

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

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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 mor-

tality 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.¹ Distinguishing NSTI from simple cellulitis and abscesses can be difficult. Previous studies from our institution have indicated that an admission serum

The mortality rate for NSTI remains high, ranging from 24% to 34%, and has not changed significantly for several decades.⁴ 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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sodium level less than 135 mEq/L and white blood cell (WBC) count of 15 400/ μ L or more are useful in distinguishing NSTI from nonnecrotizing infections.^{2,3}

METHODS

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 underserved and uninsured patients. A retrospective analysis was performed of all NSTIs seen at Harbor-UCLA Medical Center between 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 operative and pathologic findings.

Clinical data collected included age, race, medical history, physical examination findings, radiographic findings, cause of infection, and primary site of infection. Additional admission variables recorded included vital signs; levels of serum sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, lactic acid, and albumin; base excess or base deficit; WBC count; and anion gap. Intraoperative cultures were recorded and classified as gram positive, gram negative, mixed gram positive/gram negative/anaerobic, methicillin-resistant *Staphylococcus aureus*, and *Clostridium* species. Other data collected included duration of symptoms before presentation to the emergency department (ED), length of time from presentation and to surgical consultation by the ED physicians, total length of time from arrival at the ED to surgical debridement, and the need for skin grafting. 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 translated into a native SAS (SAS Institute Inc, Cary, North Carolina) format by means of DBMS/Copy (Dataflux Corp, Cary). Descriptive statistics were calculated for all variables. Numerical variables were compared by using the nonparametric Wilcoxon rank sum test and are reported as medians. Categorical or nominal variables were compared by the χ^2 test or Fisher exact 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 multivariable decision tree approach to modeling. It is a form of recursive partitioning in which the population of patients is sequentially divided into smaller and smaller groups, based on the values of observed predictor variables, with each group increasingly 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 suited 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 overfits the available information.⁵ 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, analogous 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 identified. The median age was 43 years, and 85 (69%) were

male. The most common comorbidity was diabetes mellitus, occurring in 45 (38%). The most common identifiable source of the necrotizing infection was intravenous injection of illicit drugs, reported in 39 (31%). An additional 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 extremity, 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 crepitation 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 $\geq 15\,400/\mu\text{L}$), including 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* species.

PATIENT TREATMENT

The median time from presentation in the ED until examination 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 debridements 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 number 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 mortality included a history of cancer, being transferred from an outside hospital, intravenous drug abuse, involvement 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 differences with respect to other variables, including admission serum sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, calcium, glucose, lactic acid, and albumin levels; anion gap; WBC count; microbiologic findings; number of debridements; need for amputation; and timing of surgical evaluation and treatment.

Table. Univariate Analysis for Death

	Died (n = 21) ^a	Survived (n = 103) ^a	P Value
Age, y	48 (42 to 54)	42.5 (36 to 53)	.07
Sex, No. (%) M	14 (66)	70 (68)	
Diabetes mellitus, No. (%)	4 (24)	41 (40)	.20
IVDA, No. (%)	14 (67)	25 (26)	<.001
Chemotherapy, No. (%)	2 (10)	1 (1)	.07
Corticosteroids, No. (%)	0	2 (2)	>.99
Cancer, No. (%)	3 (14)	2 (2)	.03
Liver disease, No. (%)	7 (7)	2 (10)	.60
Hepatitis, No. (%)	1 (5)	13 (13)	.50
HIV infection, No. (%)	0	6 (6)	.60
Transferred from outside hospital, No. (%)	7 (35)	13 (13)	.02
Timing of management			
Time from ED arrival to surgery evaluation, min	157 (71 to 360)	216 (105 to 409)	.40
Time from surgery evaluation to OR, min	240 (148 to 488)	245 (150 to 410)	.90
Total time from ED arrival to OR, min	382 (276 to 608)	566 (370 to 880)	.08
Admission laboratory values			
Sodium, mEq/L	131 (126 to 132)	131 (127 to 135)	.30
Potassium, mEq/L	4.2 (3.8 to 4.5)	4.3 (3.8 to 4.8)	.90
Sodium-to-potassium ratio	30 (28 to 35)	31.4 (26.4 to 36.3)	.80
Chloride, mEq/L	98 (92 to 102)	97 (93 to 102)	.70
Bicarbonate, mEq/L	21 (17 to 23)	22 (20 to 25)	.09
SUN, mg/dL	23 (13 to 34)	17 (12 to 27)	.07
Creatinine, mg/dL	1.1 (0.8 to 2.2)	1.10 (0.8 to 1.4)	.60
Calcium, mg/dL	8.2 (6.8 to 8.7)	8.1 (7.8 to 8.7)	.30
Glucose, mg/dL	127 (83 to 257)	141 (109 to 364)	.30
Anion gap, mEq/L	12 (9 to 15)	11 (9 to 14)	.30
Base excess, mEq/L	-8.35 (-13 to -5.1)	1.9 (-2.8 to 4.4)	.009
Albumin, g/dL	2.35 (1.6 to 2.7)	1.95 (1.6 to 2.7)	.60
WBCs/ μ L	26 800 (11 300 to 56 400)	18 300 (12 800 to 25 000)	.06
Lactic acid, mg/dL	72.1 (71.2 to 73.0)	18.9 (15.3 to 53.2)	.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.

^aWhere not otherwise specified, values are given as median (interquartile range).

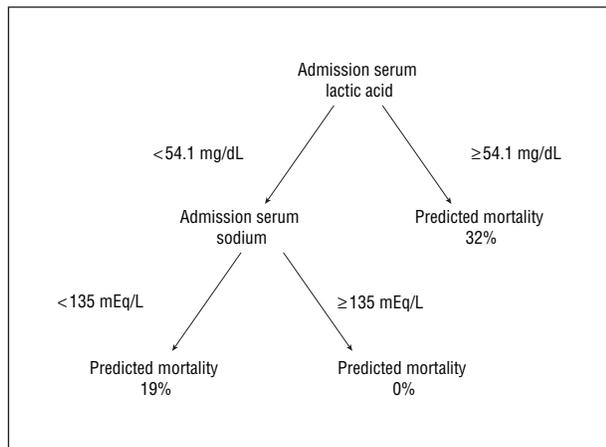


Figure. Classification and regression tree analysis for mortality. To convert lactic acid to millimoles per liter, multiply by 0.111.

CART ANALYSIS

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 (6 mmol/L) had a mortality of 32% (8 of 25). Pa-

tients with a serum lactate level less than 54.1 mg/dL combined with a serum sodium level of less than 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. 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 [6 mmol/L]) 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 col-

leagues.⁶ 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 can 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.^{2,7,8} In many cases, the inciting factors are not identified. Hard clinical signs, such as crepitation, 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.^{9,10} 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 al² 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/ μ L 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 al⁷ 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 al¹¹ 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,¹² 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/ μ L, serum creatinine level greater than 2 mg/dL (177 μ mol/L), and heart disease were predictors of death in another large study.⁶ Wong et al¹⁰ 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.¹³⁻¹⁷ These effects may be mediated by complement activation.¹⁸ 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.¹⁹⁻²¹ 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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DISCUSSION

William Schecter, MD, San Francisco, California: Necrotizing soft-tissue infections, a poorly understood group of infections most prevalent among injection drug users, alcoholics, and impoverished obese diabetic patients, has a wide spectrum of both clinical presentation and clinical course. This retrospective review of 124 patients with NSTI treated between 1997 and 2006 at Harbor-UCLA Medical Center identified a serum lactate level greater or equal to than 6 mmol/L and a serum sodium less than 135 mEq/L as simple and accurate tests to predict mortality in this group of patients. A simple rapid test to identify high-risk soft-tissue infection patients would be extremely helpful in selecting patients for rapid aggressive therapy, which might further reduce the mortality rate, which, at 17% in this series, is low compared with many other studies.

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 45% 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 2½ hours and the median time from ED presentation to operative debridement was 8½ 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 underresuscitation?

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 hypotension 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 my 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 Schechter brings up, of the importance of the Surviving Sepsis Campaign, and with this Dr Schechter 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 the OR in our study was only about 8 hours. When you look at previous studies, 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 Schechter. 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 debriding, 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 Schechter 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 Schechter is correct that the ED itself does not send the serum lactate the minute the patient hits the door, and this blood test was triggered by our surgery residents, usually 2 or 3 hours later. So it isn't truly an admission value from the moment the patient comes into the hospital.

Regarding his comments about the systolic blood pressure, yes, it was significant on univariate analysis but did not come out on the CART analysis, and, interestingly, overall very few of the patients with NSTI truly come in markedly hypotensive. So I don't believe blood pressure is a good discriminator. Regarding why serum sodium level is a predictor of death and is a predictor of NSTI, we have several theories. One is that severe sepsis is associated with adrenal insufficiency, which has been demonstrated in other studies. Another possible explanation is that studies have shown that sepsis may induce an inappropriate ADH response. Further, some experimental models have shown that sepsis leads to a change in membrane permeability of muscle cells, causing an influx of sodium into the

cells, resulting in an increase in intracellular sodium. Finally, we think that the marked third spacing associated with this disease process combined with the patient at home perhaps taking in free water may lead to hypovolemic hyponatremia.

Thank you, Dr Schechter, for your comments.

Jan K. Horn, MD, San Francisco, California: I would like to congratulate you on your further attempts to give us better insights into how we might identify patients at risk. Certainly in our institution, we have observed very early mortality in these patients. In other words, some patients spiral into this septic pathway following debridement and are dead within less than 24 to 36 hours. Given your findings, perhaps initial treatment of septic shock is more important than debridement of the infection. Perhaps we have to give consideration to better preoperative preparation and reestablishment of a better physiologic status before we operate on these patients. With that in mind, have you considered altering the approach to your management so that you ensure that they are physiologically more stable when you take them to the OR?

The other comment I would make is that we don't consider the fact that the patients may come into the hospital at any point in the process of the infectious problem. We don't account for how much time they have been brewing the infection prior to their arrival. We only become concerned about the time in 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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