ORIGINAL ARTICLE

Patient Characteristics and Outcomes in Necrotizing Soft-tissue Infections: Results from a Prospective Cohort Study in a Tertiary Care Center Intensive Care Unit in South India

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Abstract

Background: Necrotizing soft tissue infections (NSTIs) are life-threatening infections characterized by progressive destruction of muscle, fascia, and overlying subcutaneous tissue. Prospective studies in the field are few, and data from the Indian subcontinent are bleak. Prompt diagnosis and timely treatment are critical for optimal outcomes. The aims of this study are to provide detailed information on the clinical profile of patients with NSTIs and to identify predictors of mortality in order to pick up reversible factors that may improve outcomes.

Materials and methods: This study was a prospective cohort study of adult patients with NSTIs in a tertiary center in South India. All patients who were admitted to the surgical intensive care unit (ICU) of the institute with a diagnosis of NSTI were screened and enrolled. All patients were managed according to the local protocol for treatment of NSTIs and intensive care support.

Results: In our cohort of patients, simple and multiple logistic regression analysis showed that four factors, namely, AKIN stage 3, shock, need for mechanical ventilation for more than 3 days, and low serum albumin values were found to be significantly associated with higher mortality.

Conclusion: The successful management of these patients calls for early diagnosis, resuscitation, surgical debridement, appropriate and timely antibiotics, and early ventilatory weaning before multi-organ failure associated with shock and AKI occurs.

Keywords: AKIN stage 3, Hypoalbuminemia, Mechanical ventilation, Necrotizing fasciitis, Shock.

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Introduction

Necrotizing soft tissue infections (NSTIs) are life-threatening infections characterized by progressive destruction of muscle, fascia, and overlying subcutaneous tissue.[1,2] The incidence of necrotizing fasciitis ranges from 0.3 to 15 cases per 100,000 population.[1,3] Unlike other infections, even when prompt surgery, adequate antibiotic cover, and intensive care support are provided, morbidity and mortality are high and the quality of life among survivors can be severely impaired.[2] Polymicrobial necrotizing fasciitis usually occurs in older adults and individuals with underlying comorbidities, most importantly diabetes mellitus.[1] Conversely, monomicrobial necrotizing fasciitis (most commonly caused by Group A *Streptococcus*) can occur in any age group and even in the absence of comorbidities. Prospective studies in the field are few, data from the Indian subcontinent are bleak, and current knowledge is largely derived from retrospective single-center studies.[4] Awareness, prompt diagnosis, and timely treatment are critical for optimal outcomes. The aims of this study are to provide detailed information on the clinical profile of patients with NSTIs and to identify predictors of mortality in patients presenting at a tertiary-level center in South India in order to pick up some reversible factors that may improve outcomes.

Materials and Methods

This study was a prospective cohort study of adult patients with NSTIs in a tertiary center in South India. It was launched after securing approval from the institute's research board and ethics committee (IRB number 10898). All patients who were admitted to the surgical ICU of the institute with a diagnosis of NSTI were screened and enrolled after obtaining informed consent from the patient or their legal surrogate. Patients were referred to ICU from the emergency department, ward, or operation theater (after surgery). The diagnosis of necrotizing fasciitis was made clinically and was confirmed by the surgeon doing the primary operation (based on findings of necrotic or deliquescent soft tissue with undermining of the surrounding tissue). All patients were managed according to the local protocol for treatment of NSTIs and intensive care support. In our institute, cases of severe NSTIs mandate treatment with beta lactams and beta lactamase

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inhibitors (e.g., piperacillin, tazobactam) or carbapenems (e.g., meropenem or ertapenem) along with clindamycin as empirical antibiotic therapy and immediate surgical consultations for debridement or amputation. Methicillin-resistant *Staphylococcus aureus* (MRSA) cover with glycopeptide class of antibiotics was used when clinicians felt there was a risk for the same, such as in recent hospitalization or colonization (as MRSA rates in the hospital are less than 10% of all isolates). The study was conducted in the surgical ICU of this teaching hospital, which is a 13-bedded facility with 95% occupancy.

We recorded details of patients being admitted in the surgical ICU with a diagnosis of skin or soft tissue infections, and analyzed variables related to clinical features, laboratory data, microbiological data, and details regarding resuscitation, organ failure, and management.

The primary objective of the study was to discern predictors of hospital mortality related to NSTIs. We also intended to describe clinical characteristics of patients with a diagnosis of NSTI needing ICU admission. An exploratory analysis was performed to study associations between all baseline and treatment characteristics and death in the hospital.

Inclusion criteria: The inclusion criteria were as follows:

- Age more than 16 years
- Patients with a primary diagnosis of necrotizing skin and soft tissue infection, regardless of site of infection

Exclusion criteria: Patients not willing to give consent for enrolment in the study, pregnancy, and with hematological disease were excluded.

Statistical Methods

A mortality rate of 10% was taken for calculation of sample size based on the anticipated current mortality rate.[5] A minimum of 100 subjects was needed to detect adverse outcomes of 15% with an absolute precision of 7% and 95% CI. Descriptive variables were represented using mean ± SD for continuous data and frequency (%) for categorized data. Univariate relations with mortality were explored using the Student's *t*-test or Chi-square test.

Results

During the study period, a total of 1,457 patients were admitted in the ICU, out of which 100 had NSTIs (6.8%). The baseline characteristics of the patients are shown in Table 1.

Out of the 100 patients recruited, 65 were male, and 34 patients out of the 100 died in hospital (mortality rate, 34%). The mean age was found to be 56.6 (±11) years. Their median APACHE score was 17 (12–24). The median number of days of symptoms prior to presentation to the hospital was 7 (0–14).

The most common comorbidity noted among these patients was diabetes mellitus (66% of patients). Thirty-four patients had type I infection (polymicrobial), and 37 patients had type II infection (beta-hemolytic *Streptococcus* or *S. aureus* sp.). Cultures did not yield any organism in the rest of the patients. The multidrug resistance rate (MDR) was 20%. The vast majority (90%) of the patients had an NSTI of their lower limbs.

The patients needed a median of 1 (1–3) surgeries, and 48 patients needed amputation of their limb. Median number of days of mechanical ventilation requirement was 2 (1–3) days. Seventy-six patients were in shock and required vasopressors, and seven patients were in AKIN stage 3 requiring dialysis. Twenty-two patients had possible toxic shock syndrome. No patient was administered intravenous immunoglobin (IVIg).

Analysis of variables in the survivors and nonsurvivors found that age, gender, days of symptoms, APACHE score on admission to ICU, infection type, and location of infection did not impact the survival rates. Neither did surgical factors like number of surgeries performed or need for amputation significantly affect survival.

As can be seen from Table 2, in our cohort of patients, simple and multiple logistic regression analysis showed that four factors, namely, AKIN stage 3, shock, need for mechanical ventilation for

Table 1: Baseline characteristics

Baseline characteristics	*Values*
Age (Mean ± SD)	56.6 ± 11
Male (%)	65
Female (%)	35
Median days of symptoms before surgery (IQR)	7 (3–14)
Diabetic (%)	66
Body part involved	
Lower limb	90
Upper limb	2
Groin	7
Chest	1
Type of infection	
Type I	35%
Type II	37%
No growth	28%
Multidrug-resistant infections	34%
APACHE score—Median (IQR)	17 (12–24)
Shock	76%
Mechanically ventilated	21%
AKI	59%
Median serum bilirubin (IQR)	0.94 (0.57, 1.95)
Serum albumin (Mean ± SD)	2.4 (0.7)
Median number of surgeries (IQR)	1 (1–2)
Mechanical ventilation days (IQR)	2 (1–3)
Length of stay in ICU (days) (IQR)	3 (2–5.25)
Mortality	34

APACHE, acute physiology and chronic health evaluation; IQR, interquartile range

Table 2: Association between outcome (death/alive) and risk factors using simple and multiple logistic regression

Factors	*OR (95% CI)*	*p value*
AKIN stage		
Stage 3	2.47 (1.02, 5.95)	0.04
Shock		
Patients in shock	3.26 (1.01, 10.48)	0.04
Serum albumin	0.43 (0.22, 0.85)	0.01
Number of mechanical ventilation days		
3 days	2.94 (1.15, 7.51)	0.02

Table 3: Comparison between survivors and nonsurvivors

	Death (n = 34)	*Alive (n = 66)*	
Variables	*n (%)*	*n (%)*	*p value*
Age (years)‡	56.6 (10.6)	56.6 (11.3)	0.98
Sex			
Male	22 (64.7)	43 (65.2)	0.97
Female	12 (35.3)	23 (34.8)	
Days of symptoms before surgery*	7 (3, 13.3)	7 (3, 14)	0.76
Diabetes mellitus			
Yes	22 (64.7)	43 (65.2)	0.96
No	12 (35.3)	23 (34.8)	
Region			
Lower limb	31 (91.2)	61(92.4)	1.00
Others	3 (8.8)	5 (7.6)	
Infection type			
Type I	14 (41.2)	21 (31.8)	0.62
Type II	12 (35.3)	25 (37.9)	
No growth	8 (23.5)	20 (30.3)	
MDR			
No multidrug resistance	23 (67.6)	43 (65.2)	0.80
Multidrug resistance present	11 (32.4)	23 (34.8)	
Number of surgeries*	1 (1, 2)	1 (1, 2)	0.13
Need for amputation			
Yes	14 (41.2)	34 (51.5)	0.33
No	20 (58.8)	32 (48.5)	
Shock			
Yes	30 (88.2)	46 (69.7)	0.04
No	4 (11.8)	20 (30.3)	
AKI			
Yes	18 (52.9)	41 (62.1)	0.38
No	16 (47.1)	25 (37.9)	
AKIN stage			
Early renal failure	19 (55.9)	50 (75.8)	0.04
Late group	15 (44.1)	16 (24.2)	
Serum bilirubin*	0.94 (0.54, 2.1)	0.93 (0.59, 1.93)	0.74
Serum albumin‡	2.2 (0.72)	2.6 (0.69)	0.009
Mechanical ventilation (days)*	2 (2, 4)	2 (0.75, 2)	0.002
Days in ICU*	5 (2, 7)	3 (2, 5)	0.07

‡Values are presented as mean (SD) and *p* value is obtained from Student's *t*-test; *Value is presented as median (25th percentile, 75th percentile) and *p* value is obtained from nonparametric Mann–Whitney *U* test; values are presented as number (percentage) and *p* value is obtained from Chi-square test

more than 3 days, and low serum albumin values were found to be significantly associated with higher mortality.

Discussion

In this prospective cohort study conducted in the surgical ICU of a tertiary center in South India, we observed that patients with NSTI were mostly male (65%) and the mean age was 56.6 (±11) years. The mortality rate in our series was 34%, which was very high. About 66% of our patients were observed to be diabetic. The median APACHE score on admission to the ICU was 17 (12–24). It was found that 35 patients had a type I infection (polymicrobial) and 37 patients had type II infection (beta-hemolytic *Streptococcus* or *S. aureus* sp.) whereas the rest had no growth from cultures sent for microbiology. About 92% of patients had infection involving the lower limbs and the patients needed a median of 1 (1–3) surgeries (including revision surgeries). About 48% of the cohort finally needed amputation of the limb to control infection. The median number of days of mechanical ventilation requirement was 2 (1–3) days and a high proportion of these patients suffered from shock (76%) requiring vasopressors and acute kidney injury.

The main findings of our study are not surprising in that they indicate that major organ dysfunction, namely renal, circulatory, and respiratory failure have a profound effect on outcomes with NSTIs as can be seen in Table 3. However, the study helps us understand the magnitude of their individual effects through multiple logistic regression analysis and adds to the volume of data available on the outcomes of this disease, which has local, regional, and even international relevance. These findings may help in prognostication, triage of patients, and better utilization of resources. The effect of

hypoalbuminemia on outcomes with this specific disease seems to be a novel finding with very sparse available literature on the subject. It also perhaps, offers a therapeutic angle in order to attempt to improve the management of this disease.

Adopting an evidence-based approach to the management of NSTIs is complicated as the spectrum of morbidity and mortality is severe, the disease is uncommon, and much data available are retrospective. A review of 27 case series with 862 patients estimated mortality to be 32%.[6] Several more recent series, including an analysis of over 10,000 patients have reported mortality rates between 10 and 20%.[7–9] The mortality in our series, however, was found to be higher at 34%. This could be explained by the relatively late presentation of patients to the hospital for medical care as the median number of days of symptoms prior to surgery was 7 days, which is common in our setting due to various factors like poor socioeconomic status, poor health facilities, and lack of familiarity of the disease in local practitioners.[10] The mortality is commensurate with the median APACHE score of 17 (12–24) in our patients, which was higher than observed in other studies on similar patients from the West.[11]

The relatively high premorbid rate of type II diabetes mellitus is similar to that in other published series.[12,13] This reflects the high incidence of diabetes mellitus in our country as a whole and especially the state of Tamil Nadu where the prevalence among adults above 20 years of age is more than 10.5 per 100 persons.[14] This would have affected the distribution of sites of infection. In our study, it was observed that there was a predilection for lower limb involvement with 92% of patients presenting as such, which has been borne out in previous studies as well.[11,15]

It was found that 35 patients had type I infection and 37 patients had type II infection whereas the rest had no growth from cultures sent for microbiology. Studies from the Indian subcontinent and the West have widely varying data with regard to microbiological etiology for NSTIs. Singh et al. from India reported in their series that bacteria were identified in 84% of patients. From that series, 14 patients (22%) had a single organism isolated whereas 2–9 organisms were isolated in the remaining 51 patients (78%).[16] Similarly other series have shown polymicrobial infections were found in 50–55% of patients, 40–45% had a monomicrobial infection and no microbes were identified in the remaining 6%.[17] About 19% of isolates incubated beta-hemolytic streptococci and 16% grew *S. aureus.* The predominance of streptococcal and staphylococcal infections is similar to that in previous series published from India.[16] The predominance of streptococcal infections in this series was at odds with data from another series from Asia,[18] highlighting the importance of local data when instituting a policy for the management of NSTIs. About 7% of isolates incubated MRSA whereas 13% incubated multidrug-resistant nonfermenting gram-negative bacteria. The MDR among the organisms isolated was 20%. This information is useful for formulating local and regional antibiotic guidelines.

Our patients needed a median of 1 (1–3) surgeries (including revision surgeries). About 48% of them finally needed an amputation of limb to control the infection. Case series have found that when patients had a higher median number of total surgical procedures performed, mortality rates were significantly lower.[9,19] This underlines the fact that aggressive debridement of all necrotic tissue until healthy, viable tissue is reached remains the cornerstone of management of these infections. Inspection and debridement in the operating room may need to be continued very regularly until necrotic tissue is no longer present.[20] For severe necrotizing infection involving the extremities, an amputation may be an aggressive but necessary procedure to control the infection.[21]

Various studies have shown that factors associated with increase mortality include age >60 years, white blood cell count >30,000/μL, serum creatinine >2.0 mg/dL, streptococcal toxic shock syndrome, clostridial infections, infections of the head, neck, thorax, or abdomen, and delay in surgery for more than 24 hours.[8,22,23] In our study, we found that patients in AKIN stage 3 (OR 2.47, 95% CI 1.02–5.95; p= 0.04), shock (OR 3.26, 95% CI 1.01–10.48; p = 0.04), low serum albumin (OR 0.43, 95% CI 0.22–0.85; p = 0.01), and need for mechanical ventilation more than 3 days (OR 2.94, 95% CI 1.15–7.51; p = 0.02) were significantly associated with higher mortality. These findings underline the need for rapid diagnosis and definitive treatment of these patients to achieve favorable outcomes. Adequate management of early shock and renal failure as well as lung-protective ventilation with early weaning protocols may impact outcomes favorably.

There are potential advantages to administering albumin during severe sepsis. Albumin is the main protein responsible for plasma colloidal osmotic pressure;[24] it also acts as a carrier protein for endogenous and exogenous compounds;[25] it acts as a scavenger of reactive oxygen[26] and nitrogen species,[27] operates as a buffer molecule for acid–base equilibrium,[28] and maintains the endothelial glyocalyx.[29] Studies have shown that albumin administration can improve organ function in critically ill patients who are hypoalbuminemic[29] and a predefined subgroup analysis of the saline versus albumin fluid evaluation (SAFE) study showed that patients with severe sepsis receiving albumin were at a lower, although not significantly lower, risk for death than those receiving normal saline.[30] The role of albumin as a fluid of resuscitation in patients with NSTIs is an area that will need more research. Perhaps albumin's favorable effects on regional and systemic blood flow has some role.

In addition, recent work from Scandinavian countries has studied cohorts of patients who were given hyperbaric oxygen therapy and IVIg therapy,[4] which our patients did not have access to. A recent meta-analysis showed that the administration of IVIg in patients with NSTIs receiving clindamycin was associated with a reduction in mortality rate from 33.7 to 15.7% in patients with toxic shock syndrome.[31] Toxic shock can be difficult to distinguish from septic shock, especially because skin changes may not be universal and difficult to detect in the subcontinental population. The incidence of possible toxic shock syndrome in our cohort was 22%. No patient was given IVIg due to affordability and late presentation. This therapy could have improved outcomes in our patients.

Our study was conducted in a single center and hence has limited generalizability. The strengths of our study include its prospective design, large sample size, and a high rate of follow up.

Conclusion

NSTIs account for a significant burden of ICU admissions. The successful management of these patients calls for early diagnosis, resuscitation, surgical debridement, appropriate and timely antibiotics, and early ventilatory weaning before multi-organ failure associated with shock and AKI occurs. The role of albumin in improving outcomes in this disease needs to verified by controlled studies.

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