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Necrotizing Soft Tissue Infections: APACHE II Score, Dissemination, and Survival

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Abstract
Background First described more than a century ago, necrotizing soft tissue infections (NSTIs) continue to cause high mortality and morbidity. The aim of this study was to elucidate the factors affecting the outcome of patients presenting with an NSTI.
Methods To determine the factors affecting mortality from NSTIs, the records of 67 patients were retrospectively assessed for the following parameters: age, sex, time between initiation of symptoms and admission to the clinic, presence of systemic coexisting disease, APACHE II score, origin of infection, dissemination of the NSTI, and method of therapy.
Results The patients were 41 men (61.2%) and 26 women (38.8%) with a mean age of 54.9 ± 1.73 years. The overall mortality rate was 49% (33/67). Multivariate analysis determined that APACHE II scores of 13 or higher ($p = 0.001$) and NSTI dissemination ($p = 0.02$) were risk factors affecting the mortality of patients with NSTIs.
Conclusion By considering these two factors, more accurate outcome prediction may be possible, which may be useful for directing the management of patients with NSTIs.

It has been more than a century since Joseph Jones first described necrotizing soft tissue infections (NSTIs). Despite the development of various classification systems and progress in surgical management, NSTIs continue to have high mortality and morbidity rates and pose enormous diagnostic and therapeutic challenges [1]. Although the basics of NSTI management are well defined [2], the survival of patients with NSTIs also depends on factors outside of treatment [3].

The NSTI mortality rates vary from 0% to 76% among published patient series [1–28]. This wide range reflects the highly variable characteristics of the disease, which prevent clinicians from making an accurate risk analysis. Many studies have sought to determine the factors affecting NSTI outcome, and patient-related factors have been found to be as effective as treatment in promoting survival [1–3, 7, 9, 11–13, 17, 19, 20, 27–29]. For this reason, in the present study, we used the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) scoring system, which evaluates patients' acute and chronic health status, to predict the outcome for patients with NSTIs [19]. We then used multivariate analysis in 67 patients with NSTIs to investigate the relative effectiveness of the APACHE II scoring system and other clinical factors in predicting outcome.

Methods

The medical records of 67 consecutive patients presenting with NSTIs to the Department of General Surgery, Uludag University Medical Faculty between January 1986 and December 2002, were retrospectively examined. Fifty-three patients had been referred from other medical centers.

APACHE II scores were calculated using patient admission data. Upon admission, each patient was initially treated with empiric broad-spectrum parenteral antibiotics,

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most frequently penicillin combined with a third-generation cephalosporin or gentamicin combined with metronidazole or clindamycin. Initial surgical débridement was performed within the first 12 hours after admission. Microbial culture specimens obtained in the operating room during each débridement sequence directed later antibiotic management. Surgical débridement was repeated after 24 hours. If infection persisted, additional débridement were performed every 48 hours. Wound closures were routinely changed daily and additionally as necessary. Surgical débridement was continued until fully healthy tissue was obtained macroscopically or negative tissue cultures were obtained. When tertiary wound closures were not possible, skin grafting was used. A temporary colostomy was constructed in selected cases. Hyperbaric oxygen therapy was not used. Patients with severe disease or in poor condition were treated in the intensive care unit (ICU). Malnourished patients were supported by enteral nutrition via an oral or nasoenteral route whenever possible and by parenteral nutrition when enteral nutrition was inadequate.

To determine the factors affecting mortality due to NSTIs, patient records were assessed for the following parameters: age, sex, interval between symptom onset and first therapeutic intervention, presence of systemic preexisting disease such as diabetes mellitus (DM) or atherosclerotic vascular disease, APACHE II score, origin of the infection, extent of disease, and method of therapy (number of surgical débridements and additional surgical procedures). Need for the ICU and/or a ventilator, the number of days spent in the ICU, and the length of hospital stay were also recorded. Because it was not possible to obtain the results of all microbial cultures, this parameter was not included in the analysis.

The NSTIs were categorized into four main groups according to the type of lesion from which they derived. The first three groups included anorectal, skin (e.g., furuncle, intramuscular injection), and urogenital NSTIs. The remaining infections, including three cases of unknown origin, were categorized as ''other.''

The extent of each patient's NSTI was determined using the Lund and Browder burn area chart, which is used to estimate burn size [30]. With this chart, the trunk, extremities, thighs, scrotum, hands, feet, neck, and head are separately assessed for burn injury (Fig. 1). NSTIs were defined as local if the disease originated and remained confined to one of these body regions. NSTIs that spread to another body region were defined as disseminated.

To determine the factors affecting mortality rate, a univariate analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 10.0 (SPSS, Chicago, IL, USA). Significant factors in the univariate analysis were then used to produce a multivariate analysis model. A value of $p < 0.05$ was regarded as significant. Receiver operating characteristics (ROC) analysis was used to calculate the threshold APACHE II score for mortality. The chi-squared test was used to compare categorical variables. The *t*-test was used to compare group means. Statistics are presented as the mean ± SEM unless otherwise noted.

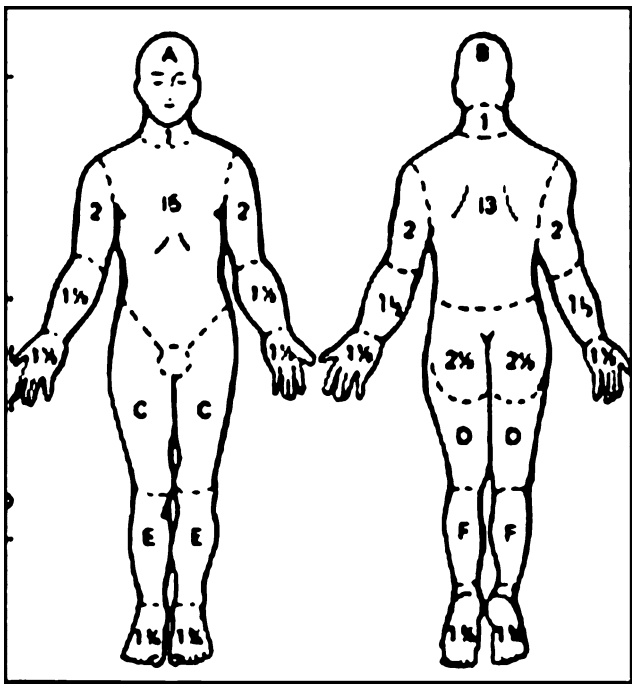

Fig. 1 Lund and Browder burn area chart

Results

Epidemiologic results

The patients were 41 men (61.2%) and 26 women (38.8%). The mean age of the patients was 54.9 ± 1.73 years. Advanced age was associated with higher mortality rates. The mortality rates were 33% and 71% among patients younger and older than 60 years, respectively. Delay in treatment initiation was approximately 7.35 days for survivors and 6.58 days for nonsurvivors ($p = 0.351$).

Approximately half of the patients (51%) had DM type II. Atherosclerotic vascular disease was the second most common coexisting disease (13%). Other specific co-morbid conditions were malignancy ($n = 7$), hypertension ($n = 3$), cerebrovascular accident ($n = 2$), chronic renal failure ($n = 2$), rheumatoid arthritis ($n = 1$), Crohn's disease ($n = 1$), and aplastic anemia ($n = 1$).

The overall mean APACHE II score was 13.9 ± 1.01. The mean APACHE II scores were 8.5 ± 0.73 for survivors

Table 1 Association between NSTI dissemination and mortality

Extent of disease	Survivors No.	Nonsurvivors No.	Total No.
Local	19 (79%)	5 (21%)	24 (36%)
Disseminated	15 (35%)	28 (65%)	43 (64%)
Total	34 (51%)	33 (49%)	67 (100%)

and 19.6 ± 1.34 for nonsurvivors. ROC analysis revealed a threshold APACHE II score for mortality of 13. The mortality rate for patients with an APACHE II score of 13 was 21%, whereas the mortality rate for patients with a score of 14 or higher was 86% ($p = 0.001$). All patients with an APACHE II score of 20 or higher ($n = 18$) died.

The NSTIs were most frequently anorectal in origin. The origins of anorectal NSTIs were perianal abscesses ($n = 22$), rectal cancer ($n = 2$), and hemorrhoidectomy complications ($n = 1$). The origins of skin NSTIs were furuncles ($n = 13$), intramuscular injection ($n = 5$), and decubitus ulcer ($n = 2$). The origins of urogenital NSTIs included Bartholin cystic abscess ($n = 5$), prostatectomy complication ($n = 1$), urethral stricture ($n = 1$), bladder cancer ($n = 1$), and nephrostomy complication ($n = 1$). NSTIs categorized as ''other'' were caused by trauma ($n = 4$), operative complications (one appendectomy, one inguinal hernia repair, and one jejunostomy) ($n = 3$), strangulated inguinal hernia ($n = 1$), Crohn's disease ($n = 1$), psoas abscess ($n = 1$), and unknown origin ($n = 3$).

Approximately 36% of the patients had a local NSTI, and 64% had disseminated NSTI. Disseminated NSTI was closely associated with a high mortality rate ($p = 0.02$) (Table 1).

The mean number of débridements was 1.4 and did not differ between survivors and nonsurvivors. A total of 24 patients required a temporary colostomy. Of these 24 patients, 10 died, and the colostomies of the remaining 14 patients were removed 3 months after wound closure. Other additive procedures were small bowel resection ($n = 2$), orchiectomy ($n = 2$), below-knee amputation ($n = 1$), and hip disarticulation ($n = 1$). One patient, who developed an NSTI as a result of cancer of the distal rectum, underwent abdominoperineal rectum resection after treatment of the NSTI. Fourteen survivors required skin grafting for wound closure.

The overall mortality rate was 49% (33/67). Fifteen patients died during the first 24 hours of admission as a result of septic shock. Sixteen patients died as a result of multiple organ failure (MOF), and two patients died from cardiogenic shock.

Of the 67 patients, 31 required intensive care. The mean lengths of stay in the ICU were 7.72 ± 1.6 days for nonsurvivors and 5.27 ± 1.6 days for survivors; the difference was not statistically significant ($p > 0.05$). The mean duration of hospital stay was 17.6 days for the overall group; it differed significantly between survivors (26.61 ± 3.1 days) and nonsurvivors (7.08 ± 1.6) ($p < 0.001$). The need for intensive care also differed significantly between survivors ($n = 10$) and nonsurvivors ($n = 21$) ($p < 0.001$), as did ventilator need (survivors, $n = 2$; nonsurvivors, $n = 15$ patients) ($p < 0.001$).

Table 2 Univariate logistic regression analysis of 67 patients

Factor	Coefficient	p	95% CI
Sex	0.95	0.109	0.82–8.20
Age >60 years*	1.69	0.030	1.26–23.80
Delay in management	0.67	0.371	0.51–7.49
Diabetes mellitus	1.45	0.540	0.96–19.20
APACHE II score >13*	4.03	0.001	5.61–56.30
Origin of infection	1.47	0.600	0.98–19.80
NSTI dissemination*	4.02	0.001	5.59–55.80
Temporary colostomy	0.64	0.355	0.50–7.25

CI: confidence interval; APACHE: Acute Physiology, Age, and Chronic Health Evaluation; NSTI: necrotizing soft tissue infections

*$p < 0.05$

Table 3 Multivariate logistic regression analysis of 67 patients

Factors	Coefficient	p	Odds ratio	95% CI
Age >60 years	1.23	0.065	3.8	0.48–24.20
APACHE II score ≥13*	4.00	0.001	14.2	3.84–77.60
Disseminated disease*	1.69	0.020	6.3	1.64–23.90

*$p < 0.05$

Logistic regression analysis results

Eight variables (age, sex, time between symptom onset and admission to the clinic, presence of systemic coexisting disease, APACHE II score, origin of infection, dissemination of NSTI, and method of therapy) were analyzed with univariate logistic regression to examine their influence on mortality. This analysis identified three factors that significantly affected patient survival: age, APACHE II score, and NSTI dissemination (Table 2).

However, multivariate analysis determined that only an APACHE II score of ≥13 ($p = 0.001$) and NSTI dissemination ($p = 0.02$) were significant risk factors affecting mortality (Table 3). Age was not an independent risk factor ($p = 0.065$).

Discussion

The overall mortality rate in our study was 49%. The mean expected mortality rate from NSTIs worldwide is approx-

imately 25% [5] but varies widely from 0% to 76% [1–28]. In our series, the main determinants of death were high APACHE II scores and disseminated disease. The other main factor to be considered was the age of the patients.

The age of patients with NSTIs has been changing. When describing Fournier's gangrene, John Alfred Fournier [6] identified three main properties: ''unknown origin, young age, and male gender.'' However, almost every recent paper about NSTIs reports a higher age group and increased mortality with advanced age [21–23]. Today, age >60 years is accepted as a predisposing factor for NSTIs [17, 23]. In our study, univariate analysis identified an association between age and prognosis, but multivariate analysis did not support this finding. When co-morbid conditions predisposing to NSTIs are considered, the negative impact of age is not surprising, as these conditions are usually observed in association with advanced age. The most common coexisting diseases in our series were diabetes mellitus (51%) and atherosclerotic vascular disease (13%), which are general diseases of old age.

Outcome prediction is an important issue for NSTIs, as for every serious medical condition. In our study we used the APACHE II scoring system to predict patient outcome, as did Pesa and Howard [20]. The APACHE II scoring system is widely used to predict the outcome of critical systemic diseases such as acute pancreatitis [19]. It has three main parts, which address the patient's acute physiological status, age, and chronic health status. Other scoring systems that have been studied include the APACHE I score and Fournier's Gangrene Severity Index (FGSI) [4, 19, 20, 31]. APACHE I was used by Freeman et al. [31] to predict survival of patients with NSTIs. However, APACHE I was found to be too complex for routine use and was later modified by Knaus et al. [19] for use with NSTIs as well as other critical systemic diseases. Laor and colleagues [32] developed FGSI to predict outcome for patients with Fournier's gangrene, and some studies have found this index to be useful [33, 34]. FGSI was derived from the APACHE II scoring system and may also be used for NSTI outcome prediction, but it scores only the acute physiological status. It must be remembered that NSTIs are systemic infections localized to a particular body region. Thus, patient age and chronic health status are as important as the acute physiological status, which is why we insist on using the APACHE II scoring system to predict the outcome of NSTI. Our finding of a strong association between APACHE II scores and NSTI outcome supports this practice. Altogether, 86% of the nonsurvivors had an APACHE II score of 13 or more, and all patients with APACHE II scores >20 died. The APACHE II score was also one of two independent risk factors identified by multivariate analysis.

Dissemination of NSTI is a sign of advanced disease [3]. Our finding of a negative impact of NSTI dissemination on survival replicates previous findings [1–3, 11, 17]. The multivariate model in our study identified NSTI dissemination as an independent risk factor ($p = 0.02$; odds ratio = 6.3).

In our series, the main cause of death among nonsurvivors who died within 1 week after admission was septic shock. MOF was the main cause of late mortality (after the first week). Patients who died during the late period had higher APACHE II scores and disseminated NSTI. The reason for this finding is uncertain. However, as necrotizing fasciitis covers a larger area, the cytokine response likely increases, which might lead to a pathological cytokine response in acutely or chronically weakened bodies (patients with an APACHE II score >13) and progression to MOF.

The mortality rate in this study is higher than the expected worldwide mortality rate of 25% [5]. Our institution is a tertiary referral center, and 80% of the patients were referred to our clinic from other medical centers at a time when some were already in advanced stages of the disease. However, there was no significant difference between the mean delay times of treatment initiation for survivors and nonsurvivors. This fact excludes the effect of the delay in treatment on outcome for our patients. When the 15 patients who died during the first 24 hours of admission are excluded from analysis, the mortality rate becomes 34.6% (18/52). In fact, this finding may highlight an important problem by showing that the NSTI is not well recognized by physicians of first and secondary health centers in our area.

NSTIs of the perianal region are easier to manage than ones located elsewhere. However, in our study, patients with perianal NSTIs had high APACHE II scores and mortality rates. Of the 22 patients with perianal NSTIs, 10 died. Four of these nonsurvivors died during the first 24 hours of admission, and additional three patients died during the first 4 days after admission. This is due to the patients' late referral to our clinic from other health centers. The mean APACHE II scores for nonsurvivors and survivors with perianal NSTIs were 18 and 7, respectively.

These data once again remind us of the importance of early diagnosis and initiation of treatment for NSTIs. When an infectious lesion is observed in a patient of advanced age with a serious systemic disease (e.g., DM, atherosclerotic vascular disease) or compromised immune system [human immunodeficiency virus (HIV), advanced cancer], the possibility of NSTI development must be considered. These patients should be closely observed even if the lesion seems harmless. It must be remembered that NSTIs may present as simple skin lesions initially and that systemic signs are an indication of advanced NSTI.[8] Surgical exploration of the suspected lesions may be advocated for such patients. Although this may disturb the patient somewhat, in most instances it can be life saving.[23]

Our study does have some limitations. First, the data were retrospectively collected from patient files and thus had no randomization. This raises the probability of type I errors and risk of bias. The absence of autopsy proof of the cause of death also weakens the power of our results. Although the policy for treating NSTIs is well described in our institution, there still may have been inconsistencies among the surgeons who treated these patients.

Conclusions

Although the delay in treatment does not significantly differ between survivors and nonsurvivors in our study, the high mortality rate and high APACHE II scores of our patients stress the devastating results of delaying the initiation of treatment. Moreover, our results identify two main factors affecting the outcome for patients with NSTI: dissemination of NSTI, which reflects the stage of the disease, and the APACHE II score, which reflects the patient's acute and chronic health status. By considering these two factors, more accurate outcome prediction may be possible, which may be useful for directing the management of patients with NSTIs.

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