Use of Admission Serum Lactate and Sodium Levels to Predict Mortality in Necrotizing Soft-Tissue Infections

Arezou Yaghoubian, MD; Christian de Virgilio, MD; Christine Dauphine, MD; Roger J. Lewis, MD, PhD; Matthew Lin, MD

Hypothesis: Simple admission laboratory values can be used to classify patients with necrotizing soft-tissue infection (NSTI) into high and low mortality risk groups.

Design: Chart review.

Setting: Public teaching hospital.

Patients: All patients with NSTI from 1997 through 2006.

Interventions: Variables analyzed included medical history, admission vital signs, laboratory values, and microbiologic findings. Data analyses included univariate and classification and regression tree analyses.

Main Outcome Measure: Mortality.

Results: One hundred twenty-four patients were identified with NSTI. The overall mortality rate was 21 of 124 (17%). On univariate analysis, factors associated with mortality included a history of cancer ($P = .03$), intravenous drug abuse ($P < .001$), low systolic blood pressure on admission ($P = .03$), base deficit ($P = .009$), and elevated white blood cell count ($P = .06$). On exploratory classification and regression tree analysis, admission serum lactate and sodium levels were predictors of mortality, with a sensitivity of 100%, specificity of 28%, positive predictive value of 23%, and negative predictive value of 100%. A serum lactate level greater than or equal to 54.1 mg/dL (6 mmol/L) alone was associated with a 32% mortality, whereas a serum sodium level greater than or equal to 135 mEq/L combined with a lactate level less than 54.1 mg/dL was associated with a mortality of 0%.

Conclusions: Mortality for NSTIs remains high. A simple model, using admission serum lactate and serum sodium levels, may help identify patients at greatest risk for death.

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Necrotizing soft-tissue infections (NSTIs) are rare, rapidly progressive infectious processes that primarily involve the fascia and the subcutaneous tissue. The infection often leads to thrombosis of the cutaneous microcirculation, severe sepsis, and multisystem organ failure. Approximately 500 to 1500 cases are reported in the United States annually. Distinguishing NSTI from simple cellulitis and abscesses can be difficult. Previous studies from our institution have indicated that an admission serum sodium level less than 135 mEq/L and white blood cell (WBC) count of 15,400/µL or more are useful in distinguishing NSTI from nonnecrotizing infections.

The mortality rate for NSTI remains high, ranging from 24% to 34%, and has not changed significantly for several decades. The prognosis depends on accurate diagnosis and immediate institution of appropriate treatment, which includes broad-spectrum antibiotics and wide surgical debridement. Thus, identifying patients at highest risk for death may have important therapeutic implications. The purpose of the present study was to determine predictors of mortality for NSTI by means of univariate and multivariate analysis, specifically, classification and regression tree (CART) analysis.

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The study was approved by the institutional review board of the Los Angeles Biomedical Institute at Harbor-UCLA Medical Center. The hospital is managed by the Los Angeles County
Department of Health Services and primarily treats under- 
served and uninsured patients. A retrospective analysis was per- 
formed of all NSTIIs seen at Harbor-UCLA Medical Center be- 
tween January 1, 1997, and December 31, 2006, by review of 
discharge diagnoses using a computerized database. Patients 
were identified by International Classification of Diseases, Ninth 
Revision codes for fields pertaining to NSTI, and the diagnosis 
was confirmed by review of medical records, including opera- 
tive and pathologic findings.

Clinical data collected included age, race, medical history, 
physical examination findings, radiographic findings, cause of in- 
fected, and primary site of infection. Additional admission vari- 
ables recorded included vital signs; levels of serum sodium, 
potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, 
laetic acid, and albumin; base excess or base deficit; WBC count; 
and anion gap. Intraoperative cultures were recorded and class- 
ed as gram positive, gram negative, mixed gram positive/ 
gram negative/anaerobic, methicillin-resistant Staphylococcus au- 
reus, and Clostridium species. Other data collected included 
duration of symptoms before presentation to the emergency de- 
partment (ED), length of time from presentation and to surgical 
consultation by the ED physicians, total length of time from ar- 
ival at the ED to surgical debridement, and the need for skin graft- 
ing. The number of debridements required was recorded, as was 
the need for major amputation. The main outcome measure was 
in-hospital mortality. A secondary outcome measure was need 
for major extremity amputation.

Patient data were collected in an Excel database (Microsoft 
Excel; Microsoft Corp, Redmond, Washington) and trans- 
lated into a native SAS (SAS Institute Inc, Cary, North Caro- 
olina) format by means of DBMS/Copy (Datalux Corp, Cary). 
Descriptive statistics were calculated for all variables. Numeri- 
cal variables were compared by using the nonparametric Wil- 
coxon rank sum test and are reported as medians. Categorical 
or nominal variables were compared by the χ² test or Fisher 
extact test, as appropriate. Univariate analyses were performed 
to determine factors associated with a complication. P < .05 was 
considered to be significant.

Multivariate analysis was performed by CART analysis, a mul-
tivariable decision tree approach to modeling. It is a form of re- 
cursive partitioning in which the population of patients is se- 
quently divided into smaller and smaller groups, based on the 
values of observed predictor variables, with each group increas- 
ingly homogeneous with respect to the outcome of interest (eg, 
in-hospital mortality). Compared with logistic regression, CART 
analysis is better suited to searching a large number of candidate 
variables without risking overfitting the data and is naturally suita- 
ded to detecting interactions between variables. A CART analysis 
begins with building multiple candidate decision trees, some of which 
may overfit the data, and then uses cross validation to “prune” 
the candidate trees, until the resulting decision tree no longer over- 
fits the available information. In the current study, however, the 
number of subjects with in-hospital mortality was not sufficient 
to support the full cross-validation approach to CART analysis.

Therefore, the current analysis involves the development of an 
“exploratory” decision tree, which has not been cross-validated. 
The resulting decision tree must be considered preliminary, ana- 
gous to a multivariable regression model that has not yet been 
validated by independent data.

RESULTS

PATIENT DEMOGRAPHICS

One hundred twenty-four patients with NSTI were iden-
tified. The median age was 43 years, and 85 (69%) were 
małe. The most common comorbidity was diabetes melli-
tus, occurring in 45 (38%). The most common identifi-
able source of the necrotizing infection was intravenous 
injection of illicit drugs, reported in 39 (31%). An addi-
tional 16 (13%) reported recent trauma. In 53 patients 
(43%), however, the cause of infection was unknown. The 
most common location of the NSTI was the lower ex-
trmity, found in 64 patients (52%).

DIAGNOSIS OF NSTI

Hard signs of NSTI were present in 55 of 124 patients (44%), 
including gas on radiograph in 24 (19%), bullae in 21 (17%), 
skin necrosis in 11 (9%), and crepitance in 9 (7%). One 
hundred twelve patients (90%) met one of our previously 
described admission laboratory criteria associated with NSTI 
sodium level < 135 mEq/L or WBC count ≥ 15 400/µL, 
cluding 97 (78%) with a sodium level less than 135 mEq/L 
and 77 (62%) with a WBC count of 15 400/µL or more. Of 
the 69 patients who did not have hard signs, 62 (90%) met 
one of the laboratory diagnostic criteria.

MICROBIOLOGIC FINDINGS

The organisms cultured were gram positive in 58 
(47%), gram negative in 8 (76), and mixed flora in 24 
(19%). Methicillin-resistant S aureus was cultured in 21 
(17%), and 3 (2%) had a culture positive for Clostridium 
spcies.

PATIENT TREATMENT

The median time from presentation in the ED until ex-
mamination by a surgeon was 210 minutes (interquartile range [IQR], 105-389 minutes). The median time from 
ED presentation to operating room was 510 minutes (IQR, 345-870 minutes). Eighteen of 124 (15%) underwent a 
major extremity amputation. The median number of de-
bridements was 2 per patient (IQR, 1-2). Forty-five (36%) 
underwent split-thickness skin grafting during the same 
admission. The median number of days in the intensive 
care unit was 3 (IQR, 1-6), and the median total num-
ber of days in the hospital was 13 (IQR, 7-27). There were 
21 deaths, for an overall mortality rate of 17%.

UNIVARIATE ANALYSIS OF PREDICTORS 
OF MORTALITY

On univariate analysis, factors associated with mortal-
ity included a history of cancer, being transferred from 
an outside hospital, intravenous drug abuse, involve-
ment of the anterior abdominal wall (20 [16%] vs 4 [3%]; 
P = .05), admission systolic (107.5 vs 123 mm Hg; P = .03) 
and diastolic (52 vs 71 mm Hg; P = .03) blood pressure, 
admission temperature (37.0°C vs 37.5°C; P = .02), and 
admission base deficit (Table). There were no differ-
ences with respect to other variables, including admi-
sion serum sodium, potassium, chloride, bicarbonate, urea 
nitrogen, creatinine, calcium, glucose, lactic acid, and 
albumin levels; anion gap; WBC count; microbiologic find-
ings; number of debridements; need for amputation; and 
timing of surgical evaluation and treatment.

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On CART analysis, 2 admission variables, serum lactate and sodium levels, were predictors of mortality (Figure). Patients with a lactate level greater than or equal to 54.1 mg/dL (≥54.1 mg/dL) had a mortality of 32% (8 of 25). Patients with a serum lactate level less than 54.1 mg/dL (<54.1 mg/dL) combined with a serum sodium level of less than 135 mEq/L (<135 mEq/L) had a mortality of 19% (13 of 70). On the other hand, the mortality was 0% (0 of 28) for patients with both a lactate level less than 54.1 mg/dL and a serum sodium level greater than or equal to 135 mEq/L (≥135 mEq/L).

The model had a sensitivity of 100% (95% confidence interval [CI], 0.84-1.00), a specificity of 28% (95% CI, 0.19-0.37), and a corresponding positive predictive value of 23% (95% CI, 0.14-0.32) and negative predictive value of 100% (95% CI, 0.88-1.00) for mortality.

**COMMENT**

Necrotizing soft-tissue infections remain a highly lethal disease. The present study of 124 patients with NSTI found a mortality of 17%. On CART analysis, 2 admission laboratory variables, an elevated serum lactate level (≥54.1 mg/dL) and decreased serum sodium level (<135 mEq/L), were included in a decision tree to predict an increased risk of death. The mortality in the present series is on the low end of reported studies and is similar to the 16.9% mortality reported by Anaya and colleagues.

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### Table. Univariate Analysis for Death

<table>
<thead>
<tr>
<th></th>
<th>Died (n = 21)</th>
<th>Survived (n = 103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48 (42 to 54)</td>
<td>42.5 (36 to 53)</td>
<td>.07</td>
</tr>
<tr>
<td>Sex, No. (%) M</td>
<td>14 (66)</td>
<td>70 (68)</td>
<td>.20</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>4 (24)</td>
<td>41 (40)</td>
<td>.07</td>
</tr>
<tr>
<td>IVDA, No. (%)</td>
<td>14 (67)</td>
<td>25 (26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chemotherapy, No. (%)</td>
<td>2 (10)</td>
<td>1 (1)</td>
<td>.07</td>
</tr>
<tr>
<td>Corticosteroids, No. (%)</td>
<td>0</td>
<td>2 (2)</td>
<td>&lt;.09</td>
</tr>
<tr>
<td>Cancer, No. (%)</td>
<td>3 (14)</td>
<td>2 (2)</td>
<td>.03</td>
</tr>
<tr>
<td>Liver disease, No. (%)</td>
<td>7 (7)</td>
<td>2 (10)</td>
<td>.60</td>
</tr>
<tr>
<td>Hepatitis, No. (%)</td>
<td>1 (5)</td>
<td>13 (13)</td>
<td>.50</td>
</tr>
<tr>
<td>HIV infection, No. (%)</td>
<td>0</td>
<td>6 (6)</td>
<td>.60</td>
</tr>
<tr>
<td>Transferred from outside hospital, No. (%)</td>
<td>7 (35)</td>
<td>13 (13)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Timing of management**

- Time from ED arrival to surgery evaluation, min: 157 (71 to 360) vs. 216 (105 to 409), P = .40.
- Time from surgery evaluation to OR, min: 240 (148 to 488) vs. 245 (150 to 410), P = .90.
- Total time from ED arrival to OR, min: 382 (276 to 608) vs. 566 (370 to 880), P = .08.

**Admission laboratory values**

- Sodium, mEq/L: 131 (126 to 132) vs. 131 (127 to 135), P = .30.
- Potassium, mEq/L: 4.2 (3.8 to 4.5) vs. 4.3 (3.8 to 4.8), P = .90.
- Sodium-to-potassium ratio: 30 (28 to 35) vs. 31.4 (26.4 to 36.3), P = .80.
- Chloride, mEq/L: 98 (92 to 102) vs. 97 (93 to 102), P = .70.
- Bicarbonate, mEq/L: 21 (17 to 23) vs. 22 (20 to 26), P = .09.
- SUN, mg/dL: 23 (13 to 34) vs. 17 (12 to 27), P = .07.
- Creatinine, mg/dL: 1.1 (0.8 to 2.2) vs. 1.1 (0.8 to 1.4), P = .60.
- Calcium, mg/dL: 8.2 (6.8 to 8.7) vs. 8.1 (7.8 to 8.7), P = .30.
- Glucose, mg/dL: 127 (83 to 257) vs. 141 (109 to 364), P = .30.
- Anion gap, mEq/L: 12 (9 to 15) vs. 11 (9 to 14), P = .30.
- Base excess, mEq/L: -3.35 (-13 to -5.1) vs. 1.9 (-2.8 to 4.4), P = .009.
- Albumin, g/dL: 2.35 (1.6 to 2.7) vs. 1.95 (1.6 to 2.7), P = .60.
- WBCs/µL: 26 800 (11 300 to 56 400) vs. 18 300 (12 800 to 25 000), P = .06.
- Lactic acid, mg/dL: 27.1 (7.2 to 73.0) vs. 18.9 (15.3 to 53.2), P = .20.

**Abbreviations:** ED, emergency department; HIV, human immunodeficiency virus; IVDA, intravenous drug abuse; OR, operating room; SUN, serum urea nitrogen; WBCs, white blood cells.

SI conversion factors: To convert SUN to millimoles per liter, multiply by 0.357; creatinine to micromoles per liter, multiply by 88.4; calcium to millimoles per liter, multiply by 0.25; glucose to millimoles per liter, multiply by 0.0555; lactic acid to millimoles per liter, multiply by 0.111.

*Where not otherwise specified, values are given as median (interquartile range).*

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**Figure.** Classification and regression tree analysis for mortality. To convert lactic acid to millimoles per liter, multiply by 0.111.
leagues. The lower mortality in these 2 reports may reflect the high volume of patients seen, which has subsequently led to earlier recognition and diagnosis, prompt and aggressive therapy with broad-spectrum antibiotics, and aggressive debridement, as well as improvements in care in the intensive care unit.

The diagnosis of NSTI may be challenging because it may be difficult to distinguish from cellulitis or a simple abscess. Conditions associated with NSTI include intravenous drug abuse, diabetes mellitus, malignancy, other immunosuppression, and obesity. In many cases, the inciting factors are not identified. Hard clinical signs, such as crepitance, bullae, necrosis, and subcutaneous air on radiographs, help to establish the diagnosis; however, these signs are often not present at the time of initial examination. In the present study, only 44% had such hard signs. Recent studies have identified admission laboratory values that may help discriminate between necrotizing and nonnecrotizing infections. Wall et al found that an elevated admission WBC count and a decreased serum sodium level were associated with NSTI. The predictive value of a WBC count greater than 15,400/µL or a serum sodium level less than 135 mEq/L, which were derived by CART analysis, were subsequently validated in a second group of patients with NSTI, with a negative predictive value of 99% and positive predictive value of 26%. More recently, Wong et al identified 6 independent variables (total WBC count and levels of hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein) to discriminate between NSTI and nonnecrotizing soft-tissue infection. The total score had a range of 0 to 13, and patients were categorized according to the risk of NSTI among 3 groups. After internal validation, Wong and colleagues showed that, for intermediate- and high-risk patients (score, >6), the score had a positive predictive value of 92% and a negative predictive value of 96%.

Several studies have analyzed factors predictive of death in necrotizing infections. Bilton et al noted that patients undergoing early and aggressive therapy had a mortality of 4.2% as compared with 38% mortality with delayed or inadequate preliminary therapy. Elliott et al, in a study of 198 patients, found 7 factors associated with an increased mortality, including age, female sex, extent of infection, delay in first debridement, elevated serum creatinine level, elevated blood lactate level, and degree of organ system dysfunction. Elevated WBC count greater than 30,000/µL, serum creatinine level greater than 2 mg/dL (177 µmol/L), and heart disease were predictors of death in another large study. Wong et al reported that a delay in surgery of greater than 24 hours was associated with an increased risk of death. Interestingly, in the present study, patients who died trended toward having a shorter interval from presentation in the emergency department to operation than survivors (382 minutes [IQR, 276-608 minutes] in nonsurvivors vs 566 minutes [IQR, 370-880 minutes] in survivors; $P = .08$). Because most patients in the present study underwent debridement within 14 hours of presentation, the findings suggest that timing of surgical debridement, provided it is performed within 8 to 12 hours, does not affect mortality. Furthermore, we have empirically observed that, in the most septic patients, the process of surgical debridement appears to induce a worsening septic response, with the development of intraoperative hemodynamic instability. This would suggest that future therapy should be targeted toward modulating the septic response before debridement.

Through CART analysis, we created a simple model for predicting mortality, using admission serum sodium and lactate levels. The model had a sensitivity of 100%, specificity of 28%, positive predictive value of 23%, and negative predictive value of 100%. The association between elevated serum lactate level, low serum sodium level, and increased mortality can potentially be explained by several mechanisms. Sepsis leads to increased muscle glucose uptake, increased lactate production and decreased utilization, an increase in the calculated ratio of muscle membrane permeabilities to $Na^+$ and $K^+$, and an increased intracellular $Na^+$ concentration. These effects may be mediated by complement activation. In addition, sepsis has been linked to an increase in antidiuretic hormone level as well as adrenocortical insufficiency, both of which may lead to hyponatremia. Finally, severe NSTIs lead to marked third spacing of fluids, which may be replaced by free water, leading to hypovolemic hyponatremia. All of the foregoing factors are contributory causes for the hyponatremia and lactic acidosis observed in NSTIs, and, given the findings of this study, they seem to be potential markers of increased mortality.

In conclusion, we present, to our knowledge, one of the largest series of patients with NSTI and one of the first studies to use CART analysis to predict mortality. The proposed model has a high sensitivity and high negative predictive value. A prospective study is currently under way at our institution to validate this preliminary model. In addition, further studies are needed to determine whether additional interventions targeted to the high mortality risk group can lead to improved outcomes.

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Correspondence: Christian de Virgilio, MD, Department of Surgery, Harbor-UCLA Medical Center, 1000 W Carson St, Campus Box 25, Bldg 1-E, Torrance, CA 90509 (cdevirgilio@labiomed.org).

Author Contributions: Study concept and design: Yaghoubian, de Virgilio, and Dauphine. Acquisition of data: Yaghoubian, Dauphine, and Lin. Analysis and interpretation of data: Yaghoubian, de Virgilio, Dauphine, and Lewis. Drafting of the manuscript: Yaghoubian, de Virgilio, Dauphine, and Lin. Critical revision of the manuscript for important intellectual content: Yaghoubian, de Virgilio, and Lewis. Statistical analysis: de Virgilio and Lewis. Administrative, technical, and material support: de Virgilio.

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Previous Presentation: This paper was presented at the 2007 Pacific Coast Surgical Association Meeting; February 18, 2007; Kohala Coast, Hawaii; and is published after peer review and revision. The discussions that follow this article are based on the originally submitted manuscript and not the revised manuscript.
The authors employed statistical methodology called classification and regression tree analysis to determine the value of the serum lactate level and hyponatremia in predicting an increased risk of mortality. Given the fact that I was challenged by grade school arithmetic, I would not dare to discuss the merits of the statistical methodology and invite my more mathematically gifted friends to comment from the floor. However, I have treated many patients with NSTIs and would like to put these findings in context.

The authors point out that 43% of their patients presented with no discernible cause for the infection and that only 44% had findings classically associated with NSTI; air in the soft tissues, skin bullae, and skin necrosis. The subtlety of presentation often leads to a delay in recognition of the gravity of the infection by clinicians in the ED inexperienced with this entity. Sometimes, even the most experienced clinicians are fooled. In this series, the median time from ED presentation to surgical consultation was 2.5 hours and the median time from ED presentation to operative debridement was 8.5 hours. We are not told what is happening during this period. Question No. 1: Are the patients receiving antibiotics and aggressive goal-directed fluid therapy based on the Guidelines of the Surviving Sepsis Campaign? Or are they, as I suspect, sitting in the ED with a fluid drip, awaiting either a correct diagnosis or an open operating room (OR)?

Furthermore, we are not told at what point during this process the serum lactate is measured. Question No. 2: Is the serum lactate measured on initial presentation to the ED or is it measured, as I suspect, sometime later when the true nature of the infection is finally recognized after a period of underrecognition? I presume the statistical analysis ruled out a correlation between hypotension, tachycardia, and an elevated serum lactate level. In fact, in this study, on univariate analysis, both blood pressure and base deficit were correlated with the mortality rate. Not surprisingly, I found that patients with upper-extremity NSTI who presented with shock have a higher mortality rate, which I published in a paper decades ago in the *Journal of Hand Surgery*. I have observed more recently that patients with leukocytosis in excess of 25,000/µL have a poor prognosis.

One can easily understand the importance of the serum lactate level as a measure of global hypoperfusion and resulting anaerobic metabolism as a predictor of mortality. The reason that hyponatremia is a significant predictor of mortality is less clear. Question No. 3: Could these patients have a relative degree of adrenal insufficiency? If so, perhaps the antidiuretic hormone (ADH) response to hyponatremia is more robust than the aldosterone response to the renin-angiotension system, resulting in retention of more free water than salt. It would be interesting to study the cortisol, ADH, and renin-angiotension system in these patients.

Finally, we are still left with the enigma of why we are unable to rescue some patients irretrievably sucked down the vortex of the cytokine cascade, even after major amputation removes the source of the infection from the body, while other patients survive after receiving seemingly similar therapy.

I enjoyed this well-presented paper and learned the prognostic importance of hyponatremia in this group of patients. Early recognition and immediate aggressive antibiotic, resuscitative, and surgical therapy remain a challenge. Question No. 4: Do the authors recommend immediate measurement of serum lactate and sodium levels for all patients with soft-tissue infection presenting to the emergency department?

**Dr de Virgilio**: I want to again thank the Pacific Coast Surgical Association for the opportunity to present our paper and to Dr Schecter for his thoughtful comments and review of the manuscript. Again, I also wanted to compliment our intern, Dr Yaghoubian, for a great presentation.
I have to say, first off, we are fortunate at Harbor-UCLA in that we have our coauthor, Dr Lewis, who is a seasoned statistician as well as an ED physician who is well versed in CART analysis. I have to myself profess that CART analysis is not my personal expertise; however, my understanding from him is that a big advantage of the CART analysis is its ability to uncover complex interactions between predictors, which may be difficult or impossible to uncover using traditional multivariate techniques. I also want to note that CART analysis is what we used originally to derive our sodium and WBC count predictors for distinguishing necrotizing and nonnecrotizing infections. We are certainly aware, as Dr Schecter brings up, of the importance of the Surviving Sepsis Campaign, and with this Dr Schecter brings up a very important point. Was the severity of the sepsis in these patients recognized early, and, as such, was appropriate therapy initiated immediately? Admittedly, the present study being retrospective, we did not record the amount of fluids given in the ED, or the timing of the institution of fluids or antibiotics. However, I will say that since we published 6 years ago the importance of recognizing the sodium and the WBC count as features of NSTIs, our own ED and our own surgery residents have been primed to recognize NSTIs, so in general, once we see that low sodium level in a patient with a soft-tissue infection, the residents jump on this and institute aggressive intravenous (IV) antibiotics and fluids.

Another important point to mention is that the median time from presentation to OR is as long as 2 days, so I believe that we have made important strides in getting these patients to the OR quickly. Our mortality, as pointed out, was 17%, which is lower than in most previous studies and similar to the study by Anaya and colleagues. But the question really remains, can we do better? I think we can, and I agree with Dr Schecter. New modalities such as the use of stress corticosteroids or recombinant activated protein C are things that were certainly underutilized in our study and bear further merit.

One observation, however, that we have noted is that we have patients who present to the ED with severe necrotizing fasciitis who are hemodynamically stable, yet the moment you take them to the OR and start debridging, they become quite unstable, as if the process of the debridement incites even a more severe septic reaction. So I think we need to do something different than what we are doing now.

Dr Schecter points out the importance of the admission WBC count. Likewise, patients in our study with astronomically high WBC counts tended to have higher likelihood of dying, on univariate analysis, and I think this is an important issue. White blood cell count just did not come out as a significant predictor on CART analysis. Regarding the serum lactate, Dr Schecter is correct that the ED itself does not send the serum lactate to the OR, so it isn't truly an admission value from the moment the patient comes to the hospital prior to debridement. Yet, the infection may have been present for many days. We don't have any way to account for that. I also believe that the virulence of the organism is important, and yet we have no way to measure virulence. In your study you reported a mixture of different kinds of organisms. Is there any correlation between the different patterns of infection and the outcome?

Dr de Virgilio: I think you really, in my opinion, hit the nail on the head because some of the earlier studies that emphasized the importance of early debridement had a median time of up to 2 days before they were debrided. What they found was that if surgical debridement was delayed beyond 24 hours after admission, there was an increased mortality. Now that we are recognizing necrotizing fasciitis sooner and our median time to OR was 8 hours, we've hit an impasse with respect to improving mortality. Thus, I think you are absolutely right. I think we need a paradigm shift in how we approach these very septic, ill patients, and I don't know that we are really benefiting these patients by rushing them to the OR so quickly when they are floridly septic. As I mentioned, once the debridement process begins, it's almost as if that itself induces an even worsening sepsis. I think we do need to take a different approach in these patients and focus more on the resuscitation and on the medical optimization and take a few more hours before we do the debridement.

With regard to your comment on the number of days prior to presentation, we observed in our study that the median number of days of symptoms prior to presentation to the ED was 3. So you are right, the infection is not something that has been going on for just a very brief time, which again points out that perhaps we need to focus a little bit more on the medical management before rushing to the OR.

Sam Wiseman, MD, Vancouver, British Columbia: On the univariate analysis, it was quite striking that the IV drug use was such a strong predictor of mortality; there was a P value of less than .0001. I was just hoping that you could comment, even though it seemed to lose significance by CART analysis, should a history of IV drug use lead to a very urgent surgical consultation in patients with soft-tissue infections who present to the emergency department? The other question connected to that is, do you have data on human immunodeficiency virus (HIV) status on your patient population? Were there immunosuppressed patients, and do they potentially represent a confounding variable in your study?
Dr de Virgilio: Thank you for those questions. Yes, as you pointed out, IV drug abuse was a significant factor on univariate analysis, and our original interest in this area of research came from the fact that we had many patients transferred to us from outside hospitals with IV drug abuse, with a misdiagnosis of a simple shooter’s abscess that needed drainage. We noted very high WBC counts in many of them, and in the OR discovered that they had necrotizing fasciitis. So you are right that when you see an IV drug abuser who comes in with a very high WBC count or low sodium level, you really have to jump on these patients. However, again, with the multivariate analysis, IV drug abuse was not a predictor of mortality in the model.

I should note that CART analysis is different than standard multivariate regression analysis in that it creates hundreds of different potential decision trees until it creates the best model. It also does not simply enter factors that were significant on univariate analysis; it analyzes all variables and looks at the interrelationship between variables when creating the tree.

With respect to the HIV, we did not specifically look at HIV, but the overall number of HIV-positive patients in our study, from what I recall, was low.

J. Augusto Bastidas, MD, Los Gatos, California: This is a very nice paper in a very difficult patient population. There are data that show a clearance of lactate predicts mortality. Do you have that data in your group?

Dr de Virgilio: No, unfortunately, we did not specifically look at that variable.

Dr Bastidas: My second question is, if a patient has a low lactate level and an appropriate sodium level, do you do anything differently? Are these patients then not put into the intensive care unit (ICU)? If not, then why measure lactate at all once you have made the diagnosis?

Dr de Virgilio: I think that the impetus behind this study is really the fact that our overall results with improving mortality over the last few decades have not gotten better, and so to me this study points out that we need to be doing something different in the presurgical approach to these patients. All of these patients in our institution are going to the ICU, too, so it is not a matter of triaging for the ICU; it’s really more that we need to look at better ways of presurgically managing these patients in order to try to target an improved mortality.

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