Predictors of Mortality and Limb Loss in Necrotizing Soft Tissue Infections

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Hypothesis: Necrotizing soft tissue infections are associated with a high mortality rate. We hypothesize that specific predictors of limb loss and mortality in patients with necrotizing soft tissue infection can be identified on hospital admission.

Design: A retrospective cohort study.

Setting: A tertiary care center.

Patients: Patients with a diagnosis of necrotizing soft tissue infection during a 5-year period (1996-2001) were included. Patients were identified with *International Classification of Diseases, Ninth Revision* hospital discharge diagnosis codes, and diagnosis was confirmed by medical record review.

Interventions: Standard current treatment including early and scheduled repeated debridement, broad-spectrum antibiotics, and physiologic and nutritional support was given to all patients.

Main Outcome Measures: Limb loss and mortality.

Results: One hundred sixty-six patients were identified and included in the study. The overall mortality rate was 16.9%, and limb loss occurred in 26% of patients with extremity involvement. Independent predictors of mortality included white blood cell count greater than $30000 \times 10^3/\mu L$, creatinine level greater than 2 mg/dL (176.8 µmol/L), and heart disease at hospital admission. Independent predictors of limb loss included heart disease and shock (systolic blood pressure <90 mm Hg) at hospital admission. Clostridial infection was an independent predictor for both limb loss (odds ratio, 3.9 [95% confidence interval, 1.1-12.8]) and mortality (odds ratio, 4.1 [95% confidence interval, 1.3-12.3]) and was highly associated with intravenous drug use and a high rate of leukocytosis on hospital admission. The latter was found to be a good variable in estimating the probability of death.

Conclusions: Clostridial infection is consistently associated with poor outcome. This together with the independent predictors mentioned earlier should aid in identifying patients on hospital admission who may benefit from more aggressive and novel therapeutic approaches.

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THERE ARE APPROXIMATELY 500 to 1500 cases of necrotizing soft tissue infection (NSTI) per year in the United States.[1] The cumulative mortality rate is approximately 24% to 34%[2-19] and has not changed significantly from that reported by Joseph Jones,[20] a confederate army surgeon, who first reported 2642 cases of "hospital gangrene" in 1871 with a mortality rate of 46%.

See Invited Critique at end of article

In an attempt to better define the different entities within NSTI and to better stratify them according to prognosis, multiple classification schemes have been proposed.[19,21-23] Different reports have described classification schemes by anatomical level of involvement (skin and subcutaneous tissue, subcutaneous tissue and fascia, and muscle), microbiologic characteristics (bacterial synergistic gangrene, streptococcal gangrene, and clostridial or fungal infections), or whether surgical management is required.[19,21,24-26] However, none of these classifications have been universally adopted and none allow a relatively simple means to classify patients on their initial examination, rendering their clinical utility rather limited. Furthermore, treatment strategies generally involve the same principles for all NSTI (early diagnosis, surgical debridement, broad-spectrum antibiotics, and physi-

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ologic and nutritional support), making these classification schemes less relevant.

However, identifying specific characteristics evident on initial examination that portend a higher risk of adverse outcomes may aid in classifying patients according to prognosis and in determining which patients may warrant more aggressive surgical interventions or which may be candidates for trials evaluating novel therapeutic approaches.

The purpose of this study was to define the incidence of poor outcomes (death and limb loss) in a cohort of patients with NSTI and, specifically, to identify predictors of mortality and limb loss evident at initial examination.

METHODS

SUBJECTS

Patients admitted to Harborview Medical Center, Seattle, Wash, with a diagnosis of NSTI during a 5-year period (May 1996-July 2001) were included in the study. Harborview Medical Center is a county hospital and a tertiary referral care center that serves patients from the states of Washington, Wyoming, Alaska, Montana, and Idaho. Patients with NSTI were treated using a standardized approach that included early and scheduled repeated debridements in concert with aggressive physiologic and nutritional support in the intensive care unit. Empirical broad-spectrum antibiotics were given to all patients, with narrowing of the spectrum once the predominant organisms were identified. Hyperbaric oxygen therapy was not routinely used.

Patients were identified by *International Classification of Diseases, Ninth Revision* codes for fields pertaining to NSTI, and diagnosis was confirmed by medical record review. The diagnosis was established by the presence of necrotic tissue at the time of surgery or by its presence as described in pathologic specimen reports (including autopsy reports). Once these criteria were met, patients were included in the study, and no further inclusion or exclusion criteria were used.

A detailed medical record review was performed by a trained abstractor to capture demographic information and preexisting conditions. The primary site of infection as well as presumed cause of infection were also abstracted and categorized. Site of infection was divided into head and neck, chest, abdomen, perineum, buttocks, and extremities while cause of infection was classified as either chronic wound and/or ulcer, injection relative to intravenous drug use, boil and/or furuncle, bite, idiopathic, trauma, postoperative wound infections, perirectal abscess, and other. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the severity of multiple organ failure were also captured. For the latter, the continuous scale of Marshall et al[27] was used.

Physiologic parameters on hospital admission included systolic blood pressure, heart rate, and temperature in degrees Celsius. Laboratory values recorded on hospital admission included white blood cell (WBC) count; hematocrit; bicarbonate, sodium, and creatinine levels; and anion gap value.

Microbiologic results were recorded for patients with initial cultures positive for organisms. Results were classified according to the type of infection, monomicrobial vs polymicrobial, and specific rates for the following groups of microorganisms were recorded: *Staphylococcus,* β-hemolytic streptococci (not Enterococcus), *Clostridium,* Enterococcus, gram-negative bacteria, anaerobes (not *Clostridium*), fungus, and other.

Treatment variables included information on the timing of surgery and the number of procedures during the hospital stay.

Antibiotic treatment strategies were also recorded including use of 1 or multiple antibiotics and the specific antibiotics used. Lastly, data on the use of additional therapeutic strategies, such as intravenous immunoglobulin and hyperbaric oxygen, were recorded.

Outcome variables recorded included data pertaining to length of hospital stay, mortality, and limb loss. The latter pertained to patients with an extremity as the primary site of infection.

STATISTICAL ANALYSIS

To identify factors associated with either mortality or limb loss, we first performed a series of univariate analyses using the χ^2 test for categorical data and the *t* test for continuous variables. Variables with a *P* value <.10 were subsequently included in a multivariate analysis to identify independent predictors of adverse outcomes using a stepwise logistic regression model with a *P* value for removal from the model of >.05. Continuous variables were dichotomized when included in the model. Results are presented as odds ratios and 95% confidence intervals. The analysis for predictors of limb loss was limited to those patients with an extremity as a primary site of infection. All statistical analyses were performed using Stata version 8 (Stata, College Station, Tex).

RESULTS

DEMOGRAPHICS, PREEXISTING CONDITIONS, AND CLINICAL CHARACTERISTICS

One hundred sixty-six patients treated for NSTI at Harborview Medical Center during this 5-year period were identified and included in the study. **Table 1** shows demographic and clinical characteristics as well as preexisting conditions of the cohort and compares these variables in survivors and nonsurvivors. The mean (SD) age of the cohort was 45.6 (15.0) years, and 100 (60.2%) were male. Information about referral was available for 150 patients of which 123 (82%) were transferred from another institution. None of these variables were significantly different for survivors vs nonsurvivors, although age older than 65 years was associated with limb loss (*P*=.10).

Intravenous drug use was the most prevalent preexisting condition in this population of patients, with 49 patients (29.5%) actively using intravenous drugs (predominantly heroin) (Table 1). When comparing preexisting conditions in survivors and nonsurvivors, rates of intravenous drug use, chronic renal insufficiency, and heart disease were significantly higher in nonsurvivors. Additionally, only heart disease demonstrated a significant association with limb loss (data not shown).

The most common site of infection was the extremities, affecting 96 patients (57.8%), followed by the abdomen and perineum (20 patients [12.1%] each) (Table 1). Mortality was significantly higher in patients with extremities as the primary site (*P*=.04). Injection drug use was the most common cause of infection in this population (49 patients [29.5%]). This etiology was more likely to be associated with death when compared with other causes (*P*=.03) while postoperative infections were associated with a higher rate of survival (*P*=.09). No specific etiology was associated with an increased risk of limb loss. **Table 2** shows demographic and clinical charac-

Table 1. Demographic and Clinical Characteristics and Preexisting Conditions of Patients With Necrotizing Soft Tissue Infection*

Variable	All Patients (n = 166)	Survivors (n = 138)	Nonsurvivors (n = 28)	P Value†
Age, y, mean (SD)	45.6 (15.0)	44.8 (15.0)	49.3 (15.0)	.20
Men	100 (60.2)	83 (60.6)	17 (60.7)	.99
Medical comorbidities‡				
None	114 (68.7)	98 (71.0)	16 (57.1)	.14
Diabetes mellitus	32 (19.3)	26 (18.8)	6 (21.4)	.70
Immunosuppression	5 (3.0)	4 (2.9)	1 (3.6)	.80
COPD	9 (5.4)	6 (4.3)	3 (10.7)	.17
Heart disease	10 (6.0)	6 (4.3)	4 (14.3)	.04
CVD	3 (1.8)	2 (1.4)	1 (3.6)	.40
Malignancy	4 (2.4)	3 (2.2)	1 (3.6)	.60
Renal insufficiency	1 (0.6)	0	1 (3.6)	.02
Intravenous drug use	49 (29.5)	37 (26.8)	12 (42.9)	.09
Site of infection				
Head and neck	8 (4.8)	7 (5.1)	1 (3.6)	.70
Chest	5 (3.0)	5 (3.6)	0	.30
Abdomen	20 (12.1)	19 (13.8)	1 (3.6)	.13
Perineum	20 (12.1)	19 (13.8)	1 (3.6)	.13
Buttocks	17 (10.2)	13 (9.4)	4 (14.3)	.40
Extremity	96 (57.8)	75 (54.3)	21 (74.9)	.04
Cause of infection				
Chronic wound and/or ulcer	12 (7.2)	9 (6.5)	3 (10.7)	.40
Injection	49 (29.5)	37 (26.8)	12 (42.9)	.09
Boil and/or furuncle	18 (10.9)	16 (11.6)	2 (7.1)	.40
Bite	2 (1.2)	2 (1.5)	0	.50
Idiopathic	30 (18.1)	25 (18.1)	5 (17.9)	.90
Trauma	27 (16.3)	24 (17.4)	3 (10.7)	.30
Postoperative wound infection	19 (11.4)	19 (13.8)	0	.03
Perirectal abscess	1 (0.6)	1 (0.7)	0	.60
Other	8 (4.8)	5 (3.6)	3 (10.7)	.30

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease.
*Distribution by mortality (univariate analysis). Values are expressed as number (percentage) of patients unless otherwise indicated.
†P value is based on a comparison between survivors and nonsurvivors.
‡Some patients had more than 1 comorbidity.

teristics of patients with NSTI of the extremities specifically.

PHYSIOLOGIC PARAMETERS AND LABORATORY RESULTS

Table 3 shows physiologic parameters and laboratory results at the time of initial examination. There were no differences in physiologic parameters on hospital admission in survivors compared with nonsurvivors; however, the presence of shock (systolic blood pressure<90 mm Hg) on hospital admission was associated with an increased risk of limb loss ($P = .02$).

Mean WBC count on hospital admission was significantly higher in nonsurvivors ($29\,500 \times 10^3/\mu L$ vs $18\,300 \times 10^3/\mu L$; $P < .001$), as well as the mean hematocrit (39.2% vs 33.7%; $P = .003$) and creatinine level (2.3 mg/dL [203.32 μmol/L] vs 1.4 mg/dL [123.76 μmol/L]; $P = .01$). No statistically significant difference was seen for any of these values in patients who had limb loss vs those who did not.

Initial mean APACHE II and multiple-organ dysfunction syndrome scores (within first 48 hours) for all patients were 19.2 and 5.4, respectively. After univariate analysis, an APACHE II score higher than 20 was associated with a 14.2-fold greater risk of death ($P < .001$) and

a multiple-organ dysfunction syndrome score higher than 5 with a 16.6-fold greater risk of death ($P < .001$).

MICROBIOLOGIC FINDINGS

Table 4 shows the distribution of microorganisms in all patients and compares survivors with nonsurvivors. Data regarding the implicated organism were available in 149 patients. Most (57% [85/149]) of the infections were polymicrobial. When comparing survivors and nonsurvivors, monomicrobial infections were more frequent in nonsurvivors (58.3% [14/24] vs 40% [50/125]; $P = .09$)

A total of 272 isolates were found. The most frequent bacteria isolated was *Staphylococcus* (21.7% [59/149]) followed by gram-negative bacteria (18.4% [50/149]) and β-hemolytic streptococci (not enterococcus) (17.3% [47/149]). Of all the isolates, only clostridial were highly associated with mortality and limb loss.

TREATMENT

One hundred sixty-three patients (98.2%) underwent surgical treatment. The remaining patients either refused surgery or died during the initial resuscitation period. The mean time to operation from hospital admission was 0.95

Table 2. Demographic and Clinical Characteristics and Preexisting Conditions of Patients With Necrotizing Soft Tissue Infection of the Extremities*

Variable	Extremity Infection (n = 96)	No Extremity Infection (n = 70)	P Value†
Age, y, mean (SD)	45.7 (14.0)	45.5 (17.0)	.84
Men	60 (63)	40 (57)	.44
Medical comorbidities‡			
None	68 (70)	46 (65)	.50
Diabetes mellitus	18 (19)	14 (20)	.80
Immunosuppression	1 (1)	4 (5)	.08
COPD	5 (5)	4 (5)	.80
Heart disease	7 (7)	3 (4)	.40
CVD	3 (3)	0	.13
Malignancy	1 (1)	3 (4)	.17
Renal insufficiency	0	1 (1)	.20
Intravenous drug use	39 (41)	10 (14)	<.001
Cause of infection			
Chronic wound and/or ulcer	7 (7)	5 (7)	.90
Injection	39 (41)	10 (14)	<.001
Boil and/or furuncle	5 (5)	13 (18)	.006
Bite	2 (2)	0	.20
Idiopathic	18 (19)	12 (17)	.80
Trauma	18 (19)	9 (13)	.30
Postoperative wound infection	5 (5)	14 (20)	.003
Perirectal abscess	0	1 (1)	.20
Other	2 (2)	6 (8)	.02

Abbreviations: See Table 1.
*Values are expressed as number (percentage) of patients unless otherwise indicated.
†P value is based on a comparison between survivors and nonsurvivors.
‡Some patients had more than 1 comorbidity.

day, and although it was shorter in nonsurvivors, this was not statistically significant (0.56 vs 1 day; P=.40). The mean number of procedures performed for the whole cohort was 3.6; 2.1 for nonsurvivors and 3.9 for survivors.

Information on antimicrobial therapy was available for 155 patients. Of these, 136 patients (87.7%) received combination antimicrobial regimens, most commonly penicillin, clindamycin, and gentamicin. There was no significant association between antimicrobial choices and adverse outcomes. A very small proportion of patients received either intravenous immunoglobulin (n=13; 7.8%) or hyperbaric oxygen (n=8; 4.8%), precluding any assessment of their relationship to outcome.

OUTCOMES

The overall mortality rate in this cohort was 16.9% (n=28). Early deaths (within 4 days of hospital admission) occurred in 18 patients (64%), and the remainder died between days 9 and 52. Mean length of stay for nonsurvivors was 11.7 days vs 30.7 days for survivors (P<.001). Limb loss occurred in 25 patients (15.1%) or 26% (25 of 98) of the patients with an extremity as the primary site of infection.

STEPWISE LOGISTIC REGRESSION

Table 5 shows the variables included in the logistic regression model for predictors of mortality and limb loss.

After multivariate analysis, specific independent predictors were identified (**Table 6**). Predictors of mortality included WBC count greater than $30000 \times 10^3/\mu L$, creatinine level greater than 2 mg/dL (176.8 µmol/L), clostridial infection, and the presence of heart disease on hospital admission. Independent predictors of limb loss were shock on hospital admission, heart disease, and clostridial infection.

Clostridial infection was identified as a predictor of poor outcome. To more easily identify patients with clostridial infection at the time of initial examination, we compared clinical and laboratory variables in those with and without clostridia. Patients with a history of intravenous drug use and those with a higher WBC count were more likely to have a clostridial infection (**Table 7**). Also, patients with clostridial infection had a higher APACHE II score and were more likely to have limb loss or die.

The specific correlation between mortality and WBC count on hospital admission (a predictor of mortality and a surrogate for clostridial infection) is clearly shown in the **Figure**.

COMMENT

This is one of the largest series of patients with NSTI published to date and the largest one focused on identifying independent predictors for mortality. Our population of patients is heterogeneous, although a high proportion of patients with intravenous drug use as an etiology are included (29.5%). We describe the overall rate of limb loss in patients with NSTI to be 15.1% (26% for those with extremity infections) and, for the first time, identify predictors for this outcome including shock on hospital admission and preexisting heart disease. We also show a low overall mortality rate of 16.9% and found WBC count and creatinine level on hospital admission, as well as the presence of heart disease, to be independently associated with mortality. Clostridial infection was shown to be independently associated with both limb loss and mortality.

The mortality of patients in this series is significantly lower than that of recent and similar larger published studies.[10-18] This may be related to the high volume of patients with this diagnosis referred to our institution. Increased awareness of the fatality associated with this disease may lead to earlier and more aggressive surgical intervention. Bilton et al[28] clearly show how aggressive and early surgical management was associated with a better outcome. They compared patients with necrotizing fasciitis according to the adequacy of surgical therapy (complete and early debridement) and divided patients into 2 groups. Those who underwent delayed or inadequate preliminary therapy had a mortality rate of 38.0% vs 4.2% in those who underwent early and aggressive therapy. Although our study did not show statistically significant differences in outcomes based on the length of time from hospital admission to initial operation, surgical treatment in our patients was instituted within 24 hours of hospital admission for most patients, a mean time significantly lower when compared with similar series (McHenry et al,[10] 45 hours; Elliott et al,[12] 1.7 days;

Table 3. Mean Physiologic Parameters and Laboratory Findings of Patients With Necrotizing Soft Tissue Infection on Hospital Admission*

Variable	All Patients (n = 166)	Survivors (n = 138)	Nonsurvivors (n = 28)	P Value†
Physiologic variables				
Systolic blood pressure, mm Hg	120.9 (25.0)	121.8 (24.0)	116 (31.0)	.40
Heart rate, beats per min	108.1 (21.0)	107.5 (22.0)	112.1 (20.0)	.30
Temperature, °C	36.8 (1.9)	36.9 (1.9)	36.4 (1.6)	.17
APACHE II score‡	19.2 (11.0)	16.8 (9.0)	31.2 (12.0)	<.001
MODS score‡	5.4 (4.9)	4.4 (4.4)	10.7 (3.8)	<.001
Laboratory variables				
WBC count, $\times 10^3/\mu L$	20.1 (14.0)	18.3 (10.0)	29.5 (23.0)	<.001
Hematocrit, %	34.6 (8.5)	33.7 (7.5)	39.2 (11.0)	.003
Bicarbonate level, mEq/L	24.0 (8.5)	24.4 (9.0)	21.9 (4.1)	.20
Sodium level, mEq/L	132.0 (9.8)	131.8 (11.9)	132.0 (9.8)	.60
Creatinine level, mg/dL	1.58 (1.6)	1.44 (1.5)	2.3 (1.9)	.01
Anion gap value, mEq/L	6.3 (6.1)	6.0 (6.0)	8.4 (6.5)	.16

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; MODS, multiple-organ dysfunction syndrome; WBC, white blood cell.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.
*Distribution by mortality (univariate analysis). Values are expressed as mean (SD) unless otherwise indicated.
†P value is based on a comparison between survivors and nonsurvivors.
‡Scores within the first 48 hours of hospital admission.

Table 4. Microbiologic Findings in Patients With Necrotizing Soft Tissue Infections*

Microbiologic Finding	All Patients (n = 149)	Survivors (n = 125)	Nonsurvivors (n = 24)	P Value†
Polymicrobial infection	85.0 (57.0)	75.0 (60.0)	10.0 (41.7)	.09
Monomicrobial infection	64.0 (43.0)	50.0 (40.0)	14.0 (58.3)	.09
Total isolated organisms	272.0 (100)	323.0 (100)	40.0 (100)	
Staphylococcus	59.0 (21.7)	51.0 (22.0)	8.0 (20.0)	.30
Gram-negative bacteria	50.0 (18.4)	43.0 (18.5)	7.0 (17.5)	.50
β-Hemolytic streptococci (not enterococcus)	47.0 (17.3)	42.0 (18.1)	5.0 (12.5)	.17
Clostridium	29.0 (10.6)	18.0 (7.8)	11.0 (27.5)	.001
Anaerobes (not Clostridium)	20.0 (7.4)	19.0 (8.1)	1.0 (2.5)	.13
Enterococcus	17.0 (6.3)	15.0 (6.5)	2.0 (5.0)	.50
Fungus	5.0 (1.8)	5.0 (2.2)	0	.30
Other	45.0 (16.5)	39.0 (16.8)	6.0 (15.0)	.40

*Distribution by mortality (univariate analysis). Values are expressed as number (percentage) of patients.
†P value is based on a comparison between survivors and nonsurvivors.

Bosshardt et al,[13] 116 hours for nonsurvivors). Early consideration of the diagnosis and surgical treatment continues to be the mainstay in the treatment of these entities. Recent studies, as well as better technology (eg, magnetic resonance imaging), have also aided in shortening the time to diagnosis and the ability to differentiate soft tissue infections from those with a component of necrosis and need for surgery.[29,30]

Various series have attempted to identify risk factors for mortality in patients with NSTI. Independent predictors of mortality previously published include age, female sex, number of medical comorbidities, diabetes mellitus, peripheral vascular disease, blood pressure on hospital admission, temperature on hospital admission, acidosis, creatinine level on hospital admission, lactate level, infections involving Clostridium, group A β-hemolytic streptococci or mucormycosis, delayed surgical treatment, and organ failure on hospital admission.[10,12,13,17] The results from all of these series are contradictory, how-

ever, and only a few factors are found to be consistent across studies, a reflection of the diverse populations studied, the different variables included in each study, and the relatively small sample sizes. Unlike prior studies, we focused on predictors that are easily identifiable at initial examination so that patients could be stratified early in their course.

Patients with a WBC count greater than $30\,000 \times 10^3/\mu L$, those with heart disease, and those with a creatinine level greater than 2 mg/dL (176.8 µmol/L) on hospital admission were found to be at higher risk of death. Patients with heart disease and shock on hospital admission had a higher risk of limb loss. Patients with clostridial infection had a 4-fold risk of mortality and limb loss together. This relatively simple discriminator—clostridial or nonclostridial infection—and the prognosis associated with these 2 types of NSTI call for a more parsimonious classification scheme. However, clostridial infections are not easily discernable from non-

Table 5. Variables Included in the Multivariate Analysis for Limb Loss and Mortality and Their Corresponding *P* Value (After Univariate Analysis)

Variable	Limb Loss *P* Value*	Mortality *P* Value
Age	.10	NS
Heart disease	.02	.04
Chronic renal insufficiency	NS	.02
Intravenous drug use	NS	.09
Extremity site	NS	.04
Injection (intravenous drug use)	NS	.09
Postoperative wound infection	NS	.03
Shock (SBP<90 mm Hg) at hospital admission	.02	NS
WBC count at hospital admission	NS	<.001
Hematocrit at hospital admission	NS	.003
Creatinine level at hospital admission	NS	.01
Clostridial infection	.008	.001

Abbreviations: NS, not significant and hence not included in model for logistic regression; SBP, systolic blood pressure; WBC, white blood cell.
*Only patients with extremity infection were included in the analysis.

Table 6. Independent Predictors of Mortality and Limb Loss in Patients With Necrotizing Soft Tissue Infection*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Mortality		
WBC count >30 000 × 10^3/μL	3.7 (1.2-11.7)	.02
Creatinine level >2.0 mg/dL at hospital admission	3.1 (1.1-9.4)	.03
Heart disease	4.7 (1.0-21.5)	.04
Clostridial infection	4.1 (1.3-12.3)	.01
Limb loss†		
Shock at hospital admission	5.9 (1.3-26.0)	.02
Clostridial infection	3.9 (1.1-12.8)	.03
Heart disease‡	5.0 (0.9-29.0)	.07

Abbreviation: WBC, white blood cell.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.
*Stepwise logistic regression.
†Only patients with extremity infection were included in the analysis.
‡Independent predictor although it did not reach strict statistical significance given the small number of patients.

Table 7. Characteristics and Outcomes in Patients With and Without Clostridial Infection at Hospital Admission*

Variables	Clostridial Infection (n = 29)	No Clostridial Infection (n = 137)	*P* Value
Age, y, mean (SD)	49 (16)	45 (16)	.20
Men	21 (72)	79 (58)	.15
Intravenous drug use	15 (52)	34 (25)	.004
Heart disease	2 (7)	8 (5.8)	.80
Extremity site†	20 (69)	82 (60)	.30
Shock (SBP<90 mm Hg)	3 (10)	12 (8)	.79
Creatinine level >2 mg/dL	5 (17)	31 (23)	.52
Sodium level <130 mEq/L	8 (28)	40 (29)	.86
Bicarbonate level, mEq/L, mean (SD)	23 (4)	24 (9)	.56
WBC count, × 10^3/μL, mean (SD)	26.5 (21.0)	18.8 (12.0)	.008
Monomicrobial infection	14 (48)	50 (36.5)	.10
MODS score, mean (SD)	6.7 (5.5)	5.2 (4.8)	.14
APACHE II score, mean (SD)	23 (14)	18 (10)	.05
Outcomes			
Mortality	11 (38)	17 (12)	.001
Limb loss‡	9 (45)	16 (19.5)	.008

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; MODS, multiple-organ dysfunction syndrome; SBP, systolic blood pressure; WBC, white blood cell.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.
*Values are expressed as number (percentage) of patients unless otherwise indicated.
†Only patients with extremity infection were included in the analysis.
‡Includes only patients with extremity infection as primary and secondary sites of infection.
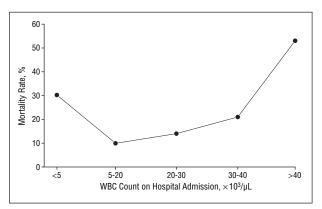

Figure. Predicted mortality rate for patients with necrotizing soft tissue infection according to white blood cell (WBC) count on hospital admission.

clostridial infections on hospital admission. For this reason, we identified specific factors that prove to be highly associated with clostridial infection, including intravenous drug use and high WBC count, on hospital admission. We also found that WBC count on hospital admission, an independent predictor of mortality and a factor highly associated with clostridial infection, could be used to estimate the risk of mortality in patients with NSTI on hospital admission (Figure). Heart disease was also found to be an independent predictor for mortality and limb loss. The fact that this specific medical comorbidity was present for both models (limb loss and mortality) should help in identifying patients with higher risk of poor outcomes from the initial examination. It is not clear, however, why heart disease in particular may be related poorly with these 2 outcomes; it may be that pa-

tients with peripheral vascular disease frequently have associated heart disease and a higher risk of limb loss, which has some association with increased mortality.[21] In our series, monomicrobial infections were more common than previously reported and also associated with a higher mortality rate. However, this result proved to be nonsignificant after multivariable analysis and is possibly due to the high frequency of clostridial infections in this cohort, which were more frequently monomicrobial and highly associated with poor outcome.

Because of its retrospective nature, this study has several limitations. For example, it is difficult to discern between diabetic foot infections and NSTI in patients with

diabetes mellitus, which might affect rates of limb loss. However, only 5 patients in our cohort were diabetic, and these patients had high APACHE II and multiple-organ dysfunction syndrome scores and a mortality rate of 60%, attesting to the severity of illness in these patients and most consistent with NSTI.

In summary, we present one of the largest series of patients with NSTI. We show low mortality and limb loss rates, probably related to the high frequency with which these entities are seen at our institution and to earlier diagnosis and debridement. We identify specific predictors of limb loss and mortality for patients with NSTI and propose to classify all of these entities into clostridial and nonclostridial NSTI. Additional independent predictors can be used to further assess the risk of poor outcomes. Specifically, patients with intravenous drug use and a high WBC count have a particularly high association with clostridial infection, and using this information may help in identifying higher-risk individuals on hospital admission (likely clostridial infection). The WBC count on hospital admission can also be used to predict mortality. This information should aid in establishing which patients may benefit from more aggressive and novel therapeutic approaches, in establishing clearer indications when considering amputation, and also in identifying target patients for clinical studies that attempt to better delineate the role of novel treatment strategies.

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T he mortality of necrotizing soft tissue infections has declined to 20% or less. Surgeons have made important contributions to disease management by establishing the principles of early recognition, adequate resuscitation, initiation of broad-spectrum antibiotics, and prompt debridement. No doubt, advances in diagnostic testing (computed tomography and magnetic resonance imaging) and the use of repeated operative debridement for source control,[1] as advocated in this study, contribute to the improved results. The mortality of these infections also depends on the presence of comorbid diseases, bacterial virulence (particularly, *Streptococcus pyogenes* and clostridia), and the genetically programmed response to severe infection.

This large series of patients with necrotizing soft tissue infections identifies a white blood cell count higher than $30000 \times 10^3/\mu L$, serum creatinine level higher than 2 mg/dL (176.8 µmol/L), and heart disease as predictors of mortality. The first 2 parameters were strongly associated with clostridial infection, the only microbiologic predictor of mortality and limb loss. The predictive value of these observations is difficult to determine because the frequency of the perturbed laboratory abnormalities was not stated and heart disease occurred in only 10 patients. A disproportionate number of patients had infections due to intravenous drug use and only one third had associated comorbid diseases. These differences in patient populations have been associated with better survival in previous studies. The percentage of body surface area involved by infection and the presence of acidosis, which have been demonstrated to influence mortality by other investigators, were not evaluated. Identification of disease through pathology reports and *International Classification of Diseases, Ninth Revision*–based coding may have added patients whose physicians would not have classified as affected with this potentially devastating disorder.

The early identification and treatment of necrotizing soft tissue infections has been our most important contribution to improved patient outcomes. Each thoughtfully done study like this one advances our understanding of this disease. Definition of the genetic factors affecting bacterial virulence and unique patient response will likely open the door for improved therapies and provide a quantum reduction in mortality.

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