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Chance to cut: defining a negative exploration rate in patients with suspected necrotizing soft tissue infection

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ABSTRACT

Background Necrotizing soft tissue infections (NSTI) are aggressive infections associated with significant morbidity and mortality. Despite multiple predictive models for the identification of NSTI, a subset of patients will not have an NSTI at the time of surgical exploration. We hypothesized there is a subset of patients without NSTI who are clinically indistinguishable from those with NSTI. We aimed to characterize the differences between NSTI and non-NSTI patients and describe a negative exploration rate for this disease process.

Methods We conducted a retrospective review of adult patients undergoing surgical exploration for suspected NSTI at our county-funded, academic-affiliated medical center between 2008 and 2015. Patients were identified as having NSTI or not (non-NSTI) based on surgical findings at the initial operation. Pathology reports were reviewed to confirm diagnosis. The NSTI and non-NSTI patients were compared using χ^2 test, Fisher's exact test, and Wilcoxon rank-sum test as appropriate. A p value <0.05 was considered significant.

Results Of 295 patients undergoing operation for suspected NSTI, 232 (79%) were diagnosed with NSTI at the initial operation and 63 (21%) were not. Of these 63 patients, 5 (7.9%) had an abscess and 58 (92%) had cellulitis resulting in a total of 237 patients (80%) with a surgical disease process. Patients with NSTI had higher white cell counts (18.5 vs. 14.9 k/mm^3, p=0.02) and glucose levels (244 vs. 114 mg/dL, p<0.0001), but lower sodium values (130 vs. 134 mmol/L, p≤0.0001) and less violaceous skin changes (9.2% vs. 23.8%, p=0.004). Eight patients (14%) initially diagnosed with cellulitis had an NSTI diagnosed on return to the operating room for failure to improve.

Conclusions Clinical differences between NSTI and non-NSTI patients are subtle. We found a 20% negative exploration rate for suspected NSTI. Close postoperative attention to this cohort is warranted as a small subset may progress.

Level of evidence Retrospective cohort study, level III.

BACKGROUND

Necrotizing soft tissue infections (NSTI) are rare, aggressive soft tissue infections with significant mortality if not appropriately diagnosed and expeditiously treated surgically. There are 500–1500 cases diagnosed annually[1–3] with an incidence of 0.04 per 1000 person-years,[1 3 4] which continues to increase.[3] NSTIs remain challenging to diagnose given their rarity and wide range of clinical presentations that result in a lack of specific diagnostic criteria.[3 5–13]

Multiple predictive models have been proposed to assist with distinguishing NSTI from other soft tissue infections.[8 14 15] Although initially promising, subsequent studies have struggled to validate these models.[6 9 12 16–20] Several authors acknowledge the key to diagnosis is a high index of suspicion.[1 5 8–10 12 17 18 20] Due to the increased mortality associated with delay in surgical debridement,[1 5 7 10 11 14 21–24] recent guidelines recommend operative debridement within 12 hours of diagnosis.[5]

We recognized that despite using predictive models and having a mature experience with this disease process, a subset of patients taken to the operating room for the diagnosis of NSTI did not have one at exploration. We hypothesized that patients with negative operative explorations were clinically indistinguishable from those patients with an NSTI. The purpose of this study was to compare patients with and without a diagnosis of NSTI at surgical exploration and to describe a rate of negative exploration for this disease.

METHODS

Patients and setting

Our institution is a county-funded, academic-affiliated, level 1 trauma center. After institutional review board approval, we performed a retrospective analysis of a prospectively maintained trauma and acute care surgery database. We evaluated all adult patients aged 18 years or older undergoing surgical exploration for NSTI at our institution between July 2008 and June 2015. The diagnosis of NSTI was based on intraoperative findings including obliteration of soft tissue planes, dishwater fluid, or necrosis of the skin, subcutaneous tissue, fascia, and/or muscle requiring debridement for source control. NSTI diagnosis was subsequently confirmed by review of final surgical pathology reports. Patients were classified as non-NSTI if there was no necrotic soft tissue to debride, consistent with the diagnosis of cellulitis, or if there was incidental finding of an abscess. Non-NSTI patients had an incision made, the wound probed, and then the wound packed with saline or Betadine-soaked gauze. At least two investigators reviewed operative reports and pathology to assure accuracy of patient classification in NSTI and non-NSTI cohorts. Wet gangrene from diabetic foot ulcers that were

isolated to the toes or distal foot was treated as a different entity from NSTI. For inclusion, patients had to show evidence of infection tracking proximally along the extremity. Patients were excluded if they were less than 18 years old, pregnant, prisoners, or declined surgical intervention in lieu of comfort care.

Demographic and admission data collected included patient gender, age, and the medical comorbidities of diabetes, congestive heart failure, cirrhosis, HIV, steroid use, current chemotherapy, and intravenous drug use. Location of the infection (trunk, pelvis/perineal/perianal, upper extremity, lower extremity), duration of symptoms, physical examination findings (crepitus, bullae, violaceous changes), vital signs, and severity of infection (presence of septic shock) were recorded. We evaluated admission laboratory values (complete blood count and chemistry panel). Blood and wound culture results were assessed, as well as the number of operative debridements and if amputation was required. An operation was counted as a debridement if tissue was debrided in an effort to gain source control. Subsequent surgical procedures such as wound VAC changes, amputation formalizations, or skin grafts were not included in this study.

We assessed if the patient had an NSTI or not (non-NSTI) at the time of operation and compared the two groups. The primary outcome was presenting clinical differences between the two groups. Secondary outcome data collected included in-hospital mortality, length of intensive care admission, and length of hospitalization. A rate of negative exploration was calculated based on findings at the first exploration. Finally, patients who were initially classified as non-NSTI and later diagnosed with NSTI on subsequent operative intervention were noted.

Statistical analysis

Statistical analysis was performed using SAS V.9.4 (SAS Institute). Categorical variables were described as ratios and percentages and compared using Fisher's exact test as appropriate or as ORs with 95% CIs. Continuous variables were described as median values with IQRs and compared using the Wilcoxon rank-sum test with Hodges-Lehmann estimator to calculate the median difference and its 95% CIs. P values less than 0.05 were considered significant.

RESULTS

Patient characteristics

During the 7-year study period, 295 patients were taken to the operating room for a suspected NSTI. During the initial operation, 232 patients (78.6%) were diagnosed with an NSTI and 63 (21.4%) were not. Of these 63 patients, 5 (7.9%) had an abscess and 58 (92.1%) had cellulitis resulting in a total of 237 (80.3%) patients with a surgical disease process. Eight patients initially diagnosed with cellulitis had an NSTI diagnosed on a second operation, but were still quantified as a negative exploration.

Patients were predominantly male (n=219, 74.2%) with a median age of 50 years (table 1). The most common comorbidity was diabetes mellitus, occurring more than twice as often in patients with NSTI compared with non-NSTI patients (65.9% vs. 30.2%, p<0.0001). There were no significant differences in other comorbidities between the groups.

The most common location for NSTI was the lower extremity (62.0%) followed by the pelvis/perineum (24.4%). Lower extremity infections accounted for the highest number of negative explorations, and yielded a negative exploration rate of 27.3% (50/183). Conversely, the pelvis/perineum had the lowest rate of negative exploration at 6.9% (5/72). There were 12 patients who had an NSTI affecting more than one region of their body.

Patients with NSTI had a longer duration of symptoms (5 vs. 3 days, p=0.004), but there was no difference in vital signs (temperature, heart rate, respiratory rate) at the time of surgical consultation. On physical examination, crepitus was more common in the NSTI group (15.1% vs. 3.2%, p=0.009), but violaceous skin changes were more common in the non-NSTI group (9.1% vs. 23.8%, p=0.004). The frequency of bullae did not differ between the groups. There was no significant difference in the rates of septic shock between the two cohorts.

Laboratory and microbiology

With regard to presenting laboratory values, patients with NSTI had more leukocytosis (p=0.02), lower sodium values (p=0.0001), and higher glucose levels (p<0.0001) (table 2). Though statistically different, the IQRs indicate the wide range of variability for both patients with NSTI and without. There was no significant difference in the percentage of bands or corrected sodium between the two cohorts. C-reactive protein is not routinely collected at our institution, so it was not possible to calculate Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scores for these patients.

Blood cultures were collected on 272 patients (92.2%) and were positive in 54 patients (19.8% of collected blood cultures) (table 2). The frequency of positive blood cultures was similar for both NSTI and non-NSTI patients (p=0.5). Blood culture organisms were compared with organisms found on wound cultures, which were collected at presentation or during operative debridement. There were a total of seven patients (three NSTI, four non-NSTI) who had positive blood cultures, but no wound cultures taken. Of the remaining 47 blood culture-positive patients, 30 (63.8%) grew the identical organism in their wound culture, herein defined as pathologic blood culture. There was no difference in the rate of pathologic blood cultures between NSTI and non-NSTI patients (p=0.65).

Wound cultures were obtained from 272 patients (92.2%) and were polymicrobial in 43.4% (table 3). Polymicrobial infections were significantly more common in patients with NSTI (p<0.0001). Monomicrobial isolates frequently associated with NSTI (*Streptococcus* sp and methicillin-resistant *Staphylococcus aureus*) were with found equal frequency in both groups. Other pathogens significantly more common in patients with NSTI were *Streptococcus viridans*, oxacillin sensitive *S. aureus*, *Enterococcus* sp, and Gram-negative rods (p<0.05). Diphtheroids, *Enterococcus*, and *Candida* were only isolated in patients with NSTI.

Surgical treatment and outcomes

Among all patients, the median number of debridements was 1, but patients with NSTI had more debridements compared with the non-NSTI cohort (p<0.001) (table 4). The number of debridements ranged from 1 to 9 in the NSTI cohort, and 1–4 in the non-NSTI cohort. A total of 62 amputations (21.0%) were performed, with significantly more amputations performed for patients with NSTI (p<0.0001). Overall in-hospital mortality was 9.8% and did not differ between NSTI and non-NSTI patients (p=0.6). Patients with NSTI had a longer intensive care unit length of stay (ICU LOS) (p=0.03) and a longer overall LOS (p=0.0002).

A unique subset are the eight patients initially diagnosed with cellulitis who had an NSTI diagnosed on return to the operating room due to failure to improve (persistent

Table 1 Demographic and clinical data

Variable	All patients n=295	NSTI n=232	Non-NSTI n=63	P value
Sex, n (%)				
Female	76 (25.8)	56 (24.1)	20 (31.7)	0.2
Male	219 (74.2)	176 (75.9)	43 (68.3)	
Age, median (IQR) years	50 (41–56)	50 (42–56)	50 (37–60)	0.8
Comorbidity, n (%)				
Diabetes mellitus	172 (58.3)	153 (65.9)	19 (30.2)	<0.0001
Congestive heart failure	18 (6.1)	14 (6.0)	4 (6.3)	1.0
Intravenous drug use	18 (6.1)	14 (6.0)	4 (6.3)	1.0
Cirrhosis	17 (5.8)	13 (5.6)	4 (6.3)	0.8
Steroids	12 (4.4)	9 (3.9)	3 (4.8)	0.7
HIV	5 (1.7)	4 (1.7)	1 (1.6)	1.0
Chemotherapy	2 (0.7)	1 (0.4)	1 (1.6)	0.4
Location of soft tissue infection, n (%)				
Upper extremity	28 (9.5)	20 (8.6)	8 (12.7)	0.3
Lower extremity	183 (62.0)	133 (57.3)	50 (79.4)	0.001
Pelvic, perineal, perianal	72 (24.4)	67 (28.9)	5 (7.9)	0.0004
Trunk	26 (8.8)	23 (9.9)	3 (4.8)	0.3
Duration of symptoms, median (IQR) days	4 (3–7)	5 (3–7)	3 (1–7)	0.004
Vitals, median (IQR)				
Temperature (°C)	37.2 (36.7-38.1)	37.2 (36.7-38.1)	37.3 (36.9-38.1)	0.2
Heart rate	101 (91–114)	101 (91–115)	100 (88–109)	0.3
Respiration rate	18 (17–20)	18 (17–20)	20 (18–21)	0.4
Physical examination, n (%)				
Bullae	55 (18.6)	40 (17.2)	15 (23.8)	0.3
Violaceous	36 (12.4)	21 (9.1)	15 (23.8)	0.004
Crepitus	37 (12.5)	35 (15.1)	2 (3.2)	0.009
Illness severity, n (%)				
Septic shock	44, (15.3)	35, (15.6)	9, (14.3)	1.0

NSTI, necrotizing soft tissue infection.

leukocytosis, fevers, hypotension, and/or progression of cutaneous changes). These eight patients were predominantly male (75%) with a median age of 40 years. The most common infection site was the lower extremity (87.5%). There was no predominant organism identified. Two patients presented in septic shock—one of whom had *Escherichia coli* bacteremia and the other whose wound culture grew group A *Streptococcus*. These two patients account for the two patients in the non-NSTI group that progressed to amputation. This patient with group A *Streptococcus* also represents the single mortality

Table 2 Laboratory data

Variable	All patients n=295	NSTI n=232	Non-NSTI n=63	P value
Laboratory, median (IQR)				
White blood cell (k/mm^3)	18.1 (12.6–23.9)	18.5 (13.5–24.4)	14.9 (11.9–22.7)	0.02
Bands (%)	17 (10–30)	16.5 (9–30)	17.5 (12–26)	0.7
Sodium (mmol/L)	131 (127–135)	130 (127–134)	134 (131–136)	<0.0001
Corrected sodium (mmol/L)	134 (131–137)	134 (131–137)	134 (132–137)	0.7
Bicarbonate (mmol/dL)	22 (20–25)	22 (20–25)	22 (20–26)	0.6
Creatinine (mg/dL)	1.2 (0.9–1.8)	1.2 (0.9–1.8)	1.3 (0.9–2.0)	0.6
Glucose (mg/dL)	183 (114–361)	244 (131–393)	114 (102–136)	<0.0001
Lactate (mmol/L)	1.7 (1.3–2.5)	1.7 (1.3–2.6)	1.8 (1.3–2.3)	0.6
Blood culture positive, n (%)	54/272 (19.8)	44/213 (20.7)	10/59 (17.0)	0.5
Pathologic blood culture, n (%)	30/47 (63.8)	27/41 (65.8)	3/6 (50.0)	0.65

NSTI, necrotizing soft tissue infection.

Table 3 Microbiology data

Wound culture, n (%)	All patients n=272	NSTI n=222	Non-NSTI n=50	P value
Polymicrobial	118 (43.4)	112 (50.5)	6 (12.0)	<0.0001
Group A *Streptococcus*	31 (11.4)	23 (10.4)	8 (16.0)	0.3
Group B *Streptococcus*	26 (9.6)	23 (10.4)	3 (6.0)	0.4
Streptococcus viridans	42 (15.4)	40 (18.0)	2 (4.0)	0.01
Streptococcus other	14 (5.2)	10 (4.5)	4 (8.0)	0.3
MRSA	31 (11.4)	27 (12.2)	4 (8.0)	0.6
OSSA	58 (21.3)	54 (24.3)	4 (8.0)	0.01
STACN	49 (18.0)	42 (18.9)	7 (14.0)	0.5
Diphtheroids	15 (5.5)	15 (6.8)	0 (0)	0.1
Enterococcus	36 (13.2)	36 (16.2)	0 (0)	0.0008
GNR	94 (34.6)	88 (39.6)	6 (12.0)	0.0001
Candida	7 (2.6)	7 (3.2)	0 (0)	0.4
Other	41 (15.1)	39 (17.6)	2 (4.0)	0.01

GNR, gram negative rods; MRSA, methicillin-resistant Staphylococcus aureus; NSTI, necrotizing soft tissue infection; OSSA, oxacillin sensitive Staphylococcus aureus; STACN, Staphylococcus coagulase negative.

in the cohort. There was another patient with group A *Streptococcus* who did not die.

DISCUSSION

This study emphasizes that despite best surgical judgment and the use of predictive models, there are a number of patients who will not have an NSTI at the time of surgical exploration. Our study is unique in that our patients all went to operation with a working diagnosis of NSTI—that is, the diagnosis of cellulitis or abscess occurred at the time of operation (and not pre-emptively). Our study adds to existing literature that the differences between patients with NSTI and non-NSTI can be extremely subtle, and we propose that there may be an acceptable rate of negative exploration for this disease process. For us it was 20%.

Previous work corroborates the difficulty in expediently diagnosing NSTI. Only 14% to 39% of necrotizing fasciitis is correctly identified at initial presentation.[7 14 25 26] Our study is unique in that we expanded our study group beyond necrotizing fasciitis to all NSTI. Further, our study indicates that even experienced clinical judgment can be wrong. Other surgical disease processes with diagnostic challenges, such as appendicitis, have been extensively studied with a historical negative appendectomy rate of approximately 15%.[27–29] Over time, groups at increased risk of negative appendectomy such as women and children have been identified,[27–32] and the overall rate of negative appendectomy has declined to 3% to 4%.[29 30] Our study establishes an overall negative exploration rate of 20%, which with time may be validated or refuted and improved by subsequent research.

In this study, patients operated on for NSTI were clinically similar preoperatively regardless of their intraoperative findings. They had indistinguishable degrees of fever and tachycardia, with remarkably similar rates of septic shock. 'Hard signs' of NSTI such as bullae, violaceous changes, and crepitus were seen in both groups. Some studies consider hard signs a late finding in NSTI and report them in less than half of patients.[1 2 6 7 9 10 12 14 15 33] Fernando *et al* found that the lack of pathognomonic physical examination findings was insufficient to rule out NSTI.[17] We found relatively low numbers of these signs in our patients as well, but even more importantly, we demonstrate that these hard signs can also be present in patients with non-NSTI further confusing the diagnosis.

Similar to prior studies, we found the lower extremity to be the most common site of NSTI.[7 11–13 26 33–37] Pelvic, perineal, and perianal presentations were significantly more common in the NSTI cohort, and this region had the lowest rate of negative exploration (6.9%). It is unclear the full reason for these trends, but surgeons may have a lower threshold to explore an extremity. Alternatively, Fournier's may represent a unique disease entity or the perineum a unique environment that predisposes the patient to NSTI. Larger numbers would be needed, but it is possible that differing body areas also have varying 'acceptable' rates of negative exploration.

Notable laboratory differences in the patients with NSTI included more profound leukocytosis and hyponatremia. When looking at the IQRs, however, there is considerable overlap between the two groups, thus although statistically significant,

Table 4 Outcomes

Variable	All patients n=295	NSTI n=232	Non-NSTI n=63	P value
Number of debridements, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	<0.0001
Amputation, n (%)	62 (21.0)	60 (25.9)	2 (3.2)	<0.0001
Mortality, n (%)	29 (9.8)	24 (10.3)	5 (7.9)	0.6
ICU LOS, median (IQR)	2 (0–5)	3 (0–5)	0 (0–6)	0.03
LOS, median (IQR)	15 (8–25)	16 (9–28)	10 (6–18)	0.0002

ICU, intensive care unit; LOS, length of stay; NSTI, necrotizing soft tissue infection.

these differences do not seem clinically relevant. Patients with negative explorations had leukocytosis up to 23 000 and were consistently mildly hyponatremic after correcting for glucose levels, just like patients with NSTI. Thus, whereas leukocytosis and hyponatremia have been integrated into multiple predictive models of NSTI,[8 14 15] we find that they also occur in patients without NSTI.

The relative incidence of polymicrobial versus monomicrobial infections varies considerably,[6] but polymicrobial infections are often the most common etiology of NSTI.[1 3 5 7 9 11 12 21 22 34 37] Diabetes has been associated with polymicrobial NSTI infections, and the higher prevalence of diabetes in our NSTI group likely contributed to the relatively higher frequency of polymicrobial infections.[36] Monomicrobial isolates previously associated with NSTI (*Streptococcus* and *S. aureus* sp) were also seen in the non-NSTI cohort. Why the same causative organism results in varying degrees of virulent infections remains unclear. This is likely attributable to host factors that have yet to be fully elucidated and an area for future research.[34]

The cohort of eight patients who had initial operative diagnoses of cellulitis and then returned to the operating room due to failure to improve is a small, but fascinating group. We found no specific trends to predict who these patients would be. They had no unique demographics or clinical presentations, and their pathogens represented a varied microbiology. Only one of these patients died, so this group was not the source of similar mortality we reported for the NSTI and non-NSTI patients. Although one assumption is that the surgeon missed the diagnosis during the first operation, it should be recalled that this was the main intent of the operation so probing and evaluating for tissue viability was the standard. Alternatively, this cohort could support the concept that NSTIs are an evolving disease process and further explain what other authors have reported as a delay to diagnosis. We use this data to recommend that surgeons continue to follow patients who they determined to have a negative exploration and go back for further exploration if the patient fails to improve.

Patients with NSTI and those with negative explorations had similar mortalities indicating the severe cellulitis can also be a serious disease process. The increased number of debridements and amputations in the NSTI cohort is likely secondary to the destructive nature of NSTI and the need to gain surgical source control. Increased ICU LOS in NSTI may reflect the time needed to obtain source control or advanced wound care needs. The overall increased LOS is likely secondary to numerous factors as patients with NSTI require substantial resources during their treatment.[3 14 15] This includes reoperation (debridements, wound VAC changes, and skin grafts), need for physical therapy, and patient disposition issues.

Limitations to this study include that it is retrospective in nature and conducted at a single institution. Our institution is a safety-net hospital and patients may present later in their disease course. We may also have different thresholds to operate on patients with suspected NSTI than other institutions. A final potential criticism of this study is that we do not routinely use the absolute value of LRINEC in making a decision to operate. As an experienced trauma and acute care surgery service, a negative LRINEC score would not dissuade our team from operating on a patient in septic shock with findings concerning for NSTI.

CONCLUSIONS

Physical examination findings and predictive lab models fail to identify every patient with NSTI. The clinical differences between patients who have an NSTI and those who do not are subtle—they present similarly, grow common causative organisms, and have equivalent mortality rates. Surgical exploration remains the gold standard for diagnosis and should not be delayed if there is a high index of suspicion. Our institution found a 20% negative exploration rate. As some negative explorations later progressed to NSTI, we recommend ongoing vigilance by the surgical team until clinical improvement is seen. We advocate for future multi-institutional studies to validate an acceptable negative exploration rate in patients suspected to have an NSTI.

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