ANNALS OF SURGERY
Vol. 225, No. 5, 554–569

Mortality Determinants in Massive Pediatric Burns

An Analysis of 103 Children with ≥80% TBSA Burns (≥70% Full-Thickness)

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Objective
Survivors and nonsurvivors among 103 consecutive pediatric patients with massive burns were compared in an effort to define the predictors of mortality in massively burned children.

Summary Background Data
Predictors of mortality in burns that are used commonly are age, burn size, and inhalation injury. In the past, burns over 80% of the body surface area that are mostly full-thickness often were considered fatal, especially in children and in the elderly. In the past 15 years, advances in burn treatment have increased rates of survival in those patients treated at specialized burn centers. The purpose of this study was to document the extent of improvement and to define the current predictors of mortality to further focus burn care.

Methods
Beginning in 1982, 103 children ages 6 months to 17 years with burns covering at least 80% of the body surface (70% full-thickness), were treated in the authors' institution by early excision and grafting and have been observed to determine outcome. The authors divided collected independent variables from the time of injury into temporally related groups and analyzed the data sequentially and cumulatively through univariate statistics and through pooled, cross-sectional multivariate logistic regression to determine which variables predict the probability of mortality.

Results
The mortality rate for this series of massively burned children was 33%. Lower age, larger burn size, presence of inhalation injury, delayed intravenous access, lower admission hematocrit, lower base deficit on admission, higher serum osmolarity at arrival to the authors' hospital, sepsis, inotropic support requirement, platelet count <20,000, and ventilator dependency during the hospital course significantly predict increased mortality.

Conclusions
The authors conclude that mortality has decreased in massively burned children to the extent that nearly all patients should be considered as candidates for survival, regardless of

age, burn size, presence of inhalation injury, delay in resuscitation, or laboratory values on initial presentation. During the course of hospitalization, the development of sepsis and multiorgan failure is a harbinger of poor outcome, but the authors have encountered futile cases only rarely. The authors found that those patients who are most apt to die are the very young, those with limited donor sites, those who have inhalation injury, those with delays in resuscitation, and those with burn-associated sepsis or multiorgan failure.

In children, massive burns over 80% of the total body surface area (TBSA) that are mostly third-degree burns have in the past been associated with almost certain death. Treatment in specialized burn centers, however, has so influenced survival in such massive burns that many now live. New and innovative techniques, such as early excision and grafting,[1,2] institution of appropriate nutritional support,[3] aggressive therapy for respiratory injury,[4] and prompt recognition and treatment of burn-related infections,[5] have played major roles in improved burn survival. The challenges that remain to further increase survival now could be better defined. Determination of which patients would be expected to die even with modern critical care techniques and burn wound management is important, because aggressive support should not be removed from a patient who is fully able to survive and lead a productive life. However, the point at which further treatment is futile should be well defined to avoid prolonged and unnecessarily painful deaths.[6]

Traditionally, burn size and age along with the presence or absence of inhalation injury have been used as the primary predictors of mortality after thermal injury. Other factors that are known during transport and at the time of hospital admission, such as delays in resuscitation and initial responses to therapy, may help to predict accurately those who are likely to die. Measures of sepsis and organ function often occur before death is imminent and could be useful in predicting futility of further care. In an effort to determine predictors of mortality, we compared initial presentation characteristics, transport-related variables, initial laboratory tests, and hospital course measurements in survivors and nonsurvivors of a series of 103 consecutive pediatric patients with >80% TBSA burn and >70% TBSA third-degree burn treated by a uniform protocol.

METHODS

Patient Care

Of two thousand eight hundred ninety patients admitted to the Shriners Burns Institute, Galveston Unit, between July 1982 and September 1996, one hundred three patients, ages 5 months to 17 years, sustained burns of >80% TBSA with >70% TBSA full-thickness. Survivors were compared to nonsurvivors to determine what findings would predict a high risk of mortality.

Patients were referred from the southern and western United States, Mexico, and Central and South America. The children were transported primarily by air accompanied by a physician, nurse, and respiratory therapist from our institute. All full-thickness burns were excised by one of three surgeons within 48 hours of admission. Harvested autografts taken at 0.8 one thousandths of an inch with a Padgett electric dermatome (Padgett, Kansas City, MO) were meshed 4:1 using a Brennen mesher (Brennen Medical, St. Paul, MN) and were covered with 2:1 meshed cadaveric allograft (UTMB Skin Bank, Galveston, TX). Meshed 2:1 cadaveric skin was used to cover all excised areas for which no autograft was available. Donor sites on the patients were covered with Scarlet Red (Sherwood, St. Louis, MO). All remaining second-degree areas were covered with a mixture of half 1% silver sulfadiazine cream (Marion–Merrill–Dow, Kansas City, MO) and half 1% nystatin ointment (Pharmatek, Huntington, NY). All patients underwent bronchoscopy at the first operation to identify airway injury. Patients were returned to the operating room every 5 to 10 days for further autografting after donor sites had healed. Broad-spectrum perioperative antibiotics were used in every case. In grafting, the hands were covered with sheet grafts or 2:1 mesh autograft without overlay. The face and neck were treated initially by application of a mixture of half 2% polymyxin B-bacitracin ointment (Burroughs Wellcome, Morris Plains, NJ) and half 1% nystatin ointment, then covered with sheet graft after separation of the eschar. Enteral nutrition was supplied to meet predicted requirements (Table 1). When ventilatory assistance was required, pressure or volume control ventilation was provided by means of a Servo C ventilator (Siemens, Danvers, MA) in all but one patient, who was ventilated with a percussive VDR ventilator (Percussionaire, Sandpoint, ID). All patients with identifiable inhalation injury were treated with nebulized heparin (100 units/kg per dose) and 20% acetylcysteine (Dey Laboratories, Napa, CA).

Factors Significant to Mortality-Independent Variables

We divided the treatment of burn injury into four relevant periods, and independent variables measured within

Presented at the 108th Annual Meeting of the Southern Surgical Association, December 1–4, 1996, Palm Beach, Florida.

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Accepted for publication December 13, 1996.

Table 1. GALVESTON SBI NUTRITIONAL REQUIREMENT FORMULA

Age (yr)	kcal Required	Protein (g/kg/day)
0–12	1800 kcal/m^2 BSA/24 hr + 2200 kcal/m^2 BSA burned/24 hr	1–2
12–18	1500 kcal/m^2 BSA/24 hr + 1500 kcal/m^2 BSA burned/24 hr	1–2

BSA = body surface area.

these periods were chosen that would represent valid physiologic events affecting mortality. These variables were grouped into categories corresponding to these periods. The periods were, in order, injury characteristics at the time of burn, transport-related variables, admission measurements, and hospital course events (Table 2).

In previous studies, initial characteristics at the time of injury have been shown to predict mortality, and this was defined in our first period of care. The variables that we chose included age, presence of inhalation injury, total burn size, full-thickness burn size, and gender. By our definition, the second period of care was during initial evaluation and transport, where institution of resuscitation and transport time to treating facilities are likely to affect outcome. Here the variables that we chose were time to intravenous access, time from burn to hospital admission, and resuscitation volume. The third period of care was during actual hospital admission, where measures of the adequacy of resuscitation and intravascular volume are likely to predict outcome. The measured variables that we chose included hematocrit, base deficit, and serum osmolarity. The fourth period of care was during the hospital course. We chose to divide this period into two categories, the first category including variables representing sepsis and nonpulmonary organ failure, and the second category to denote pulmonary failure. We performed this in an effort to retain significance of nonpulmonary organ failure variables in the logistic regression analysis, because the signs of lung failure were by colinear relations likely to diminish any effect of the other signs of organ failure. Our chosen variables for sepsis and nonpulmonary organ failure were the development of sepsis, serum creatinine level above 2.0 mg/dL, inotropic support requirement, and platelet count $<20{,}000/mm^2$. The percent of days that a ventilator was required in the first 28 days was used as the variable for pulmonary failure.

Burn size was determined by means of age-appropriate diagrams by one of three attending surgeons. Inhalation injury was defined as evidence of airway injury on bronchoscopy combined with a requirement of mechanical ventilation for greater than 72 hours with a P_a/F_IO_2 <300. Time to intravenous access was defined as the time in hours to start of reliable venous catheterization with infusion of intravenous solutions. Resuscitation volume was calculated by determining the total resuscitation fluid given in the first 24 hours postburn divided by the TBSA, fraction of TBSA burned, and time in hours (total volume [mL]/TBSA [m^2]/fraction TBSA burn/time [hours]). This expression places more emphasis on larger resuscitation volumes for increasing burn size. As a hypothetical example, for a 2.0-m^2 TBSA patient with an 80% TBSA burn who received 15,000 mL in the first 24 hours, the resuscitation volume per hour would be 391 mL/m^2 burn/hour. If the same patient received a 95% TBSA burn and the same amount of fluid, the resuscitation volume per hour would be 328 mL/m^2 burn/hour. In those patients who had the first excision and grafting procedure <24 hours after the injury, the fluid received before going to the operating room was divided by the appropriate number of hours. Time of transport was the time in hours from injury to arrival at our institution.

The presence of pathogenic bacteria on blood culture in conjunction with leukocytosis or leukopenia, hyperthermia or hypothermia, and tachycardia was used to define sepsis. A serum creatinine of >2.0 mg/dL was used as a measure of renal failure. Inotropic support requirement was defined as the use of continuous intravenous cardiac pressor agents for >6 hours to maintain a mean arterial pressure within normal range for age. Thrombocytopenia was defined as a confirmed platelet count of $<20{,}000/mm^2$ during the hospital course. The number of ventilator days up to 28 was divided by the number of hospital days, again not to exceed 28, to arrive at an index of ventilator dependency in the first month. This index will differentiate those with only perioperative ventilatory support from those with prolonged ventilatory requirements because of pulmonary fail-

Table 2. VARIABLES DIVIDED INTO TEMPORAL CATEGORIES FOR MULTIPLE LOGISTIC REGRESSION ANALYSIS

Model(s)	Independent Variables
Category 1: At injury	Age, inhalation injury, TBSA burn, TBSA full-thickness burn, sex
Category 2: Transport	Time to reliable IV access, fluid received in the first 24 hr
Category 3: Admission	Admission hematocrit, base deficit, serum osmolarity
Category 4: Hospital course	Sepsis, serum creatinine >2.0 mg/dL, inotropic support requirement, platelet count $<20{,}000/mm^2$, ventilator dependence

TBSA = total body surface area; IV = intravenous.

ure. The mean length of hospitalization for nonsurvivors of 28 days was chosen as the upper limit of days for this index to lessen the contribution of survivors with long periods of convalescence.

Data Analysis

All values are expressed as mean ± standard error of the mean or percentages. Each of the variables was tested for differences between survivors and nonsurvivors by univariate statistical methodology with significance accepted at $p < 0.05$ (chi square, Bonferroni's test between groups based on the binomial distribution, Student's t test, or Mann–Whitney rank–sum test where appropriate). A pooled cross-sectional multivariate logistic regression analysis was used to test the hypothesis that the four temporal groups of variables affect the probability of mortality. This was performed using the Statistical Analysis System Package (SAS, Cary, NC). For this analysis, the dependent variable was mortality, and our model determined the log odds of increased mortality given the independent variables. Specifically, the model estimated was,

$$\log(\pi_i/1 - \pi_i) = \log O_i = \alpha + \beta_i(I_i) + \beta_2(T_i) + \beta_3(A_i) + \beta_4(H_i) + C + E \quad (1)$$

where $\log O_i$ is the log odds of a high mortality rate, $\beta_1(I_i)$ is the vector of the injury characteristics variables, $\beta_2(T_i)$ is the vector of the transport variables, $\beta_3(A_i)$ is the vector of the admission variables, and $\beta_4(H_i)$ is the vector of the hospital course variables. C is the control variable, and E is the error term. To determine the significance of each variable, the chi square probability (p) value, which within multiple logistic regression corresponds to a standard probability value, was calculated for all variables in an analysis within their assigned category, and significance was accepted at 0.05. This chi square probability value is reported in the tables for each independent variable in addition to the probability value from standard univariate analyses.

In conjunction with the above models, nested models based on sequential addition of significant variables along each additional time course were determined. This was performed by adding significant independent variables from the subsequent category to those of the previous model (*e.g.*, category 2 variables were added to category 1 variables to form cumulative model 1, category 3 variables were added to cumulative model 1 to form cumulative model 2, etc.). Further analyses lead to models containing only the significant variables described in the regression equations. When variables were colinear, the strongest reasonable variable was retained. Variables that lost significance in progressive equations, even if significant within their category, were eliminated. White noise tests, including a concordance value, were performed to verify the results.

Because this analysis is not experimental, constancy of treatment and the breadth of measurements were used as controls. All factors affecting mortality were defined and measured as discussed in the independent variable section. All other factors that potentially affect mortality were constant across patients.

To determine whether the survival rate has improved since 1984, time was divided into 3-year intervals and compared using only complete years. To determine if TBSA burn was associated with length of stay in survivors, the length of hospital stay per percentage of TBSA burned was regressed over the range of burn sizes by linear regression. With the increasing use of recombinant human growth hormone in this population since 1988, we sought to determine its effect on mortality by comparing its use in survivors and nonsurvivors.

RESULTS

Injury Characteristics

One hundred three patients were identified with burns of >80% TBSA and >70% full-thickness. The mortality rate in this patient group was 33%. The mean age was 6.4 ± 0.45 year (range, 0.5–17 years), the mean total burn size was 88% ± 1 TBSA (range, 80–100%), and the mean full-thickness burn size was 85% ± 1 TBSA (range, 70–100%). Seventy-six were males, and 27 were females. Inhalation injury was present in 60 of the 103 patients. The injury characteristics and probability values for both univariate analysis as well as comparisons within the framework of a model for determining the effect of the combined variables on the log odds of mortality expressed as chi square probability values are listed in Table 3.

When age and mortality were compared (Fig. 1), mortality was 57% for children 2 years and younger (n = 28), 27% for those 3 to 10 (n = 56), and 16% for those 11 to 18 years of age (n = 19). The age group 0 to 2 was significantly different from the other age groups. When mortality was compared to burn size (Fig. 2), the 80% to 85% TBSA burns had a 19% mortality (n = 43), 86% to 90% TBSA burns had a 31% mortality (n = 26), 91% to 95% TBSA burns had a 45% mortality (n = 20), and those with 96% to 100% TBSA burns had a 69% mortality rate (n = 13). The 80% to 85% group is significantly different from the 96% to 100% group, and if patients with 80% to 90% TBSA burns are compared to those with 91% to 100% TBSA burns, there also is a significant difference between groups.

All independent variables except gender distribution were significant and had the predicted signs in the logistic regression. Increased TBSA burn and TBSA third-degree burn were both predictive of increased mortality. As expected, these two variables were highly colinear; there-

Table 3. PATIENT CHARACTERISTICS

	Age (yr)	Sex	TBSA Burned (%)	TBSA Full-Thickness Burn (%)	Inhalation Injury (%)
Survivors (n = 69)	7.1 ± 0.5	49 males, 20 females	87 ± 1	82 ± 1	51
Nonsurvivors (n = 34)	4.9 ± 0.8	27 males, 7 females	90 ± 1	89 ± 1	74
Univariate p value	0.009	0.501	0.004	<0.001	0.046
Chi square p value (multivariate analysis)	0.016	0.08	0.004	0.007	0.032

TBSA = total body surface area.

fore, TBSA burn was selected for inclusion in the multiple regression models and equations. The log odds of high mortality is expressed by the following equation fitted from the data where p is the conditional probability of mortality and inhalation injury is 0 or 1 for absence or presence of injury, respectively.

$$\log(p/1 - p) = -10.92 - 0.14(\text{age}) + 0.12(\text{TBSA burned}) + 1.12(\text{inhalation injury}) \quad (2)$$

The concordance for this equation with observed responses was 78%. This model predicts that the probability of death increases with lower age, larger TBSA burn, and presence of inhalation injury.

Transport Variables

During transit, the mean time to start of a reliable venous catheter was 1.2 ± 0.2 hour for all patients. The total fluid received in the first 24 hours indexed to burn area per hour was 448 ± 20 mL/m^2 burn per hour (Table 4). More than 70% of the patients arrived at our hospital within 48 hours of burn with an equal distribution between survivors and nonsurvivors. A delay in starting an

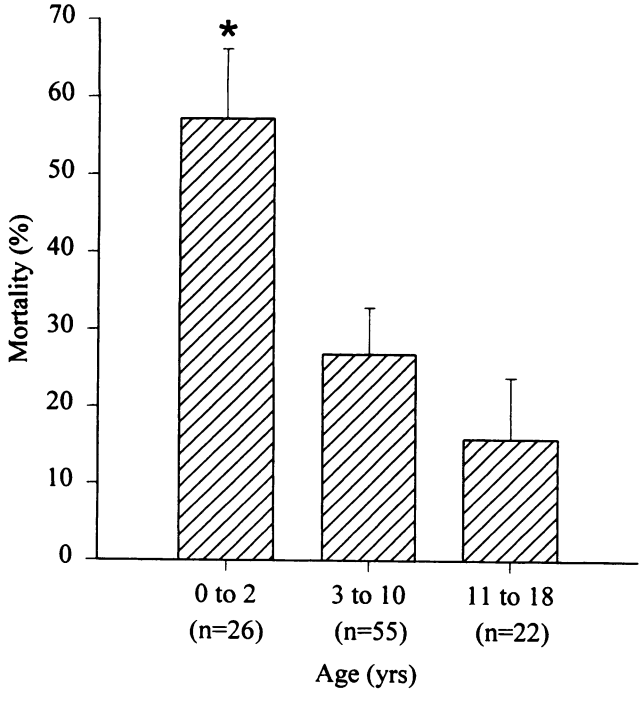

Figure 1. Mortality in burns >80% total body surface area for various ages. Significant difference from other groups is denoted by an asterisk (*). Values represent mortality rate standard error of the mean based on the binomial distribution. Mortality decreases with increasing age.

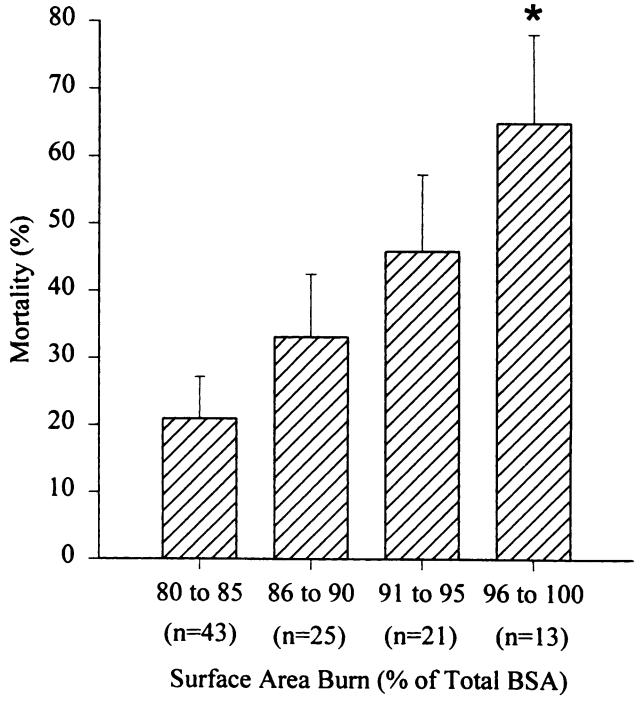

Figure 2. Mortality for increasing burn size. A significant difference from the 80% to 85% group is denoted by an asterisk (*). Values represent mortality rates with standard error of the mean based on the binomial distribution. Mortality increases with increasing burn size.

Table 4. CHARACTERISTICS OF TRANSPORT BETWEEN GROUPS

	Time to IV Start (hr)	IV Fluid in the First 24 hr (mL/hr/m² burn)	Transport Time <48 hr (%)
Survivors (n = 66)	0.6 ± 0.2	431 ± 20	49/69 (71%)
Nonsurvivors (n = 34)	2.2 ± 0.5	487 ± 51	25/34 (74%)
Univariate p value	<0.001	0.210	0.429
Chi square p value (multivariate)	0.004	0.277	0.247

IV = intravenous.

Table 5. ADMISSION VALUES FOR SURVIVORS AND NONSURVIVORS

	Hematocrit (%)	Base Deficit (mEq HCO_3)	Serum Osmolarity (mOsm/mL)
Survivors	38 ± 1	−4.5 ± 0.5	290 ± 1
Nonsurvivors	33 ± 1	−7.6 ± 1.0	308 ± 6
Univariate p value	0.021	0.002	0.001
Chi square p value (multivariate)	0.028	0.036	0.018

intravenous line of >1 hour was identified in 14 (21%) of 66 survivors and in 21 (62%) of 34 nonsurvivors. A delay in intravenous access of >2 hours was identified in 8 (12%) of 66 survivors, and in 11 (32%) of 34 nonsurvivors. When the delay is displayed graphically (Fig. 3), it is evident that the greatest survival benefit is obtained by beginning resuscitation fluid within the first hour after injury.

Only the time to intravenous access is significant among these independent variables in both analyses. We could find no difference between groups in time to transport to our hospital or fluid received in the first 24 hours evaluated either independently or with other variables.

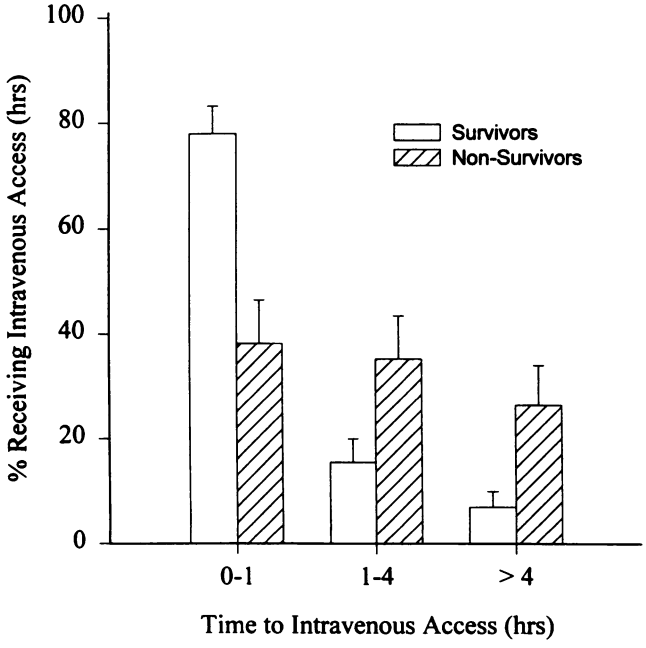

Figure 3. Time to intravenous access in survivors and nonsurvivors. Mortality increases with delays in starting an intravenous line and instituting volume resuscitation.

The log odds of high mortality using the significant variable in this category is expressed by the following equation:

$$\log(p/1 - p) = -2.27 + 0.39(\text{time to intravenous access}) \quad (3)$$

The concordance for this equation with the observed responses is 73.3%. When these variables are combined with the first category, time to intravenous access was found to be significant and with the predicted sign. Inhalation injury was not significant with the addition of the other variables. When time to start of resuscitation was added to the sequential regression equation, the log odds of high mortality is expressed by the following equation:

$$\log(p/1 - p) = -9.91 - 0.13(\text{age}) + 0.11(\text{TBSA burned}) + 0.34(\text{hours to IV start}) \quad (4)$$

A concordance of 79% with the observed responses was calculated for this model. At this point in the course of burn injury, the significant predictors of mortality in our equation are decreasing age, increasing burn size, and increasing interval of time to intravenous resuscitation.

Admission Measurements

At the time of hospital admission, the mean hematocrit for both groups was 37% ± 1%, the base deficit was −5.5mEq HCO_3 ± 0.5, and the serum osmolarity was 296 mOsm/mL ± 3 (Table 5). All variables in this category were found to be significant between groups and in predicting the probability of mortality. The log odds of high mortality based on variables within this category is expressed by the following equation:

$$\log(p/1 - p) = -6.12 - 0.05(\text{admission hematocrit}) - 0.11(\text{base deficit}) - 0.02(\text{serum osmolarity}) \quad (5)$$

Table 6. HOSPITAL COURSE VARIABLES

	Serum Creatinine >2.0 mg/dL	Inotropic Support	Sepsis	Platelets <20 × 10^3/mm^2	Ventilator Dependence (% days on ventilation during first 28 days)
Survivors	2/69 (3%)	2/69 (3%)	4/69 (6%)	4/68 (6%)	21 ± 4
Nonsurvivors	11/34 (32%)	18/34 (53%)	14/34 (41%)	16/32 (50%)	83 ± 6
Univariate p value	<0.001	<0.001	<0.001	<0.001	<0.001
Chi square p value (multivariate)	0.45	0.041	0.004	0.022	<0.001

The concordance of this model with the observed responses is 75%. When these variables were combined with the previous nested significant independent variables, only serum osmolarity remained significant between the groups because of the highly colinear relations between hematocrit, serum osmolarity, and base deficit. Colinearity implies that the involved variables are closely associated, and including all of them is redundant and dilutes the measurement of the relevant physiologic response by adding degrees of freedom. Any one of these variables could be chosen to represent this response; however, serum osmolarity was chosen as the strongest predictor, perhaps because of its higher variance. The logistic regression equation combining the effects of the first three periods is expressed in the following equation:

$$\log(p/1 - p) = -15.15 - 0.15(\text{age}) + 0.10(\text{TBSA burned}) + 0.29(\text{hours to IV start}) + 0.02(\text{serum osmolarity}) \quad (6)$$

The concordance in this model with the observed responses is 81%. For these variables, all the patients had arrived to the burn unit. The significant independent variables that remained were age, burn size, and time to resuscitation and serum osmolarity.

Hospital Course Measurements

During the hospital course, 18 (17.5%) of the 103 children became septic, a serum creatinine >2.0 mg/dL developed in 13 children (12.6%), 20 (19.4%) required inotropic pressor support for >6 hours, and 18 (19.8%) of 20 had platelet counts <20,000/mm^2. Eleven (85%) of 13 patients with a serum creatinine >2.0 mg/dL, 18 (90%) of 20 with pressor support requirement, 14 (78%) of 18 with sepsis, and 16 (80%) of 20 with a platelet count <20,000/mm^2 were nonsurvivors (Table 6). In this category, all of the independent variables were significant by univariate analysis; however, serum creatinine >2.0 mg/dL was not significant in the multivariate analysis. The logistic regression equation defining this category is as follows with 0 or 1 for absence or presence of inotropic support requirement, sepsis, or a platelet count <20,000/mm^2, respectively:

$$\log(p/1 - p) = -1.83 + 0.24(\text{inotropic support requirement}) + 2.03(\text{sepsis}) + 1.61(\text{platelets} < 20{,}000) \quad (7)$$

The concordance for this equation is 71% with the observed responses. When the above variables were added to the previous nested significant variables, inotropic support requirement, sepsis, and platelet count <20,000 were found to be significant. Time to intravenous access and serum osmolarity were found to be colinear with the addition of the above variables. Time to intravenous access was the stronger of the two, and when this was entered into the model without serum osmolarity, it remained significant. The log odds of high mortality based on all nested significant variables and the predicted sign are as follows:

$$\log(p/1 - p) = -14.30 - 0.18(\text{age}) + 0.15(\text{TBSA}) + 0.38(\text{time to IV}) + 0.31(\text{inotropic support}) + 1.96(\text{sepsis}) + 1.87(\text{platelets} < 20{,}000/mm^2) \quad (8)$$

where 0 or 1 is the presence or absence of serum creatinine >2.0 mg/dL, inotropic support, sepsis, and platelets <20,000/mm^2, respectively. A concordance value of 91% was seen with this model compared to the observed responses.

In the first 28 days of the hospital course, the mean percentage of days that a ventilator was required was 42% ± 4%. The survivors required ventilator support for 21% ± 4% of days in the first month, and nonsurvivors required ventilator support for 83% ± 6% of days in the first month (Table 6). There was a highly significant difference between groups by univariate analysis. When entered into the multivariate logistic regression, it again was highly significant. The logistic regression defining this variable on the probability of mortality is:

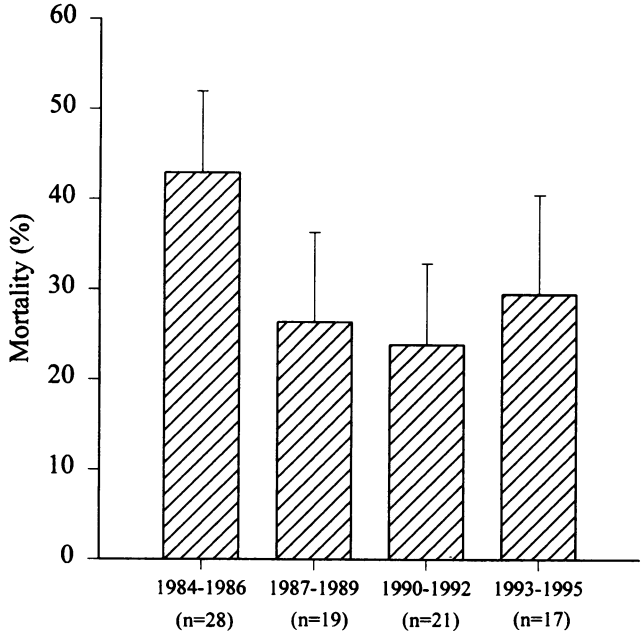

Figure 4. Percent of mortality from 1984 to 1996. No difference could be found between periods by Bonferroni's test on 0.975 confidence interval based on the binomial distribution.

$$\log(p/1 - p) = -2.96 + 4.37(\%\text{ days requiring ventilatory support in the first 28/100}) \quad (9)$$

The concordance for this equation is 86% with the observed responses. In the final cumulative nested model, TBSA burn, time to intravenous access, serum osmolarity, and inotropic support requirement did not remain significant. This left age, sepsis, and ventilator requirement as the significant variables in this model. The logistic regression equation combining the effects of all periods is expressed as follows:

$$\log(p/1 - p) = -3.59 - 0.21(\text{age}) + 3.25(\text{sepsis}) + 4.84(\%\text{ days requiring ventilatory support in the first 28/100}) \quad (10)$$

The concordance for this equation is 96% with the observed responses.

Survival Rate Over Time, Length of Hospital Stay, and Growth Hormone

Survival rate was compared during 3-year intervals, and no difference between periods could be shown (Fig. 4). When the length of stay per percentage of TBSA burn was compared to burn size in survivors, the linear regression showed a significant correlation with $p < 0.05$. This is represented graphically by histogram in Figure 5. The equation describing the relation is:

$$\text{length of stay/\% TBSA burn} = -1.33 + 0.02(\%\text{ TBSA burn}) \quad (11)$$

This regression indicates that length of stay increases as burn size increases. We could find no difference in survival with the use of recombinant human growth hormone.

DISCUSSION

Advances in burn care have produced an increase in the survival rate of severely burned patients. In this study of 103 children with >80% TBSA burn and >70% TBSA full-thickness admitted between 1982 and 1996, the mortality rate was 33%, providing evidence that continuing improvements in burn wound management and care of the critically ill have made a dramatic impact. This study indicates that patients who would be predicted to die by the classic criteria of age, burn size, and inhalation injury now are surviving, thus continued efforts to provide aggressive treatment and identify new areas for improvement should be emphasized.

Initially, Bull and Squire[7] defined prediction of mortality after burn based on age and burn size. At the time of the report by Bull and Squire,[7] an 80% TBSA burn in a

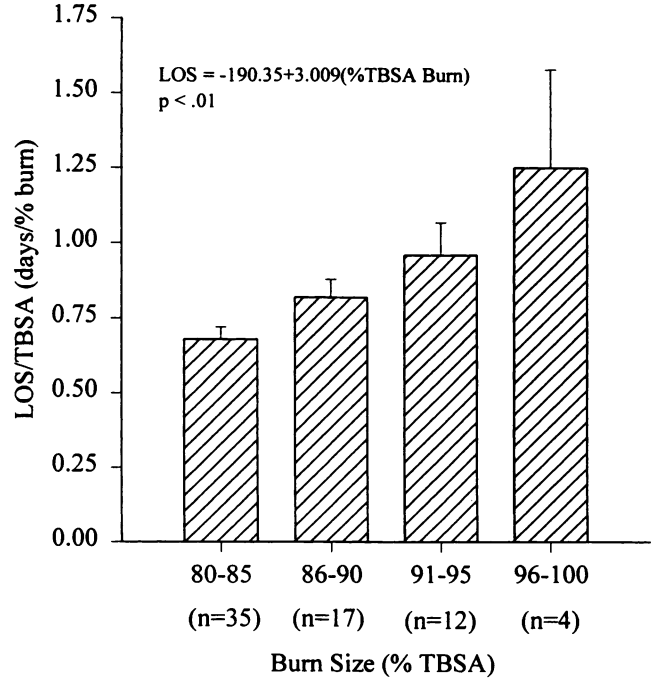

Figure 5. Length of hospital stay for various burn sizes. Larger burn size results in incrementally longer hospital stays per percent burned area as defined by the linear regression equation.

patient of any age was considered a fatal injury. Nearly 40 years later, the importance of other factors, such as preadmission shock,[1] inhalation injury,[8,9] sepsis,[10] and thrombocytopenia[11] have been identified. Over time, reports have shown sequential improvements in mortality with advances in burn care.[10,12,13] However, even with these improvements, the latest comprehensive review from the American Burn Association Patient Registry reports an 80% mortality rate for all >80% TBSA burns (range, 1–75 years of age). The rate was even higher for those younger than 20 years of age.[14] This is no longer true as shown in the current study where an improvement in mortality rates is reported for pediatric burn patients.

Patients in this study have been observed prospectively since a major change in practice at our institution in 1982. At that time, we began treating all major burns by excising completely the full-thickness area within 48 hours of admission to our hospital and documenting the progress of those who survived over time. Since our initial report in 1986,[15] we have treated more than 80 patients using the same techniques and believe that this is the major contributor to increases in survival. This conclusion is supported by several other authors.[1,2,9,10,12] In addition, no changes in mortality were shown from 1984 to 1996. Perhaps this is because of uniformity among the three surgeons practicing at the burn center during the time since the technique of massive early excision and cadaveric overgrafting has been practiced.

The relation of age and mortality shows that there is a marked increase in mortality in children younger than 2 years of age compared to those older than 2 years of age (Table 3, Equation (1), Fig. 1). This was shown to be highly significant by the univariate analysis and is corroborated in the multivariate analysis. Age was one of two variables that remained significant throughout the cumulative model development and is in keeping with larger studies of all burn sizes in larger populations.[16] This emphasizes the need to focus studies on the care of the very young. However, it must be stressed that the mortality rate was 57% even for children younger than 2 years of age, giving each of these patients a real probability of survival with this magnitude of injury.

Burn size also is a highly significant variable affecting mortality, even in this limited patient group. The increasing severity of injury by more skin loss exposes the largest burns to more operations, longer lengths of stay, and more complications, thus increasing the mortality rate. With increasing burn size, the degree of skin loss makes the available donor skin very small, and multiple operations using the same area for donor site will be required for coverage of the entire large wound area. We found that increasing burn size increases the length of stay per percentage of burn in a linear fashion. We would expect that this would rise exponentially at the extreme of burn size (>98%); however, we could not show this because of the small number of patients in this group. Cultured epidermis may lessen the load on the donor site and was used in six survivors and one nonsurvivor in this study to decrease theoretically the length of stay because of limited donor site.

In 1986, we reported that children with burns >80% TBSA collected between 1981 and 1984 with a significant inhalation injury had a mortality rate of nearly 75%.[8] In this report, 74% of the patients who died had an inhalation injury; however, 51% of the survivors also had an inhalation injury; only 42% of the patients with a significant inhalation injury died. Thus, inhalation injury alone, when considered in this massively burned pediatric population, is no longer a strong predictor of mortality. This may be because of multiple improvements in the clinical management of smoke inhalation injury during the current period or that the mortality rate for burn size is high, and the effect of inhalation injury that has been identified in smaller burns is masked within the increased risk of mortality in large burns. Another explanation is the protective effect offered by massive cutaneous injury and the subsequent immunocompromised state on development of lung injury. In animal studies, it has been shown that receiving a burn before smoke inhalation injury reduces lung damage compared to those of animals receiving the burn after smoke injury.[17]

A delay in fluid resuscitation not surprisingly is a major contributor to mortality in massive burns. The amount of fluid lost in the first 24 hours through the burn wound and into normal tissues as a result of increased systemic capillary permeability has been shown to be 2000 mL/m^2 TBSA plus 5000 mL/m^2 TBSA burned.[18] This corresponds to 530 mL/hour per m^2 TBSA for a 2.0-m^2 patient with an 87% TBSA burn. This patient, if placed in the nonsurvivor group, would fall behind by 1060 mL if resuscitation was delayed 2 hours, which is equal to 28% of the total circulating volume. Volume contraction of this magnitude may, when finally resuscitated, contribute to perfusion–reperfusion injury,[19] thus activating neutrophils and releasing free radicals that could contribute to a systemic inflammatory response. In our multivariate logistic regression analysis, the most significant contributor to mortality among the resuscitation measurements was not the amount of fluid given in the first 24 hours, but how soon after the injury fluid was started. The challenge that this represents to the burn community is to provide better communication to emergency care responders, emphasizing institution of resuscitation immediately during the treatment of the thermally injured.

In our data set, there was no difference between survivors and nonsurvivors in time of transport to our facility. More than 70% of both groups were transported within 48 hours, and >84% were transported within 96 hours.

This finding is of particular importance when the distance to specialized centers is considered, and shows that widely dispersed units can properly handle massive burns, because the time needed to transport should not affect outcome greatly. These patients were referred from locations up to 2000 miles away, and no difference could be found. These data then would suggest that adequate care at the area of injury is of vital importance before and during transport to a specialized facility. In both groups, there were some patients who were transported more than a week after injury, which makes these data follow a nonparametric distribution, and thus these data were not reported with a mean and standard error.

A lower base deficit and an increased serum osmolarity at the time of admission to our institute in nonsurvivors are consistent with shock in the early resuscitation period contributing prominently to mortality. The lower hematocrit in the nonsurvivor group is somewhat puzzling but may be explained by hemolysis, which is known to occur in massive burns[20] or in part to the higher resuscitation requirements that occur in those who initially were in shock and in whom a significant acidosis developed. The lack of concurrence of hematocrit and osmolarity would argue for the former explanation. In our analysis, serum osmolarity was a statistically stronger predictor than either base deficit or hematocrit, which may be because of the greater range of values encountered with this measurement. This underscores that the statistical finding of the greater significance of serum osmolarity should not cause underestimation of the importance of hematocrit and acid-base measurements in determining the severity of injury in burned patients.

The development of sepsis in burns historically has been a significant cause of mortality. Linares,[21] in his review of 115 pediatric burn autopsies, found that 86 (75%) of the deaths had sepsis as the primary cause of death. This still is true in this massive burn group but to a lesser extent, because only 41% of the nonsurvivors had a septic episode. Perhaps of even more significance is the fact that only 17% of the entire population studied ever became septic. We attribute this remarkable decrease in mortality to infectious causes to better use of topical and systemic antimicrobials[5] and, more importantly, to the aggressive use of early excision and grafting of the entire burn wound.

In this study, it was found that the development of serum creatinine of >2.0 mg/dL was significantly different between survivors and nonsurvivors by univariate analysis; however, we could not show the same difference using multivariate statistics. This is likely because of the relations between the variables being such that other findings of delays in resuscitation and organ failure measured in this study occurred in conjunction with an elevation in creatinine, and the other variables were associated more highly with mortality. This would cause serum creatinine >2.0 mg/dL to be less significant as a predictor of mortality than were the other variables, and for these reasons, serum creatinine >2.0 mg/dL was dropped from the multivariate regression equations. This finding should not diminish the importance of renal failure in the massively burned, because we have shown that it does occur more often in nonsurvivors, and should be avoided vigorously if possible and supported aggressively if encountered.

Not surprisingly, the percentage of time on the ventilator in the first 28 days was highly significant between groups and in predicting the probability of death, emphasizing that pulmonary failure is a major contributor to mortality in this group. Over the past several years at our institution, the predominate cause of death in massive burns has changed in distribution from that of overwhelming sepsis to complications of ventilatory support of severe pulmonary failure.[21] The large contribution of prolonged ventilator dependence and the smaller contribution of inhalation injury to prediction of mortality in this study should focus attention on pneumonia and acute lung injury from inflammatory mediators as targets for advancement in burn care. This is corroborated by the finding that inhalation injury was present in fewer than half of those patients with severe pulmonary failure in another series of burned patients.[22] The development of pneumonia has been found to add between 20% and 60% to the expected mortality of burned patients.[23]

Increasing serum creatinine, inotropic support requirement, and thromocytopenia are clear harbingers of multiorgan failure in burn patients that often lead to mortality in not only burn patients, but in all other disease and injury processes as well. Some of the early parameters are redundant with later outcomes. We found that time to intravenous access was associated highly with admission serum osmolarity, base deficit, and the development of renal failure during the hospital course. These associations should emphasize their proper use and interpretation as early indicators of organ dysfunction.

An analysis of mortality in this patient group using univariate statistics can be misleading because of interactions between the variables. Multivariate logistic regression has been used previously to examine the relations of independent variables in determining survival in burn patients.[2,24] This technique was used to compute models of prediction for mortality in the massively burned children described in this article. The equations presented can be used to calculate the risk of mortality in patients between 0 and 18 years of age with >80% TBSA burns, of which at least 70% TBSA is full-thickness. Second-degree injuries are less severe, heal faster, and require less treatment and therefore will have a better survival rate. The use of these models to predict mortality in those with primarily partial-thickness burns would overestimate mortality.

The concordance values that are reported are a measure of the difference in the observed responses from random values placed into the model, showing that the model predicts the outcome variable better than chance. The distance of this value from 50% should increase as the model improves, as has been shown here. There is no satisfactory "goodness of fit" measure for multivariate logistic regression analysis, and these reported concordance values show that the models elevate the prediction of mortality away from the range of "white noise." Another assessment of these models is a chi square value for the covariates, which for all models was <0.009.

Survival improvement of this magnitude brings the question of who should be treated and who should receive comfort care. Our data show that most children even with massive burns will live. In an example of a 5-year-old child with a 90% TBSA burn with inhalation injury, the predicted probability of death based on our equation is 57%. If initial treatment was complicated by a delay in starting an intravenous treatment for 3 hours, mortality probability would be 59%. Further, if at admission, he had a serum osmolarity of 310 mOsm/g, the predicted mortality would be 54%. During the hospital stay, if the patient required inotropic support for more than 6 hours and became septic as identified on blood culture results, his predicted mortality would be 85%. Finally, if he required ventilatory support for the first 3 weeks of his hospitalization, the predicted mortality would be 97%. Futility of medical care has been defined by some as a point where a 95% mortality can be predicted. Only the younger of our patients met that criteria if a mortality prediction was made using these equations and then only after the addition of parameters indicating sepsis and organ failure. Our data bring to light the question of the justification of only comfort care in the setting of massive burns in children and suggest that this practice should be abandoned in favor of care at a specialized burn center.

We have followed the progress of survivors in this study with systemic standardized assessments of psychosocial adaptation and functional ability to determine the long-term outcome after severe burn injury.[25] We consistently have found that the children as a group perform as well as those age-matched peers in terms of emotional and social adjustment, cognitive performance, self-esteem, and life satisfaction. Most recently, we examined the standardized assessments of survivors of burns in this study group at 1, 5, and 10 years after injury and again found in preliminary data analysis that the survivors are no more distraught psychologically and no less competent in social and academic endeavors than those of their age-matched peer group. We must, of course, continue to evaluate the outcomes over time, but the evidence to date is that these patients can achieve a quality of life that they find satisfying.

It is concluded that even the largest burn in the youngest patient should be resuscitated as early as possible after injury and the patient transferred to specialized burn centers. Here, every attempt should be made to institute aggressive treatments designed to restore the patient to society as a functioning and productive individual. The prediction equations presented are not to provide a qualification for comfort care but to provide timely warning as to what pathology needs proper attention and to give some advance insight into how and what therapy might be most beneficial. Prompt intravenous access and resuscitation, aggressive operative therapy, and the avoidance of sepsis and organ failure by meticulous critical care should enable any child with almost any burn size to live.

Acknowledgments

The authors thank Drs. A. D. Mason and Judah Rosenblatt for their generous assistance with the statistical analysis and Dr. Patricia Blakeney for her analysis of psychosocial outcomes. The authors also thank Marc Nicoli, Roque Ramirez, Marc Jeschke, Doriad Jarrar, Meelie Debroy, Sina Matin, and Edgar Pierre for their assistance in data acquisition.

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Discussion

DR. WILLIAM W. MONAFO: (St. Louis, Missouri): Dr. Griffen, Dr. Copeland, Fellows, and Guests. These are wonderful results and Dr. Herndon is to be congratulated. Financiers keep score with money, and burn surgeons tend to keep score with mortality data. The message Dr. Herndon concluded with, that there is no such thing as a hopelessly burned child in 1996 (at least on day one) is the message to take home.

The manuscript goes through a number of multivariant analyses to identify determinants of mortality. If I understand it correctly, sepsis and oliguric renal failure accounted for about three quarters of the deaths, findings that have been reported over and over again previously. It is a familiar litany.

I think that from a perspective point of view, we have to understand that these patients represent only 4% of all the patients that were treated in Galveston during this study period. Although mortality is still high, it is approaching acceptable levels, as we have just heard. This should point us, as you saw in scarred patients, toward focusing future efforts on improving life quality. Yes, mortality is still an issue, but disfiguring scars are the major source of morbidity that these patients carry through their lifetime. There is no good animal model of hypertrophic scar, and this has severely interfered with our efforts to understand and control it.

The manuscript attributes much of the good survival in these patients to the aggressive or, I might even say, hyperaggressive surgical approach that was used. These wounds were excised within 48 hours.

That approach, in patients with 85% or 90% burns, is logistically demanding and taxes hospital resources. The conclusion that the aggressive surgical approach used in these patients is mainly responsible for the mortality needs to be viewed with some skepticism. There is no control group, and it is well known that results in most illnesses improve with time. This has been especially true during the last two decades with improvements in critical and supportive care.

I cannot refrain from mentioning that 18 years ago we recorded a modest series of adult patients with an average burn size of 91.5%. We had a survival rate of 50%. This was 18 years ago, and none of these patients were treated with the method you heard today; instead, the deep burns were excised in stages over several weeks. We should, therefore, be a bit cautious about accepting the contribution of early wound excision to the mortality data.

I have just one question. In the patients less than two years of age, was blood pressure and urine output looked at early on with respect to the delay in the beginning of intravenous fluid administration?

I would like to thank the Association for the privilege of the floor.

DR. WILLIAM G. CIOFFI (Providence, Rhode Island): Dr. Griffen, Copeland, Members, and Guests. Dr. Herndon is to be congratulated for illustrating that survival from massive thermal injury, once thought to be the exception, is now common. Certainly, his results are equal to or exceed all previous published reports.

He has identified both prospective and retrospective predictors of survival, and I have several questions concerning this.

I am surprised that the time post-burn of arrival to the burn center had no impact on survival, given the observed importance of aggressive early resuscitation. I would like you to comment on that.

Does a certain percentage of the non-survivors never reach the burn center and, thus, a certain amount of bias is introduced?

All predictors require prospective validation. Have you done it either at your institution or at another?

In the paper you state that the predictor may be used to assess whether continued aggressive care is futile, and I wonder if you have applied the predictor in this manner.

Despite your excellent results, some patients still die. And given the substantial negative impact of prolonged ventilatory support, what do you propose to change improved survival in this cohort?

Lastly, as mentioned by Dr. Monafo, outcome can be measured in many ways, and you have focused on survival. I would be very interested in the functional results in terms of psychological as well as physical disability by a non-biased observer.

Thank you.