patients treated with HBOT and conservative surgery, seven
died; in six treated with HBOT and aggressive surgery, two died), support the idea that HBOT should not replace aggressive surgery [44]. Brown compared HBOT and debridements with debridements alone and reported a mortality of 30% compared with 42%, fewer debridements (2.4 versus 1.3), and a similar length of hospital stay [45]. In spite of the physiological justification for the use of HBOT in NSTI, the results of the studies presented so far are inconsistent. Therefore, the recommendation is to perform randomized, prospective studies providing statistically significant evidence before recommending HBOT as standard therapy [46].

3. Antibiotic treatment

Initial therapy is usually empirical, but should ensure coverage of Gram-positive and negative cocci and anaerobes. The initial specific antibiotic can vary, but a combination of a penicillin or cephalosporin, aminoglycoside, and clindamycin or metronidazole is usually administered to cover anaerobes. When cultures are available, antibiotic therapy should be as specific as possible. If the microbiological studies are negative, the antibiotic treatment can be changed depending on the patients’ clinical evolution. Finally it is important to note that the thrombosis of the superficial vessels that occurs in the NSTI limits penetration of the antibiotic into the infected area. Therefore, given the suspicion of NSTI, aggressive surgical treatment should not be delayed until the results of antibiotic treatment become available; ultimately, the debridement of all the necrotic tissue is the most important prognostic factor in NSTI [47].

4. Immunoglobulin treatment

Streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis caused by group A streptococci are rapidly invasive and are associated with high morbidity and mortality. Group A streptococcus secretes several exotoxins with superantigenic activity which play an important role in the pathogenesis of these infections. Superantigens do not conform to the usual rules of antigen presentation and processing; they cause a powerful activation of T cells and antigen-presenting cells, and consequently an excessive production of pro-inflammatory cytokines. For its part, the M protein, in addition to its known anti-phagocytic activity, induces vascular damage. Experience with the use of intravenous polyspecific immunoglobulin G (IVIG) in patients with STSS is growing [48]. The mechanism of action of IVIG includes inhibition of the activity of the superantigen neutralizing the antibodies, opsonization by M specific antibodies, and a general anti-inflammatory effect. Currently, studies advocate aggressive surgical treatment when necrotizing fasciitis is suspected. However, in a retrospective descriptive study, Norrby-Teglund reported the successful management of seven patients with NSTI due to group A streptococcus with a medical regimen; surgery, when performed, was not aggressive [49]. In that study, seven patients who had positive cultures of group A streptococcus at the site of infection and/or in blood, and two or more of the following conditions – temperature above 38°C or below 36°C, bpm > 90, rpp> 20, PaCO2< 32 mmHg, leukocytes > 12,000/mm3 or < 4000/mm3, > 10% immature band forms, and who had two or more organ failures and/or hypotension unresponsive to fluid therapy – were selected between November 1992 and February 2002 to receive high doses of IVIG (defined as 2g/kg, and the drug used was Gamimune N). Three patients required non-invasive surgery, one of them a second debridement, and in another necrotizing fasciitis was confirmed by histopathological examination. Four of the patients presented hemodynamic improvement within 24 h of IVIG administration, and only two of the seven required a second dose. All patients survived, and the mean hospitalization time was 30 days. Considering that six out of the seven patients had STSS, and that a mortality rate of 67% has been reported in patients presenting STSS and necrotizing fasciitis, the fact that seven patients survived without invasive surgery is a particularly interesting finding.

The suggestion is that the use of IVIG may allow an initial management with non-aggressive surgery or without surgery at all, thus reducing the need for amputation or repeated, aggressive debridements in these patients who are often hemodynamically unstable. The authors acknowledge that the study suggests a "wait and see" policy in one type of patient with necrotizing soft tissue infections, which goes against the standard treatment proposed in the current literature. Furthermore, the study is limited in terms of sample size and is retrospective and observational, but the possibility that initial conservative management using IVIG reduces morbidity by avoiding the use of aggressive surgery in these hemodynamically unstable patients and does not increase mortality merits further analysis.

5. Surgical treatment

Treatment of necrotizing soft tissue infections is primarily surgical, since surgery is the most important modifiable prognostic factor in this rapid, aggressive disease [2, 50]. When the level of suspicion is high, surgery must be performed immediately in the operating room. The procedure consists of the removal of all devitalized and necrotic tissue and drainage of all planes until viable tissue is found.
Debridement should start with a resection of the skin and of all the non-viable subcutaneous tissue. A microbiological analysis should be performed at this stage even in the absence of accumulated pus in the macroscopic study. Often a characteristic "dish water pus" is found above the fascia. The fasciotomy should extend as far as the viable tissue, as indicated by bleeding, dissection resistance, and color. A microbiological and pathological examination of the resected fascia should also be performed. On occasion the underlying muscle is affected, and so it should be explored for signs of viability (bleeding, contractility, consistency, color). Non-viable muscle should be debrided (Fig 7). Profuse pulsatile irrigation is performed throughout the debrided area with 6-9 l of saline solution.

The vast majority of authors recommend routine surgical revision within 24 hours. Many cases will require two or three more debridements, which are always performed in the operating room under fully aseptic conditions. If the postoperative evolution is satisfactory, the wound in the affected area is closed. This will usually require coverage grafts. In many series, amputation of the affected limb is necessary in up to 60% of cases.

CONCLUSIONS

When necrotizing fasciitis is diagnosed, antibiotic treatment should never be considered as a replacement for surgical debridement. The recommended antibiotic treatment regimen should cover the main causative organisms, and so must be broad spectrum (either a combination of a third generation cephalosporin + clindamycin or metronidazole, or a carbapenem or piperacillin-tazobactam monotherapy) [4,5,8,12,13]. This treatment will be continued until the culture and pathology results are available, which will give us the definitive diagnosis. The value of adjunctive therapies (HBOT and immunoglobulins) has not been amply demonstrated; they can be performed if available, but they should not interfere in the standard treatment protocol of surgery plus antibiotics. Because there are no definitive complementary tests, rating scales such as the LRINEC score have been designed to aid decision-making [6,7,9]. However, in the early hours of evolution the analytical parameters may be within normal ranges [36-39] and the most important guide is the high index of suspicion (due to the presence of disproportionately intense pain, skin changes and rapid evolution of the disease both locally and generally), since prompt surgical treatment is essential. In doubtful cases, repeated assessment of the evolution and the response to empiric antibiotics is recommended and the option of urgent surgical debridement should be kept open. The most important prognostic factors are patient’s age, comorbidity, and debridement, the last one being the only one that is modifiable [2-5,10]. During the hospital stay, the patient must undergo repeated surgical procedures: debridement and/or amputation depending on the evolution, and the closure of the wounds which often requires soft tissue reconstruction [4,5].
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