Continuous Renal Replacement Therapy Improves Survival in Severely Burned Military Casualties With Acute Kidney Injury

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Background: **Acute kidney injury in severely burned patients is associated with high mortality. We wondered whether early use of continuous renal replacement therapy (CRRT) changes outcomes in severely burned military casualties with predetermined criteria for acute kidney injury.**

Methods: **Between November 2005 and June 2007, casualties admitted to our burn intensive care unit after sustaining burns in Iraq and Afghanistan, who subsequently developed acute kidney injury or circulatory shock or both, underwent CRRT. Baseline demographic, laboratory, and hemodynamic parameters were recorded. Both 28-day mortality and in-hospital mortality were evaluated and compared with a consecutive group of burn casualties with greater than 40% total body surface area (TBSA) burns, acute kidney injury, or nephrology consultation in the 2 years before the existence of our CRRT program.**

Results: **One hundred forty-seven severely burned military casualties were admitted to our intensive care unit before CRRT program initiation, and 102 were admitted after CRRT program initiation. Before the CRRT program, 16 patients were identified as having >40% TBSA burns with kidney injury with or without nephrology consultation (control group); 18 were treated with CRRT since (CRRT group). Groups were similar for %TBSA, %full-thickness TBSA, incidence of inhalation injury, blood urea nitrogen, creatinine, and Injury Severity Score. Of the CRRT patients, seven soldiers were treated for isolated acute kidney injury, whereas 11 were treated for a combination of acute kidney injury and shock. The dose of therapy was 50.2 ± 13 mL/kg/h with a treatment course of 5.2 ± 3 days. Of the 11 patients in the CRRT group treated for shock, eight were off vasopressors by 24 hours and the remaining three within 48 hours. None of the patients in the control group were placed on renal replacement therapy with nephrology consultation in eight patients. Both 28-day mortality (22% vs. 75%, $p = 0.002$) and in-hospital mortality (56% vs. 88%, $p = 0.04$) were lower in the CRRT group compared with that in the control group.**

Conclusion: **Aggressive application of CRRT in severely burned casualties with kidney injury significantly improves survival.**

Key Words: **Intermittent hemodialysis, Continuous renal replacement therapy, Burn, Nephrology, RIFLE.**

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Acute kidney injury is a common and important problem in the critically ill patient. This is also true for burn patients, in whom previous studies have reported its incidence to be between 1% and 30%. Once acute kidney injury is established, it causes a substantial increase in morbidity, health care costs, and mortality; its impact on mortality in burn patients is extremely high, between 80% and 100%.[1–7] This enormous burden that acute kidney injury brings upon the health care system has triggered intensive investigation aimed at elucidating the mechanisms implicated in the pathogenesis of acute kidney injury and at improving outcomes. However, we have not yet reaped the expected clinical benefits from the fundamental insights gained of acute kidney injury; mortality remains exceedingly high in these patients. Part of the impediment in progress has been in our lack of a uniform set of criteria for diagnosing and stratifying the severity of acute kidney injury. This lack of uniform diagnostic criteria not only contributes to the variability in the incidence and mortality reported in previous studies, but also makes them very difficult to compare. Recently, a new stratified scoring system based on increasing severity of acute kidney injury called the "RIFLE classification" (Risk, Injury, Failure, Loss, End-stage) has been proposed[8] and increasingly validated in various patient populations.[9] This classification was recently applied by Coca et al.[10] in burn patients, who found that the incidence of acute kidney injury was 27%, and it carried with it a mortality rate of 73% in the patients with the most severe acute kidney injury (requiring dialysis). Consequently, it is clear that the

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diagnosis of severe acute kidney injury is associated with a dismal prognosis, especially in the severely burned, despite the widespread application of new renal replacement strategies.[4,10] This suggests that we still do not know how to optimally treat these patients; there is no consensus with regard to the optimal modality of renal replacement therapy, timing of initiation of therapy, or dose of therapy.[3,4,11–17]

The United States Army Institute of Surgical Research Burn Center is the sole burn treatment facility in the Department of Defense serving active duty personnel in addition to its role as the regional burn center for South Texas. Since the beginning of 2003, our burn center has admitted nearly 600 military casualties sustaining burns in Iraq and Afghanistan. Before November 2005, only conventional intermittent hemodialysis (IHD) services were available for those who developed acute kidney injury. However, critically ill burn patients with acute kidney injury are often not suitable candidates for IHD because acute kidney injury commonly develops in conjunction with circulatory shock in these patients. Thus, many of these patients have difficulty tolerating IHD because of hemodynamic compromise. This, in turn, leads to suboptimal delivery of dialysis; in fact, a number of patients were not offered hemodialysis because of concerns as to whether they would tolerate IHD, or questions as to the potential benefits versus risks of IHD. During the last few decades, a more gentle form of renal replacement therapy, continuous renal replacement therapy (CRRT), has become widely available throughout the United States. CRRT offers several potential advantages in the management of severe acute kidney injury in burn patients. It is slow and continuous, consequently allowing for very efficient metabolic clearance and ultrafiltration of fluids, while minimizing hemodynamic compromise. This permits ongoing optimization of fluid and metabolic management without limiting nutritional support.[18] For these reasons, an intensivist-driven CRRT program was developed in our burn intensive care unit (BICU) and our first patient treated in November 2005 (Fig. 1). The purpose of this study was to evaluate and report the impact of this therapy in our severely burned military casualties who develop acute kidney injury.

Fig. 1. *Burn patient receiving continuous renal replacement therapy (CRRT).*

PATIENTS AND METHODS

Study Population

The study population consisted of 246 consecutive military casualties admitted to our BICU between March 2003 and June 2007, after sustaining burns in Iraq and Afghanistan; 102 were admitted after November 2005, when our CRRT capabilities became available. The CRRT group consisted of 18 consecutive military burn casualties with acute kidney injury (with or without circulatory shock) who underwent CRRT using the Prismaflex system (Gambro, Lund, Sweden) using 1.4-m^2 polyarylethersulfone filters. The control group consisted of consecutive historical controls, matched by % total body surface area (TBSA) and Injury Severity Score (ISS) that were selected from the period before November 2005 by performing a query of our burn center trauma registry. All military casualties with greater than 40% TBSA burns and a diagnosis of renal failure were included in the control group. Sixteen patients were identified after excluding one patient who was brain dead on arrival to our BICU. Civilian admissions to the BICU were excluded from this analysis.

Data Collection

Electronic medical records for these patients were reviewed to extract baseline patient characteristics, hemodynamic and laboratory parameters, and outcome variables. Injury Severity Scores (ISS), prospectively tabulated in our trauma registry, were extracted for both the CRRT group and the control group. Other severity scores (Acute Physiology and Chronic Health Evaluation II,[19] multiple-organ dysfunction syndrome [MODS],[20] and Sepsis-related Organ Failure Assessment [SOFA][21,22]) were calculated during our chart review. For the CRRT group, all scores were tabulated using the physiologic parameters present on the first day CRRT was initiated (time zero, T0). For the control group, T0 was assigned on the day the diagnosis of renal failure was determined or the day nephrology consultation was initiated. The RIFLE classification was used to categorize severity of acute kidney injury based on the previously described criteria in both groups at T0.[8] In this classification, risk (R) is defined

as an increase in serum creatinine by 50% or urine output of less than 0.5 mL/kg/h for 6 hours; injury (I) is defined as an increase in creatinine by 100% or a urine output less than 0.5 mL/kg/h for 12 hours; and failure(F) is defined as an increase in serum creatinine by 200% or urine output less than 0.3 mL/kg/h for 24 hours or anuria for 12 hours.

Statistical Analysis

Outcome measures of interest for comparison included 28-day mortality as well as in-hospital mortality. Data were analyzed using SAS, version 9.1 (SAS Institute, Cary, NC). Comparisons were made between the CRRT group and the control group. Data are presented as mean ± SD. Multiple logistic regression analysis was used to determine the effect of such variables as age, %TBSA, %full-thickness TBSA, inhalation injury, ISS, RIFLE classification, need for pressors, and treatment group on the risk of death. Continuous variables were compared via paired Student's t test. χ^2 testing was used to compare categorical variables. All testings were two-tailed, with $p < 0.05$ considered significant. Where appropriate, ϕ and Spearman's correlation studies were performed. Kaplan-Meier estimates of survival were constructed to compare the in-hospital mortality for the CRRT group versus historical control via stratified log-rank test.

RESULTS

Table 1 demonstrates that the groups were similar in %TBSA burned, %full-thickness TBSA, incidence of inhalation injury, pressor need, RIFLE classification, blood urea nitrogen level, and creatinine level. Although not significant, there was a trend toward the control group being slightly older. The groups were also similar in all measures of illness severity.

Table 1 Population Comparison

	Control Group (n = 16)	CRRT Group (n = 18)	p
Age	30 ± 8	26 ± 3	0.06
%TBSA	65 ± 14	68 ± 17	NS
%Full thickness	54 ± 24	58 ± 16	NS
Inhalation injury, %	75	56	NS
Pressors, %	75	61	NS
RIFLE classification	I (n = 6), F (n = 10)	I (n = 5), F (n = 13)	NS
Blood urea nitrogen (T0)*	55 ± 23	55 ± 21	NS
Creatinine (T0)*	2.9 ± 1	3.4 ± 1.6	NS
ISS†	41 ± 16	39 ± 14	NS
Acute Physiology and Chronic Health Evaluation II‡	37 ± 8	34 ± 5	NS
MODS‡	13 ± 4	12 ± 3	NS
SOFA‡	13 ± 4	13 ± 3	NS

* T0 = Day of CRRT initiation, diagnosis of renal failure, or nephrology consultation.
† Calculated at admission.
‡ Calculated at T0.
NS indicates not significant.

The therapy characteristics of the CRRT group are described in Table 2. All patients were initiated on therapy for rapidly deteriorating renal function as exhibited by RIFLE criteria. All were categorized as RIFLE-F or RIFLE-I in the presence of shock (i.e., need for pressors) before initiation of therapy. All but two patients received continuous venovenous hemolfiltration. Continuous venonvenous hemodiafiltration was prescribed for two patients for better electrolyte balance. Average prescribed dose of therapy as determined by the ultrafiltration rate was 50 ± 13 mL/kg/h. Average treatment duration was a median of 5 days (range, 2–13) using a 1.4-m^2 polyarylethersulfone filter. Eight patients (44%) required more than one session of therapy because of the development of acute kidney injury later in their hospitalization. One patient required CRRT on three different occasions each time with renal recovery. Only the first session of therapy was included for our comparison of baseline characteristics, organ severity, and mortality against control. All the survivors recovered renal function to near baseline.

Figure 2 compares the number of patients on pressors in each group at T0, 24 hours, and 48 hours. Twelve patients in the control group were in circulatory shock at the time of diagnosis. In these patients, pressor requirement did not change at 24 hours. One patient was off pressors at 48 hours

Table 2 CRRT Treatment Characteristics

	CRRT Group
Indication	RIFLE-I with shock (need for pressors) or RIFLE-F
Mode	Continuous venovenous hemolfiltration (n = 16), continuous venonvenous hemodiafiltration (n = 2)
Prescribed dose	50 ± 13 mL/kg/h
Regional anticoagulation	Citrate (n = 15), none (n = 3)
Duration	5 (2–13) days
Multiple sessions	44% (n = 8)

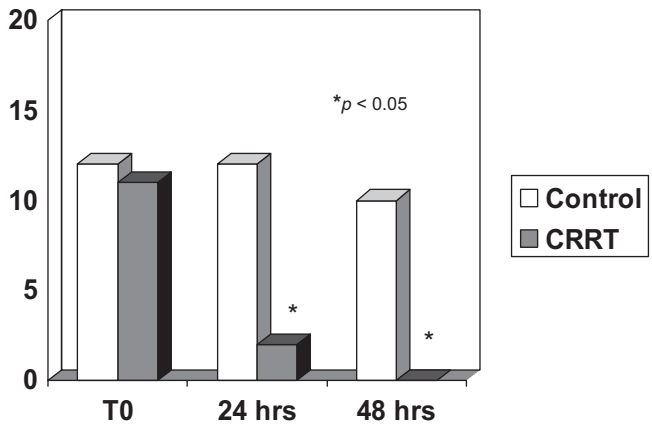

Fig. 2. *Number of patients on pressors in continuous renal replacement therapy (CRRT) and control groups at day 1 (T0), 24 hours, and 48 hours.*

whereas another did not survive past 24 hours. Of the 11 patients in the CRRT group treated for shock, eight were off vasopressors by 24 hours and the remaining three within 48 hours. There was a positive association between persistent need for pressors at 48 hours and death with a ϕ-coefficient of 0.449 ($p = 0.009$).

In half the control patients (8 of 16), nephrology consultation was requested. Of these, three patients eventually recovered their renal function, one later died. Three patients met criteria but were too unstable for IHD, and two died before they met criteria. None were placed on hemodialysis. The other control patients either recovered their renal function and later died of other causes or died before nephrology could be involved.

Both 28-day mortality (22% vs. 77%, $p = 0.002$) and in-hospital mortality (56% vs. 88%, $p = 0.04$) were lower in the CRRT group compared with the control group (Fig. 3). The Kaplan-Meier survival curve detected a significantly higher rate of survival in the CRRT group compared with control (Fig. 4) out to almost a year.

Multiple logistic regression analysis demonstrated only a trend toward the control group having a higher risk of death odds ratio 5.67 (95% confidence interval 0.974–32.198), $p = 0.054$. None of the other variables analyzed approached significance.

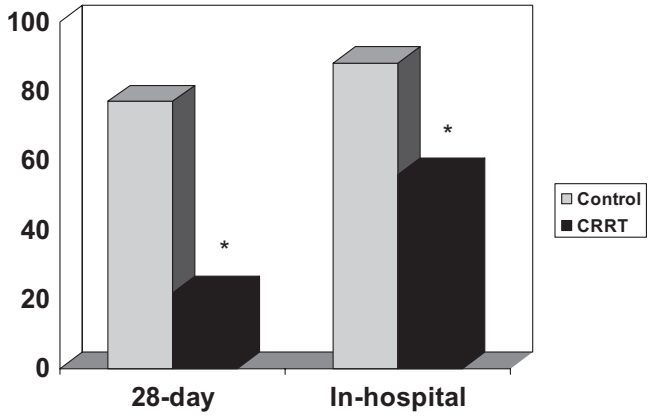

Fig. 3. *In-hospital and 28-day mortalities for continuous renal replacement therapy (CRRT) and control groups (*p < 0.05).*

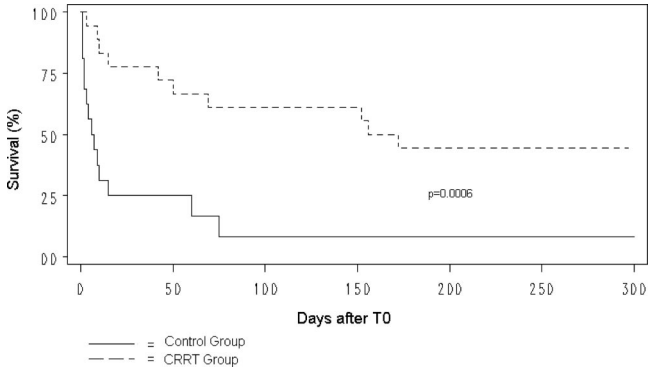

Fig. 4. *Kaplan-Meier estimates of survival for continuous renal replacement therapy (CRRT) and control groups.*

DISCUSSION

Despite recent advances in burn care, the diagnosis of acute kidney injury has been associated with a dismal prognosis in burn patients with no change in outcome over time.[1–7] We found that early and aggressive intervention with CRRT in a critically ill burn population with a high risk of death was associated with a rapid improvement in hemodynamic stability (they were able to be weaned off pressors quickly) and a markedly better survival than a closely matched historical cohort. Thus, our study indirectly answers a few questions while raising several others regarding renal replacement therapy in critically ill burn patients with acute kidney injury.

The first issue that this study addresses is whether we should be aggressive about offering renal replacement therapy to these patients. We think that the answer is unequivocally yes. The reason for our contention is that survival in our CRRT group (which represents aggressive therapy) was markedly higher than that in the control group. In this respect, it is important to note that all the patients in the CRRT group were initiated on CRRT early during their course of acute kidney injury, and they were prescribed higher doses of hemofiltration (~50 mL/kg/h) to ensure adequate clearances, whereas none of the patients in our control group received any form of renal replacement therapy. The reasons that the controls were not offered renal replacement therapy were as follows. Traditional indications for acute renal replacement include presence of uremic symptoms, drug overdose, and treatment of unresponsive acidosis, refractory electrolyte abnormalities, and fluid overload. However, these indications are empirical and subjective, and are rarely met in critically ill burn patients. Moreover, those with unresponsive acidosis and severe electrolyte imbalance commonly also have concomitant hemodynamic instability that makes therapy with IHD more difficult (this was the only renal replacement modality available to us during that timeframe). Thus, one can understand why none of the eight patients in our control group were placed on renal replacement therapy despite being seen by nephrologists. As evidenced by the high mortality in this group, it is clear that most burn patients will die before meeting traditional criteria for initiating renal replacement therapy, suggesting that earlier initiation is desirable.

There is no consensus as to when to initiate renal replacement therapy in critically ill patients with acute kidney injury. However, several studies suggest that starting early may be beneficial.[16,23–27] For instance, Piccinni et al.[24] evaluated the effect of early isovolemic hemofiltration (EIHF) in 80 oliguric patients with septic shock and acute lung injury. Half the patients received EIHF (45 mL/kg/h applied within 12 hours of ICU admission for 6 hours followed by conventional hemofiltration; 20 mL/kg/h for a minimum of 3 days),

whereas classic acute kidney injury criteria were used to guide initiation of therapy in the control group (at 20 mL/kg/h). There was a marked improvement in essentially all the clinical outcome parameters measured in the EIHF group compared with the control group, including pulmonary function (defined by the Pao_2/FiO_2 ratio at 48 hours), hemodynamic parameters (lower heart rate, higher mean arterial pressure, higher systemic vascular resistance, and lower noradrenaline dose), ventilator dependence, duration of mechanical ventilation, ICU stay, and hospital stay. In this respect, it is interesting to note that our patients also demonstrated significant hemodynamic improvement within 48 hours of starting CRRT. This may have been because of the early initiation of CRRT or the "high dose" of hemofiltration used (discussed below). Despite these promising findings, not all studies have reported positive results. Bouman et al.[28] compared three renal replacement strategies—early high-volume hemofiltration, early low-volume hemofiltration and late low-volume hemofiltration—on patients with circulatory and respiratory failure complicated by early oliguric acute kidney injury. In this prospective randomized, two-center study, 28-day survival did not differ with either high-volume hemofiltration or early initiation of hemofiltration. However, all three of their groups had distinctly high survival rates (74%, 69%, and 75% 28-day survival, respectively) compared with other studies (18%–58%);[4,17,29] thus, it would be difficult to detect a beneficial effect of any therapeutic maneuver in this study. Because the patient populations seem to be quite different, particularly in their severity of illness, it is highly unlikely that these results can be extrapolated to a population with a high risk of death, such as the severely burned patients with acute kidney injury.

Another potential contributing factor to the increased survival in our CRRT patients may be the relatively high dose of therapy delivered. Indeed, there are several studies that have found that dose of therapy impacts survival. Ronco et al.[17] reported in a well-done randomized controlled study that increasing the dose of hemofiltration from 20 mL/kg/h to 35 mL/kg/h improved survival in ICU patients with acute renal failure. Similarly, Saudan et al.[30] recently performed a prospective randomized trial and found that adding a mean dialysis dose of 18 $\pm$ 5 mL/kg/h to a mean ultrafiltration dose of 24 $\pm$ 6 mL/kg/h (total hemodiafiltration dose was 42 $\pm$ 5 mL/kg/h) significantly improved 3-month survival compared with hemofiltration alone at 25 $\pm$ 5 mL/kg/h (59% vs. 34%; $p = 0.0005$). This survival benefit of higher doses of clearance in patients with acute kidney injury has also has been suggested for IHD.[31] Although the data may still not be definitive, we agree with the notion that the best evidence to date supports the use of at least 35 mL/kg/h for continuous venovenous hemolfiltration and continuous venonvenous hemodiafiltration, or daily hemodialysis.[32] In addition, it is possible that even higher doses may be of further benefit in our specific patient population because they are highly catabolic and have increased inflammation (with concomitant increases in circulating cytokines). In this respect, it is interesting to note that in Ronco et al.'s study[17] the highest dose of hemofiltration (45 mL/kg/h) did not impact overall survival, but it significantly increased it in the subgroup of patients with sepsis. Furthermore, several experimental and clinical studies have suggested that doses of at least 50 mL/kg/h (or 4–5 L/h) via a convective-based therapy are required to sufficiently "clear" inflammatory mediators in septic shock, and that this nonspecific "cytokine removal" is associated with positive physiologic effects, including improvement of hemodynamic instability.[33–41] Our CRRT group received a mean ultrafiltration dose of 50 $\pm$ 13 mL/kg/h (those who were on pressors before the initiation of CRRT received a slightly higher dose of 54 $\pm$ 14 mL/kg/h). Hemodynamic improvement was demonstrated in all patients requiring pressors before initiating therapy. By comparison, those on pressors at T0 in the control group generally remained on pressors at 48 hours (Fig. 2). Persistent need for pressors at 48 hours was associated with death. Although this association does not demonstrate a causal relationship, we think that a survival impact may be related to the reversal of shock via treatment with high-volume hemofiltration, as previously suggested by Honore and Joannes-Boyau.[35] It is tempting to speculate that the higher mortality rates of 73% to 82% (even with renal replacement therapy) reported in prior studies of burn patients with severe acute kidney injury[4,10] may in part be because of the lower doses of renal replacement therapy delivered. If cytokine removal turns out to be an important component of CRRT in these patients, then other methods of cytokine modulation (i.e., high flux membranes, hemoadsorption, and plasmapheresis) may become particularly important in treating these patients. Clearly, continued molecular, animal, and human studies are warranted to investigate the reproducibility and mechanism of this effect.

The limitations of our study are those that are inherent to any retrospective study. The control group, although a carefully matched historical cohort, was identified by the diagnosis of renal dysfunction extracted from our trauma database. This was cross-referenced with a list of patients for whom nephrology was consulted. This list was further cross-referenced with a list of patients with >40% TBSA burns. Although those with nephrology consultation were all identified by the query, it is possible that patients with renal dysfunction, who would have otherwise been placed on CRRT had the capability been available, may have been missed. This possibility is further amplified by the fact that the incidence of acute kidney injury seems to have increased from 11.8% to 17.6% during the study period. Although this difference did not reach statistical significance ($p = 0.1963$), this trend suggests the potential for bias introduced in favor of the CRRT group. Second, because the patients were not prospectively randomized, it is possible that there were subtle differences in their baseline characteristics that were not detected, which may have altered their predicted survival. However, this possibility is unlikely to explain the large

difference in mortality between the groups because the severity of illness (as determined by four distinct scoring scales) was not different between the groups. In this respect, it is also possible that the cause of the acute kidney injury may have been different between groups [ischemic vs. nephrotoxic acute tabular necrosis], which would also alter the predicted survival. Although the actual causes of the patients' acute kidney injury are not possible to obtain, the presumed mechanism of injury was ischemic in the majority; thus, it is unlikely that differences in the cause of acute kidney injury could account for the large differences in survival between the groups. Another possible explanation for the improved survival is the possibility that other aspects of burn care may have evolved at the same time. However, during the time period evaluated, staff turnover was minimal and surgical and wound care management did not change. Other than the introduction of CRRT in the BICU, there were no other significant changes implemented during this time period. Still, we must assume that other aspects of burn care may have improved during the 4-year span. Finally, it is important to point out that our study was not intended to compare whether CRRT is superior to IHD in the treatment of critically ill burn patients with acute kidney injury. We simply report our results of an aggressive therapeutic strategy in treating these complex patients using CRRT as a tool to deliver uncompromising renal replacement therapy. We chose this modality because of its aforementioned advantages over traditional IHD in these patients (particularly because of its lack of detrimental hemodynamic effects), and because hemofiltration-based therapies (especially at higher doses) may also add the potential effect of removal of inflammatory mediators abundant in circulatory shock.[33–41] It is possible that similarly positive results can be achieved with other renal replacement modalities such as daily IHD, or sustained low-efficiency dialysis, which is sometimes referred to as extended daily dialysis.[42] Further studies are clearly warranted to determine whether there is a difference between therapies.

CONCLUSION

Given the obvious clinical impact of renal replacement in the management of severe acute kidney injury, no prior study has ever compared renal support via any method of delivery to no support. Patients in our control group had various reasons for not meeting criteria for renal replacement. Those who did meet criteria were either too hemodynamically unstable to tolerate IHD or died before therapy could be initiated. Patients with severe burns are prone to overwhelming sepsis and rapid deterioration. The development of acute kidney injury in this setting is often sudden in onset with rapid progression to death before uremia or other traditional indications have had a chance to set in. It is likely that early and aggressive application of any hemodynamically tolerated mode of renal replacement at a sufficient dose can impact outcome in this setting. In our ICU, early and aggressive application of CRRT in severely burned casualties with acute kidney injury improved survival when compared with a closely matched historical cohort who did not receive renal replacement. An aggressive approach, regardless of mode of therapy, is likely needed in severely burned patients with acute kidney injury. Waiting until "traditional" indications are met, perhaps reasonable in other critically ill populations, only results in a high death rate in the burn population. Prospective randomized trials are needed to determine the mechanism, optimal timing, dose, and mode of therapy in this population with a high risk of death.

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DISCUSSION

Dr. Robert M. Perkins (Walter Reed Army Medical Center, Washington, DC): Chung et al. report their experience with the introduction of a CRRT program at a regional burn center caring primarily for burn trauma patients evacuated from Iraq and Afghanistan. Their retrospective, observational analysis, using historical controls who did not receive renal replacement therapy, identified survival differences favoring the CRRT group. They conclude that aggressive introduction of renal replacement therapy in burn patients with acute kidney injury improves survival.

Military conflicts have played a central role in the development of renal replacement therapy since the last half of the 20th century. The earliest crude estimates of mortality associated with renal failure in the critically injured were derived from analyses of data from World War II and Korea.[1,2] The very poor prognosis associated at that time with the development of oligoanuria, coincident with or subsequent to penetrating or burn trauma, has not improved substantially during the decades since, and is still generally recognized to be greater than 50%. The introduction in Korea in 1952 of a dedicated renal team near the area of combat capable of providing renal replacement therapy, as an alternative to conservative medical management alone, produced modest improvements in these dismal statistics; yet, death still remained a more likely outcome than survival for patients with posttraumatic acute renal failure.[3] Studies of post-traumatic renal failure from Vietnam confirmed mortality rates greater than 60%.[4] A similar poor prognosis is still ascribed today to the general population of ICU patients with acute kidney injury.[5] With respect to this study by Chung et al., these older reports are of more than historical interest, for the current analysis supports (and extends to a burn population specifically) the aforementioned findings of Teschan and Conger, among others, that renal replacement therapy improves survival of these critically injured patients when compared with medical management alone.

The current focus of renal replacement research for the management of acute kidney injury in the critically ill is focused on determining the optimal modality and dose of

renal replacement therapy, the optimal clinical threshold at which to initiate therapy, and the appropriate indications for initiating renal replacement therapy. Expected in the near-term are the results of the large, Veterens Administration/ National Institutes of Health collaborative Acute Renal Failure Trail Network (ATN) study, an interventional trial enrolling more than 1,000 subjects randomized to different doses of renal replacement therapy and using both convective and diffusive modalities in each arm.[6] The ATN trial tests the hypothesis that more intensive renal replacement therapy will improve 60-day all-cause mortality. Importantly, it will include an analysis comparing costs and cost-effectiveness associated with different intensities of therapy. After half a century of experience with renal replacement therapy in the critically ill, the nephrology and critical care communities eagerly await answers to these very basic questions.

Several observations serve as cautionary points when interpreting the data presented by Chung et al. First, the use of historical controls, because of the likelihood of significant bias inherent to all studies using noncontemporaneous controls, obligates the authors to thoroughly demonstrate the between-group similarity of all parameters potentially impacting mortality. Were the causes of renal failure primarily ischemic or nephrotoxic ATN, and were the numbers of each similar between groups? What were the rates of oligoanuria, and are there differences in the rates of renal recovery between the two groups? These are examples of variables impacting mortality for which we do not have data for purposes of comparison. Additionally, in the CRRT group, what criteria were used to initiate renal replacement therapy? To establish RIFLE scores at T0, for example, what criteria were used to determine baseline serum creatinine values? Additionally, T0 occurred by hospital day 7 in two thirds of the CRRT group, compared with just one third of the control group, suggesting important differences in the clinical course, length of hospitalization, or cause of renal failure between the two groups of patients. More generally, given the small study population, it is likely that type-II errors obscure differences in baseline characteristics between the two groups, for which group statistics are only provided for a limited number of variables.

Given the rapidity with which the Army Medical Department has implemented improvements in trauma care during the conflicts in Iraq and Afghanistan during the past several years, it is likely that other factors beyond the introduction of the CRRT program have impacted the survival of these patients, when compared with a historical control group. Improvements in wound care generally, and burn care specifically, are notable in this regard.

For these reasons, caution is therefore advised before concluding that the specific CRRT regimen used by Chung et al. is solely responsible for the improved survival herein reported. Nonetheless, the reported mortality rates in the CRRT group are impressively low, some of the lowest reported historically in an extremely high-risk population of patients. Although we should not yet ascribe this finding to their CRRT program alone, the authors rightly call for definitive, randomized trials to confirm improved survival rates and to identify contributory factors, particularly in light of the rather impressive survival of their series of patients.

Dr. Kevin K. Chung (US Army Institute of Surgical Research, Fort Sam Houston, TX): We thank Dr. Perkins for his thoughtful discussion of our article. He is correct in advising cautious interpretation of our findings. The flaws identified are pertinent and expose the shortcomings of a retrospective study with its perceived bias unavoidable. Clearly, many issues with regard to timing of initiation, mode, and dose need further prospective study. Some will be answered by the ATN trial cited by Dr. Perkins. We have modified the paragraph in our Discussion section to elaborate on these limitations. However, the one issue that seems undisputed (and therefore we would like to continue to emphasize) is that some form of renal support (regardless of mode and dose) is likely better than no treatment (i.e., medical management alone) when dealing with a high-risk population who develops acute kidney injury.

In our burn ICU, before the development of our CRRT program, at the very core of many disputes over whether a burn patient with acute kidney injury should be placed on renal replacement, stood two issues: perceived efficacy and hemodynamic tolerability. In a few patients, the notion of medical futility was invoked as a reason not to initiate therapy. Although it may have been appropriate when the patient had finally reached that point of no return, perhaps early intervention could have had a lifesaving impact. In others, hemodynamic tolerability of therapy, regardless of mode, was questioned. Not only was CRRT, with the mode and dose used in our study, hemodynamically tolerated, all patients requiring vasopressors upon initiation of therapy came off support by 48 hours. Undeniably, CRRT was hemodynamically tolerated, if not therapeutic with a non-renal effect.

Like many others, we are left with many unanswered questions. How would sustained low-efficiency dialysis or extended daily dialysis compare with CRRT? What is the optimal dose of therapy? What is the best fluid? What artificial kidney membrane is most efficacious? Does therapeutic plasma exchange have a role in patients with septic shock and acute kidney injury? A few things, however, are crystal clear. In the most severely burned, development of acute kidney injury is associated with an unacceptably high death rate. Waiting until "traditional indications" are met to initiate renal support will result in death for most. An alternative approach is needed. We think we have such an approach albeit one that demands further study.

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