

# Can necrotizing soft tissue infection be reliably diagnosed in the emergency department?

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## ABSTRACT

Necrotizing soft tissue infections (NSTIs) are associated with a high mortality and require prompt recognition and treatment, consisting of aggressive surgical debridement and critical care support. Diagnosis is a key step, which is generally made in the operating room (OR), but the decision to debride requires guidance. This is frequently made on clinical grounds, but NSTI can be occult in presentation and several other infective processes can mimic NSTI. It is unknown whether the various scoring systems described in the literature can enable clinicians to reliably diagnose NSTI in the emergency department, rather than the OR. The topic was debated at the 36th Annual Point/Counterpoint Acute Care Surgery Conference and the following article summarizes the discussants points of view along with a summary of the evidence.

**Level of evidence** Level III.

## INTRODUCTION

Necrotizing soft tissue infections (NSTI) constitute a life-threatening surgical disease which requires rapid identification and aggressive surgical debridement.<sup>1</sup> The incidence in the USA is around 0.04 cases per thousand patient years, which is increasing for reasons unknown.<sup>2</sup>

Microbiologically, NSTI can be classified into three types.<sup>1,3</sup> Type 1 infections are polymicrobial in origin and are most common; anatomically, these tend to affect the perineum and truncal regions. Type 2 infections are considered monomicrobial, caused by agents such as *Staphylococcal*, *Streptococcal* and *Clostridia* species. Such infections may also precipitate toxic shock syndrome adding to the complexity and severity of the presentation. Type 3 infections are controversial and constitute the least frequently observed group, mediated by *Vibrio vulnificus*, accessing the body via a break in the skin exposed to seawater.

Pathologically, these organisms invade the subcutaneous tissues, often producing endotoxins and exotoxins, causing the ischemic necrosis of tissue and systemic compromise, often at a prodigious rate.<sup>1</sup> The mainstay of therapy remains aggressive surgical debridement in parallel with broad-spectrum antibiotic administration and end-organ support.

Early diagnosis is critical and linked to outcome.<sup>4-6</sup> The most common physical manifestation of NSTI is erythema, pain and swelling. ‘Classical’ features such as crepitus and hypotension occur in less than 50% of cases, prompting a drive for additional methods to score the likelihood of

NSTI. Several scores have been developed which include laboratory indices and features on radiographic imaging.<sup>7,8</sup>

It is unknown whether the knowledge from such scores can be used in the emergency department (ED) to support the diagnosis of NSTI. This article is a summary of the debate on this subject, held during the 36th Annual Point/Counterpoint Acute Care Surgery Conference.

## NSTI CAN BE RELIABLY DIAGNOSED IN THE ED (ABRIDGED SUMMARY)

**Dr Kimberly Davis MD, MBA, Professor of Surgery, Yale School of Medicine**

NSTIs represent an infrequently encountered, but rapidly progressive soft tissue infection, which requires prompt diagnosis and aggressive surgical debridement. Diagnosis requires a high index of suspicion, as delays in treatment are associated with greater morbidity. Although clinical signs can be varied, several clinical tests have been used to generate predictive tools for NSTI.

Wong and colleagues have proposed the ‘laboratory risk indicator for necrotizing fasciitis’ (LRINEC) score. This involves the assessment of C-reactive protein (CRP), white cell count (WCC), hemoglobin, sodium, creatinine and glucose and the assignment of a score, depending on the level of the variable. A score of >6 is highly suggestive of an NSTI.

The strength of this score appears to be in identifying patients where there is a very high or low suspicion of NSTI. Although this has some obvious practical significance, it leaves a middle group of patients where the diagnosis remains uncertain. This is where imaging can play a significant role.

Radiology has traditionally had a limited role to play in NSTI diagnosis, but the advent of widely accessible cross-sectional imaging has changed this paradigm. Although MRI offers high-resolution soft tissue imaging, CT is timely, widely available and amenable to rapid interpretation by non-radiologists, until formal reporting.

A CT scoring system has been described for use in patients with equivocal physical and laboratory findings based on the presence of fascial air, edema, fluid tracking and lymphadenopathy. A score greater than 6, generated a high sensitivity and specificity for NSTI.

In summary, diagnosis of NSTI requires a high index of suspicion and early surgical exploration is required; however, in equivocal cases, laboratory and imaging scoring systems can be used in the ED to assess the likelihood of the need for debridement.

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## NSTI CANNOT BE RELIABLY DIAGNOSED IN THE ED (ABRIDGED SUMMARY)

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The optimum method of diagnosing an NSTI is surgical exploration and direct inspection of the tissue, leading to the aggressive surgical debridement of dead and devitalized tissue as appropriate. Although the concept of a diagnostic algorithm that can be undertaken in the ED is conceptually attractive, no scoring system is sufficiently sensitive or specific to risk application in this disease process. Moreover, scoring systems risk introducing delays, although tests are performed and can confuse practitioners by generating decision paralysis.

When considering laboratory indices, numerous tests have been evaluated. A WCC >14 achieves a diagnostic sensitivity of 81% and a specificity of 76% for NSTI, but will still miss an unacceptable proportion of NSTI diagnoses. The LRINEC score attempts to address this shortcoming by evaluating several laboratory tests, but even a high score (>6) attains a sensitivity of 92% and a specificity of 96% by the describing authors but has not been replicated in the follow-up studies.

Imaging has similar issues, with plain radiography demonstrating a less than 25% accuracy in identifying subcutaneous gas. Furthermore, the absence of gas does not permit the exclusion of NSTI. CT scanning achieves a sensitivity of 80%, which can be raised to 86% by assessing multiple features. MRI is reported to attain a 100% sensitivity and 86% specificity; however, this is a scarce resource and takes time to acquire the images.

Surgical exploration remains the gold standard for the diagnosis of NSTI. Laboratory and imaging tests can demonstrate the extent of disease and quantify physiological compromise, but patients with suspected NSTI belong in the operating room (OR). Clinicians must be judicious in their application of further tests in a disease whose mortality is time dependent.

### EVIDENCE SUMMARY

The severity of NSTI was recognized as early as 500 BC by Hippocrates, who described numerous deaths from whole-body erysipelas incurred by a trivial injury.<sup>9</sup> The incidence of NSTI varies considerably across the world from as low as 0.3 per 100 000 in Norway to 15.5 per 100 000 in Thailand.<sup>12</sup> This can be partly explained by the difference in risk factors for NSTI across the globe which include heterogeneous groups such as large penetrating wounds, exposure of wounds to seawater, skin breaches from insect bites and childbirth and immunocompromised states.<sup>10</sup>

The clinical course typically observed in the USA is of a minor skin breach, allowing bacteria to gain entry resulting in a monomicrobial or polymicrobial infection.<sup>1</sup> Ischemic tissues, such as in peripheral vascular disease, have a predilection for anaerobes, which drives the development of gas gangrene. Once bacteria burden increases and there is the release of exotoxins, various pathological effects can be noted. The aggregation of platelets and leukocytes damage endothelial integrity producing local edema. As swelling increases, ecchymoses and bullae appear, along with the progressive invasion of the infection into the deeper tissue layers. Thrombosis of larger vessels can occur, producing ischemic necrosis of all tissue layers.

The mortality following NSTI can be high, at 29%,<sup>4 11</sup> which in the setting streptococcal infection with toxic shock syndrome or septic shock, increases to 38% and 45%, respectively.<sup>11 12</sup> Optimal survival is dependent on early recognition and aggressive surgical debridement. The initial debridement

is often extensive and generally patients require multiple OR trips for serial debridement. Large open wound can be managed by topical negative pressure dressings until subsequent plastic surgical reconstruction.

The timing of the initial surgery appears to be important, although this has not been studied comprehensively and there is no consensus on specific time goals beyond 'as soon as possible'. This issue is partly confounded by a lack of standard timing definitions—does the clock start on suspicion of diagnosis, admission to hospital or onset of symptoms? Different studies apply different definitions.

A retrospective study of 65 patients from a single US center demonstrated that survivors (71%) of NSTI has shorter times (hours) to debridement compared with non-survivors (25 vs 90;  $P < 0.001$ ).<sup>4</sup> More recently, the experience from New Zealand was reported in a 20-patient series, which reported an 8.3% survival rate following median time to debridement of 20 hours.<sup>5</sup> The most recent assessment of time to debridement assessed 87 patients with NSTI, dichotomized into early (<6 hours) or late ( $\geq 6$  hours) debridement. Although the early cohort ( $n = 40$ ) had a lower mortality of 7.5% compared with the late cohort ( $n = 47$ ) of 17%, it did not achieve statistical significance.<sup>6</sup> The issue of timing remains poorly understood and there are many confounding factors such as time to antimicrobial therapy and fluid resuscitation; however, safe practice involves rapid access to surgery.

Despite these established management principles for NSTI, diagnosis remains difficult, both in terms of occult presentations and mimics.<sup>1</sup> Fever can be absent due to the administration of antipyretic or infection with *Clostridium sordellii*, which is a rare necrotizing infection characterized by a persisting apyrexia. Severe pain from an NSTI may be erroneously ascribed to musculoskeletal strains or venous thrombosis, especially when the infection spontaneously originates from within deep compartments. Crucially, where the pain is out of proportion to the clinical findings, an astute clinician will consider NSTIs in their differential diagnosis.

Furthermore, several conditions can mimic the initial presentation of NSTI, clouding the diagnostic pathway. Severe candidiasis of the groin, cutaneous necrosis in calciphylaxis, stasis dermatitis and cellulitis can appear similar to NSTI. Important discriminators can be elucidated from the patient history such as comorbid conditions and concomitant medication use.

Efforts have been made to enhance diagnostic confidence with the use of laboratory indices; however, no single value has been found to be reliable.<sup>13</sup> The LRINEC score was developed to overcome these shortcomings by incorporating several weighted values.<sup>7</sup> These investigators used data from 89 patients with a confirmed NSTI and 225 patients with non-NSTI cutaneous sepsis to develop a regression model of factors predictive of NSTI. Ultimately, they included WCC, hemoglobin, sodium, glucose creatinine and CRP level. Patients with a score higher than six are at high risk of NSTI, with the original authors presenting a positive predictive value (PPV) of 92.0%, negative predictive value (NPV) of 96.0% and area under the curve (AUC) of 0.976.

This score has been evaluated in several settings which has yielded a spread of predictive values ranging from a PPV of 57%–92% and an NPV of 86%–92%.<sup>14–16</sup> This variation is likely reflective of the differing rates of NSTI in the studied cohorts which generally used a convenience sample of non-necrotizing infections. This scoring is not infallible and appears to work best where the clinical features are ambiguous and there is time to obtain laboratory investigations. A recent re-examination

of this score suggested that the historical description of ‘pain out-of-proportion’ along with a CRP greater than 150 mg/L was comparable to the LRINEC score.<sup>17</sup>

Imaging is another diagnostic modality to consider. Plain films have been demonstrated to be of low sensitivity and specificity and should not be used in the diagnosis of NSTI but may be useful in certain patient groups such as intravenous drug users to identify foreign bodies. Cross-sectional imaging appears to have some promise. CT seems to be the most clinically available, with images that are rapidly acquired and interpretable by surgeons. The first reported series of 67 patients with NSTI who underwent CT scanning as part of their management concluded that CT was 100% sensitive and 81% specific.<sup>18</sup> Those investigators concluded that CT could reliably exclude NSTI. The features specifically assessed were soft tissue asymmetry, muscle necrosis, gas and fluid collections.

The findings of this study were confirmed and extended by a group which examined a series of 305 patients undergoing CT imaging for NSTI assessment.<sup>8</sup> Using these data, the authors synthesized a weighted scoring system based on the presence of fascial air, muscle/fascial edema, fluid tracking, lymphadenopathy and subcutaneous edema. A value greater than six or greater had a sensitivity of 86.3%, a specificity of 91.5% with an AUC of 0.928.

Although the presented evidence is compelling, most studies are collected retrospectively and the few studies with a control group generally rely on patients with non-NSTI, which can introduce significant heterogeneity. To address this issue, a large prospective observational study is currently underway in Northern Europe called the Immune Failure in Critical Therapy study.<sup>19</sup> This project aims to recruit 400–500 patients collecting data on several diagnostic, treatment and outcome variables.

## CONCLUSION

NSTI can rapidly progress to a life-threatening septic process, unless its evolution is curtailed by aggressive surgical debridement. Key to this is prompt diagnosis which can be straightforward in typical cases where patients present with classical features, but mimics and occult disease can confuse diagnostic accuracy. Several scoring systems which can be practicably applied in the ED, have been proposed, based on laboratory indices and cross-sectional imaging, but no test is infallible. Clinicians need to exercise a high threshold for considering the diagnosis of NSTI, use scoring systems judiciously, but fundamentally, surgical exploration remains the diagnostic gold standard.

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