Necrotising Soft Tissue Infection–Risk Factors for Mortality

ABSTRACT
Necrotising Soft Tissue Infection is a rapidly progressing fatal disorder, the prognosis of which depends on early diagnosis and management.

Objective: In this study, our objective was to assess the factors contributing to mortality due to NSTI.

Methods: A retrospective review of the records of all patients with NSTI involving fascia, skin or muscle between January 2007 and December 2011, was performed. The aetiology, predisposing factors, risk factors, causative microbiological organisms and the clinical outcomes associated with mortality were studied.

Statistical Data: Descriptive statistics comprising of proportion(%) presented. Chi–square test was employed to assess the statistical significance in the distribution of various known risk factors between the survivors and non–survivors. A ‘p’ value less than 0.05 was considered significant.

Results: Sixty patients records were reviewed. Fifty-one patients (85%) were males and nine (15%) were females. Mean age was 46.57 years (+/- 20.60) ranging from 15–83 years. All the patients were treated by debridement & wide spectrum antibiotics.

INTRODUCTION
Necrotising soft tissue infections comprise a spectrum of disease entities that are characterized by extensive, rapidly progressive soft tissue necrosis that usually involves the fascia and sub–cutaneous tissue, but can also affect the skin and the muscle [1]. It was first described by Hippocrates circa in 500 BC [2]. Necrotising fasciitis had been described in medical texts since 1871 [3] and in surgical literature since 1924 [4]. Mortality is directly proportional to time of intervention and increases with the depth of various known sites of infection. Mortality ranges from 8.7% [5] to 73%. Streptococcal toxic shock syndrome is associated with a mortality rate of up to 80% [6]. Individual factors that have been implicated to increased mortality from NSTI includes increasing age, diabetics mellitus, peripheral vascular disease, obesity, chronic renal failure, HIV, alcohol abuse, IV drug abuse, abscess, blunt or penetrating trauma, insect bite, surgical incision and delaying surgical debridement etc. Unfortunately, the small number of patients reported in most series of NSTIs has precluded the definitive identification of risk factors for mortality.

A clinical score that categorises patients with NSTI according to the risk of death was created by Anaya et al., [7], which used simple variables, all available at the time of first assessment. Despite the plethora of risk factors, there is no specific inciting event identified in 25% to 50% of patients. Early diagnosis and a regime of vigorous resuscitation, nutritional support, broad spectrum antibiotics and aggressive debridement with re–exploration are crucial in patient management. The aim of this study was to assess the risk factors associated with mortality due to NSTI.

MATERIAL & METHODS
A retrospective record review of all patients with NSTI involving the fascia with or without the muscle necrosis, who were treated at M.S. Ramaiah teaching hospital between Jan 2007 and Dec 2011, was done. Patients were identified using a computer–generated search through the medical records department. NSTI was defined by the presence of necrosis of the subcutaneous tissue & fascia with variable involvement of the skin & muscle clinically.

Medical records were reviewed for the following data: Age, gender, aetiology of bacterial infection, predisposing factors like, DM, PVD, IV drug abuse, alcoholism, hypoalbuminemia, other immune-compromised conditions, co-morbid illness, anatomic sites of infection, clinical manifestation of infection, lab findings, time from hospital admission to operation, bacteriology, number of operative debridements, need for amputation, presence of MOF & mortality.

The anatomic site of infection was classified as trunk, extremity (upper limb or lower limb) & perineum. Post-Operative NSTI was defined as NSTI that occurred following a recent operative incision. Leucocytosis was defined as WBC count > 10,000c /cu.mm; anemia if Hb was < 10g/dl; hyponatremia if sodium was < 134mg/ dl. All patients were treated by aggressive resuscitation, surgical debridement with re-exploration if required, intravenous antibiotics like cephalosporins or carbapenems depending on the severity of Mono-microbial atiology being found in 27 patients (63.3%) and polymicrobial culture was isolated in 13 patients (36.7%), with E-coli and staphylococci being the most common organisms to be isolated. In most patients, multiple debridements were done. The overall mortality rate was estimated to be 25%. Age, aetiology, diabetes mellitus, hypoalbuminemia, alcohol, site of infection, bacteriology etc. were the risk factors associated with mortality, that were evaluated. Diabetes mellitus was the most common associated risk factor found in 32 patients (53.3%), though not statistically significant. Increasing age (>50 years, p value = 0.016), raised Serum Creatinine (>1.2mg/dl, p-value = 0.023) and delayed surgical intervention (>24 hours p value= 0.006) were the risk factors associated with Mortality in NSTI that were statistically significant.

Conclusion: Despite the use of appropriate antibiotic treatment, aggressive debridement & resuscitation, NSTI still leads to a high mortality & morbidity. In this series, there is high mortality associated with increasing age, raised serum creatinine and delayed surgical intervention. The mortality rate (25%) is comparable to other studies.
the disease, with clindamycin and metronidazole, the dose of which were adjusted according to patient’s renal function, nutritional support and early soft tissue coverage. The antibiotics were later changed according to culture and sensitivity report.

RESULTS

Sixty patients were treated altogether. Fifty-one patients (85%) were males and 9 patients (15%) were females. Mean age was 46.57 years (+/- 20.60), ranging from 15 to 83 years. Thirty-eight patients were operated within 24 hours of admission and 25 were operated after 24 hours of admission. All patients presented with pain and tenderness, the duration ranging from 5 days to 2 years, but most of them presented within 15 days.

Twenty-one patients (35%) were febrile at the time of presentation with a body temperature >100°F. Skin changes in the form of erythema, redness, blisters, necrotic patches etc. were seen in 56 patients (93.3%). Fifteen patients (25%) presented with MOF in the form of renal failure, ARDS or hepatic derangement.

Most of the patients i.e., 32 patients (53.3%) presented with the spontaneous onset of symptoms. Minor trauma leading to NF was found in 4 patients (6.66%). Surgical trauma i.e., NSTI arising due to post-surgical causes was seen in 7 patients (11.6%) and 2 patients (3.33%) presented with history of insect bites.

All the 15 patients (25%) who presented with Fournier’s gangrene had history of abscess or minor wounds at the onset. DM was the most common co-existing predisposing factor; other co-morbid factors were peripheral vascular disease, COPD, CRF and paraplegia [Table/Fig-1].

Lower limb was the most common site of involvement found in 34 patients (56.6%). Perineum was the next common site, seen in 15 patients (25%). Seven patients (11.6%) had their abdominal wall involved. They were post-surgical patients who had undergone the abdominal surgeries elsewhere. Four patients presented with NF of the upper limb (6.66%) [Table/Fig-1].

Laeukocytosis was found in 58.3% (n=35), 21 patients (35%) presented with anaemia, 20 patients (33.3%) presented with a raised creatinine. In 18 patients (36%), Sodium was found to be low. Liver function test was altered in 18 patients [Table/Fig-2]. Polymicrobial organisms were found in culture in 13 patients (25%). Seven patients (11.6%) had their abdominal wall involved. They were post-surgical patients who had undergone the abdominal surgeries elsewhere. Four patients presented with NF of the upper limb (6.66%) [Table/Fig-1].

MORBIDITY & MORTALITY

Thirty-five patients underwent debridement within 24 hours of admission. Out of whom, 25 patients (71.5%) were treated and discharged while 10 patients died (28.5%). Twenty-five patients were debrided after 24 hours, but within 48 to 72 hours; 20 of them (80%) were treated and discharged, while 5 patients died (20%). They were the patients who had a dilemma in diagnosis and were operated once the clinical features flared up. Thirty-four patients required single debridement, out of whom, 8 patients (25%) died. Twenty-one patients required multiple debridements, the mean number of operative procedures being 3.24 ± 1.0 and 7 patients (25%) died in this group. The average hospital stay of each patient was 45 days (excluding the patients who were discharged against medical advice and those who died). The antibiotics commonly used empirically were cephalosporins or piperacillin and tazobactum or carbapenems with clindamycin and metronidazole depending on severity. They were later changed according to culture & sensitivity. Diversion colostomy was done in two patients with perineal infection. Amputation was done on five patients with lower limb infection; all were diabetic and had myonecrosis. Patients who had Post-Operative NSTIs had abdominal wall reconstruction using polypropylene mesh at a later date.

The overall mortality rate was 25% (n=15). Early mortality, which was defined as death within ten days of the first debridement
occurred in twelve patients, which was due to overwhelming sepsis. Death occurred due to ARDS or acute renal failure. One patient with COPD died of pneumonia.

Three patients died after 10 days of the first debridement (mean 22.5 days, range 12 to 33 days), out of which two patients died of late multi-system failure and 1 patient died of renal failure. Out of the 15 patients who died, 8 patients isolated monomicrobial organisms, one patient isolated polymicrobial organism and no growth was found in 5 patients (p value = 0.07). However, as anaerobic culture was not done, it was possible that even these 5 patients who did not grow any organisms could have had an anaerobic bacterial infection or could have incurred production of toxins. Atioli, DM, hypoalbuminemia, anatomic site of infection, bacteriology, associated myonecrosis did not significantly impact on outcome. Factors that had a statistically significant impact on outcome in patients with NSTIs and those that approached statistical significance are listed in [Table/Fig-1 & 2].

**DISCUSSION**

Classic symptoms associated with NSTI are pain, anxiety & diaphoresis, which worsen rapidly [2]. There may be a history of trauma/break in the skin continuity within the 48 hours preceding the onset of symptoms, and there will be tenderness beyond redness, which is very classical. But only 10 to 40% of patients present with classic history [2]. Pain is usually out of proportion to physical findings, however in some patients there may be little or no pain. All patients presented with pain and tenderness in this study. A history of minor trauma was noted in only 4 (6.66%) patients but a history of surgical trauma was noted in 7 patients (11.66%).

Local erythema & swelling is the most common signs of NSTI. Skin changes will be evident only once corresponding skin ischemia occurs, usually later in the disease progression [2]. Most of the patients presented to us at this stage, as ours is a tertiary referral centre. The most common atiology of NSTI in our series is idiopathic (53.3%) while post-operative atiology was reported by Mc Henry et al. [1]. This was followed by perianal abscesses (25%) resulting in NF of perineum.

Various bacteriologic agents have been identified in patients with NF. The organisms isolated from the tissue were most commonly *E. coli* (n=11) either alone when monomicrobial infections occurred or in association with other organisms when polymicrobial infections were present especially when the lower limb was involved. *Staphylococcus* was the most common organism isolated from abdomen wall NF. The 25% mortality rate in this series compares favourably with other reports of patients with NSTI [Table/Fig-4]. Reports have suggested that patients with NF of the extremities have an improved survival compared to those with involvement of other areas [8,9,10]. In this series there were 38 extremity infections (LL=34, UL=4) with a death rate of 16.6% (n=10). Perineum was involved in 15 patients with 4 deaths (26.6%), comparable with 21.6% recorded by Ghnnam W M in 74 cases in 2010 [11]. In most series perineum is most commonly involved. In six patients muscles were involved and five patients underwent amputation. In seven patients trunk was involved with one death.

Stone et al., [12] reported 63% of the deaths from NSTI within 7 days of hospital admission and Rouse et al., [6] found that 45% of deaths from NSTI occurred within 10 days of initial debridement and resulted from either persistent infection after inadequate debridement or rapidly progressive septicemia. In our series 80% (n=12) of the patients had died with in 10 days due to overwhelming sepsis. Remaining 3 patients died after 10 days of first debridement due to late multi-system failure. More recently Hakan Yanar et al., [13] reported a mortality of 40% in a series of 35 patients. Statistical analysis of the potential risk factors for mortality from NSTI demonstrated that only a raised serum creatinine (> 1.2 mg/dl, p=0.023), age more than 50 years (p=0.016) and debridement after 24 hours (p value-0.006) were associated with unfavorable outcome with statistical significance. They were associated with advanced disease and more fulminant infection. The duration of symptoms amongst non-survivors ranged from 2 to 25 days (average of 13.5 days). All except 2 patients presented within 1 week of symptoms. Altered LFT, MOF at the time of presentation, no isolation of organism from culture, presence of comorbid conditions were the other factors that approached statistical significance in patients who died of NSTI. Mortality rates have been reported to be especially high in the presence of increasing age [7]. Rea and Wyrick [14] reported a mortality rate of 67% in patients more than 50 years of age and mortality rate of 4% in patients less than 50 years of age [9]. Our results were comparable with other studies like that of Mc Henry et al., [1,15] where in time of admission to operation, percentage of body surface area involved, presence of comorbid conditions and increasing age have had statistical significance in the outcome. The other risk factors for NSTI are PVD & diabetes [14]. The most common co-morbid condition associated with NSTI in our series was DM, which was seen in 32 patients (53.3%); 22 of these patients (68.6%) were treated and discharged & 10 patients (31.2%) died. The death rate was 31% among the diabetics & 17.9% among non diabetics. Though the death rate was higher among the diabetics, it was not statistically significant (p-value = 0.23) as also reported by David et al., [15].

All patients were treated by aggressive resuscitation, surgical debridement with re-exploration if necessary, I.V. antibiotics, nutritional support & early soft tissue coverage. All patients in this series had a diagnosis of NSTI that was confirmed by pathologic studies or documented clinically by the presence of liquefactive necrosis of the fascia, which allowed the surgeon to pass a blunt instrument or hand freely along the normally adherent tissue planes. The muscle involvement was clinically confirmed by the dusky appearance or muscle being replaced by slough [2].

Our data supports a policy of early exploration for all the patients in high risk groups, presenting with severe pain, particularly if accompanied by cellulitis, local skin changes or crepitus, immediately or later if there is a diagnostic dilemma or those in whom cellulitis progresses. Variability in the rate of development of NSTI was originally described by Wilson in 1942 [5]. He noted that the infection might affect an entire extremity within 24 hours or slowly progress over several weeks. In other patients the disease was dormant and then spreads rapidly without any readily apparent reason. This could be the atiology in most of our patients who presented with spontaneous onset.

The factors that cause NSTI to be aggressive or even lethal within 24 hours in some patients, but remain relatively unaggressive in others remain unidentified [16]. The virulent phase of this disease must be diagnosed quickly and accurately. Securing a diagnosis non-invasively is very difficult; this contributes to diagnostic delay, thus delaying treatment, resulting in death [17]. Exploration and fascial examination of the suspicious areas can be easily performed under local anaesthesia at the bedside by incision and inspection of the fascia noting the colour, odour, presence of necrosis and status of fascial planes. After diagnostic delay, the most common pitfall in treatment is inadequacy and delay in the surgical debridement.

The results of this study indicated that NSTI is no more an uncommon disease and therefore calls for a high index of suspicion as early interventions can reduce mortality. Definitive treatment includes a unified plan consisting of vigorous pre-operative resuscitation, broad-spectrum antibiotics, early and aggressive surgical debridement, re-exploration at 24 hours and thereafter as needed, nutritional support and early soft tissue coverage. The use of hyperbaric oxygen is controversial and was not undertaken in
our patients. The limitation of the study is that it is a retrospective study and results were tabulated based on the available data.

CONCLUSION

These results indicate that prompt recognition and early debridement of NSTI can potentially improve the outcome of this serious disease. Despite the use of appropriate antibiotic treatment, aggressive debridement, & aggressive resuscitation NSTI still has a high mortality & morbidity. Increasing age, raised creatinine and delay in the first debridement were associated with unfavorable outcome in this study. Many other parameters that were compared did not show much significance as reported in others studies.

REFERENCES