Outcome of Patients with Toxic Epidermal Necrolysis Syndrome Revisited

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Toxic epidermal necrolysis syndrome is an uncommon, acute, life-threatening, medication-induced disorder with a reported mortality rate of 20 to 60 percent. Different variables have been identified as risk factors. The extent to which these variables, when combined, affect the mortality and outcome in toxic epidermal necrolysis syndrome patients has not yet been reliably defined. Because of the high mortality rate, the logistic analysis of studied variables was performed to see whether a prognostic algorithm could be developed to aid the management of these patients. Thus, a retrospective review of 56 consecutive toxic epidermal necrolysis syndrome patients treated over a period of 13 years was undertaken in the authors' burn center. The demographics included age, sex, race, and total body surface area involved. The other variables studied were comorbidities, sepsis, steroid administration, and the interval between onset of rash and burn center admission. Data were subjected to Fisher's exact test and logistic analysis. Thirty-six patients (64.3 percent) were alive and 20 (35.7 percent) died. Univariate analysis indicated that the male/female ratio was 12:24 for survivors and 9:11 for nonsurvivors ($p = 0.4$). The white/nonwhite ratio was 80 percent for survivors and 54 percent for nonsurvivors ($p = 0.58$). The median age was 48.4 ± 22.8 years (survivors, 41.7 ± 22.0; nonsurvivors, 60.5 ± 19.5; $p = 0.002$). Total body surface area involvement for survivors was 56.9 ± 32 and 77.7 ± 21 for nonsurvivors ($p = 0.005$). The presence of one or more comorbidities between the two groups differed (53 percent survivors and 90 percent nonsurvivors, $p = 0.007$), indicating eight times higher odds of dying in their presence. The average time between the onset of symptoms and admission to the burn unit was 5.25 ± 3.4 days for survivors and 7.15 ± 4.5 days for nonsurvivors ($p = 0.08$). The presence of sepsis (19.4 percent survivors, 95 percent nonsurvivors, $p < 0.001$) decreased odds for survival by a factor of 79. Steroids given as a single dose or multiple doses before the patient's transfer to the burn unit were not significantly associated with death (44 percent survivors, 65 percent nonsurvivors, $p = 0.14$). A multivariate logistic regression model yielded odds ratios of 1.11 (95 percent confidence interval, 1.03 to 1.19) for age in years, 304 (95 percent confidence interval, 8.83 to 10,400) for the presence of sepsis, and 1.03 (95 percent confidence interval, 0.99 to 1.08) for body surface area in percent. All those entering the burn unit with sepsis died. Equivalently, no survivors had sepsis before admission to the burn unit, whereas 55 percent of nonsurvivors had sepsis before admission and 40 percent developed sepsis after admission. When investigating the effect of age and sepsis, no patients over age 60 ever having sepsis survived, whereas all those who were under 60 and without sepsis survived. Likewise, all patients whose age was over 60 and whose total body surface area involved was over 60 percent died. The main factors contributing to the mortality from toxic epidermal necrolysis syndrome, when considering covariates separately, are the presence of sepsis at any time (odds ratio, 79), the presence of comorbidities (odds ratio, 8.05), age, and total body surface area, whereas multivariate models suggested age (odds ratio per year of additional age, 1.11), total body surface area (odds ratio per additional percent of body surface area, 1.03), and the presence of sepsis (odds ratio, 304). By using the actual coefficients in the logistic model, the log odds that the patient will die as the result of his or her condition can be summarized in the following formula: −11.5 + (10 percent of the patient's age + 3 percent of total body surface area + 5.75 if sepsis is present). The awareness of the importance of these covariates, and their early recognition as risk factors, should offer a focused approach to the patients' management and improve their outcome. (*Plast. Reconstr. Surg.* 110: 768, 2002.)

Toxic epidermal necrolysis syndrome, originally described in the mid-1950s, has been classified into two distinct types, I and II.[1] Type I, also known as the staphylococcal scalded skin syndrome, is caused by staphylococcal endotoxin, and is a distinct syndrome. The level of

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skin involvement here is intraepidermal, and is a clinically milder form than type II. An uneventful recovery usually follows treatment with antistaphylococcal antibodies.[2] Type II is an uncommon, acute, life-threatening condition that involves sloughing of the skin at the dermal-epidermal junction, with or without associated mucositis, and carries a mortality rate of 20 to 60 percent.[3] A variety of similar syndromes (erythema multiforme majus, erythema multiforme exudativum, Lyell disease, and Stevens-Johnson syndrome) share the histopathologic features of toxic epidermal necrolysis syndrome. The epithelial loss induced by these syndromes predisposes the patient to bacterial and fungal infections, and respiratory, gastrointestinal, nutritional, and ocular complications.[4] The most common cause of toxic epidermal necrolysis syndrome is attributed to a drug reaction, although viral, bacterial, and fungal infections and neoplastic disease have also been implicated.[5] In most patients, the disease presents with influenza-like prodromal symptoms, followed within hours or days by a rash, then by bullae that progress over a day or two to a more generalized epidermal slough. Moderate digital pressure over skin causes flaccid bullae that extend, termed a positive Nikolsky sign. The mucosal involvement usually precedes surface epithelial lesions.[6] Over the course of several days, progressive neutropenia and thrombocytopenia may develop which, together with septic complications, contribute to multisystem organ failure and death in 20 to 60 percent of toxic epidermal necrolysis syndrome patients.

Current reports on toxic epidermal necrolysis syndrome indicate a wide variety of variables that affect the outcome in these patients. Although the treatment of toxic epidermal necrolysis syndrome patients at burn centers can differ markedly from other centers, most of the authors agree that better outcome is expected if an expeditious transfer to a burn center is available, if corticosteroid administration is omitted, and if appropriate wound care and vigorous nutritional support are provided.[1,7-10] To date, no quantitative correlations have been developed to indicate to what extent each variable present in toxic epidermal necrolysis syndrome patients (age, sex, sepsis, steroids, total body surface area, or comorbidities), taken individually or combined, contributes to outcome. Therefore, we have undertaken this study in our burn center to clarify this question.

Methods

A retrospective review of 56 consecutive toxic epidermal necrolysis syndrome type II patients over a period of 13 years (1985 to 1998) was undertaken at the Baltimore Regional Burn Center. At admission to the burn intensive care unit, patient care was provided by a specialized multispecialty burn team.[8] Briefly, all toxic epidermal necrolysis syndrome patients with involvement of 20 percent or more of total body surface area admitted to the burn intensive care unit received a standard resuscitation protocol. History, clinical examination, biopsy, and histopathologic evaluation in each patient confirmed the diagnosis of toxic epidermal necrolysis syndrome. Initially, all wounds were débrided and cleaned. After that, 1% silver sulfadiazine (Silvadene, Hoechst Marion Roussel, Inc., Kansas City, Kan.) cream with sterile dressings was applied and changed at least daily. Alternatively, a nanocrystalline silver dressing (Acticoat, Smith & Nephew, London, United Kingdom) was applied, wetted about three times a day with sterile water, and replaced every 3 to 4 days. Further débridements, whirlpool, and use of biologic skin substitutes were used on an individual basis, and most patients were treated on a low-pressure bed system.

Chart Review

The following data were recorded: age, sex, race, and comorbidities. If, at the time of admission to the burn unit, toxic epidermal necrolysis syndrome patients had other medical problems, their comorbidities were entered only if they were not related to the cause of toxic epidermal necrolysis syndrome; for example, if a patient developed toxic epidermal necrolysis syndrome as a result of the administration of phenytoin for a seizure disorder, then the seizure disorder did not, per se, constitute a comorbidity for the purpose of this study. Comorbidities encountered in a group of toxic epidermal necrolysis syndrome patients included renal failure, diabetes, hypertension, seizures, chronic obstructive pulmonary disease, asthma, cirrhosis of the liver, and autoimmune conditions. The total body surface area involved was calculated according to the exfoliated open surface, using a Lund-Browder chart.[11] The other variables studied were the actual time elapsed from onset of

symptoms (the date of detection of the initial rash) to admission to the burn unit, sepsis (its presence before, at the time, and after admission), and steroid administration before admission. Sepsis was defined as the presence of two or more of the following: rectal temperature greater than 38.5°C, positive blood culture, white blood cell count greater than 12,000 or less than 4000, metabolic acidosis, homodynamic instability (systolic blood pressure less than 90 mmHg or greater than or equal to 40 mmHg decrease from baseline), altered mental status, and hypoperfusion with organ dysfunction. Its treatment included standard intensive unit care, empiric support, and antibiotics consistently administered as indicated. No intravenous immunoglobulins were given to these toxic epidermal necrolysis syndrome patients. In addition, no patient received steroids at admission to the burn unit except for rapid taper when deemed necessary. The above-mentioned variables were compared between the group of patients who survived and those who did not. Survivors were followed for 90 days after discharge to ensure that no deaths occurred in that period.

Statistical Analysis

Data were analyzed with Stata software (Stata Corporation, College Station, Texas). Individual covariates were compared between the two groups of patients in the study using Fisher's exact test for dichotomous covariates, and two-sample t tests for continuous covariates. The final logistic regression model, containing age, presence of sepsis at any time, and total body surface area, had been suggested by the investigators at the start of the analysis. Other models that included covariates listed as significant in the univariate analyses were investigated but discarded, because they added no additional utility. A value of $p < 0.05$ was considered statistically significant.

Results

The outcome for these 56 patients indicated that 36 patients survived (64.3 percent) and 20 patients did not. The cause of the mortality of 35.7 percent was most commonly multiple system organ failure (in the presence or absence of sepsis, failure of two or more system organs requiring support or treatment). The mean age in our group of 56 patients was 48.4 ± 22.8 years (survivors, 41.7 ± 22.0; nonsurvivors, 60.5 ± 19.5). A rank-sum test for differences in the median age showed that the difference was statistically significant ($p = 0.002$). The male/female ratio was 12:24 and 9:11 ($p = 0.4$), whereas the ratio between white and nonwhite (African-American or Asian) was 16:20 and 7:13 ($p = 0.58$) for survivors and nonsurvivors, respectively. The total body surface area studied for these two groups of patients was 56.9 ± 32 and 77.7 ± 21, respectively ($p = 0.005$) (Table I).

The presence of one or more comorbidities differed significantly between the two groups (53 percent survivors and 90 percent nonsurvivors, $p = 0.007$), dividing the odds of survival by 8.05 times (Table II). Likewise, the presence of sepsis greatly influenced survival (19.4 percent of patients who survived, and 95 percent of patients who died had sepsis, $p < 0.001$), increasing the odds for dying by a factor of 79. No survivors had sepsis before and only 19.4 percent developed sepsis after admission to the burn unit. In contrast, 55 percent of nonsurvivors had sepsis before and 40 percent after admission. The average time from the onset of symptoms to admission to the burn unit was 5.25 ± 3.4 days for survivors and 7.15 ± 4.5 days for nonsurvivors ($p = 0.08$). Steroids, given as single or multiple doses before the transfer of the patient to the burn unit, were not significantly associated with survival (44.4 percent of survivors, 65 percent of nonsurvivors, $p = 0.15$).

The above results, although interesting in

TABLE I

Demographic Characteristics of Toxic Epidermal Necrolysis Syndrome Patients

	All Patients	Survivors	Nonsurvivors	*p* Value
No. of patients	56	36	20	–
Age (years)	48.4 ± 22.8	41.7 ± 22	60.5 ± 19.5	0.002*
Sex (male/female)	21:35	12:24	9:11	0.4
Race (white/nonwhite)	25:33	16:20	7:13	0.58
Total body surface area (%)	64.3 ± 30	56.9 ± 32	77.7 ± 21	0.005*

* $p < 0.01$.

TABLE II

Important Variables for Survival in Toxic Epidermal Necrolysis Syndrome Patients

	All Patients (%)	Survivors (%)	Nonsurvivors (%)	p Value
Onset to admission (days)	5.92 ± 3.9	5.25 ± 3.4	7.15 ± 4.5	0.08
Sepsis (total)	26/56 (46.4)	7/36 (19.4)	19/20 (95)	0.002*
Before admission	11/56 (19.6)	0/36 (0)	11/20 (55)	
After admission	15/56 (26.8)	7/36 (19.4)	8/20 (40)	
Comorbidities	37/56 (66)	19/36 (53)	18/20 (90)	0.004*
Steroids (total)	29/56 (51.8)	16/36 (44.4)	13/20 (65)	0.15

* $p < 0.01$.

understanding effects of individual covariates, cannot be used to build a predictive model. To this end, various multiple logistic regression models were investigated. The model that had been suggested at the start of the analysis, which included age, presence of sepsis, and total body surface area, turned out to be quite a good model. This model yielded odd ratios of 1.11 (95 percent confidence interval, 1.03 to 1.19) for age in years, 304 (95 percent confidence interval, 8.83 to 10,400) for the presence of sepsis, and 1.03 (95 percent confidence interval, 0.99 to 1.08) for body surface area in percent. The last variable was not significant at the 0.05 level, but was kept in the model because it approached significance. It had a one-sided p value of 0.08 against the natural alternative that more burns increase the odds of death. Despite its high univariate association with survival, the presence of comorbidities added little to the model given above ($p = 0.32$). The use of steroids was nonsignificant in the multivariate model, just as it was when considered alone. No other covariates were found to be significant in the multivariate setting. Therefore, the odds of dying are multiplied by 1.11 for each additional year of age, by 1.03 for each additional percent of body surface area, and by 304 if the patient develops sepsis. These results were used to create a predictive model for the log odds of death, similar to that given by Ryan et al.[12] The predicted log odds that the patient will die, given his or her condition, are as follows: −11.5 + (10 percent of the patient's age + 3 percent of total body surface area + 5.75 if sepsis is present). To find the odds themselves, this result would then be exponentiated.

It was interesting to note that all 11 patients who were transferred to the burn unit with sepsis died. When the sample was split on the basis of age and development of sepsis, all those who were over 60 with sepsis died, and all of those who were under 60 and sepsis-free survived. When the sample was divided on the basis of age and total body surface area involved, all those who were over 60 and whose total body surface area involved was over 60 died (all but one developed sepsis).

Discussion

Toxic epidermal necrolysis syndrome remains an acute, life-threatening condition that carries a mortality rate of 20 to 60 percent (35.7 percent in this series). Current clinical experience indicates that early referral to a tertiary care center experienced in burn management, abstinence from steroid use, sepsis prevention, and an aggressive empiric wound-oriented intensive care management increases survival in toxic epidermal necrolysis syndrome patients. To create a prognostic algorithm that would predict the outcome, and thus facilitate the treatment, the above detrimental variables for toxic epidermal necrolysis syndrome patients were united in the logistic model as we have described. Our review indicates that in a multivariate model, significant correlates of mortality were age and sepsis, whereas total body surface area approached significance. The presence of comorbidities was an individually significant variable, although this significance evaporated in the multivariate setting.

The correlation of total body surface area and mortality has been previously reported by Revuz et al. in 87 consecutive patients with a 25 percent mortality rate and an average of 39 percent total body surface area involvement.[13] Similar findings were suggested by Murphy et al. in 44 toxic epidermal necrolysis syndrome patients.[14] Our data also found total body surface area involved to be an individually significant variable. Logistic analysis indicated that its univariate significance was in great part attributable to its positive association with both age and the probability of developing sepsis. It

was included in the final model because the predicted probabilities of death, rather than individual coefficients in the model, were of primary importance.

We and other authors have previously reported that the delay in transfer has a detrimental effect on survival in toxic epidermal necrolysis syndrome patients.[8,14] The current data indicate that time from the onset of symptoms to the admission to the burn intensive care unit was quite close between survivors and nonsurvivors (5.25 versus 7.15 days), and it was not significantly different. We explain this with the fact that nonsurvivors were admitted within a much shorter time frame in the current study compared with previous studies, where that time was almost twice as long. Therefore, although statistical significance was not reached in this series, we still strongly support an expeditious referral/admission of these patients. In addition, it is important to note that the patients in this study (with a 35.7 percent mortality rate) present the sickest subgroup of toxic epidermal necrolysis syndrome patients, who need burn intensive care unit admission. This is in contrast to the vast majority of toxic epidermal necrolysis syndrome patients with mild symptoms that are successfully treated as outpatients.

As previously indicated by other authors, age is also a significant variable in the survival of patients suffering with toxic epidermal necrolysis syndrome.[4,14] Our data confirm that older toxic epidermal necrolysis syndrome patients are at higher risk of dying. As stated in the Results section, there were many variables that by themselves were related to the odds of dying after developing toxic epidermal necrolysis syndrome. However, to have a predictive model, a multivariate model composed of age, sepsis, and total body surface area is preferred. Inclusion of any of the race, gender, comorbidity, and steroid variables led to no new models with additional significant coefficients. The former were simply unrelated to mortality, so their addition to any multivariate models would have little utility. Thus, the presence of comorbidities, although highly related when considered by itself (increased odds ratio by 8.05), added little to the original model, because of the high correlation of age and comorbidities. In real terms, because increasing age is associated with increasing comorbidities, age contains most of the information, which is contained in the comorbidities, and hence inclusion of the latter adds little to the model. Hence, the final, highly predictive model uses age, sepsis, and total body surface area involved.

In summary, the main factors contributing to mortality in toxic epidermal necrolysis syndrome patients are the presence of sepsis at the time of admission to the burn unit (odds ratio, 304), age (odds ratio per year of additional age, 1.11), and total body surface area involved (odds ratio per additional percent of body surface area, 1.03). Although the presence of comorbidities (odds ratio, 8.05) and the use of steroids (odds ratio, 2.32) are individually important, they lose their significance when combined with other variables. By using the actual coefficients in the logistic model, the log odds that the patient will die as the result of his or her condition can be summarized in the following formula: -11.5 + (10 percent of the patient's age + 3 percent of total body surface area + 5.75 if sepsis is present). By considering these covariates, we hope to offer an easier assessment of the patient's prognosis and better problem-oriented management that could improve the patient's outcome.[9,12]

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