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Hold the pendulum – Rates of acute kidney injury are increased in patients who receive resuscitation volumes less than predicted by the Parkland equation

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Abstract

Objective—To determine whether restrictive fluid resuscitation results in increased rates of acute kidney injury (AKI) or infectious complications.

Summary Background Data—Studies demonstrate that patients often receive volumes in excess of those predicted by the Parkland equation, with potentially detrimental sequelae. However, the consequences of under-resuscitation are not well-studied.

Methods—Data were collected from a multicenter prospective cohort study. Adults with greater than 20% total burned surface area injury were divided into three groups based on the pattern of resuscitation in the first 24 hours: volumes less than (restrictive), equal to, or greater than (excessive) standard resuscitation (4-6cc/kg/%TBSA). Multivariable regression analysis was

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employed to determine the effect of fluid group on AKI, burn wound infections (BWI), and pneumonia.

Results—Among 330 patients, 33% received restrictive volumes, 39% received standard resuscitation volumes, and 28% received excessive volumes. The standard and excessive groups had higher mean baseline APACHE scores (24.2 vs 16, $p<0.05$ and 22.3 vs 16, $p<0.05$) than the restrictive group, but were similar in other characteristics. After adjustment for confounders, restrictive resuscitation was associated with greater probability of AKI (OR 3.25, 95% CI 1.18, 8.94). No difference in the probability of BWI or pneumonia among groups was found (BWI: restrictive vs standard OR 0.74, 95%CI 0.39,1.40, excessive vs standard OR 1.40, 95%CI 0.75,2.60, pneumonia: restrictive vs standard, OR 0.52, 95% CI 0.26, 1.05; excessive vs standard, OR 1.12, 95% CI 0.58, 2.14).

Conclusions—Restrictive resuscitation is associated with increased AKI, without changes in infectious complications.

Graphical Abstract

This retrospective cohort study demonstrated that resuscitation of burn injured patients with volumes less than predicted by the Parkland equation results in significantly increased rates of acute kidney injury. No association between resuscitation volumes and burn wound infections or pneumonia was identified.

INTRODUCTION

The administration of intravenous fluids to patients after burn injury forms the cornerstone of resuscitation. The goal of fluid resuscitation is to maintain vital organ perfusion while avoiding excessive edema formation. Clinically, this is often a difficult balance to achieve, due to the physiological consequences of burn injury. The capillary damage caused by thermal injury leads to extravasation of plasma into burned tissues, resulting in intravascular depletion of oncotic proteins and large interstitial fluid shifts.[1,2] These changes render patients prone to both edema and hypovolemia simultaneously. Under-resuscitated patients may develop shock, while over-resuscitation may deplete intravascular proteins, worsening edema formation.

The unique fluid requirements of burn injured patients have led to the development of formulae aimed at predicting the specific fluid volumes required for resuscitation. While many formulae exist, the Parkland formula has traditionally been accepted as the best estimate of fluid requirements in the first 24 hours after burn.[3] An international survey of burn professionals in 2009 found that 70% used the Parkland formula in their resuscitation protocols.[4] Despite the widespread use of the Parkland formula in institutional protocols, 55-100% of patients receive more fluid than predicted by Parkland.[5-7] This excess administration of fluids is a recent phenomenon that has been termed “fluid creep”.[3,8]

Several theories have been proposed to explain fluid creep: overestimations of burn size, overzealous pre-hospital fluid administration, failure to titrate fluid volume to urine output, and increasing opioid use during resuscitation.[3] This aggressive fluid resuscitation has been associated with increased risk of complications such as abdominal compartment syndrome,

cerebral edema, pulmonary edema and acute respiratory distress syndrome (ARDS).[9] These data have prompted some authors to re-evaluate what constitutes an optimal fluid volume for resuscitation.[6] There is no consensus regarding what constitutes more conservative resuscitation, and while the morbidity associated with under-resuscitation is recognized, this is less well characterized. Small cohort studies suggest that resuscitation with volumes less than Parkland is safe, and potentially beneficial.[10] However, data from large prospective studies is lacking, and the threshold at which morbidity occurs due to under-resuscitation is unknown.

A feared consequence of under-resuscitation in burn patients is acute kidney injury (AKI). AKI is a recognized complication of burn injury; its incidence and significant impact on mortality have been well characterized.[11-14] The prevalence of AKI in burn patients varies depending on criteria used, however a recent meta-analysis reported a median prevalence of 14.5% and median associated mortality of 77%.[11] These studies are largely retrospective, and employ varying definitions of AKI. To date, no studies have been conducted to specifically determine the impact of fluid resuscitation volumes on subsequent development of AKI. Our study aimed to determine whether a restrictive approach to fluid resuscitation results in an increased incidence of AKI in adults admitted for treatment of acute burn injury.

METHODS

Study overview

This is a retrospective cohort study where the exposure of interest is the resuscitation volume received in the first 24 hours after burn injury. We sought to determine if there was an association between the volume of resuscitation fluid administered relative to the Parkland equation and rates of AKI. This study was performed as part of the multicenter Inflammation and Host Response to Injury (Glue Grant) study. The institutional review boards of the participating institutions (University of Texas Medical Branch, Galveston, TX; Loyola University Medical College, Chicago, IL; University of Texas Southwestern, Dallas, TX; University of Washington Seattle, Seattle, WA; Massachusetts General Hospital, Boston, MA) each approved this study.

Patients

The cohort included patients aged ≥18 years, who were admitted to a participating hospital no later than 96 hours after burn injury between 2004 and 2011. Patients with greater than 20% total burned surface area (TBSA) and injury requiring at least one surgical intervention were included. Patients in whom treatment was deemed futile were excluded. All hospitals followed standard operating procedures generated by participating investigators of the burn patient-oriented research core.[15] Included in these protocols was a fluid resuscitation protocol mandating that fluid administration should be based on 2-4cc/kg/%TBSA and titrated to urine output.

Patients were retrospectively stratified into three groups according to the volume of crystalloid they received as resuscitation during the first 24 hours after admission. Any fluid

received prior to admission, and any colloid received during the first 24 hours was not included. Patients were assigned to the restrictive group if they received less fluid in the first 24 hours of hospitalization than predicted by the Parkland equation (i.e. <4cc/kg/%TBSA); patients who received volumes equivalent to standard resuscitation (i.e. 4-6cc/kg/%TBSA) were assigned to the standard group, and patients who received volumes in excess of standard resuscitation (i.e. >6cc/kg/%TBSA) were assigned to the excessive group. We considered standard resuscitation as between 4 and 6 cc/kg/%TBSA, reflecting both the commonly used Parkland equation as well as multiple previous studies demonstrating average fluid requirements in this range.[16-20] Patient demographics, injury characteristics (date of injury, burn size and depth, presence of inhalation injury), resuscitation volumes (colloid and crystalloid), highest and lowest creatinine, need for dialysis, and outcomes (infection, complications, death) were recorded throughout hospitalization.

Outcomes

The primary outcome of interest for all groups was the rate of AKI. Secondary outcomes included rates of both pneumonia and burn wound infections, as both clinical experience and the literature suggest that there might be an association between resuscitation volumes and subsequent infectious complications. For the purposes of this study, AKI was defined as an absolute creatinine greater than 1.5 mg/dL at any point during hospitalization. RIFLE criteria[21] were not applied, as data regarding baseline creatinine and urine output were not recorded. Burn wound infections and pneumonia were defined according to standardized consensus definitions in the study standard operating procedures.[15,22] Acute respiratory distress syndrome was defined as Pa02/FiO2 ≤300 and bilateral pulmonary infiltrates. Intra-abdominal pressure was measured in all patients; abdominal compartment syndrome was defined as intra-abdominal pressure greater than 20mmHg. Multi-organ failure was defined as a Denver score greater than 3.

Statistical Analysis

Baseline characteristics and outcomes were compared between the three groups. Differences between groups were calculated using one-way ANOVA for continuous variables, chi-squared tests for categorical variables, and Kruskal-Wallis tests for count data. Post-hoc analyses were performed using the Bonferroni method. The odds of AKI, burn wound infections, and pneumonia were determined using individual logistic regression models adjusting for age, sex, TBSA, inhalation injury, APACHE II score,burn mechanism, and treatment center. Covariates were chosen for inclusion in each model based on the change in estimate approach, with a 10% change in the parameter estimate taken as the cutoff for inclusion in the model.[23] The association of fluid strata with each outcome is presented as odds ratios, along with their 95% confidence intervals.

RESULTS

Over an 8-year period, 330 patients meeting inclusion criteria were admitted to the participating institutions. Overall, 33% (n =109) of patients received 24-hour fluid volumes less than predicted by Parkland, 39% (n =128) received standard resuscitation volumes, and 28% (n=93) received volumes in excess of standard. Groups were similar in age, gender,

TBSA, and burn depth (Table 1). The distribution of patients across resuscitation groups varied by institution; at two centers, the majority of patients received standard resuscitation; at one center, the majority of patients received restrictive resuscitation; at the remaining two centers patients were distributed evenly across each resuscitation group. At baseline, the mean weight of patients in the excessive group was significantly less than the standard or restrictive groups: 75.7 kg vs 83.6 or 89.9, respectively ($p<0.05$). Mean APACHE II scores were significantly higher in the excessive and standard groups relative to the restrictive group (24.2 vs 16, $p<0.05$ and 22.3 vs 16, $p<0.05$). Rates of inhalation injuries were significantly different across groups; the rate in the standard group was significantly higher than both the restrictive (48% vs 26%, $p<0.0001$) and excessive groups (48% vs 43%, $p<0.001$). The excessive group also had a higher rate of inhalation injury than the restrictive group (26% vs 43%, $p<0.001$). The average fluid volume received (SD) was 2.8 (0.9) cc/kg/%TBSA in the restrictive group, 4.9cc (0.6) /kg/%TBSA in the standard group, and 7.8 (2.1) cc/kg/%TBSA in the excessive group.

Outcome Analysis

The hospital course of each group is summarized in Table 2. The overall crude rate of AKI and burn wound infections was similar across groups, while rates of pneumonia were significantly lower in the restrictive group compared to both the standard and excessive groups (28% vs 56%, $p<0.001$ and 28% vs 59%, $p<0.001$). The standard and excessive groups had similar rates of pneumonia (56% vs 59%, $p=0.66$). Among patients who developed AKI, 27% (n=13) received dialysis; 7 patients (58%) were in the restrictive group, compared to 3 (20%) in the standard group and 3 (30%) in the excessive group. The incidence of mortality among patients with AKI was significantly higher than among those without AKI (35% vs 17%, $p=0.01$). Median LOS/%TBSA was significantly different among the groups, being lowest in the restrictive group (0.75, IQR 0.71) and highest in the excessive group (1.41, IQR 1.00).

Crude bivariate comparisons were conducted across each group for several inpatient complications: abdominal compartment syndrome (ACS), acute respiratory distress syndrome (ARDS), bacteremia, sepsis, multiorgan failure (MOF) and death (Table 3). No significant differences were found between groups in rates of ACS, sepsis, MOF or death. Significant differences between groups were identified in rates of both ARDS and bacteremia; higher rates of ARDS were observed in both the standard and excessive groups compared to the restrictive group, while higher rates of bacteremia were observed in the standard group relative to the restrictive group.

A multivariable logistic regression analysis was performed to evaluate the effect of fluid resuscitation group on rates of AKI after adjusting for the effects of several potential confounders (Table 4). After adjusting for age, sex, TBSA, burn mechanism, inhalation injury, APACHE II score and treatment center, resuscitation with restrictive volumes was associated with a significantly greater probability of AKI (OR 3.25, 95% CI 1.18-8.94).

A multivariable logistic regression analysis was similarly performed to model burn wound infections and pneumonia. After adjusting for sex, TBSA, inhalation injury,burn mechanism and center, there was no significant association between resuscitation strategy and the risk of

burn wound infections (restrictive vs standard, OR 0.74, 95% CI 0.39-1.40; excessive vs standard, OR 1.40, 95% CI 0.75-2.60) (Table 5). There was also no significant association between groups and the rate of pneumonia (restrictive vs standard, OR 0.52, 95% CI 0.26, 1.05; excessive vs standard, OR 1.11, 95% CI 0.59, 2.14) after adjusting for age, TBSA, inhalation injury, burn mechanism, APACHE score and center (Table 6).

DISCUSSION

We performed a retrospective cohort study investigating the association of resuscitation volumes on subsequent development of AKI among patients admitted for treatment of burn injuries greater than 20% TBSA. After adjusting for injury severity, patients who were resuscitated with volumes of crystalloid that are less than 4cc/kg/%TBSA have increased rates of AKI compared with patients who receive volumes equal to or greater than 4cc/kg/%TBSA. Given the growing body of literature supporting more restrictive fluid regimens, it is important to recognize the clinical consequences of under-resuscitation alongside those of over-resuscitation. Of the patients who developed AKI, 27% received dialysis, the majority of whom were in the restrictive group. Dialysis may prolong hospital stay and increase the patient's risk of developing nosocomial infections or other complications. This is an important complication of under-resuscitation to consider, and future work is required to characterize the association between under-resuscitation, dialysis requirements, and patient outcomes. The rate of irreversible AKI among patients in this study is unknown.

Another goal of our study was to identify whether there was any association between resuscitation strategy and the development of burn wound infections or pneumonia. After adjusting for injury severity, no such association was present, suggesting that the volume of fluid received relative to that predicted by Parkland might not be a risk factor for later development of infectious complications. Previous studies have demonstrated that over-resuscitation is associated with increased risk of pneumonia and bloodstream infections[9]; we did not find an association between over-resuscitation and either burn wound infections or pneumonia after adjusting for injury severity, though our results do indicate a trend towards lower rates of pneumonia in the restrictive group. This variation likely represents differing analytic strategies; Klein et al reported significantly increased crude odds of pneumonia and bloodstream infections for each 5L increase in fluid received, rather than relative to standard resuscitation volumes.[9]

Overall, the average fluid volume received in the first 24 hours after injury was 5cc/kg/%TBSA, despite the recommendation of the study protocol of 2-4cc/kg/%TBSA. This is consistent with previous data demonstrating that patients receive volumes in excess of 4cc/kg/%TBSA, even in the presence of standardized protocols. We found that the protocol volume was followed in approximately one-third of cases, while one-third of patients received crystalloid volumes in excess of 6cc/kg/%TBSA. Furthermore, we observed center-level differences in resuscitation volumes, again despite the study's resuscitation protocol. Two centers favoured standard resuscitation, one center favoured restrictive, and one favoured excessive. While these differences might be in part related to varying injury severity and patient characteristics across centers, they also suggest that the existing local culture of care might be a stronger predictor of administered fluid volumes than formulaic

protocols. Each fluid group was balanced in terms of burn severity; however, APACHE II scores were significantly higher in the standard and excessive groups compared to the restrictive group. This suggests that over-resuscitation may occur in response to physiological responses evident during the resuscitation phase, while the Parkland equation predicts fluid requirements based on burn extent. The response to these physiological cues likely varies at the physician and center level, again in accordance with local cultures of care.

An evaluation of the effectiveness of the Parkland equation in predicting fluid requirements is beyond the scope of the current study. However, we have demonstrated that efforts to ameliorate fluid creep should not be so over-zealous as to swing the pendulum towards under-resuscitation; administration of resuscitation volumes less than 4cc/kg/%TBSA is associated with a higher rate of AKI. As such, a balance must be achieved between under- and over-resuscitation. Furthermore, the risks and benefits of under-resuscitation, namely increased rates of AKI with decreased rates of pneumonia, must be weighed against each other. Large prospective studies are needed to determine the morbidity and mortality attributable to each of these complications in the burn patient population. These analyses are beyond the scope of the current study.

We considered that patients with more extensive burns or inhalation injury are more likely to receive large resuscitation volumes, while these are also independent risk factors for the development of AKI.[24,25] These injury characteristics may confound the effect of fluid volume received on subsequent rates of AKI, particularly in the excessive group. To adjust for these potential differences, we considered the effect of the following confounders: age, sex, TBSA, mechanism of injury, APACHE II score, treatment center, and the presence of inhalation injury. While we have considered all known confounders in our statistical models, residual confounding of the relationship between fluid volumes and outcome might still account for the observed relationship. Potential residual confounders might include physician preferences or local culture of care.

The long-term outcomes of AKI were not explored in this study. The available data did not allow specific assessment of renal recovery or need for dialysis, as longitudinal creatinine measurements and detailed dialysis information were not recorded. The incidence of dialysis following AKI was 27%, and we are likely underpowered to detect a difference in dialysis requirement among the three groups. Previous work demonstrates that AKI is an important risk factor for morbidity and mortality in burn patients, irrespective of dialysis requirement.[11-13,26,27] Reported crude mortality rates in among burn patients with AKI range from 28 to 100%.[1]. Risk-adjusted rates of mortality are also significantly higher following AKI; Stewart et al report significantly increased probability of death with all stages of RIFLE, while Palmieri et al report significantly increased probability of death with the ‘Failure’ stage only.[2,3] Though the increased mortality associated with AKI has been clearly demonstrated, the long-term outcomes following a single episode of AKI have not been explicitly studied among burn survivors. Observational data from other patient populations suggests that patients who suffer AKI may be at increased risk for chronic kidney disease (CKD) and long-term mortality.[28,29] The risk of developing CKD is particularly evident in elderly patients.[30] Given that a single episode of AKI may increase

both in-hospital mortality and length of stay after burn injury, as well as long-term morbidity and mortality, efforts to prevent AKI secondary to under-resuscitation are justified. Future work should characterize the short- and long-term renal outcomes, including resource utilization, in burn patients with AKI.

The impact of resuscitation volume on several inpatient complications was also considered. Higher crude rates of ARDS were observed in patients who received standard or excessive resuscitation compared to those patients who received restricted resuscitation. Similarly, higher crude rates of bacteremia were observed in patients receiving standard compared to restrictive resuscitation. The impact of fluid resuscitation volumes on these important outcomes, after adjustment for patient and injury characteristics, remains to be further characterized. This will be crucial to allow more informed clinical decision-making with regards to fluid resuscitation and balance of the risks of both over- and under-resuscitation, including AKI and infectious complications.

We recognize several limitations of our current study. The lack of baseline creatinine measurements precluded application of formal AKI criteria, such as RIFLE. Our definition of AKI as an absolute creatinine greater than 1.5 mg/dL likely resulted in inclusion of only the more severe cases of AKI; thus, the overall prevalence cited here is likely an underestimate, and is lower than previous published studies. Furthermore, the timing of AKI was not considered for the purposes of our analysis – both early and late AKI were considered together, though it is recognized that under-resuscitation is more likely to be related to early AKI while late AKI is more likely related to sepsis. Only adults with burns resulting in greater than 20% TBSA injury with a need for surgical intervention were included; as such, the results may not be generalizable to the pediatric population or to patients with smaller burns. Potential misclassification bias exists, as pre-hospital fluids were not captured in the database. Some patients may have received additional resuscitation volumes prior to admission.

Future efforts should be directed at characterizing the best predictors of fluid requirements, the most accurate indicators of adequate resuscitation, and the long-term outcomes and resource utilization associated with AKI in burn-injured patients. The impact of AKI on other in-hospital outcomes, such as ICU and hospital length of stay, also remains to be elucidated. These outcomes may provide additional justification to efforts aimed at preventing AKI in burn-injured patients. As the short and long-term impacts of AKI on the outcomes of burn-injured patients are further elucidated, the significance of under-resuscitation will increasingly be recognized alongside the significance of over-resuscitation. As methods for invasive hemodynamic monitoring become more accurate and widespread, perhaps a formulaic approach to fluid resuscitation will become obsolete, in favour of goal-directed fluid therapy similar to that employed in the initial treatment of sepsis.

Overall, our study suggests that more judicious administration of resuscitation fluids is necessary; multiple studies have now demonstrated that patients receive volumes in excess of the Parkland equation. We have demonstrated that resuscitation volumes below those predicted by the Parkland equation are associated with significant increases in the rate of AKI. These results, taken together with other studies which demonstrate the harmful effects

of over-resuscitation, suggest that patients should be resuscitated with a volume of crystalloid that is at least equal to that predicted by the Parkland equation (4cc/kg/%TBSA). Consideration should only be given to administration of volumes beyond Parkland when Baxter's original criteria are met: (1) excessively deep burns with muscle necrosis, (2) inhalation injury, and (3) when there is a delay in resuscitation.[31,32] In this manner, the adverse outcomes associated with both under- and over-resuscitation will be avoided.

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Table 1

Baseline patient and injury characteristics as a function of resuscitation strategy

	Overall	Resuscitation Strategy			p-value
		Restrictive (<4cc/kg/T BSA)	Standard (4-6cc/kg/TBSA)	Excessive (>6cc/kg/TBSA)	
Total patients	330	109	128	93	
Center					<0.001
1	104 (31%)	26 (25%)	59 (57%)	19 (18%)	
2	81 (25%)	21(26%)	28 (35%)	32 (40%)	
3	87 (26%)	27 (31%)	27 (31%)	33 (38%)	
4	6 (2%)	1 (17%)	3 (50%)	2 (33%)	
5	52 (l6%)	34 (65%)	11 (21%)	7 (13%)	
Mean Age (SD)	41.3 (15.8)	40.9 (15.5)	40.8 (15.6)	42.3 (16.6)	NS
Gender (male)	247 (75%)	86 (79%)	92 (72%)	69 (74%)	NS
Mean Weight, kg (SD)	83.5 (83.5)	89.9 (21.6)	83.6 (21.1)	75.7 (17.4)	<0.001 *
Mean % TBSA, (SD)	41.0 (18.2)	42.4 (19.1)	41.8 (18)	38.1 (17.3)	NS
Mean %Total full-thickness (SD)	31.0 (19.1)	29.3 (20.1)	32.3 (17.2)	31.1 (20.3)	NS
Burn Mechanism					
Flame	276 (84%)	85 (78%)	112 (88%)	79 (85%)	NS
Flash	22 (7%)	10 (9%)	5 (4%)	7 (8%)	NS
Scald	17 (5%)	8 (7%)	6 (5%)	3 (3%)	NS
Other	15 (5%)	6 (6%)	5 (4%)	4 (4%)	NS
Inhalation injury	129 (39%)	28 (26%)	61 (48%)	40 (43%)	<0.001 †
Mean APACHE II Score (SD)	20.8 (9.2)	16.0 (8.5)	22.3 (8.8)	24.2 (8.1)	<0.001 †
Mean Initial base deficit (SD)	−5.14 (4.9)	−4.59 (5.0)	−5.41 (4.8)	−5.27 (4.9)	NS
Mean 24 Hour Fluids, L (SD)	16.4 (10.0)	10.3 (5.6)	17.2 (8.5)	22.3 (11.9)	<0.001 ‡

* Post hoc testing revealed significant differences on these values between Standard and Excessive groups

† Post hoc testing revealed significant differences on these values between Restrictive and Excessive groups

‡ Post hoc testing revealed significant differences on these values between all groups

Table 2

Resuscitation strategy and patient outcomes

	Overall	Resuscitation Strategy			p-value
		Restrictive	Standard	Excessive	
Mean Highest creatinine, mg/dl (SD)	1.15 (0.42)	1.17 (0.42)	1.09 (0.4)	1.20 (0.5)	NS
Median Hospital LOS (IQ Range)	34 (41)	26 (32)	40.5 (40)	41 (41.5)	<0.001 *
Median LOS/%TBSA		0.75 (0.71)	1.03 (0.97)	1.41 (1.00)	<0.001
Median ICU LOS (IQ Range)	26 (32)	18 (24)	33.5 (36)	26 (31.5)	0.005 *
BWI	169 (51%)	51 (47%)	65 (51%)	53 (57%)	NS
Mean Other nosocomial infections (SD)	2.4 (3.2)	1.9 (3.3)	2.6 (3.3)	2.6 (2.8)	NS
AKI	48 (15%)	17 (15%)	16 (12%)	15 (16%)	NS
Dialysis	37 (11%)	12 (32%)	15 (12%)	10 (11%)	NS
Deaths	67 (20%)	22 (20%)	28 (22%)	17 (18%)	NS

* Post hoc testing revealed significant differences on these values between Restrictive and Standard, and Restrictive and Excessive groups

Table 3

Resuscitation strategy and complications

Outcome	Overall	Resuscitation Strategy			p-value
		Restrictive	Standard	Excessive	
Pneumonia	158 (48%)	31 (28%)	72 (56%)	55 (59%)	<0.001 *
Abdominal compartment syndrome	11 (3%)	2 (2%)	4 (3%)	5 (5%)	NS
ARDS	107 (32%)	22 (20%)	46 (35%)	39 (42%)	0.003 *
Sepsis	37 (11%)	12 (11%)	17 (13%)	8 (9%)	NS
Bacteremia	92 (28%)	21 (19%)	42 (32%)	29 (31%)	0.048 †
Multiorgan Failure [1]	91 (28%)	28 (26%)	40 (31%)	23 (25%)	NS
Death	67 (20%)	22 (20%)	46 (35%)	39 (42%)	NS

[1] Maximum Denver Score ≥4

* Significant difference between Restrictive and Standard, and Restrictive and Excessive groups

† Significant difference between Restrictive and Standard groups

Table 4

Factors associated with AKI*

Predictor	Adjusted Odds Ratio (95% CI)	P value
Fluid group[1]		
Restrictive	3.25 (1.18, 8.94)	0.02
Excessive	1.03 (0.41, 2.59)	0.95
Age (per year)	1.02 (1.00, 1.05)	0.05
Female sex	0.35 (0.12, 1.01)	0.05
APACHE II score (per 1 unit)	1.17 (1.10, 1.25)	<0.001
TBSA (per % increase)	0.98 (0.96, 1.01)	0.22
Inhalation injury	1.25 (0.52, 2.97)	0.61
Burn Mechanism[2]		
Flash	6.68 (1.90, 23.49)	0.003
Scald	1.82 (0.18, 18.14)	0.61
Other	2.61 (0.48, 14.15)	0.27
Treatment Center[3]		
1	0.71 (0.25, 1.96)	0.51
2	0.47 (0.15, 1.48)	0.19
3	2.49 (0.19, 32.97)	0.49
4	1.00 (0.29, 3.48)	0.99

*Multivariable logistic regression model

[1]Reference = Standard

[2]Reference = Flame

[3]Reference = Center 5

Table 5

Factors associated with BWI

Predictor	Adjusted Odds Ratio (95% CI)	p value
Fluid group[1]		
Restrictive	0.74 (0.39, 1.41)	0.36
Excessive	1.40 (0.75, 2.61)	0.29
Female sex	1.28 (0.73, 2.24)	0.39
TBSA (per % increase)	1.02 (1.01, 1.04)	0.006
Inhalation injury	1.79 (0.97, 3.32)	0.06
APACHE II Score (per 1 unit)	1.01 (0.97, 1.04)	0.74
Burn Mechanism[2]		
Flash	1.08 (0.36, 3.21)	0.89
Scald	1.34 (0.44, 4.07)	0.61
Other	0.56 (0.16, 1.96)	0.37
Treatment Center[3]		
1	3.36 (1.68, 6.69)	0.001
2	0.70 (0.36, 1.35)	0.28
3	0.71 (0.10, 4.87)	0.73
4	3.37 (1.46, 7.80)	0.004

* Multivariable logistic regression model

[1]Reference = Standard

[2]Reference = Flame

[3]Reference = Center 5

Table 6

Factors associated with pneumonia

Predictor	Adjusted Odds Ratio (95%CI)	p value
Fluid group[1]		
Restrictive	0.52 (0.26, 1.05)	0.07
Excessive	1.12 (0.59, 2.14)	0.73
Age (per year)	1.01 (1.00, 1.03)	0.06
TBSA (per % increase)	1.03 (1.01, 1.06)	0.001
Inhalation injury	1.56 (0.83, 2.93)	0.16
APACHE II score (per 1 unit)	1.07 (1.03, 1.12)	0.001
Burn Mechanism[2]		
Flash	0.50 (0.17, 1.51)	0.22
Scald	0.37 (0.09, 1.53)	0.17
Other	0.46 (0.11, 1.91)	0.28
Treatment Center[3]		
1	1.08 (0.51, 2.25)	0.85
2	1.00 (0.48, 2.06)	0.99
3	1.42 (0.14, 14.31)	0.76
4	0.26 (0.10, 0.69)	0.007

* Multivariable logistic regression model

[1]Reference = Standard

[2]Reference = Flame

[3]Reference = Center 5