Resolution of Sepsis-Associated Acute Kidney Injury: Association with Emergency Department Fluid Management Patterns

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Abstract

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Background: Sepsis is the most common cause of acute kidney injury (AKI). AKI is associated with poor outcomes including progression to chronic kidney disease, increased intensive care unit and hospital length of stay, and mortality. Recent evidence suggests that trajectory of AKI (duration and resolution/persistence), rather than KDIGO stage, is associated with these poor outcomes. Fluid management decisions made during early resuscitation have the potential to improve AKI trajectory in patients with sepsis.

Objective: To examine the association between emergency department (ED) fluid management patterns and AKI resolution in a cohort of ED patients with septic shock.

Methods: Retrospective cohort study of 292 patients with septic shock identified in the ED at an academic county hospital in Seattle, WA from 2009 -2015. Multivariable relative risk regression was used to examine the association between two exposures; 1) total resuscitation volume administered in the ED and 2) total volume of Lactated Ringer's solution administered in the ED, and the outcome of unresolved AKI at the earliest of death, discharge, or hospital day 5.

Measurements and Main Results: Two-hundred six patients (71%) had sepsis-associated AKI and 83 (28%) had unresolved AKI. Patients with unresolved AKI were older, had more comorbidities, and were more severely ill. Mortality during the first 5 hospital days was more common among patients with unresolved AKI (34%) than those with resolved AKI (<1%) or no AKI (<1%). There was a trend toward decreased risk of unresolved AKI in patients receiving larger total ED resuscitation volumes. Each liter of Lactated Ringer's solution administered in the ED was associated with a 24% decreased relative risk of unresolved AKI (95%CI 5%-39%, P=0.02).

Conclusions: In this cohort, increased volume of Lactated Ringer's solution in the ED was independently associated with decreased risk of unresolved AKI. This result supports the need for randomized trials comparing ED resuscitation with 0.9% saline to balanced crystalloid in patients with septic shock.

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Background

There are over 750,000 cases of severe sepsis or septic shock in the U.S. annually, and severe sepsis/septic shock has a case fatality of 20-30% [1]. Sepsis is the most common cause of AKI (AKI occurs in 50-60% of sepsis cases), and the development of Sepsis-Associated AKI (SA-AKI) during the course of sepsis increases the risk of in-hospital mortality by 6-8 fold [2, 3]. SA-AKI can be part of the multi-organ dysfunction syndrome, and is often on the causal pathway between septic shock and mortality. In addition to its association with mortality, SA-AKI is also associated with prolonged intensive care unit (ICU) and hospital length of stay, and prolonged duration mechanical ventilation [4-6]. Finally, an episode of SA-AKI can progress to chronic kidney disease (CKD) or cause worsening of existing CKD [7-10].

The most recent guidelines for staging AKI were published in 2012 by the Kidney Disease: Improving Global Outcomes (KDIGO) group [11]. While these guidelines have been extremely useful for unifying AKI definitions across studies, recent evidence suggests that the trajectory of AKI (duration and resolution vs. persistence), rather than KDIGO stage, is associated with renal and overall outcomes in patients with AKI [7, 12-15].

The pathogenesis of SA-AKI is incompletely understood, but likely multifactorial [16]. Some factors contributing to the development and outcome of SA-AKI, including macrovascular renal perfusion abnormalities, increased renal vein pressures, formation of renal parenchymal edema, inflammation, and activation of the tubuloglomerular feedback mechanism may be modifiable via fluid management decisions made early in the course of sepsis management [17-24].

Guidelines for management of sepsis and septic shock recommend early resuscitation with intravenous crystalloid [25] . Early crystalloid resuscitation can help treat the

macrovascular renal perfusion abnormalities (systemic vasodilation, hypotension, and relative hypovolemia) that contribute to SA-AKI. Nonetheless, avoiding excessive volume administration has the potential to reduce the decline in glomerular filtration rate (GFR) that can occur due to increased renal vein pressures and renal parenchymal edema. The choice of a balanced crystalloid (rather than 0.9% saline) in early sepsis has the potential to reduce inflammation, volume retention, and the effect of the tubuloglomerular feedback mechanism (already active in sepsis) on the decline in GFR [26, 27].

The purpose of this study is to evaluate associations between early fluid management practices (volume and composition of resuscitation fluid) and AKI resolution in patients admitted with septic shock.

Methods

Study Design and Subjects

We conducted a retrospective cohort study of adult patients presenting to the emergency department (ED) at an academic public hospital in Seattle, WA between June 2009 and February 2015. Patients were included if septic shock prompted ED clinicians to activate the hospital's sepsis alert protocol. Criteria for activation of this protocol included suspected infection plus hypoperfusion (mean arterial pressure < 65 mmHg, systolic blood pressure < 90 mmHg, and/or lactate > 4 mmol/L) despite fluid resuscitation (≥ 30 ml/kg of crystalloid). The sepsis alert protocol could also be activated based on attending physician judgement. Patients were excluded from this study if they were transferred from another acute care hospital, if they had end-stage renal disease on chronic maintenance hemodialysis, if they had no data available on baseline, outpatient non-emergency department creatinine measured between 7-365 days prior to their ED

presentation, or if they had only 1 creatinine measured during their hospitalization. The University of Washington Institutional Review Board approved the study with a waiver of informed consent.

Data Collection

All data were abstracted from the electronic medical record by bioinformatics personnel or trained physician or nurse abstractors. The Charlson comorbidity index was calculated from discharge diagnoses as previously described [28]. A random sample of records (6%) was reviewed by a second, blinded abstractor, with near perfect interrater agreement as measured by APACHE II patient classification K 0.91 (95% CI 0.80-1.00).

Exposures

Our exposures were total fluid volume given in the ED and total volume of Lactated Ringer's solution (LR) given in the ED. We hypothesized a U-shaped relationship between total fluid volume and unresolved AKI, such that both very low and very high total fluid volumes would be associated with poor renal outcomes. For this reason, we modeled total fluid volume as an ordered categorical variable, with 2-3.5L as the reference range.

Outcome

We defined AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria for change in creatinine from baseline [11]. Baseline creatinine was the most recent outpatient, non-emergency department creatinine drawn between 7 and 365 days prior to this ED presentation. Our primary outcome was unresolved AKI at 5 days/120 hours after ED presentation. Patients were considered to have unresolved AKI at day 5 if they met criteria for AKI within 72 hours of ED admission and the inpatient creatinine measured nearest to but not

after 120 hours since ED presentation still qualified as AKI by KDIGO criteria (≥ 0.3 mg/dL and/or ≥ 50% above baseline) [11]. Patients were also considered to have unresolved AKI if they were on renal replacement therapy (RRT) at the time of death or hospital day 5, regardless of their serum creatinine level. Patients who died or were discharged prior to hospital day 5 were assigned to the no AKI, resolved AKI, or unresolved AKI group for which they met criteria at the time of death or hospital discharge.

Other Definitions

Chronic kidney disease (CKD) was defined as a baseline creatinine that corresponded to an estimated glomerular filtration rate (eGFR) of ≤ 60 mL/min/1.73m^2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [29].

Statistical Analysis

Patients with unresolved AKI were compared to those with no AKI or resolved AKI. Continuous variables with parametric distribution were expressed as mean and standard deviation (SD) and compared in bivariate analyses using unpaired t-tests without the presumption of equal variance. Non-parametrically distributed continuous variables were expressed as median and interquartile range [IQR] and compared using Wilcoxon Rank-Sum tests. Categorical variables were expressed as number and proportion and compared using the chi-square test.

To model the association between total fluid volume or total volume of LR and unresolved AKI, we used two multivariable relative risk regression models with log-link and robust standard error estimates. We used relative risk, rather than logistic regression, because

our outcome is common and an elevated odds ratio would overestimate the relative risk. Categories of potential confounders to be included as covariates in the models were specified a priori and included age, comorbidities, and markers of severity of illness. Selected covariates included age, Charlson comorbidity index, serum lactate, mean arterial pressure, and ED length of stay. The model examining the association between volume of LR and unresolved AKI was also adjusted for volume of 0.9% saline administered in the ED.

We performed three pre-specified sensitivity analyses. First, we addressed the competing risks of AKI resolution, hospital discharge, and mortality by repeating the multivariable models and imputing extreme values (presuming that those who died within 5 days without AKI would have had unresolved AKI had they lived, and that those who were discharged alive with unresolved AKI would have had AKI resolution had they remained in the hospital). Second, we restricted our analysis to patients with KDIGO stage ≥ 2 AKI. Finally, in order to address the fact that creatinine is distributed in total body water, we adjusted all post-ED creatinine values for total fluid volume received in the ED using the equation: adjusted creatinine (Cr_{adj}) = SCr X (1+ [total ED fluid volume/TBW], where SCr is measured serum creatinine and TBW=Total Body Water = 0.60 X patient admit weight. We then redefined AKI and AKI resolution based on Cr_{adj} values, and included those variables for AKI and AKI resolution in the previously described multivariable regression models.

Results

Nine-hundred fourteen patients with septic shock were identified in the ED between June 2009 and February 2015. Of those, 622 were excluded based on the exclusion criteria listed above, leaving 292 patients for inclusion in our cohort (Figure 1). Seventy-one percent (n=206)

of these patients met criteria for AKI within 72 hours of ED presentation. The majority, 195 of 206 (95%) of these patients met criteria for AKI at the time of ED presentation. Of the 97 patients without AKI at the time of admission, only 11 of these (10%) went on to develop AKI by 72 hours. Of those with AKI, 68 (33%) had KDIGO stage 1 AKI, 61 (30%) had stage 2, and 77 (37%) had stage 3. Seven of the patients with Stage 3 AKI received renal replacement therapy during the first 5 days of hospitalization. The distribution and timing of AKI, AKI resolution, hospital discharge, and death from hospital days 1-5 are presented in Figure 2.

Of 206 patients who met criteria for AKI within 72 hours of ED presentation, 83 (40%) had unresolved AKI at the time of death, hospital discharge, or hospital day 5. The ED characteristics of patients with and without unresolved AKI are shown in Table 1. Of note, patients with unresolved AKI tended to be older, to have more pre-existing comorbidities including CKD and heart failure, to have an acidosis at the time of ED presentation (higher lactate, lower pH, lower serum bicarbonate level), and to have a lower mean arterial pressure or require vasopressor support in the ED. In unadjusted bivariate analysis, patients who went on to have unresolved AKI received less total resuscitation fluid volume (median [IQR] 3.1L [2.4-4.0] vs. 4.0L [3.0-4.0], p=0.02), and a lower volume of LR (median [IQR] 0.0L [0.0-0.8] vs. 0.8L [0.0-2.0], p<0.01) in the ED, when compared with those who had no AKI or resolved AKI.

The majority of patients received 2-3.5 (36%) or >3.5-5.0 L (40%) of fluid in the ED, with median [IQR] total fluid volume administration of 4.0L [2.9-4.8L]. Approximately half (n=140, 48%) of patients received some amount of LR in the ED. The characteristics of patients who did and did not receive LR are shown in Table S1 of the supplementary appendix. Of note, patients who received LR tended to be younger [mean (SD) 52 (14) vs. 56 (15) years, p=0.04], to have fewer comorbidities, and to have a higher initial mean arterial pressure (MAP) [mean (SD)

85 (23) vs. 77 (21) mmHg, P<0.01]. Patients receiving LR also had a higher initial serum lactate concentration [median (IQR) 4.8 (2.9-7.5) vs. 3.9 (2.1-6.8) mmol/L, P=0.04].

Figures 3-5 show the proportion of patients with unresolved AKI by volume of Lactated Ringer's solution (Figure 3), by volume of 0.9% saline (Figure 4), and by total resuscitation fluid volume category (Figure 5). These figures suggest a trend toward reduced risk of unresolved AKI in patients who received larger volumes of LR or larger total resuscitation volumes, and no clear pattern or trend in risk of unresolved AKI with increasing volumes of 0.9% saline. The multivariable relative risk regression for independent association between volume of LR and unresolved AKI suggests a 24% decreased relative risk of unresolved AKI per 1 liter increase in volume of LR [RR 0.76, 95% confidence interval (CI) 0.61-0.95, P=0.02] (Table 2). In the model for independent association between total fluid volume category and unresolved AKI, there was a trend toward increased risk of unresolved AKI in the lowest fluid volume category (<2L) and decreased risk in the two higher fluid volume categories (>3.5-5.0L and >5.0L) (Table 3).

There were 30 patients who died within the first 5 days of hospitalization (Figure 2). Of these, 28 (93%) died with unresolved AKI, one with resolved AKI and one without AKI. All other patients with no AKI or resolved AKI survived to hospital day 5. Three patients were discharged with unresolved AKI. In the sensitivity analysis imputing extreme values for patients who died without AKI or were discharged with AKI, the association between higher volumes of LR and lower risk of unresolved AKI remained (RR 0.77, 95%CI 0.61-0.97, P=0.03).

Similarly, in the model restricted to the 138 patients with KDIGO stage 2 or higher AKI, the trend toward decreased risk of unresolved AKI with higher volumes of LR and higher total fluid volumes persisted. (Supplementary Tables S2 and S3).

Weight was missing for 1 subject, and this subject was excluded from the analysis using ED-fluid-adjusted creatinine estimates. After adjusting subsequent measured creatinine values for resuscitation fluid administered in the ED, 5 subjects who were initially classified as having no AKI were re-classified as having AKI. Of these, all 5 had AKI that resolved by death, discharge, or hospital day 5. Nine patients initially classified as having resolved AKI were re-classified as having unresolved AKI after adjusting serial measured creatinine values for the total resuscitation fluid volume administered in the ED. In the multivariable regression analysis performed with these adjusted creatinine values, the association between higher volume of LR and lower risk of unresolved AKI remained (RR 0.78, 95% CI 0.63-0.97, P=0.03) (Supplementary Tables S4 and S5).

Discussion

Summary of Findings

In this single-center cohort of 292 patients with septic shock identified in the ED, 71% met criteria for AKI within 72 hours of ED presentation, and 28% had unresolved AKI at the time of death, hospital discharge, or hospital day 5. Patients in this cohort were most likely to meet criteria for AKI at the time of ED presentation, with only a minority developing AKI later in their hospitalization. Mortality was much more common in patients with unresolved AKI (34%) than those with no AKI (<1%) or resolved AKI (<1%).

Larger volumes of LR in the ED were independently associated with a decreased risk of unresolved AKI after adjusting for age, comorbidities, and markers of severity of illness. In

addition, there was a steadily decreasing risk of unresolved AKI with total resuscitation fluid volumes > 2.0L.

Comparison with Previous Studies

There is limited literature that specifically investigates the degree to which volume and/or composition of ED resuscitation fluid is associated with AKI resolution in patients with septic shock. In 2001, Rivers et al published their landmark randomized controlled trial (RCT) of early goal directed therapy (EGDT) [30]. Patients randomized to EGDT received larger volumes of fluid during the first 6 hours of therapy than those randomized to usual care [mean (SD): 5.0L (3.0) vs. 3.5L (2.4)]. Patients in the EGDT arm had a lower Multi Organ Dysfunction Score (of which serum creatinine concentration is a component) at 72 hours (5.1 vs. 6.4, $p<0.001$). In 2006 Lin et al tested a modified goal-directed protocol vs. usual care in an RTC of 224 ED patients with septic shock [31]. Patients randomized to the goal-directed therapy (GDT) protocol received more resuscitation fluid during the period of persistent shock (136.2 mL/hour vs. 88.6 mL/hour in the usual care group), and had a lower incidence of sepsis-associated renal failure than those assigned to usual care (39% vs. 55%, P=0.015). The results of these RCTs are consistent with our results showing a trend towards improved renal outcomes in patients who received larger volumes of early resuscitation fluids.

However, in the 2014 ProCESS investigators published an RCT of 1351 patients with septic shock randomized to receive EGDT, protocol-based standard therapy (PSC), or usual care [32]. Fluid volume prior to randomization plus that given in the first 6 hours after randomization differed only slightly between the arms (5.1L in the EGDT arm, 5.5L in the PSC arm, and 4.4L in the usual care arm). In a recently published an ancillary study to ProCESS, Kellum et al

reported no difference in new AKI (40.3% in EGDT, 34.9% in PSC, and 38.1% in usual care, P=0.52) or recovery from AKI (complete recovery 57.3% in EGDT, 55.2% in PSC, and 54.1% in usual care, P=0.89) [33]. Interpretation of these trials with regard to resuscitation fluid volume and renal outcomes is challenging, as fluid volume was only a portion of the study protocols. Thus, we cannot determine if fluid volume, another component of the bundle, or a combination of bundle components, was responsible for the observed renal outcomes.

With regards to fluid composition, there are multiple observational studies that observed an association between hyperchloremia or 0.9% saline (vs. balanced fluids such as LR or Plasma-lyte) and worse renal and/or overall outcomes in critically-ill patients [34-39]. These observational studies have spawned several prospective and/or randomized trials of 0.9% saline vs. balanced fluid in ICU patients. In 2012 and 2015, Yunos et. al. published two open-label prospective studies of ICU patients that sequentially compared an ICU-wide chloride-restrictive regimen (balanced fluid) to an ICU-wide chloride-liberal regimen (0.9% saline) [40, 41]. In the first study there was a reduced incidence of AKI [OR 0.52 (95% CI 0.37-0.75), and need for renal replacement therapy (RRT) [OR 0.52 (95%CI 0.33-0.81) in patients assigned to the chloride-restrictive regimen [40]. Similarly, the 2015 study (which inverted the two groups in the calculation of relative risk) observed an increased risk of AKI [HR 1.32 (95%CI 1.11-1.58), P=0.002] and need for RRT [HR 1.44 (95% CI 1.10-1.88), P=0.006) in the chloride-liberal group [41]. However, the SPLIT RCT published in 2015 showed no difference in incident AKI in those treated with Plasma-Lyte 148 vs. 0.9% saline [RR 1.04 (95%CI 0.80-1.36), P=0.77] [42]. Of note, the recently published SALT pilot study is the only RCT to report on the interaction between total fluid volume and fluid composition [43]. While the SALT primary analysis showed no association between crystalloid composition and their primary outcome (composite of

death, dialysis, or persistent renal dysfunction at 30 days), in patients receiving larger volumes of crystalloid, there was higher incidence of AKI and more receipt of new RRT in patients assigned to saline (p-value for interaction=0.026) [43].

It should be noted that none of these RCTs included resuscitation fluid administered in the ED as part of their study protocol. In addition, the patients included in the SPLIT and SALT studies had relatively low illness severity and received, on average, lower volumes of resuscitation fluid when compared to the cohort of patients with septic shock included in this study. When considering AKI resolution, it may be that the ED represents a window of opportunity during which fluid volume and type have the greatest potential to influence outcomes. Also, as suggested by the results of the SALT study, it may be that fluid composition has the greatest impact on renal outcomes in patients who receive large volumes of resuscitation fluid (such as those with septic shock).

Strengths and Limitations

We limited the cohort to patients with available baseline outpatient creatinine levels available from 7-365 days prior to ED presentation. While a strength in some ways (see below), this choice may skew our population toward having a relatively higher proportion of chronic illness. The small sample size also limited our ability to adjust for additional confounders (specific comorbidities and other markers of illness severity), and there is a possibility that the observed association is the result of residual confounding. Finally, the small number of patients who received very small or very large volumes of fluid limited our ability to assess the hypothesized U-shaped relationship between total resuscitation fluid volume and unresolved AKI.

Many studies of AKI in critical illness, including sepsis, have missing or partially missing data on pre-morbid renal function. These studies choose to navigate this missing data problem by either defining AKI as an increase in inpatient creatinine values or by imputing baseline creatinine values for those with missing data, most often assuming a baseline GFR of 75 $mL/min/m^2$. Either of these approaches is highly prone to misclassification of AKI. By limiting our cohort to patients with known baseline outpatient creatinine prior to onset of acute illness, we avoid this misclassification bias. Also, by doing so, we are able to accurately diagnose AKI based on the first creatinine drawn in the ED, to observe that the majority of patients with SA-AKI meet AKI criteria at the time of ED presentation, and to accurately report the timing of AKI, AKI resolution, hospital discharge, and death in a cohort of patients with septic shock.

Finally, we chose AKI resolution/unresolved AKI as our outcome in this study. There is a growing body of evidence suggesting that AKI trajectory (resolution/partial resolution/non-resolution), rather than KDIGO stage or highest inpatient serum creatinine, is associated with overall outcomes in critically ill patients [7, 12-15]. If, as these data suggest, most patients with SA-AKI have AKI at the time of ED presentation, then it is important to assess ED resuscitation practices for association with higher or lower likelihood of AKI resolution.

Conclusions

The majority of patients with SA-AKI met AKI criteria at the time of ED presentation. A higher volume of LR administered in the ED was associated with decreased risk of unresolved AKI in patients with septic shock. There was a trend toward decreased risk of SA-AKI in patients receiving higher volumes of total fluid administration in the ED. Time spent in the ED may represent a window of opportunity in which fluid management decisions have the potential

to influence renal outcomes. These data are suggestive, particularly given the results of ICU-based trials suggesting improved renal outcomes with balanced fluid, that ED treatment with LR (vs. 0.9% saline) may improve renal outcomes in patients with septic shock. While the results of the present study are by no means definitive, they support the need for a randomized trial of 0.9% saline vs. balanced crystalloid in ED patients with septic shock.

FIGURES

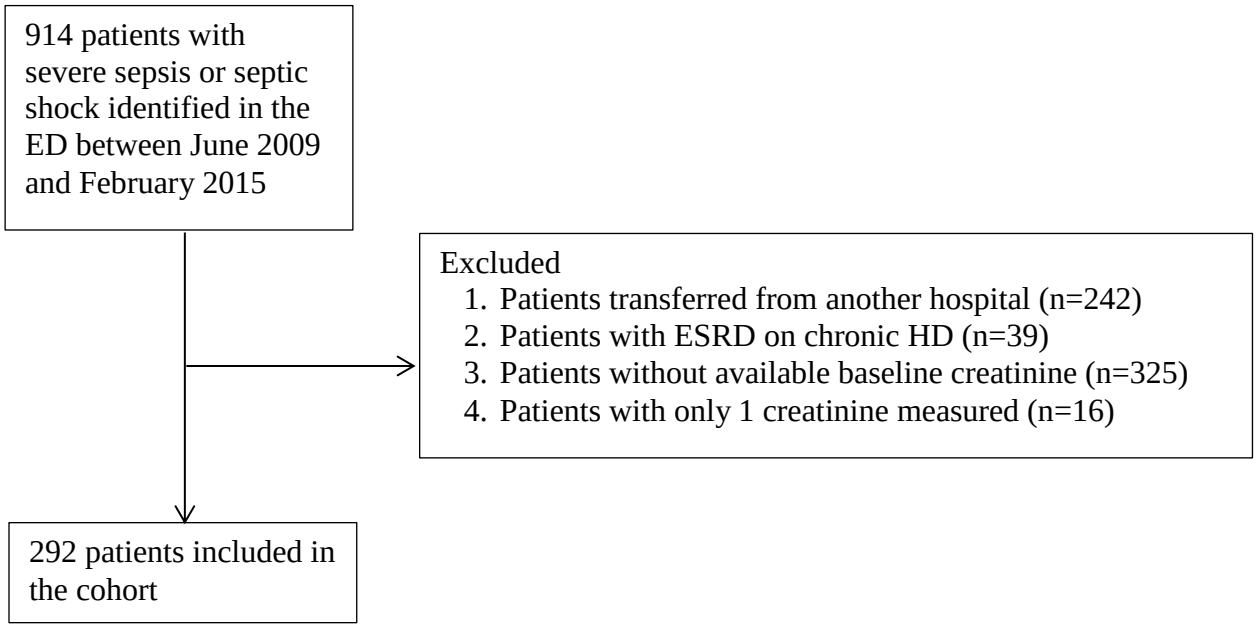


Figure 1: Cohort Selection

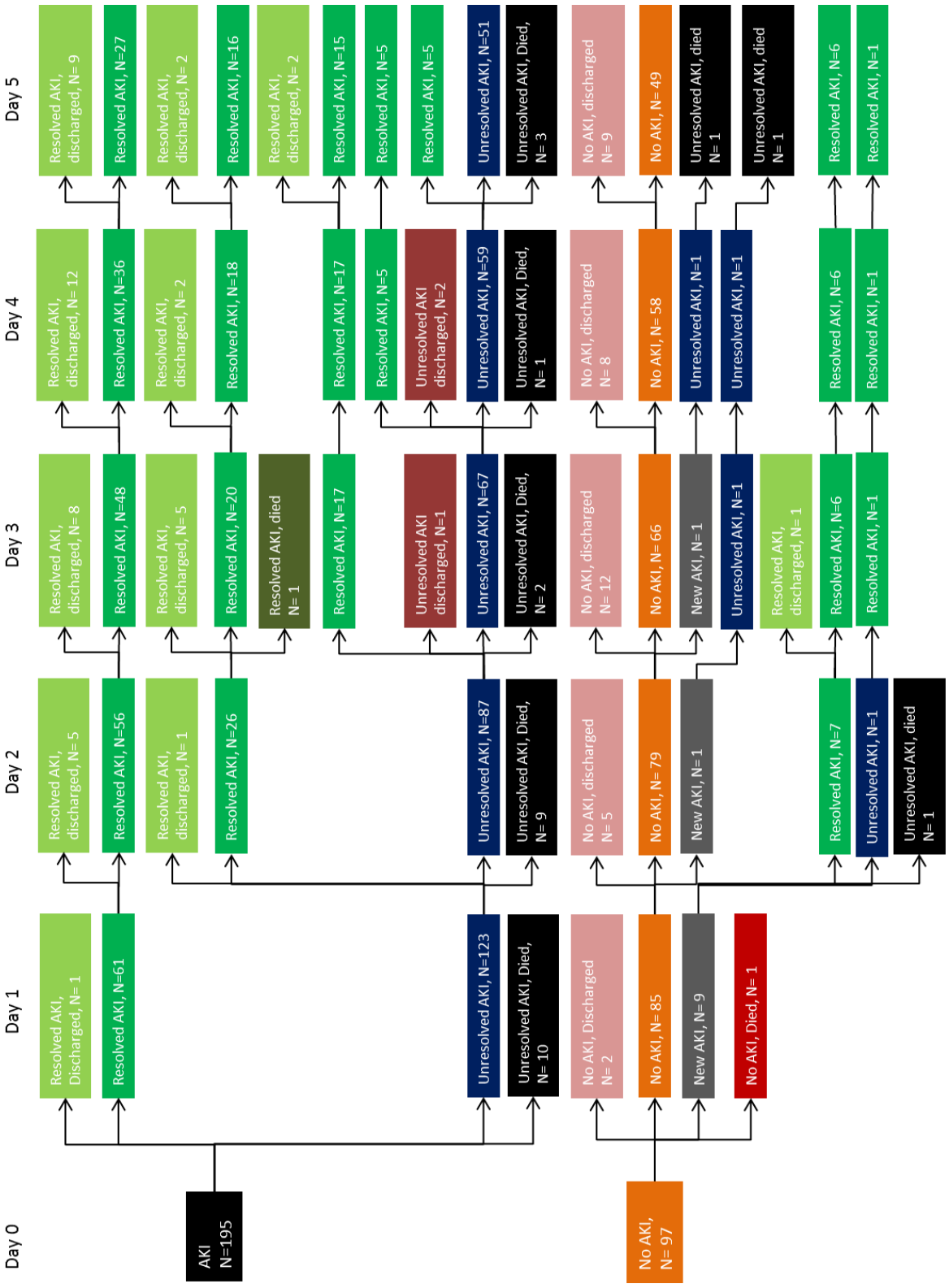


Figure 2: Flow of cohort through AKI, AKI resolution, Discharge, and Death from ED presentation (Day 0) through Hospital day 5

Figure 3

Trend toward decreased risk of unresolved AKI in patients receiving higher volumes of Lactated Ringer's solution.

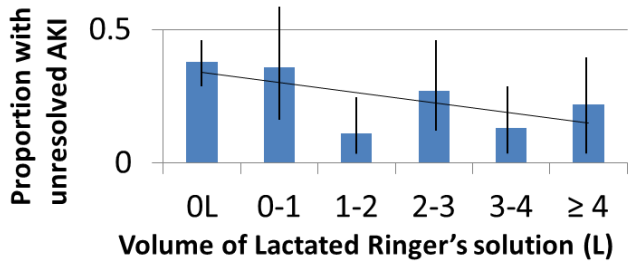


Figure 4

No trend in risk of unresolved AKI with higher volumes of 0.9% saline.

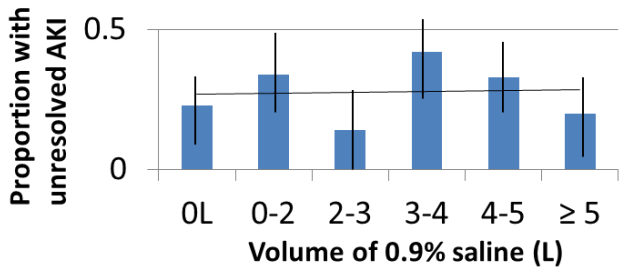
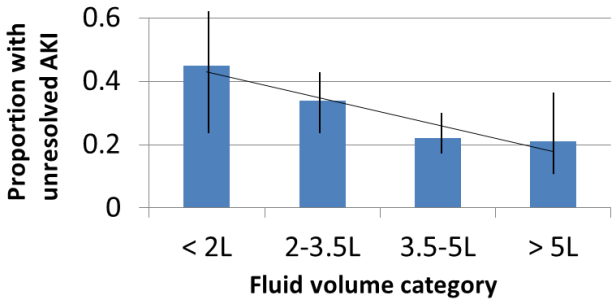


Figure 5

Proportion of patients with unresolved AKI by volume of total crystalloid administration



TABLES

Table 1: Characteristics of patients with and without unresolved AKI*			
	No AKI or Resolved AKI (n=209)	Unresolved AKI (n=83)	P-value
Demographic Information and Pre-existing conditions			
Age (years)	53 (14)	58 (15)	0.01
Male	145 (69%)	56 (68%)	0.75
Race			0.38
White	138 (66%)	50 (60%)	
Black	32 (15%)	13 (16%)	
Asian	23 (11%)	8 (10%)	
American Indian or Alaskan Native	15 (7%)	12 (14%)	
Multiracial	1 (<1%)	0 (0%)	
BMI (kg/m^2)	26.8 (7.9)	27.9 (6.6)	0.24
Admitted from nursing facility or LTAC	15 (18%)	49 (23%)	0.32
Charlson comorbidity index	2[1-3]	3[2-4]	<0.01
Chronic Kidney Disease[+]	13 (6%)	14 (17%)	<0.01
Baseline outpatient creatinine (mg/dL)	0.84 [0.70-1.00]	0.88 [0.70-1.16]	0.13
Baseline outpatient eGFR[#] ($mL/min/1.73m^2$)	102 (26)	92 (30)	0.01
Cirrhosis with complication	20 (10%)	20 (24%)	<0.01
NYHA Class 4 Heart Failure	11 (5%)	13 (16%)	<0.01
Clinical Characteristics			
Lactate (mmol/L)	3.9 [2.1-6.5]	4.9 [3.1-8.6]	<0.01
First RR in ED (breaths/min)	21 (7)	22 (8)	0.46
First SBP in ED (mmHg)	110 (28)	103 (27)	0.05
First MAP in ED (mmHg)	83 (22)	77 (21)	0.03
First HR in ED (beats/min)	112 (25)	111 (28)	0.94
Glasgow Coma Score	13 (4)	13 (4)	0.24
Sodium (mEq/L)	134 (8)	130 (14)	0.02
Chloride (mEq/L)	99 (8)	97 (9)	0.09
Potassium (mEq/L)	4.1 (1.1)	4.3 (1.3)	0.22
Bicarbonate (mEq/L)	21.6 (5.5)	18.6 (5.8)	<0.01
pH	7.34 (0.12)	7.28 (0.16)	0.01
Blood Urea Nitrogen (mg/dL)	18 [12-34]	29 [18-54]	<0.01
Creatinine (mg/dL)	1.20 [0.85-1.93]	2.30 [1.40-3.08]	<0.01
Practice Patterns			
Intubated in ED or by medics	50 (24%)	29 (35%)	0.06
Vasopressors in the ED or by medics	45 (22%)	28 (34%)	0.03
Time to vasopressors (n=73)	178 [123-273]	145 [92-211]	0.29
Time to antimicrobials (minutes) (n= 272)	135 [88-220]	115 [73-219]	0.16
Total ED Fluids (L)	4.0 [3.0-5.0]	3.1 [2.4-4.0]	0.02
Total NS (L)	3.0 [1.0-4.0]	3.0 [1.5-4.0]	0.49
Total LR (L)	0.8 [0.0-2.0]	0 [0-0.8]	<0.01
Any LR	114 (55%)	26 (31%)	<0.01
ED length of stay (minutes)	344 [255-485]	323 [235-410]	0.09

* Values provided are number(%), mean (standard deviation), or median [interquartile range]

[+] Baseline estimated glomerular filtration rate < 60 $mL/min/1.73m^2$, as estimated using the Chronic Kidney Disease Epidemiology (CKD-Epi) calculator

[#] Estimated using CKD-Epi calculator

Table 2: The association between volume of Lactated Ringer's solution and unresolved AKI at day 5 as estimated using multivariable relative risk regression.*

	Relative Risk[#]	95% Confidence Interval	P-value
Volume of Lactated Ringer's solution (L)	0.76	0.61-0.95	0.02
Volume of 0.9% saline (L)	0.95	0.94-1.07	0.40

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure, initial lactate concentration, and emergency department length of stay.
[#] Relative Risk is per 1 liter increase in volume of Lactated Ringer's solution or 0.9% saline.

Table 3: The association between total fluid volume category and unresolved AKI as estimated using multivariable relative risk regression.*

Total Fluid Volume (L)	Relative Risk	95% Confidence Interval	P-value
<2.0	1.25	0.76-2.05	0.39
2.0-3.5	Reference		
>3.5-5.0	0.67	0.44-1.02	0.06
>5.0	0.73	0.40-1.31	0.29

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure , initial lactate concentration, and emergency department length of stay.

SUPPLEMENTARY APPENDIX

Table S1: Characteristics of patients who did and did not receive Lactated Ringer's solution (LR) in the Emergency Department*			
	No LR (n=152)	Received LR (n=140)	P-value
Demographic Information and Pre-existing conditions			
Age (years)	56 (15)	52 (14)	0.04
Male	99 (65%)	102 (73%)	0.15
Race			0.60
White	98 (64%)	90 (64%)	
Black	24 (16%)	21 (15%)	
Asian	18 (12%)	13 (9%)	
American Indian or Alaskan Native	11 (7%)	16 (11%)	
Multiracial	1 (1%)	0 (0%)	
BMI (kg/m^2)	28 (8)	26 (7)	0.07
Admitted from nursing facility or LTAC	30 (20%)	34 (24%)	0.35
Charlson comorbidity index	2.5 [1-4]	2 [1-4]	0.06
Chronic Kidney Disease[+]	18 (12%)	9 (6%)	0.11
Baseline outpatient creatinine (mg/dL)	0.9 [0.7-1.1]	0.8 [0.68-1.0]	0.02
Baseline outpatient eGFR[#] ($mL/min/1.73m^2$)	95 (28)	103 (26)	0.02
Cirrhosis with complication	27 (18%)	13 (9%)	0.04
NYHA Stage 4 Heart Failure	15 (10%)	9 (6%)	0.29
Clinical Characteristics			
Lactate 1 (mmol/L)	3.9 [2.1-6.75]	4.75 [2.9-7.5]	0.04
First RR in ED (breaths/min)	21 (7)	22 (8)	0.30
First SBP in ED (mmHg)	104 (26)	113 (30)	<0.01
First MAP in ED (mmHg)	77 (21)	85 (23)	<0.01
First HR in ED (beats/min)	110 (25)	113 (27)	0.24
Glasgow Coma Scale	14 3)	12 (5)	<0.01
Sodium (mEq/L)	132 (12)	135 (7)	<0.01
Chloride (mEq/L)	97 (9)	99 (8)	0.42
Potassium	4.3 (1.2)	4.1 (1.0)	0.15
Bicarbonate (mEq/L)	21 (6)	21 (6)	0.47
pH	7.32 (0.13)	7.31 (0.15)	0.84
BUN (mg/dL)	24 [14-43]	18.5 [12-36]	0.04
Creatinine (mg/dL)	1.5 [0.99-2.78]	1.26 [0.90-2.25]	0.08
Practice Patterns			
Intubated in ED or prior to ED arrival by medics	36 (24%)	43 (31%)	0.18
Vasopressors started in the ED or prior to arrival by medics	40 (26%)	33 (24%)	0.59
Time to vasopressors (n=73)	181 [103-270]	140 [70-212]	0.29
Time to antimicrobials (minutes) (n= 272)	145 [86-239]	117 [79-188]	0.04
Total ED Fluids (L)	4 [3-4.2]	4 [2.8-5]	0.30
Total NS (L)	4 [3-4.2]	2 [0-3]	<0.01
Total LR (L)	0 [0-0]	2 [1-3]	<0.01
ED length of stay (minutes)	351 [269-499]	318 [243-434]	0.04

* Values provided are number(%), mean (standard deviation), or median [interquartile range]

[+] Baseline estimated glomerular filtration rate < 60 $mL/min/1.73m^2$, as estimated using the Chronic Kidney Disease Epidemiology (CKD-Epi) calculator

[#] Estimated using CKD-Epi calculator

Table S2: The association between volume of Lactated Ringer's solution and unresolved AKI at day 5 in patients with KDIGO Stage 2 or higher AKI*

	Relative Risk[#]	95% Confidence Interval	P-value
Volume of Lactated Ringer's solution (L)	0.85	0.70-1.04	0.11
Volume of 0.9% saline (L)	0.95	0.85-1.06	0.34

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure, initial lactate concentration, and emergency department length of stay.
[#] Relative risk is per 1 liter increase in volume of Lactated Ringer's solution or 0.9% saline.

Table S3: The association between total fluid volume category and unresolved AKI at day 5 in patients with KDIGO Stage 2 or higher AKI*

Total Fluid Volume (L)	Relative Risk	95% Confidence Interval	P-value
<2.0	1.19	0.75-1.87	0.46
2.0-3.5	Reference		
>3.5-5.0	0.79	0.54-1.17	0.24
>5.0	0.62	0.34-1.11	0.11

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure , initial lactate concentration, and emergency department length of stay.

Table S4: The association between volume of Lactated Ringer's solution and unresolved AKI at day 5 using creatinine values adjusted for total resuscitation fluid volume administered in the ED*

	Relative Risk[#]	95% Confidence Interval	P-value
Volume of Lactated Ringer's solution (L)	0.79	0.64-0.98	0.03
Volume of 0.9% saline (L)	0.99	0.89-1.11	0.87

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure, initial lactate concentration, and emergency department length of stay
[#] Relative risk is per 1 liter increase in volume of Lactated Ringer's solution or 0.9% saline.

Table S5: The association between total fluid volume category and unresolved AKI at day 5 using creatinine values adjusted for total resuscitation fluid volume administered in the ED.*

Total Fluid Volume (L)	Relative Risk	95% Confidence Interval	P-value
<2.0	1.29	0.81-2.04	0.29
2.0-3.5	Reference		
>3.5-5.0	0.81	0.55-1.19	0.28
>5.0	0.90	0.52-1.54	0.70

* Model adjusted for age, Charlson Comorbidity Index, mean arterial pressure , initial lactate concentration, and emergency department length of stay.

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