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Local Variations in the Epidemiology, Microbiology, and Outcome of Necrotizing Soft Tissue Infections: A Multi-Center Study

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Abstract

Background—Necrotizing soft tissue infections (NSTIs) are rare and highly lethal.

Methods—Retrospective chart review of patients with NSTIs treated at 6 academic hospitals in Texas between January 1, 2004 and December 31, 2007. Patient demographics, presentation, microbiology, treatment, and outcome were recorded. Analysis of variance, chi-square, and logistic regression analysis were performed.

Results—Mortality rates varied between hospitals from 9 to 25% (n=296). There was significant inter-hospital variation in patient characteristics, microbiology, and etiology of NSTIs. Despite hospital differences in treatment, primarily in critical care interventions, patient age and severity of disease (reflected by shock requiring vasopressors and renal failure post-operatively) we the re main predictors of mortality.

Conclusions—Significant center differences occur in patient populations, etiology, and microbiology of NSTIs, even within a concentrated region. Management should be based on these characteristics given that adjunctive treatments are unproven and variations in outcome are likely due to patient disease at presentation.

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Drafting of manuscript: Kao, Lew
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Summary—Significant regional inter-hospital variations occurs in patient characteristics, microbiology, etiology, and management of necrotizing soft tissue infections (NSTIs) which impact outcome.

Introduction

Necrotizing soft tissue infections (NSTIs) are rare, fulminant infections that result in significant morbidity and mortality. A review of 27 case series with 862 patients between 1980 to 1998 estimated mortality to be 32%.[1] Several recent series, including an analysis of over 10,000 patients from the Nationwide Inpatient Sample (NIS), a national discharge database, have reported mortality rates between 10 and 20%.[1–4] Long-term mortality in NSTI survivors is also increased when compared with population-based controls.[5] Furthermore, approximately 20% of NSTI patients require amputations[6–7] and 30% of patients have mild to severe functional limitations after discharge.[8]

Given the rarity of the disease and heterogeneity in its characteristics, comparison between studies is difficult. Mortality rates are dependent upon patient characteristics [2,9–15] and the etiologic microbial pathogen(s).[15–17] Additionally, there are regional differences in the epidemiology and microbiology of NSTIs[18–20] that are related to outcome. The objective of this study was to characterize the incidence, patient characteristics, epidemiology, microbiology, and outcome of patients with NSTIs at six university-affiliated hospitals in Texas. The hypothesis of the study was that the epidemiology and microbiology of NSTIs affects outcome in patients with NSTIs.

Methods

We conducted a multi-center retrospective chart review of patients diagnosed with an NSTI between January 1, 2004 and December 31, 2007. Six hospitals associated with four medical schools participated in the study – Lyndon Baines Johnson General Hospital (LBJGH) and Memorial Hermann Hospital (MHH), affiliated with University of Texas Health Science Center at Houston; the Methodist Hospital (TMH) affiliated with Weill Cornell Medical College; Ben Taub General Hospital (BTGH) and the Michael E. DeBakey Veteran's Administration Medical Center (VAMC), affiliated with Baylor College of Medicine; and University Hospital (UH) affiliated with University of Texas Health Science Center at San Antonio. LBJGH and BTGH are safety net hospitals in Harris County, Texas that share a common administration; UH is a safety net hospital in San Antonio. MHH and BTGH are the two designated Level I Trauma Centers in Houston, and LBJGH is a Level III Trauma Center. MHH and TMH are non-profit hospitals in Houston. The study was approved by the Institutional Review Boards of all hospitals and universities.

Patients with NSTIs were identified using the International Classification of Disease version 9 (ICD-9) discharge code for necrotizing fasciitis (728.86). Charts were reviewed to verify a diagnosis of NSTI based on documentation in the operative report. Data collect included: demographics, risk factors, initial presentation, laboratory values, operative findings, microbiologic results, post-operative care, hospital course, morbidity, and mortality. The Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) scores were calculated using patient admission data when available. Missing data, such as the Glasgow Coma Score and admission inspired oxygen concentration, were assumed to be normal for the APACHE II calculations unless otherwise documented.

Demographic and initial presentation data were compared between the patients at the six hospitals using analysis of variance (ANOVA) for parametric and the Kruskal-Wallis Test for non-parametric continuous variables and chi-square analysis for categorical variables

using SPSS version 17.0 (SPSS Inc, Chicago, Illinois). Univariate and multiple logistic regression analyses were performed to identify predictors of mortality. Because of the large number of independent variables, a p-value of less than 0.01 on univariate analysis was required for inclusion in the initial multiple regression analysis; stepwise regression was performed to achieve the final model. The Wald and partial deviance tests ($p \leq 0.05$) were used to assess for contribution of those variables to the overall analysis. The goodness-of-fit of the final multiple regression model was assessed using the Hosmer-Lemeshow test.

Results

Patient characteristics

A total of 296 patients had documented NSTIs – 68 at LBJGH (23%), 67 at BTGH (23%), 60 at TMH (20%), 58 at MHH (20%), 34 at UH (11%) and 9 at VAMC (3%). There was no significant trend in incidence over the four-year period. The median age was 50 years (interquartile range, IQR, 40–58). There was a significant difference in the ethnic distribution of patients at each hospital (Table 1); the three county hospitals (LBJGH, BTGH, and UH) had primarily Hispanic patients while the non-profit hospitals and the Veteran's Hospital had primarily Caucasian patients ($p<0.001$). There was a significant difference in the distribution of co-morbidities between the hospitals. In particular, TMH which is a non-profit hospital had more patients with cardiac and chronic kidney disease. The non-profit hospitals, TMH and MHH, had the highest percentage of patients transferred from other hospitals when compared with all other hospitals combined (39% vs. 2%, $p<0.001$).

Admission physiologic and laboratory values

There were several statistically significant differences between centers in a number of admission values, but there was no consistent trend between hospitals. The median APACHE II score was 13 (n=74), and the scores were not significantly different between hospitals. Other markers of disease severity such as systolic blood pressure, lactate level, base deficit, and bacteremia on admission were not significantly different between centers.

Disease characteristics

There were also significant differences in epidemiology and microbiology between hospitals. In half of the cases, no etiologic cause of the NSTI was identified. Trauma was the primary cause of NSTI in 38 cases (13%), with a greater number of cases being attributed to trauma at the two Level I Trauma Centers (BTGH and MHH). Injection was the primary cause of infection at UH in San Antonio (9/34, 26%) but accounted for a small number of cases in Houston (3/264, 1%). UH also had the highest proportion of patients with monomicrobial methicillin-resistant staphylococcus aureus (MRSA) infections and a significantly higher rate of muscle involvement.

Microbiologic data from cultures was available in 239 (91%) of cases. There were no significant differences between hospitals in the proportion of patients presenting with poly- versus mono-microbial infections (46% and 54% respectively, overall). However, there was a significant difference in the proportion of patients presenting with mono-microbial MRSA (4–41%, $p<0.001$) as well as in the proportion with mono- or poly-microbial infections and MRSA positive cultures (4–45%, $p<0.001$). MRSA was the most frequently identified organism in mono-microbial infections (35%). Other organisms identified in mono-microbial infections included gram positive cocci (methicillin-sensitive staphylococcus aureus, 16%; streptococcus – Groups B, D, not enteroccoccus, 12%; Group A beta-hemolytic streptococcus, 11%; staphylococcus non-aureus, 2%); gram-negative rods

(Klebsiella, 5%; Pseudomonas, 4%; Escherischia coli, 2%; Vibrio, 2%; and Acinetobacter, 1%); anaerobes, 5% (including Clostridium 1%); and fungi, 4%.

Over half of the patients presented with NSTIs of the extremities (56%), with a significant difference in the percentage of patients with lower extremity involvement between hospitals. Only a minority of patients had head and neck infections (6%). The remaining patients presented with infection of the trunk, perineum/scrotum, and buttock. Although the ICD-9 code for Fournier's gangrene was not included in this review, several of the patients were likely coded using the ICD-9 code for necrotizing fasciitis. These patients were included in the review.

Management

All of the patients underwent at least one operation (Table 2). The median number of debridements was 2 (IQR 1–3). A total of 9% of patients received an amputation as an initial operation, and 13% received an amputation at any time during the hospital stay. Of 106 patients who had lower extremity involvement, 29 (27%) underwent amputations. There was significant inter-hospital variability in the percentage of patients receiving an amputation at the first operation ($p=0.05$), and 92% of the variability in the percentage of patients per hospital with an initial amputation was explained by the prevalence of lower extremity involvement.

Post-operative antibiotic choices varied between hospitals. Regarding coverage for MRSA NSTIs, the proportion of patients receiving Vancomycin varied between 44% and 94% among hospitals ($p<0.001$), while the proportion receiving Linezolid varied between 3% and 22% ($p=0.14$). Fifty-six to 94% of patients received either Vancomycin or linezolid, and there was significant variability between hospitals ($p<0.001$). Other anti-MRSA agents such as dalbavancin, teavancin, daptomycin, and tigecycline were not administered frequently enough for analysis. There was no correlation between MRSA-positive cultures and administration of vancomycin, linezolid, or either of the antibiotics. There were significant differences between hospitals in antibiotics used with gram-negative activity. Four of the hospitals primarily prescribed cefepime while two of the hospitals primarily prescribed piperacillin-tazobactam. Timing of antibiotic administration with reference to culture positivity was not recorded; therefore, the impact of adequate timing of appropriate spectrum antimicrobial therapy on outcome could not be determined.

A total of 221 (75%) patients required intensive care. There were significant differences in the percentage of patients who received hyperbaric therapy, insulin infusion, and drotrecogin alpha. Only 2 hospitals offered hyperbaric oxygen (MHH and UH). Among patients at those hospitals, 6/92 (7%) received hyperbaric therapy and all of these patients survived. A total of 171 patients received insulin therapy, either subcutaneous or intravenous; 70% of diabetics received insulin therapy as compared to 30% of non-diabetics. LBJGH and BTGH did not have standardized insulin infusion orders during this time period. The maximum target glucose level differed slightly between the remaining hospitals (110 mg/dL for MHH and UH and 120 mg/dL for TMH and VAMC) Regarding drotrecogin alpha, 14 patients (5%) received it overall and there was significant inter-hospital variability in its use ($p<0.001$). The median APACHE II score did not appear to completely explain the inter-hospital variability in the use of drotrecogin alpha ($R^2=0.12$), nor did any findings associated with severe sepsis[21] such as platelet count less than 100,000 ($R^2=0.17$), bilirubin greater than 2 mg/dL (negatively associated with use, $R^2=0.21$), or creatinine > 2 mg/dL ($R^2=0.39$). Only one patient was calculated to have an APACHE II score greater than 25, which is a recommended cut-off for drotrecogin alpha administration.[22] That patient did not receive drotrecogin alpha and survived. Vasopressor use was not significantly different between hospitals (0.38). Nonetheless, there were differences between hospitals, which

could be largely explained by the percentage of patients presenting with a mean arterial pressure less than 65 mmHg, which is the recommended target by guidelines[23] (R^2=0.81).

Outcomes

The overall mortality of the series was 17% (Table 2). The median length of stay was 18 days (IQR 10–35) and the median intensive care unit (ICU) length of stay was 5 days (IQR 0–15). On univariate analysis, there were multiple predictors of mortality. The main patient characteristic associated with mortality was age (OR 1.05, 95% CI 1.03–1.07 per year). Several therapies were associated with increased mortality such as vasopressors, pulmonary artery catheterization, hemodialysis, steroids, and insulin infusion. In terms of surgical management, neither amputation at the initial operation (OR 0.64, 95% CI 0.18–2.20, p=0.48) nor colostomy formation (OR 1.76, 95% CI 0.61–5.08) were associated with improved survival. Delay in treatment by more than 24 hours was not significantly associated with mortality, but bacteremia on admission increased the odds of death by a factor of 3.39 (95% CI 1.63–7.05).

Mono-microbial MRSA infections was not significantly associated with mortality (0.32, 95% CI 0.10–1.07). The wide confidence interval suggests a small sample size. Univariate analyses of mono-microbial MRSA infections and need for vasopressors (OR 0.51, 95% 0.21–1.27, p=0.15) or post-operative renal failure requiring hemodialysis (OR 0.64, 95% 0.12–2.38, p=0.41) had similarly wide confidence intervals. There was no significant association between Group A beta-hemolytic streptococcal infections and mortality. The percentage of patients with Clostridium was too small to run a separate analysis. There was no association between classes of antimicrobial coverage and mortality. Regarding specific antibiotics, there was a significant association between imipenem and mortality (OR 3.48, 95% CI 1.43–8.49, p=0.006) likely due to the fact that it was used in 27% of cases at TMH, which had patients with a greater likelihood of pre-existing cardiac and renal disease.

On multiple regression analysis, independent predictors of mortality were: age (OR 1.05, 95% CI 1.01–1.09, p=0.01), post-operative vasopressor use (OR 28.4, 95% CI 1.35–77.8, p<0.001), and post-operative hemodialysis (OR 5.42, 95% CI 1.30–22.7, p=0.02). The overall R^2 of the model was 0.34. The Hosmer-Lemeshow test was non-significant (chi-square 10.0, degrees of freedom 8, p=0.0.26), suggesting that the model adequately fit the data.

Discussion

There have been relatively few proven advances in the treatment of NSTIs over the past several decades, which may be due to several factors. First, NSTIs are a rare disease. In a recent NIS analysis, there were 10,940 NSTI cases over four years, resulting in an incidence of 0.04% among hospitalized patients.[2] Second, the effectiveness of adjunctive treatments is entirely based on observational studies, and randomized controlled trials are lacking.[24] Lastly, heterogeneity between studies in terms of patient characteristics, bacteriology of the infections, disease severity at presentation, and critical care management make comparisons between outcomes difficult.

The overall mortality in our study was lower than that reported in earlier literature, but similar to that reported in more recent series, including a 10.9% mortality rate in the NIS analysis (2001–2004).[2] Although not statistically significant, there was variability between centers in our study with mortality ranging from 8.8% to 25.0%, unadjusted for patient characteristics or disease severity. There may be multiple reasons for the variability, including inconsistency in the definition of an NSTI which is a limitation of the retrospective study design. Another reason for variability in mortality rates were the

differences in patient characteristics. Based on the literature, predictors of outcome have included advanced age,[2,9–13] advanced disease severity on presentation as manifested by admission APACHE II score,[1] lactate level,[12–13, 25] organ failure,[2,12] evidence of sepsis or shock,[6,9, 12] and presence of co-morbidities in general[9, 14] or specifically such as cirrhosis, [15] immunocompromised state or malignancy,[10] or coronary artery disease.[6] In our series, age and severity of disease as manifested by requirements for vasopressors and hemodialysis post-operatively were independent predictors of mortality.

Other differences in outcome may be explained by the microbiology and epidemiology of the NSTIs. For example, in King County, Washington, where heroin injection is a major risk factor for necrotizing fasciitis, there is an increased prevalence of infections due to Clostridium species[6,18] and an associated increased risk for both limb loss and mortality.[6] Among patients with cirrhosis, Type II monomicrobial infections with gram negative rods such as Vibrio are more common and are associated with worsened outcomes.[19] In Houston, Texas, case series from individual centers (VAMC and BTGH) have reported an improved outcome with monomicrobial NSTIs due to Staphylococcus aureus.[16,20] The emergence of community-acquired MRSA NSTIs was first reported in 2005 by Miller *et al.*[17] and has been subsequently described as an emerging pathogen in NSTIs in other publications.[26–27] In our series, mono-microbial infections were most likely to be due to MRSA. The large proportion of these patients may account for the lower mortality rates, even though the reduction in mortality and and patients with a monomicrobial MRSA infection was not statistically significant; the sample size was too small to be confident of the results.

Lastly, another reason for differences in outcome may be related to treatment. Prompt aggressive surgical debridement and broad spectrum antibiotic therapy are the mainstays of treatment of NSTIs. Although delay in therapy can result in increased mortality,[7,13–14] it was not significantly associated with mortality in our study. However, presence of bacteremia on admission increased the odds of dying and may be a marker for delay in patient presentation, diagnosis, or surgical treatment. Unfortunately delay between onset of symptoms and treatment was not able to be quantified. Additionally, adequacy of source control was unable to be assessed and could have been a confounding factor. Regarding antibiotic choices, all hospitals stated that they had a policy of empiric coverage against MRSA and broad spectrum antibiotic use against anaerobes, gram negatives, and gram positives. However, actual usage of specific antibiotics (including those with activity against MRSA) differed significantly between hospitals. There was significant variability in critical care management across centers. The reasons were multi-factorial including center-specific differences such as the availability of resources (hyperbaric oxygen) and differences in protocols (insulin infusions) as well as patient-specific differences in the severity of disease on presentation. Lack of high quality evidence for therapeutic adjuncts may also have contributed to variability in care. For example, the evidence for drotrecogin alpha in patients with severe soft tissue infections or NSTIs is based on a small proportion of patients in the large randomized trials[22, 28] and two case reports.[29–30]

For advances to be made in NSTIs, a validated classification scheme that correlates to outcome must be developed so that between-center comparisons can be made and multi-center studies can be conducted. Classification schemes have been used to describe NSTIs, but these schemes may not correlate to outcome. For example NSTIs, can be described based on the microbiology as Type I polymicrobial or Type II monomicrobial infections. Although specific bacteria may be associated with increased mortality, the microbial subtype does not appear to correlate. Characteristics of the infection such as extent as measured by body surface area,[7] primary location,[7] and depth,[31] have been associated with mortality, but there is no validated prognostic score based on these criteria. Non-specific

scores for severity of disease, such as the APACHE II score,[1,32] have also been correlated with mortality, but are not routinely reported in all studies.

In the literature, there are two proposed models for predicting outcomes from NSTIs, one of which is the laboratory risk indicator for necrotizing fasciitis score (LRINEC),[33] which has most often been used to aid in the diagnosis of NSTIs.[34] Only one study demonstrated that a score greater than or equal to 6 predicted mortality or amputation.[33] A two-center study from Seattle and Houston (LBJGH) used a combined prediction and validation dataset and found that a score consisting of age, heart rate, temperature, white blood cell count, creatinine, and hematocrit on admission predicted mortality.[3] The score divides patients into three strata (1–3) that have predicted mortality rates of 6%, 24%, and 88%. Using the current study's database (of which there was no overlap with patients from the prior dataset), a score could be calculated for 263 patients. The mortality for the three groups were 8.2% for Group 1 (10/122), 24.1% for Group 2 (33/137), and 50% for Group 3 (2/4). While our data is consistent with the predictive score, our patient population had been partially used to develop the initial score and the score has not yet been validated in other centers.

This study was novel in that it describes the significant variability not only in presentation of NSTI patients but also in their care, even within a geographic region. Other multi-center studies have focused on the effectiveness of a single treatment modality, such as hyperbaric oxygen,[35–36] or combined center data to develop a single predictive model.[3, 9] Endorf et al compared care of NSTI patients at burn and non-burn centers.[2] However, variability in between patient populations and care at individual centers was not described. Gunter et al calculated an aggregated mortality rate from 27 case series were aggregated (n=862 patients) but was unadjusted for confounders such as center differences in care.[1] Nonetheless, our study also has limitations due to the methodological biases that accompany all retrospective reviews and the lack of standardized definitions and prognostic classification systems for NSTIs. For example, confounding due to a triage effect (e.g. patients with cardiac comorbidities being transferred to the tertiary care non-profit hospitals) cannot be excluded. Further collaborative efforts are necessary to advance the study of NSTIs and to address these limitations. The authors propose the following: (1) development of a consensus statement of standardized definitions for NSTIs, (2) collection of data in the setting of a prospective multi-center study using the standardized definitions and following evidence-based guidelines for care,[37–38] and (3) proposal of a classification system that correlates to prognosis by a panel of experts using the Delphi method and validation within the prospective study.

In conclusion, patients with NSTIs have a highly variable outcome, even within a local region, due to significant differences in patient characteristics, microbiology and epidemiology, and treatment of NSTIs. Therefore, comparison of data between series of patients should be done very carefully. Patients should be treated promptly and aggressively based on the epidemiology and microbiology of the infection as well as the severity of disease on presentation. Treatment differences may influence outcome, but comparative effectiveness studies of adjunctive treatments need to be performed in multi-center studies given the rarity of the disease. A common lexicon and validated prognostic classification scheme needs to be developed so as to improve the ability to conduct these studies.

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Table 1

Patient characteristics. Categorical variables are reported as percentages and continuous variables are reported as medians (interquartile range). Comparisons were made using chi-square for categorical variables and analysis of variance/Kruskal-Wallis test for continuous variables.

	Overall (n=296)	LBJGH (n=68)	BTGH (n=67)	MHH (n=58)	TMH (n=60)	VAMC (n=9)	UH (n=34)	p-value
Demographics								
Age (years)	50 (40–58)	49 (40–57)	48 (40–56)	48 (34–58)	55 (44–68)	60 (56–70)	43 (35–52)	<.001
Gender								
Male	62	65	70	60	43	100	65	.005
Female	38	35	30	40	57	0	35	.005
Ethnicity								
Black	24	22	30	22	30	33	3	.04
White	37	22	27	57	48	44	23	<.001
Hispanic	38	56	42	19	17	22	65	<.001
Asian	1	0	2	2	2	0	0	.87
Unknown	1	0	0	0	3	0	0	.16
Comorbidities								
Diabetes	53	57	52	38	58	56	68	.11
Liver disease	16	22	12	14	8	11	29	.07
Cardiac disease	14	3	15	14	30	11	9	.001
Pulmonary disease	6	3	3	5	10	0	15	.11
Chronic kidney disease	10	4	6	7	23	0	9	.003

LBJGH: Lyndon Baines Johnson General Hospital, BTGH: Ben Taub General Hospital, MHH: Memorial Hermann Hospital, TMH: The Methodist Hospital, VAMC: Veteran's Administration Medical Center, UH: University Hospital

Table 2

Management and outcomes.

	Overall (n=296)	LBJGH (n=68)	BTGH (n=67)	MHH (n=58)	TMH (n=60)	VAMC (n=9)	UH (n=34)	p-value
Intubation (%)	47	40	49	60	47	0	44	.02
1st operation debridement (%)	93	88	96	88	95	100	100	.12
1st operation amputation (%)	9	16	5	9	12	0	0	.05
Total # of debridements	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–4)	2 (1–3)	1 (1–2)	3 (2–4)	.002
Vasopressors (%)	22	25	15	26	27	15	11	.38
Steroids (%)	13	10	7.5	5.2	32	11.8	0	.12
Hyperbaric oxygen (%)	2	0	0	9	0	3	0	.001
Insulin drip (%)	29	29	37	26	15	27	78	.002
Drotrecogin alpha (%)	5	10	8	5	32	12	0	<.001
Mortality	17	10	12	24	25	22	9	.07
Hospital length of stay (days)	18 (10–35)	16 (10–26)	28 (15–48)	17 (12–33)	22 (11–35)	5 (3–19)	11 (7–36)	<.001
ICU length of stay (days)	5 (0–15)	6 (1–14)	9 (3–30)	4 (0–13)	5 (1–16)	0 (0–1)	2 (0–7)	<.001

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