

Determinants of Mortality in Necrotizing Soft Tissue Infections

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Abstract

Background: Necrotizing soft tissue infections (NSTI) are frequently encountered, with a high mortality despite advances in health care.

Material and Methods: Patients presenting with NSTI were prospectively followed up in an attempt to identify factors that were significantly associated with mortality.

Results: There were a total of 86 patients [65 males (75.6%) and 21 females (24.4%)] with an overall mortality of 33.7% (29 patients). The average age was 50.37 years and trauma was the commonest aetiology (34 patients, 66.7%). The average duration of symptoms prior to presentation was 10.56 days; the lower limb was most commonly involved (62 patients, 72.09%). Fifty nine patients had comorbidities (commonest being diabetes mellitus in 41). Age above 50 years, symptoms for more than 8.5 days, involved surface area more than 15.5%, of the total body surface, on-admission pulse rate more than 99 beats/minute, systolic blood pressure less than 103 mm Hg, Glasgow scale less than 12, need for inotropes, low hemoglobin, high leukocyte counts, uraemia, deranged coagulation, low serum albumin, and high levels of lactic acid were significant for mortality. On multivariate analysis, only age above 50 years, presence of acidosis and low serum albumin significantly affected survival.

Conclusion: NSTI carry high mortality. The identification of potential risk factors associated with mortality might help in guiding and optimizing the management of patients who present with NSTI.

Key words: *Soft tissue; infection; necrosis; gangrene; fasciotomy; debridement; prognosis; death*

Introduction

Severe life-threatening soft tissue infections have been recognized throughout history and have been referred to by varying terminology such as *non-clostridial gas gangrene, gangrenous ulcers, phagedaenic ulcer, putrid ulcer, or hospital gangrene*. These infections have also been classified according to anatomical site of involvement such as Fournier's gangrene (perineum), Ludwig's angina (submandibular and sublingual spaces) and Meleney's gangrene (abdominal wall). However, since necrotizing infections of all soft tissues involve a similar approach to diagnosis and treatment, regardless of anatomic location or depth of infection, the term "necrotizing soft tissue infection" (NSTI) is used to replace these varied names as well as the term "necrotizing fasciitis" that was coined by Wilson in 1952 to describe

rapidly progressive, inflammatory infections of the fascia with secondary involvement of skin, subcutaneous tissue and muscle [1,2].

The presentation of NSTI varies widely, ranging from skin and subcutaneous necrosis with muscle and fascial involvement leading to life-threatening sepsis and multi-organ failure. Although necrotizing infection leads to a massive destruction of tissues, the initial presentation is not always obvious because it may involve only the deep tissues in the early phases, leaving the overlying skin seemingly normal. This makes the diagnosis difficult and consequently delays appropriate treatment leading to extensive tissue destruction, limb loss, and high mortality [3-5]. Despite advances in understanding the natural history of disease, antibiotics, fluid and electrolytes, anaesthetic management, improved surgical technique and better critical care, the mortality remains high, with prolonged hospitalisation, limb loss, reconstructive surgery and functional limitation in survivors [5].

A number of risk factors have been documented to be associated with significant mortality over the years. Among them age (more than 60 years), intravenous drug abuse, diabetes, obesity, malnutrition, congestive heart disease, chronic pulmonary disease, peripheral vascular disease,

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chronic alcoholism, immunocompromised states such as malignancy, steroid use, transplantation, and human immunodeficiency virus infection are the most commonly cited [5-13]. Despite encountering NSTI fairly commonly, we could identify only 8 series from India from the year 2000 onwards [6-13]. Of these, one exclusively dealt with upper limb NSTI occurring in diabetic patients [6], while the others were more inclusive. The overall mortality in these studies ranged from as low as 1.85% to as high as 27%. Higher mortality was seen in patients aged more than 50 years, those with shock, diabetes mellitus, leucocytosis, jaundice, hyponatremia, hypoalbuminemia, anaemia, elevated serum creatinine, higher percentage of body surface area involved and delay in surgery [7-13].

The present study was planned with an aim of identifying potential risk factors that could be amenable to modulation for a better outcome in patients with NSTI in our set up.

Material and Methods

After Ethical Committee clearance, the study was performed prospectively on 86 consecutive patients with a clinical diagnosis of NSTI who were admitted in the Emergency Department of our hospital with the aim to find out the 30 day mortality rate and to identify any variables (clinical or laboratory) that could determine mortality. The optimum sample size for reaching statistical significance was calculated on the basis of 15% mortality, 5% level of significance and 80% power. All patients of either sex and any age presenting with NSTI and willing to participate in the study were enrolled after taking informed consent. Patients operated elsewhere before presentation, those unwilling to participate and those with localized subcutaneous infection or abscess and cellulitis without deep tissue involvement were not included.

The study was purely observational and no attempt was made to modify existing practices. Patient data such as demographics, clinical status on admission, laboratory investigations and surgery performed, were maintained prospectively and they were regularly assessed in the wards. The outcome measure was mortality; in addition to documenting in-hospital mortality, patients were followed up to 30 days after discharge.

Statistical analysis of the data was done at the end of the study using SPSS (version 22.0) by applying appropriate statistical tests depending upon the variables. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality; for normally distributed data, mean were compared using T-test; for skewed data or scores, Mann-Whitney U-test was used. For discrete categorical data, number and percentages were calculated and Chi-Square test or Fisher's Exact test were applied. Receiver

Operating Characteristic (ROC) curves were calculated to find threshold / cut-off values of significant variables using Youden's index. To find independent predictors for mortality, Logistic Regression Analysis was carried out. All statistical tests were two-sided.

A *p* value of <0.05 was considered statistically significant.

Results

General Characteristics

There were 65 male (75.6%) and 21 female (24.4%) patients (a total of 86) with an average age of 50.37 years (ranging from 12 to 86 years) and BMI of 25.17 kg/m². The overall 30 day mortality was 33.7% (29 patients). The commonest aetiology was trauma followed by spontaneous onset; the average duration of symptoms prior to presentation was 10.56 days. On admission, 32 out of 86 patients (37.2%) needed inotropic support; the average systolic blood pressure was 96.6 mm Hg, pulse rate 96.6 beats/minute, respiratory rate 20/minute and temperature 98.8 ° F. All these patients were started on empirical antibiotic therapy in the emergency and taken up for surgery at the earliest. The involved total body surface area (TBSA) was calculated using Lund and Browder chart and the average percentage of involvement was 11.89%. The lower limbs were most commonly involved (61 patients, 72.09%). Patient data is tabulated in Table 1.

Associated comorbidities

In the present series, 59 patients (68.6%) had associated comorbidities - the commonest was diabetes mellitus (DM) which was seen in 41/59 (69.49%) - of these 22 (53.6%) had isolated DM and 19 (46.3%) had diabetes mellitus associated with complications (DM+). Multiple comorbidities (diabetes, hypertension, coronary heart disease, deep vein thrombosis, peripheral vascular disease, etc.) were seen in 22/59 patients (37.29%) on presentation.

Initial Laboratory Evaluation

All patients diagnosed as NSTI underwent routine lab investigation on admission. This included haemogram, blood sugar, kidney functions, blood gas analysis, C-reactive protein (CRP), serum albumin, urine analysis, chest x-ray, electrocardiogram, hepatitis and HIV screening as well as microbial cultures from any discharge or wound.

Surgery Performed

The commonest procedures done initially were fasciotomy and debridement (in 37 patients; 43%) and fasciotomy alone (30 patients; 34.9%). Seventeen (19.8%) patients required post-operative ventilator support. Overall, 9 patients (10.4%) had limb loss and 25 patients (29.06%) needed

Table 1. Patient Demographics / Variables significant for mortality

	Total	Survivors	Non-survivors	p value	Threshold Value
Number of patients	86	57	29	-	-
Average age (years)**	50.37	47.82	55.38	0.045	50
Male / Female	65/21	45/12	20/09	-	-
Duration of symptoms (days)*	10.56	8.91	13.83	0.001	8.5
Comorbidity*	59	36	23	0.004	
Total body surface area involved (%)*	11.89	9.84	15.93	0.000	15.5
BMI (kg/m ²)	25.17	24.48	26.54	0.045	-
Pulse rate on admission (Beats/min)*	98.96	93.54	109.45	0.000	98.5
Systolic Blood Pressure on admission (mm/Hg)*	96.60	109.23	71.79	0.000	103
Respiration (breaths/min) *	20.25	19.68	21.65	0.000	20.5
Glasgow coma scale (less than 12)*	15	-	15	0.002	-
Inotropic support *	32	08	24	0.000	-
Hemoglobin (gm/dl) *	10.06	10.75	8.70	0.002	8.75
Total Leucocyte count *	17229.05	14028.07	23520	0.002	18700
Platelet count (× 103/μl)	143.39	141.44	147.24	0.931	-
Blood Urea (mg/dl)*	82.01	54.93	135.24	0.000	70.5
Serum Creatinine (mg/dl) *	1.73	1.39	2.4	0.002	2.15
Random blood sugar (mg/dl)	165.25	157.39	180.72	0.556	-
C-reactive protein (mg/dl)	236.68	228.58	252.62	0.715	-
INR *	1.26	1.172	1.435	0.000	1.23
Serum albumin (gm/dl) * #	2.73	3.11	2.0	0.000	2.55
Arterial lactate (mmol/L) *	3.40	1.72	6.69	0.000	2.15
Acidosis * #	25	03	22	0.000	pH < 7.35
Post-operative ventilation *	17	01	16	0.000	-
Hospital stay (days)	11.61	13.40	8.10	-	-

*Values found significant on univariate analysis

**Only age, low albumin and acidosis were found significant on multivariate analysis

Threshold values constructed using Receiver operating curves

redebridement over their period of stay. The average duration of stay was 11.61 days, significantly higher for survivors (13.40±10.05 days) than non-survivors (8.10±7.12 days).

Microbiology

Cultures were sent routinely from site for all patients on admission. Monomicrobial cultures were common (69 patients; 80.23%) and only 7 samples revealed polymicrobial flora. There was an overall predominance of gram negative bacilli (*Klebsiella*, *Pseudomonas*, *Acinetobacter*) seen in 46/69 patients (66.67%) of all monomicrobial cultures. Overall, *Methicillin Sensitive Staphylococcus aureus* (MSSA) was the most commonly isolated organism (14 cases, 16.28%). There were no cases of clostridial infection.

Risk Factors for Mortality

The overall 30-day mortality rate was 33.7% (29 patients). When various socio-demographic, clinical, laboratory and management related variables were analyzed between survivors and non-survivors, it was found that the mortality rate was significantly associated with the following risk factors: age above 50 years, presence of symptoms for more than 8.5 days, involved body surface area more than 15.5%, on-admission clinical parameters [pulse rate more than 99 beats/minute, systolic blood pressure less than 103 mm Hg, Glasgow scale less than 12 and the need for inotropic support], initial laboratory reports [haemoglobin less than 8.7 mg/dL, leucocytosis (above 18,700/ml), uraemia, deranged coagulation, serum albumin less than 2.5 gms/dL, and high levels of lactic acids (more than 2.15

mmol/L)]. Although elevated blood sugar on presentation was not associated with significant mortality, the presence of diabetic ketoacidosis and DM with complications showed a significantly higher mortality. Patients who underwent early surgery (within 3 hours of presentation) had a significantly better survival than those in whom surgery was delayed beyond this period.

On multivariate analysis, age (more than 50 years), hypoalbuminaemia (less than 2.5 gms/dL) and presence of metabolic acidosis (pH less than 7.35) were found to be independent predictors of mortality (Table 1).

Development of a prognostic scale

Taking the 3 factors that were significant in multivariate analysis into consideration, we devised an 'Alpha' score (Albumin, pH and Age). In "Alpha" score, a point of one was given in each of the above mentioned risk factors if they exceeded the normal range. Thus, every patient could be scored from 0 (no risk factors) to 3 (all three risk factors present). It was seen that the Alpha score was highly predictive of mortality only when all three factors were positive (Alpha 3) but the sensitivity, specificity, positive predictive value and negative predictive value fell for lower scores (Table 2).

Discussion

The mortality of NSTI still remains high, with an overall 30-day mortality rate of 33.7% (29/86 patients) in the present series which was purely observational. Various clinical, hematological and biochemical parameters were recorded on admission and patients were followed up prospectively to determine any variables contributing towards mortality (Table 1). The majority of patients were males (75.6%) but gender was not related to mortality; the average age was 50.37 years and patients aged above 50 years had a significantly higher mortality, which is similar to that reported in a few other series [5,14]. The average duration of symptoms before presentation to hospital was 10.56 days. It is well

documented that a delay in presentation increases mortality in NSTI [5,15] and the same was seen in this study as well - patients who presented after 8.5 days of onset of symptoms had a significantly higher mortality than those who presented earlier. NSTI was secondary to trauma (51 patients, 59.3%) or spontaneous (28 patients, 32.6%) in the majority of patients, similar to that seen by other authors [5,16,17]. Although few authors have reported spontaneous appearance without obvious cause [18,19], it is possible that this represents a situation where minor, unnoticed trauma may have occurred and remained neglected until the development of full blown NSTI. The other reported causes are insect bites, injection sites, surgical wounds and a source from the perianal area [5]. The most common sites of involvement were the lower limbs (72%) followed by upper extremities (11.6%), inguino-scrotal area (9.3%) and torso (4.6%). It is reported that patients with NSTI of the extremities have an improved survival compared to those with involvement of central part of body or in those with affection of the head and neck region due to proximity with various vital anatomical structures [18,20]. Mortality increased proportionally to the area involved. The mean total body surface area (TBSA) involvement in those patients who died was 15.93%, significantly higher than that of survivors (9.84%). Involvement of more than 10% of TBSA has been previously reported as an independent predictor of mortality [9,21].

The presence of multiple co-morbidities is also significant in determining mortality [5]. Diabetes mellitus (DM) was the most common co-morbidity seen (41 patients, 47.67%) in this series, with a mortality rate of 51.21% amongst diabetics and 27.5% among non-diabetics, similar to that reported by others [16,18,22].

Various other factors were also observed to be associated with mortality, but on multivariate analysis only three factors correlated significantly: age (more than 50 years), hypoalbuminaemia (less than 2.5 gms/dL) and the presence of metabolic acidosis (pH less than 7.35). This simple scale relies upon 3 values which, if analyzed, indirectly

Table 2. 'Alpha' Prognostic Scoring System (Using Albumin, pH and Age).

Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
0	3.45	56.14	3.85	53.33	38.37
1	13.79	56.14	13.79	56.14	41.86
2	24.14	89.47	53.85	69.86	67.44
3	58.62	98.25	94.44	82.35	84.88

Score 1 point for each of the following variables:

- low Albumin (less than 2.5 gms/dl)
- acidosis (pH less than 7.35)
- age (greater than 50 years)

reflect nutritional status (albumin), acute physiological status (pH) and chronic health status (age). Our attempt at validating this scale randomly throughout the same patient population revealed a high sensitivity (58.62%), specificity (98.25%), positive predictive value (94.44%), negative predictive value (82.35%) and an accuracy of 84.88 when all three factors were positive, i.e. a score of 3. However, this should not be taken as an acceptable validation of the Alpha score and ideally, an independent validation needs to be performed in a new study sample before it can come into general usage.

The present series of 86 patients of NSTI has shown a positive correlation with age, low albumin and acidosis with higher mortality, but it has its limitations as well. Firstly, these patients were treated under different surgical units and consultants, each with their own approach to antibiotic therapy, management, aggressiveness in debridement, amputations and re-debridement, whereas the others were more expectant. Since there was no standard protocol for the management of these patients, this could have affected the outcome – this study itself has shown that a delay in surgery beyond 3 hours of admission was associated with a higher mortality. Secondly, antibiotic therapy was initially empiric, with a preference for piperacillin-tazobactam and linezolid or clindamycin. Later, it was changed based on isolates and their sensitivity. Thirdly, our attempt at validating the ‘Alpha score’ within the same population is not an ideal method of doing so, and needs validation in an external cohort and comparison with standard prognostic scales such as the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score and APACHE II. Fourthly, patients were evaluated only upon admission and not followed up to see whether improvements in their parameters reflected improved survival; for example, we are unable to comment whether improvement in pH correlates with survival since this was not a focus in the current study.

However, despite these limitations, the present study has shown that NSTI still carry a high mortality; attention to managing various modifiable risk factors and optimizing these patients prior to early surgery may help in reducing associated mortality.

Ethical Approval – Informed Consent: *The authors declare that the study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Also all patients gave their written informed consent prior to their inclusion to the study.*

Conflict of Interest: *The authors declare that there is no conflict of interest.*

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