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Hypertonic Sodium Resuscitation Is Associated with Renal Failure and Death

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Objective

The use of hypertonic sodium solutions (HSS) and lactated Ringer's (LR) solution in the resuscitation of patients with major burns was compared.

Summary Background Data

Hypertonic sodium solutions have been recommended for burn resuscitation to reduce the large total volumes required with isotonic LR solution and their attendant complications.

Methods

To evaluate the efficacy of this therapy in our adult burn center, we resuscitated 65 consecutive patients with HSS (290 mEq/L Na) between July 1991 and June 1993 and compared them with 109 burn patients resuscitated with LR (130 mEq/L Na) between July 1986 and June 1988 (LR-1). A subsequent 39 patients were resuscitated with LR between September 1993 and August 1994 (LR-2).

Results

Patients receiving hypertonic sodium solutions *versus* LR-1 were similar with respect to age (46.0 *vs.* 43.6 years), total burn size (39.2% *vs.* 39.9%), incidence of inhalation injury (41.5% *vs.* 47.7%), and predicted mortality (34.6% *vs.* 30.2%). Total resuscitation volumes during the first 24 hours were lower among patients treated with HSS than those in the LR-1 group (3.9 ± 0.3 *vs.* 5.3 ± 0.2 mL/kg/%body surface area [BSA], $p < 0.05$). After 48 hours, however, cumulative fluid loads were similar (6.6 ± 0.6 *vs.* 7.5 ± 0.3 mL/kg/%BSA), and total sodium load was greater with the HSS group (1.3 ± 0.1 *vs.* 0.9 ± 0.1 mEq/kg/%BSA, $p < 0.002$). During the first 3 days after burn, serum sodium concentrations were moderately elevated in the HSS patients (153 ± 2 *vs.* 135 ± 1 mEq/L, $p < 0.001$). Patients resuscitated with HSS had a fourfold increase in renal failure (40.0 *vs.* 10.1%, $p < 0.001$) and twice the mortality of LR-1 patients (53.8 *vs.* 26.6%, $p < 0.001$). In patients resuscitated with HSS, renal failure was an independent risk factor ($p < 0.001$, by logistic regression). Analysis of these results prompted a return to LR resuscitation (LR-2). Age (41.6 ± 2.9 years), burn size (37.8 ± 3.9 %BSA), and incidence of inhalation injury (51.3%) were similar to the earlier groups. Total sodium load was less among LR-2 patients than the HSS group (0.7 ± 0.1 mEq/kg/%BSA, $p < 0.01$), but similar to the LR-1 patients. Renal failure developed in only 15.4%, and 33.3% died, similar to the LR-1 group and significantly lower than patients treated with HSS ($p < 0.001$ and $p < 0.05$, respectively).

Conclusion

Hypertonic sodium solution resuscitation of burn patients did not reduce the total resuscitation volume required. Furthermore, it was associated with an increased incidence of renal failure and death. The use of HSS for burn resuscitation may be ill advised.

The development of effective fluid resuscitation for burns has been one of the triumphs of surgical therapy over the past half century. Reports by Cope and Moore,[1] Reiss et al,[2] and Baxter et al.[3,4] have chronicled the evolution and enhanced the clinical understanding of burn resuscitation so that today, death from burn shock is routinely avoided except in those patients with the most extensive burn injuries. There are two basic approaches to burn resuscitation commonly used today. One is based on the use of isotonic salt solutions, principally lactated Ringer's (LR) solution.[4,5] This approach has been used extensively worldwide, has been endorsed by a National Institutes of Health consensus conference,[6] and is included in the American College of Surgeons' Advanced Trauma Life Support Course and in the American Burn Association's Advanced Burn Life Support Course. The other approach to burn shock resuscitation developed from the studies by Moyer et al.[7] They demonstrated the importance of the sodium ion in the resuscitation fluid and found that sodium load rather than the fluid volume was the major determinant of effective resuscitation. Using solutions with a sodium concentration of 250 mEq/L, they were able to achieve effective physiologic resuscitation with a lower total volume in the first 24 hours.[8–10] Other studies have documented the safety of this approach,[11] but not all authors have observed a net reduction in fluid requirements.[12]

Although both approaches to burn resuscitation are effective in preventing death from burn shock, to date, no studies have compared the clinical course of patients with each formula. At the University of Alabama Burn Center, we have used both isotonic and hypertonic fluid regimens in resuscitating patients with acute burn injury for the last 8 years. The purpose of this study was to review our experience and to compare the clinical course and outcome of patients resuscitated with an isotonic solution (LR) and with hypertonic sodium solutions (HSSs).

METHODS

Patients

Individuals included in this study consist of all patients admitted to the surgical intensive care unit (SICU) at the University of Alabama Hospital for burn shock resuscitation during one of three time periods. In all cases, the patient's overall burn care was managed by one burn surgeon (ARD). Wound care, the timing of burn excision and grafting, occupational and physical therapy, and nutritional support generally have been uniform over the time period of the study, except for an increasing emphasis on early enteral nutrition and earlier wound excision and skin grafting.

The three time periods included in this study were July 1986 through June 1988, July 1991 through June 1993, and September 1993 through August 1994. During these time periods, other faculty members of the Section of Trauma, Burns, and Surgical Critical Care (PQB, RCT, and LWR) participated in burn shock resuscitation and other aspects of the patient's critical care. During the first time period, all patients were resuscitated with lactated Ringer's solution (LR-1). During the second time period, hypertonic salt solutions (HSS) were used. In the third time period, patients were resuscitated again with lactated Ringer's solution (LR-2).

Fluid Resuscitation

Resuscitation of LR-1 and LR-2 patients was performed exclusively with lactated Ringer's solution, (Na = 130 mEq/L) with initial fluid needs estimated by using the Parkland formula of 4 mL/kg body weight/% body surface area (BSA) burn. Adjustments in resuscitation were made based on clinical response as manifested primarily by urine output. After the initial 24 hours of resuscitation, fluids generally were changed to a hypotonic solution (i.e., D5W), with or without colloid supplementation (i.e., 5% albumin).

Initial resuscitation of HSS patients by emergency personnel and referring physicians was with LR exclusively. However, on arrival at UAB, resuscitation was changed to a hypertonic solution: LR plus 160 mEq/L sodium acetate (NaAc, [Na] = 290 mEq/L). Initial fluid rate was based on the volume of hypertonic fluid calculated to deliver the same sodium load as estimated by the Parkland formula (0.52 mEq/kg body weight/% BSA burn). Frequent arterial blood gas and serum electrolyte values were obtained. Adjustments in fluid administration were based on clinical criteria that included acid-base status and urine output. The LR-NaAc solution was discontinued if serum bicarbonate level exceeded 30 mEq/L and resuscitation was continued with 3% NaCl (Na = 513 mEq/L), adjusted to meet similar sodium loads, pro-

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Table 1. DEFINITIONS OF ORGAN SYSTEM FAILURE

Cardiovascular system failure	Heart rate <55
	Mean arterial pressure <60 mm Hg
	Ventricular tachycardia
	Ventricular fibrillation
	Arterial pH <7.25 (with pO2 <50)
	Inotrope for CI <3.0 or MAP <60 mm Hg
Pulmonary system failure	Respiratory rate <6, >30
	Arterial pCO2 >50 mm Hg
	Ventilator dependence >4 days
	ARDS-PEEP >10 cm H2O or FiO2 >50%
Renal system failure	Urine output <480 mL/24 hrs
	BUN >100 mg/dl
	Serum creatinine >3.0 mg/dl
	Need for hemodialysis
Intestinal system failure	Ileus or feeding intolerance >5 days
	Stress ulcer requiring transfusion
	Acalculous cholecystitis
Hematologic system failure	WBC <1000
	Platelet <20000
	Hematocrit <20%
	PT/PTT >25% control
Hepatic system failure	Total Bilirubin >3.0
	SGOT twice normal (>80)
	SGPT twice normal (>90)
	Alkaline phosphatase twice normal (>230)
	GGT twice normal (>130)

vided the serum sodium remained below 160 mEq/L. If serum Na approached 160 mEq/L, resuscitation fluid was changed to an isotonic solution, usually LR.

Patient Information

The records of all burn patients cared for in the SICU in the first two time periods were reviewed, and patients treated in the third time period were followed prospectively. Demographic data for all patients were collected, including burn size, presence or absence of inhalation injury, development of pneumonia, and outcome. Organ system failure was identified using criteria summarized in Table 1. Laboratory data at admission, 24 hours, and 48 hours after injury were reviewed. Serum sodium and serum osmolarity values were recorded for the first 7 days after injury. The resuscitation fluid type and volume administered were recorded for the first and second 24-hour periods after injury. Urine output data were likewise noted.

For LR-1 patients, presence or absence of inhalation injury was based on clinical criteria, including presence of facial burns, expectoration of carbonaceous sputum, history of burn within an enclosed space, and ultimately, on the clinical judgment of the admitting physician. The suspicion of the presence or absence of inhalation injury for HSS and LR-2 patients was based on clinical criteria as in LR-1; however, definitive diagnosis in the more recent groups was established by fiberoptic bronchoscopy. Bronchoscopic criteria for inhalation injury included mucosal erythema, edema, ulceration, and submucosal hemorrhage with or without carbon deposition in the tracheobronchial tree.[13]

Calculations

In an attempt to standardize injury severity, mortality prediction was calculated based on the stepwise logistical regression analysis generated from the 1980–1984 patient experience at the U.S. Army Institute of Surgical Research, in which patient age, burn size, presence or absence of inhalation injury, and pneumonia were identified as major determinants of outcome.[14] For each group, mean values for data were calculated, as well as

Table 2. GENERAL PATIENT DEMOGRAPHICS

	LR-1	HSS	LR-2
N	109	65	39
Age (yrs)	43.6 ± 1.9	46.0 ± 2.5	41.6 ± 2.9
TBSA burn, %	39.9 ± 2.0	39.2 ± 2.7	37.8 ± 3.9
Inhalation injury frequency, % (N)	47.7 (52)	41.5 (27)	51.3 (20)
Pneumonia frequency, % (N)	11.9 (13)	29.2 (19)*	10.3 (4)†
Observed mortality, % (N)	26.6 (29)	53.8 (35)*	33.3 (13)†
Predicted mortality, % (N)	30.2 (31)	34.6 (23)	28.3 (11)
95% CI, %	23.4–36.9	25.6–43.6	17.0–39.6

Age, burn size: mean ± SEM.
CI: confidence interval.
* $p < 0.05$, LR-1 *vs.* HSS.
† $p < 0.05$, HSS *vs.* LR-2.

Table 3. FLUID RESUSCITATION DATA

	LR-1	HSS	LR-2
N	109	65	39
Fluid intake (mL/kg/%BSA)			
24 hrs	5.25 ± 0.19	3.94 ± 0.34*	3.91 ± 0.31
48 hrs	2.23 ± 0.14	2.65 ± 0.39	2.04 ± 0.23
Total (0–48 hrs)	7.48 ± 0.29	6.59 ± 0.64	5.95 ± 0.48
Na intake (mEq/kg/%BSA)			
24 hrs	0.68 ± 0.02	0.85 ± 0.08*	0.51 ± 0.04†
48 hrs	0.24 ± 0.02	0.40 ± 0.06*	0.17 ± 0.02†
Total (0–48 hrs)	0.92 ± 0.04	1.25 ± 0.13*	0.68 ± 0.05†
Urine Output (ml/kg/hr)			
24 hrs	1.20 ± 0.07	1.07 ± 0.07	1.01 ± 0.09
48 hrs	1.29 ± 0.09	1.04 ± 0.08*	0.97 ± 0.10

All values: mean ± SEM.
* $p < 0.05$, LR-1 *vs.* HSS.
† $p < 0.01$, HSS *vs.* LR-2.

Table 4. INCIDENCE OF ORGAN SYSTEM FAILURE

	LR-1	HSS	LR-2
N	109	65	39
Cardiovascular, % (N)	38.5 (42)	58.5 (38)*	30.8 (12)†
Pulmonary, % (N)	37.6 (41)	67.7 (44)*	30.8 (12)†
Renal, % (N)	10.1 (11)	40.0 (26)*	15.4 (6)†
Intestinal, % (N)	14.7 (16)	10.8 (7)	10.3 (4)
Hematologic, % (N)	15.6 (17)	27.7 (18)	17.8 (7)
Hepatic, % (N)	35.8 (39)	69.2 (45)*	48.7 (19)

* $p < 0.01$, LR-1 *vs.* HSS.
† $p < 0.01$, HSS *vs.* LR-2.

standard error of mean (SEM) using a commercial statistical software package (StatView 4.01, Abacus Concepts, Inc., Berkley, CA). Significant differences between groups were determined by a t test. For predicted mortality values, 95% confidence intervals (CI) were calculated. Analysis of important factors in patient outcome was determined using the chi square test. Equations for survival probability were derived by stepwise logistic regression analysis.

RESULTS

There were 109 patients from July 1986 to June 1988 (LR-1), 65 patients from July 1991 to June 1993 (HSS) and 39 patients from September 1993 to August 1994 (LR-2) requiring admission to the SICU (Table 2). Initial data analysis compared HSS and LR-1 patients.

Both groups were similar with respect to age (46.0 *vs.* 43.6 years; HSS *vs.* LR-1), total burn size (39.2% *vs.* 39.9%), and incidence of inhalation injury (41.5% *vs.* 47.7%); however, the incidence of pneumonia was significantly higher in the HSS group (29.2% *vs.* 11.9%, $p = 0.004$). Despite the difference in pneumonia incidence, the predicted mortality of the two groups was similar (34.6% *vs.* 30.2%). However, HSS had a significantly higher observed mortality rate than that of the earlier group (53.8% *vs.* 26.6%, $p < 0.001$).

Resuscitation data for the first and second 24-hour postburn periods, as well as cumulative data for the first 48 hours postburn are summarized in Table 3. During the initial 24 hours of resuscitation, total fluid load was significantly less for the HSS group than for the LR-1 group (3.94 *vs.* 5.25 mL/kg/%BSA, $p < 0.001$). There were no significant differences in fluid administration during the second 24 hours (2.65 *vs.* 2.23 mL/kg/%BSA), and 48-hour cumulative fluid loads also failed to achieve statistical significance between HSS and LR-1 (6.59 *vs.* 7.48 mL/kg/%BSA). Calculated sodium loads were significantly higher in HSS patients at 24 hours (0.85 *vs.* 0.68 mEq/kg/%BSA, $p = 0.013$), at 48 hours (0.40 *vs.* 0.24 mEq/kg/%BSA, $p = 0.002$), and during the entire resuscitation period when compared with the LR-1 patients (1.25 *vs.* 0.92 mEq/kg/%BSA, $p = 0.002$). Urine output was not significantly different between the two groups in the first 24 hours after burn (1.07 *vs.* 1.20 mL/kg/hour); however, patients in the HSS group had a significantly lower urine output during the second hospital day (1.04 *vs.* 1.29 mL/kg/hour, $p = 0.039$). In both groups, average urine outputs actually were higher than the goal of 0.5–1.0 mL/kg/hour.

The groups were examined with respect to the incidence of organ failure, as summarized in Table 4. Hypertonic sodium solutions and LR-1 were similar with respect to the incidence of intestinal failure (10.8% *vs.*

Table 5. DEMOGRAPHIC DATA FOR RENAL FAILURE *VS.* NO RENAL FAILURE GROUPS

	LR-1		HSS	
	No RF	RF	No RF	RF
N	98	11	39	26
Age, years	42.3 ± 2.0	55.5 ± 6.1*	40.3 ± 3.1	54.5 ± 3.6*
TBSA burn, %	37.6 ± 1.9	59.5 ± 8.0†	38.5 ± 3.6	40.4 ± 4.2
Inhalation injury frequency, % (N)	49.8 (43)	81.8 (9)†	38.5 (15)	46.2 (12)
Pneumonia frequency, % (N)	10.2 (10)	27.3 (3)	7.7 (3)	61.5 (16)†
Observed mortality, % (N)	19.4 (19)	90.9 (10)†	25.6 (10)	96.2 (25)†
Predicted mortality, %	25.0 (24)	76.8 (8)	22.8 (9)	52.3 (14)
95% CI, %	18.5–31.5	58.7–94.9	12.1–33.5	38.6–66.0

Age, burn size: mean ± SEM.
RF: renal failure.
p values are for No RF *vs.* RF subsets for each group.
* $p < 0.05$.
† $p < 0.001$.

Table 6. FLUID RESUSCITATION DATA FOR RENAL FAILURE *VS.* NO RENAL FAILURE GROUPS

	LR-1		HSS	
	No RF	RF	No RF	RF
N	98	11	39	26
Fluid intake (mL/kg/%BSA)				
24 hrs	5.29 ± 0.20	4.86 ± 0.55	3.42 ± 0.38	4.72 ± 0.63
48 hrs	2.29 ± 0.14	1.74 ± 0.60	2.75 ± 0.62	2.50 ± 0.31
Total (0–48 hrs)	7.58 ± 0.30	6.61 ± 0.99	6.16 ± 0.97	7.22 ± 0.69
Na intake (mEq/kg/%BSA)				
24 hrs	0.68 ± 0.03	0.63 ± 0.07	0.70 ± 0.09	1.08 ± 0.15*
48 hrs	0.24 ± 0.02	0.22 ± 0.09	0.36 ± 0.07	0.46 ± 0.08
Total (0–48 hrs)	0.90 ± 0.04	0.85 ± 0.15	1.05 ± 0.15	1.53 ± 0.22*
UOP (mL/kg/hr)				
24 hrs	1.25 ± 0.07	0.78 ± 0.29*	1.15 ± 0.10	0.95 ± 0.10
48 hrs	1.34 ± 0.08	0.85 ± 0.43	1.04 ± 0.10	1.02 ± 0.13

All values: mean ± SEM.
p values are for No RF *vs.* RF subsets for each group.
* $p < 0.05$.

14.7%) and hematologic failure (27.7% *vs.* 15.6%). However, HSS patients had a significantly higher incidence of cardiovascular failure (58.5% *vs.* 38.5%, $p = 0.011$), pulmonary failure (67.7% *vs.* 37.6%, $p < 0.001$), and hepatic failure (69.2% *vs.* 35.8%, $p < 0.001$). Most striking was the fourfold greater incidence of renal failure among HSS patients (40.0% *vs.* 10.1%, $p < 0.001$) when compared with LR-1 patients.

The data were further analyzed with respect to the presence or absence of renal failure; Table 5 summarizes these results. Patients who subsequently developed renal failure were significantly older than the subset of patients without renal failure in both the LR-1 group (55.5 *vs.* 42.3 years, $p = 0.038$) and the HSS group (54.5 *vs.* 40.3 years, $p = 0.005$). In the LR-1 group, other significant prognostic factors included a larger burn size (59.5% *vs.* 37.6%, $p < 0.001$) and higher frequency of inhalation injury (81.8% *vs.* 49.8%, $p = 0.017$) among patients who developed renal failure. In contrast, HSS patients with renal failure had a significantly higher frequency of pneumonia than HSS patients without renal failure (61.5% *vs.* 7.7%, $p < 0.001$); however, the severity of the initial injuries between the two subsets treated during this time were comparable because there was no difference in burn size (40.4% *vs.* 38.5%) or frequency of inhalation injury (46.2% *vs.* 38.5%). Based on these prognostic factors, predicted mortalities were greater for patients who developed renal failure when compared with those without renal failure in the LR-1 (76.8%; 95% CI, 58.7% to 94.9% *vs.* 25.0%; 95% CI, 18.5% to 31.5%) and the HSS groups (52.3%; 95% CI, 20.6% to 66.0% *vs.* 22.8%; 95% CI, 12.1% to 33.5%). More importantly, the presence of renal failure had a profound influence on the outcome of HSS patients. Although the observed mortality in LR-1 patients with renal failure was not significantly different from the value predicted (90.9% *vs.* 76.8%; 95% CI, 58.7% to 94.9%), the observed mortality in HSS patients with renal failure was significantly higher than predicted (96.2% *vs.* 52.3%; 95% CI, 20.6% to 66.0%). Among HSS patients, the development of renal failure was highly predictive of mortality when the chi square test was applied ($p < 0.001$). Additionally, when subjected to logistic regression, renal failure was found to be an independent prognostic factor in these patients ($p = 0.007$). This was true for the LR-1 group as well, but with a less profound influence on patient outcome ($p = 0.029$).

Because renal failure appeared to be a significant contributor to the difference in patient outcome between groups, we examined the association between fluid and sodium loads and the development of renal failure (Table 6). For the LR-1 group, fluid requirements were similar among patients with and without renal failure at 24 hours (5.29 *vs.* 4.86 mL/kg/%BSA) and 48 hours (2.29 *vs.* 1.74 mL/kg/%BSA). Sodium loads also were similar at 24 hours (0.68 *vs.* 0.63 mEq/kg/%BSA) and 48 hours (0.24 *vs.* 0.22 mEq/kg/%BSA) after burn. For HSS patients, fluid volume was higher in the first 24 hours (4.72 *vs.* 3.42 mL/kg/%BSA) and for the entire resuscitation period (7.22 *vs.* 6.16 mL/kg/%BSA) in patients who subsequently developed renal failure, but these differences were not statistically significant. However, patients who developed renal failure received a significantly greater amount of sodium in the first 24 hours than those without renal failure (1.08 *vs.* 0.70 mEq/kg/%BSA, $p = 0.021$). This relationship was similar for the initial 48-hour postburn period (1.53 *vs.* 1.05 mEq/kg/%BSA, $p = 0.033$). Mean urine outputs were greater than 0.5 mL/kg/hour in all patients during all time intervals, indicating more than adequate resuscitation for all groups.

Table 7. SERUM SODIUM DATA FOR RENAL FAILURE *VS.* NO RENAL FAILURE GROUPS

	LR-1		HSS	
	No RF	RF	No RF	RF
N	98	11	39	26
Serum Sodium (mEq/L)				
Admission	138.7 ± 0.4	136.7 ± 1.5	139.5 ± 0.5	139.8 ± 0.8
HD1	137.4 ± 0.3	138.8 ± 3.8	149.0 ± 1.8	158.6 ± 2.2*
HD2	134.9 ± 0.4	135.6 ± 1.9	149.4 ± 2.0	158.3 ± 1.9*
HD3	134.1 ± 0.6	137.0 ± 2.5	146.3 ± 2.1	154.3 ± 2.3*
HD4	135.1 ± 0.6	137.2 ± 3.0	145.2 ± 2.3	151.5 ± 2.3
HD5	135.7 ± 0.7	138.4 ± 3.3	141.7 ± 1.9	150.2 ± 2.5*
HD6	136.1 ± 0.7	138.2 ± 2.5	141.5 ± 2.1	148.2 ± 2.6*
HD7	135.2 ± 0.8	138.2 ± 2.2	140.3 ± 1.9	146.2 ± 2.3
ΔNa	0.5 ± 0.5	3.7 ± 2.4	10.9 ± 1.9	23.5 ± 2.2†

All values: mean ± SEM.
ΔNa = (peak Na during first post-burn week) (admission Na).
p values are for No RF *vs.* RF subsets for each group.
* $p < 0.05$.
† $p < 0.001$.

When the mean serum sodium concentrations for the first week after burn (Table 7) were examined for each of these subgroups, no significant rise in serum sodium was seen in LR-1 patients, and no significant differences between serum sodium were noted between patients with and without renal failure (Fig. 1). However, this profile was quite different in the HSS group (Fig. 2). With HSS resuscitation, mean serum sodium values peak during the first 48 hours after burn, as expected. These values slowly decreased over the next several days. However, when comparing the groups with and without renal failure, the patients who eventually developed renal failure had a more rapid and persistent rise in mean serum sodium values. These differences persisted through much of the first postburn week. The magnitude of hypernatremia (ΔNa) was calculated as the difference between serum sodium at the time of admission and peak serum sodium during the first postburn week. The value for ΔNa was significantly higher for HSS patients (15.9 *vs.* 0.8 mEq/L, $p < 0.001$). This difference was even greater for the subset of HSS patients who developed renal failure when compared with patients without renal failure (23.5 *vs.* 10.9 mEq/L, $p < 0.001$). Using the chi square test, ΔNa was highly predictive of the subsequent development of renal failure in HSS patients ($p < 0.001$). This difference in ΔNa was not observed among LR-1 patients (3.7 *vs.* 0.5 mEq/L).

A similar pattern in serum osmolarity was observed for each group (Table 8; Figs.3 and 4). When compared with patients without renal failure, mean serum osmolarity of patients who developed renal failure were similar at the time of admission, but became significantly greater as early as the first postburn day. Mean osmolarity remained significantly elevated throughout the first postburn week. Although serum osmolarity was not measured in LR-1 patients, there was no comparable difference in calculated serum osmolarity (Osm = 2[Na] + [BUN]/2.8 + [glucose]/18) within this group of patients. The magnitude of hyperosmolarity (ΔOsm) also was significantly greater among HSS patients who developed renal failure compared with patients treated during the same time period without renal failure (21.5 *vs.* 9.4 mOsm/L, $p = 0.005$). This difference was not significantly different in the earlier group (9.1 *vs.* 3.2 mOsm/L). The HSS patients who developed renal failure did so relatively early in their hospitalization (median, postburn day 7). In contrast, the median onset of renal failure for LR-1 patients was 12 days after injury (Fig. 5).

A stepwise logistic regression analysis was performed to analyze factors important in determining mortality for both groups. The probability of survival for patients in each group is expressed by the equations in Table 9. When renal failure is considered as a prognostic factor, the presence of inhalation injury and the development of pneumonia are no longer statistically important in predicting patient outcome in either group. The coefficients for the renal failure variable in these equations further emphasizes its relative greater influence on patient outcome among patients receiving HSS.

Preliminary results from the comparison of outcomes in LR-1 and HSS prompted a return to LR burn resuscitation, using similar guidelines and endpoints of resuscitation adequacy as employed with LR-1. The results of the first 39 consecutive patients treated from September 1993 to August 1994 (LR-2) are compared with patients resuscitated with HSS (Table 2). The mean age of the

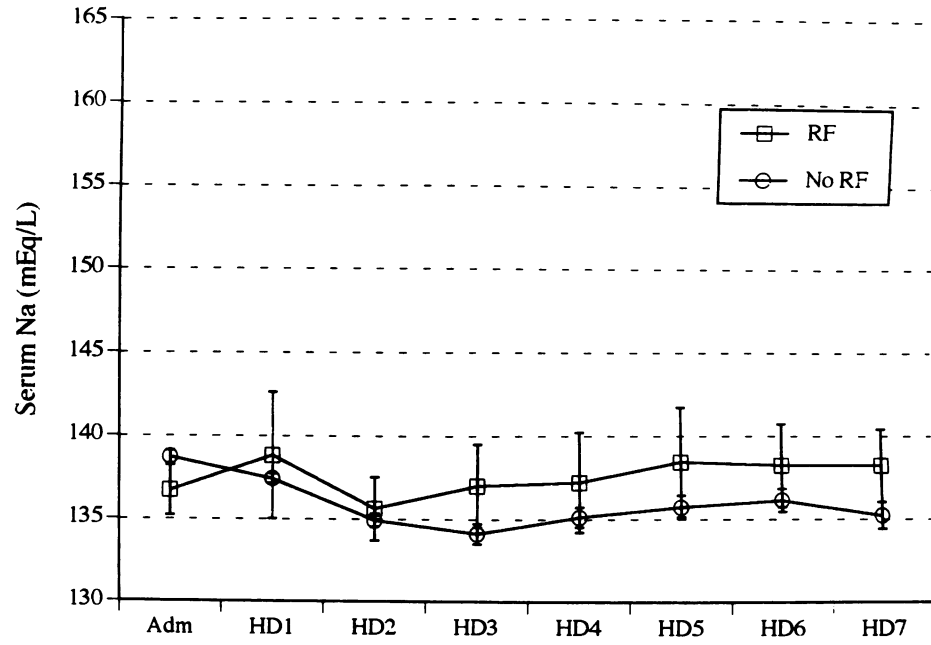

Figure 1. Mean serum sodium is similar between patients with and without renal failure for patients resuscitated with lactated Ringer's solution.

patients (41.6 ± 2.9 years), size of burn (37.8 ± 3.9 %BSA), and incidence of inhalation injury (51.3%) were similar between all groups, whereas the incidence of pneumonia was lower in the most recent group compared with the LR-1 group and was significantly lower than HSS patients (10.3% *vs.* 29.2%, p = 0.018). Fluid intake also was similar in both the first (3.91 ± 0.31 mL/kg/%BSA) and second (2.04 ± 0.23 mEq/kg/%BSA 24-hour periods (Table 3). As with LR-1, the amount of sodium administered in the first 24 hours was significantly lower than that administered with HSS resuscitation (0.51 *vs.* 0.85 mEq/kg/%BSA, p = 0.008), and this difference persisted during the second postburn day (0.17 *vs.* 0.40 mEq/kg/%BSA, p = 0.002). The incidence of renal failure (15.4% *vs.* 40.0%, p = 0.009), cardiovascular failure (30.8% *vs.* 58.5%, p = 0.002), and pulmonary failure (30.8% *vs.* 67.7%, p = 0.001) were significantly lower among LR-2 patients compared with HSS patients, but similar to that of the earlier LR-1 patients (Table 4). Observed mortality was similar to that predicted by the Shirani model (28.3%; 95% CI, 17.0% to 39.6%), and it was significantly less than the observed

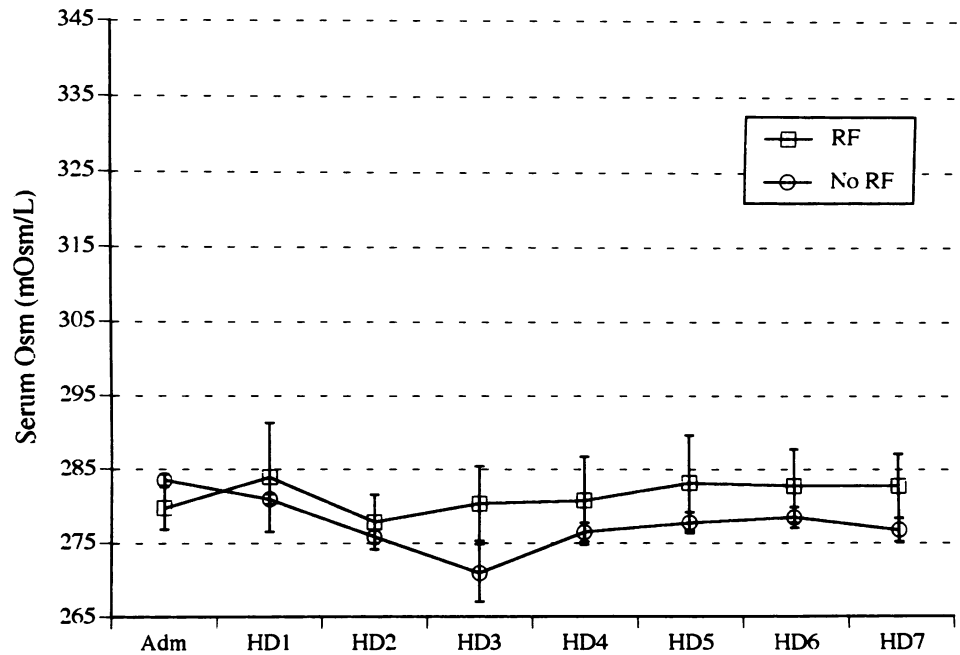

Figure 2. Mean serum osmolarity is similar between patients with and without renal failure for patients resuscitated with lactated Ringer's solution.

Table 8. SERUM OSMOLARITY DATA FOR RENAL FAILURE *VS.* NO RENAL FAILURE GROUPS

	LR-1		HSS	
	No RF	RF	No RF	RF
N	98	11	39	26
Serum Osmolarity (mOsm/L)				
Admission	283.5 ± 0.8	279.7 ± 2.9	285.0 ± 1.0	285.8 ± 1.5
HD1	280.9 ± 0.7	283.9 ± 7.4	307.0 ± 3.6	332.8 ± 3.5†
HD2	275.8 ± 0.9	277.8 ± 3.7	311.5 ± 4.2	336.8 ± 4.6†
HD3	270.9 ± 3.9	280.3 ± 5.1	302.0 ± 4.5	329.0 ± 5.1†
HD4	276.4 ± 1.3	280.7 ± 6.0	298.6 ± 4.8	324.0 ± 4.7†
HD5	277.7 ± 1.4	283.1 ± 6.5	294.3 ± 4.2	325.6 ± 5.5†
HD6	278.4 ± 1.4	282.7 ± 5.0	294.2 ± 4.3	319.4 ± 6.2†
HD7	276.7 ± 1.6	282.7 ± 4.4	293.7 ± 4.8	321.8 ± 6.2†
ΔOsm	3.2 ± 0.7	9.1 ± 4.0	9.4 ± 1.8	21.5 ± 4.1*

All values: mean ± SEM.
ΔOsm = (peak Osm during first post-burn week) (admission Osm).
p values are for No RF *vs.* RF subsets for each group.
* $p < 0.01$.
† $p < 0.001$.

mortality of patients resuscitated with HSS (33.3% *vs.* 53.8%, $p = 0.032$).

DISCUSSION

As stated by Pruitt, "the goal of resuscitation [of burned patients] should be the maintenance of vital organ function at the least immediate or delayed physiologic cost."[15] Hypertonic fluids were introduced in an attempt to ameliorate early complications associated with large volume infusion often required during "traditional" resuscitation with LR solution. Proponents suggested that patients could be adequately resuscitated either by administration of large volumes of isotonic sodium solutions or lesser volumes of hypertonic sodium solutions. Patients with extremely large burns and individuals with impaired cardiovascular reserve are among those expected to benefit most from lower volume resuscitation. Recommended guidelines for HSS resuscitation include maintaining the patient's serum sodium below 160 mEq/L, serum osmolarity below 340 mOsm/L, and urine output between 0.5 and 1.0 mL/kg/hour.[10,12] When these guidelines are adhered to, a number of series have described fewer pulmonary complications,[16] shorter postburn ileus,[17] and diminished postburn edema.[11] These observations, however, have been largely subjective and somewhat inconsistent. Improvement in overall mortality also has been suggested,[10,16] but there has been concern in the literature as to the potential for organ system dysfunction associated with hypernatremia and hyperosmolarity. Remarkably, there have been no studies directly comparing the ultimate outcomes of these two approaches to burn resuscitation. Furthermore, there is little information regarding the long-term effects of hypernatremia and hyperosmolarity in critically ill patients. Classically, complications of hypernatremia have focused primarily on its effects on the central nervous system. Acute hypernatremia can lead to dehydration and shrinkage of the brain, causing stretching and tearing of bridging dural vessels and often resulting in subarachnoid or subdural hemorrhage.[18] In addition, fatal cases of cerebral edema and permanent neurologic damage have occurred when hypernatremia has been corrected too rapidly.[19] Acute hypernatremia is associated with significant morbidity and mortality, particularly in older patients. One series of elderly patients reported a 60–70% mortality rate when serum sodium rose above 160 mEq/L.[20]

The current study was not prospective and randomized, and the patient groups in our study were separated in time. However, age, burn size, and incidence of inhalation injury were equivalent for all groups, and these are commonly regarded as the most important determinants of outcome in burn patients. The same burn surgeon directed all aspects of wound care and general management for all patients in both time periods. Fluid therapy was tightly monitored and supervised by faculty level physicians for all patients. Goals for standard resuscitation and specific guidelines for the use of HSS were met. Because of historical trends in burn care and overall progress in surgical critical care, one would expect improvement in patient outcome over the course of the study if the resuscitation methods were equivalent. The patients receiving HSS for burn resuscitation, however,

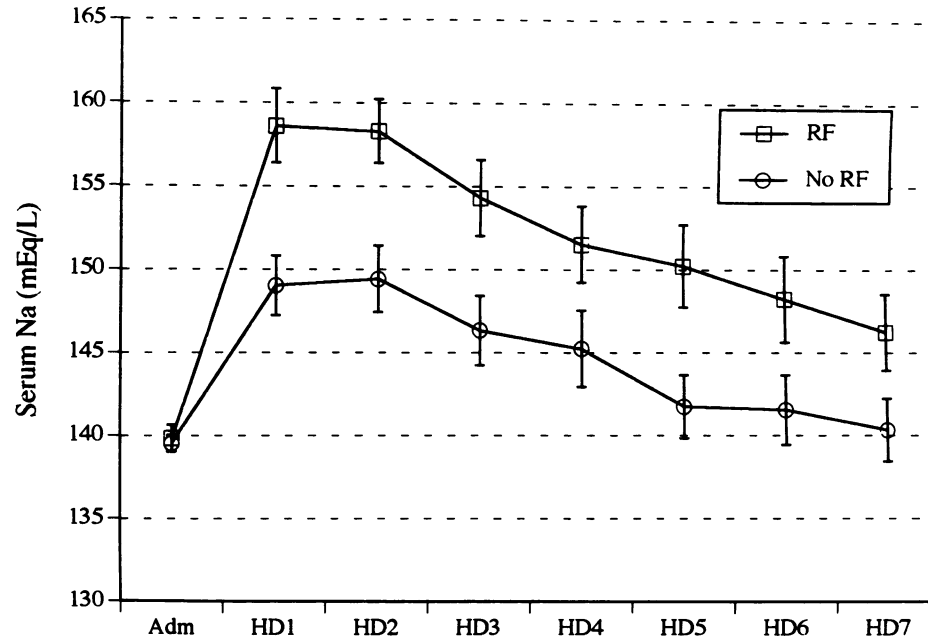

Figure 3. Mean serum sodium is significantly greater for patients developing renal failure when resuscitated with hypertonic sodium solution.

had a higher mortality than a group of intra-institutional historical controls and higher mortality than that predicted for the group based on age, burn size, presence of inhalation injury, and pneumonia as described by Shirani.[14] Because inhalation injury was confirmed by bronchoscopic criteria among patients treated more recently, the incidence of inhalation injury may have been overestimated in LR-1 patients. This could contribute to a worsened predicted mortality for that group. However, the incidence of false-positive clinical diagnoses of inhalation injury is not well described, and the potential for false-negative diagnoses exists as well. In the report by Shirani, a logistic regression equation was derived to predict the presence of inhalation injury based on clinical criteria (age, burn size, presence of facial burns, and history of injury in an enclosed space) and ultimately diagnosed either by bronchoscopy or xenon scan. When these factors are considered in our patients, the diagnosed incidence of inhalation injury for LR-1 is similar to that predicted (47.7% *vs.* 44.7%; 95% CI, 38.2% to

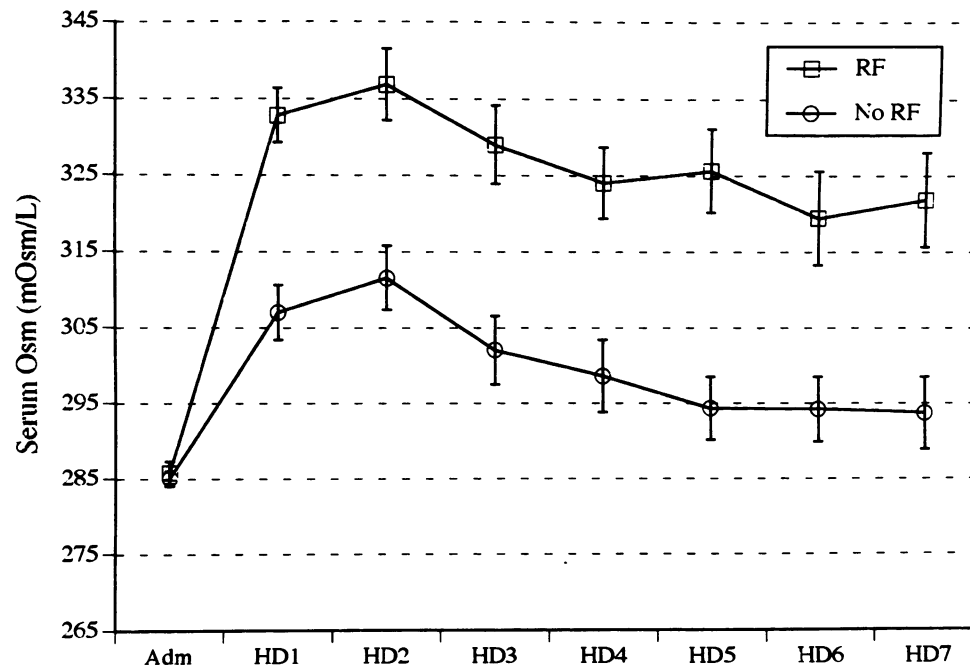

Figure 4. Mean serum osmolarity is significantly greater for patients developing renal failure when resuscitated with hypertonic sodium solution.

51.1%). Therefore, we do not believe the differences in expected and observed mortality is explained by the potential diagnostic bias between the groups.

Patients with major burns respond in a predictable physiologic manner after resuscitation with isotonic fluids such as LR. These patients exhibit a mild hyponatremia associated with a low-to-normal serum osmolarity. In the postresuscitation phase, adequate urine flow associated with a natriuresis is observed, suggesting euvolemia (normal volume status) and an absence of total body sodium deficit.[21] Because increased levels of antidiuretic hormone (ADH) have been found in patients after burn resuscitation, a syndrome of inappropriate ADH secretion was thought to exist.[22] In a more recent report, however, Cioffi et al. documented depressed total blood volumes in burn patients after resuscitation, which in turn would appropriately promote ADH release.[23]

After resuscitation with HSS, this response may be further augmented. Because hypovolemia and increased serum osmolarity both are potent stimuli of ADH release, one would expect significant elevations in ADH levels in these patients. In fact, elevated ADH levels have been documented after hypertonic resuscitation, and these levels do not decline toward normal until approximately 5 days after injury. Simultaneous measurements of atrial natriuretic peptide (ANP) revealed serum levels of ANP were low to normal at admission, with the absolute value inversely related to burn size.[24] By the fourth postburn day, ANP levels increased above normal and remain elevated for several days.[23,24] It has been observed that ADH inhibits ANP release,[24] and one might postulate that the increase in ANP occurs only after ADH levels decline. It also has been shown that serum levels of aldosterone are elevated in the early period after burn and that these levels remain persistently elevated for a week or more after injury.[23,25] Therefore, relative hypovolemia and hyperosmolarity after hypertonic resuscitation could act concomitantly to stimulate increased ADH levels and ANP inhibition. At the same time, these patients exhibit significant hyperaldosteronism. As a result, patients would be expected to develop avid and prolonged sodium retention. After hypertonic resuscitation, patients with significant hypernatremia and hyperosmolarity would be unable to excrete sodium. Therefore, serum sodium and osmolarity may remain persistently elevated, even if the tonicity of infused fluids are changed appropriately. The patient would then be subjected to the effects of prolonged exposure to potentially injurious levels of hypernatremia and hyperosmolarity. In addition, while resuscitation fluid requirements in the first 24 hours are relatively lower in patients receiving HSS, persistent hypernatremia may necessitate delayed administration of large volumes of hypotonic fluids. Proposed advantages of HSS resuscitation related to edema, pulmonary complications, and intestinal ileus may be negated by this delayed volume infusion.

These phenomena were observed in our patients. Significant hypernatremia was a common finding in patients receiving HSS, particularly in the patients who eventually developed renal failure. Also, mean serum sodium values did not fall significantly until the third to fourth postburn day. Serum osmolarity were found to follow a similar pattern, although an even longer period of time elapsed before normalization of values was observed. Patients receiving HSS trended toward increased fluid requirements by the second postburn day compared with patients receiving LR, and total fluid loads were not significantly different at the end of 48 hours.

What level of serum sodium constitutes "toxic" hypernatremia, and what is the pathophysiology of hypernatremia-associated organ failure? Shimizaki et al. have reported an inverse relationship between serum sodium levels and urine output during burn resuscitation with hypertonic saline.[16] They had difficulty maintaining an adequate urine output in their patients when serum sodium values were greater than 160 mEq/L. They recommend a shift from HSS to isotonic fluid when serum sodium rises above that level to prevent hypernatremia-associated oliguria; however, they emphasized that this transition should be gradual, to prevent cell swelling, which might occur with a rapid decline in serum osmolarity. In addition, they hypothesized that the function of the cell membrane Na pump is impaired in burned tissues, which would permit ready entry of sodium into the cell. Ono et al. have observed impaired Na-K ATPase function associated with a cutaneous burn in a rabbit model.[26] This phenomenon was partially reversible with correction of systemic acidosis through resuscitation. In another animal model, Feifel et al. reported uncoupling of mitochondrial respiration, presumably from transmembrane ATPase dysfunction.[27] Their data suggested unidentified humoral factors as being responsible for this phenomenon, implying these abnormalities are present in uninjured tissue as well. These transmembrane protein abnormalities affect the ability of hypertonic saline to act as a volume expander and also may further damage cellular respiration and physiology, resulting in significant organ dysfunction.

Our data suggest that the deleterious effects of hypernatremia occur at serum sodium levels previously thought to be safe. Even in our highest-risk group, mean serum sodium levels remained below 160 mEq/L, suggesting even moderate levels of hypernatremia result in organ system dysfunction in these patients. A major factor determining patient outcome appeared to be the presence of renal system failure. The incidence of renal failure seen in the LR-1 and LR-2 groups was similar to the 9% incidence recently reported by Peterson et al.[28] However, renal failure was four times more common in the

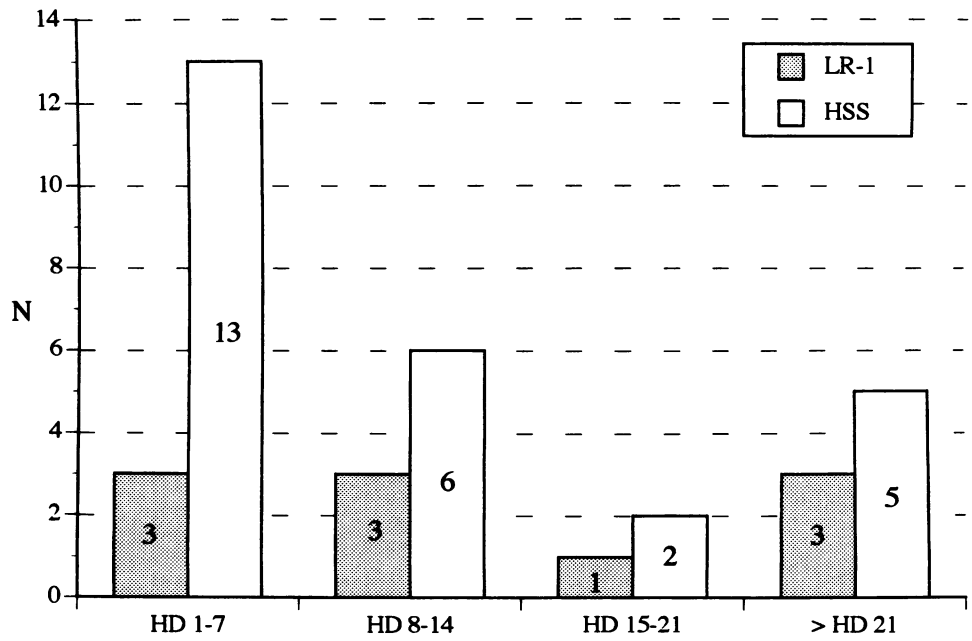

Figure 5. Onset of renal failure is within the first postburn week for half of patients resuscitated with hypertonic sodium solution.

group receiving HSS, and the development of renal failure was associated with a mortality rate impressively higher than those maintaining relatively normal renal function. Some have suggested a greater use of HSS in elderly patients because of their relative inability to tolerate large fluid loads.[9] In our series, patients developing renal failure tended to be older than patients who maintained normal renal function. When possible etiologic factors are examined, patients resuscitated with HSS who eventually develop renal failure tended to receive a larger sodium load, and subsequently developed hypernatremia of greater magnitude than patients who did not develop renal failure who were similarly treated. A fluid load of 8.3 mL/kg/%BSA would be required if this same sodium load were given as LR solution—more than twice the amount predicted by the Parkland formula. These effects are not limited to the renal system. In patients receiving HSS, 50% of patients developed failure in three or more organ systems. The poor prognosis of multisystem organ failure in intensive care unit patients and burn patients in particular is well known.[29,30]

The role of HSS in burn resuscitation should be reconsidered, particularly in the elderly and in patients with pre-existing renal disease. Because of the apparent adverse effect on patient outcome, the use of HSS as an alternative to isotonic saline solutions seems ill advised. Hypertonic sodium solutions might have some usefulness if they are limited to small-volume infusions early in resuscitation, when fluid shifts and capillary leak are greatest.[31] If HSS is used, decreased urine output during resuscitation might represent hypernatremia-associated oliguria rather than inadequate resuscitation. Thus, careful evaluation of the patient's intravascular volume status should be undertaken in this situation, and appropriate adjustments in fluid rate or composition should be made. The clinician using metabolic data as indicators of adequate resuscitation also should be cautious. Uncoupling of oxidative phosphorylation may dictate an obligate level of anaerobic metabolism with associated lactic acidemia in these patients, and normalization of acid-base parameters may be unattainable during early resuscitation. Either situation could result in inappropriate resuscitation of these patients. If HSS is used, the clinician may potentially further sodium load these patients, thereby exacerbating the deleterious effects on organ function, particularly the kidney. To date, there has been no other study directly comparing the outcomes of patients resuscitated with HSS and with isotonic salt solutions. In the absence of data demonstrating either improved or comparable outcomes, isotonic saline resuscitation should be the preferred regimen for resuscitating the thermally injured patient. Burn resuscitation with hypertonic salt solutions cannot be recommended.

We resuscitated a series of patients with hypertonic sa-

Table 9. MATHEMATICAL MODEL FOR SURVIVAL PROBABILITY

$$P = \frac{e^Y}{1 + e^Y}$$

P = expected survival (limits = 0, 1)

[LR-1] Y = 9.4748 − 0.0866 (%BSA) − 0.0874 (AGE) − 2.9816 (RF)

[HSS] Y = 17.0461 − 0.1511 (%BSA) − 0.2092 (AGE) − 8.3777 (RF)

%BSA = total burn as percent of body surface area; AGE = age in years; RF = 0, 1 (absence, presence of renal failure).

line according to published guidelines for safe and effective use of these solutions. Despite appropriate use of HSS, the expected benefit of reduced fluid volume was not observed. Hypertonic sodium solutions had an adverse effect on patient outcome; the observed mortality was much greater than predicted and greater than that of a similar group resuscitated with LR several years earlier. Both the incidence of renal failure and patient mortality decreased markedly after reinstitution of LR resuscitation.

Acknowledgments

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Discussion

DR. DAVID N. HERNDON (Galveston, Texas): Dr. Williams, Dr. Copeland, Members, and Guests. The authors are to be congratulated on an arduous review of an extensive clinical population. Most large series reviewing the cause of death in burn patients have noted a marked decrease in the incidence of acute renal failure, particularly in the first week postburn.

Three decades ago, an incidence of acute renal failure in large burns of 30% to 50% was commonplace. Today, a less than 10% incidence of this complication is usually reported. The authors were understandably concerned when they noted a 40% incidence of renal failure in their burn patients treated in their intensive care unit between July of 1991 and June of 1993. Particularly disturbing was that 13 of these 65 patients developed renal failure during the first week postburn. The most common cause of early renal failure in burns has in the past been thought to be due to failure to maintain central venous pressure, arterial pressure and urine output at sometime during the early resuscitation, most frequently prior to hospitalization, a delay in re-