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Treating Acute Kidney Injury
One Less Weapon in the Armamentarium?

Acute kidney injury (AKI), particularly when accompanied by critical illness, remains a devastating condition, and recent evidence consolidates the view that in the critically ill, AKI is associated with sepsis in more than 50% of cases (1). To date, therapy remains supportive, with little evidence that any specific therapy may influence outcome. Indeed, this is apparent when one consults the clinical guidelines for management of AKI, although within this is the recommendation that protocolized hemodynamic management for patients with septic shock be adopted (2). It is therefore timely that in this issue of the *Journal*, Kellum and colleagues (pp. 281–287) report the results of the preplanned ancillary analysis of the ProCESS (Protocolized Care for Early Septic Shock) trial (3). The authors examine the employment of protocol-based fluid resuscitation (early goal-directed treatment [EGDT]) on the development of new-onset AKI of any stage during the first 28 days of enrollment, as well as secondary outcomes, including duration of AKI, recovery of renal function, volume overload, and the need for renal support. The results of the three main studies investigating EGDT in septic shock are well documented, with no significant advantage regarding mortality or morbidity being observed (4–6). However, they did show that timely volume resuscitation and delivery of antibiotics to this patient group appear to have improved dramatically since 2001, given that the crude mortality in the usual care group was just over 18% compared with the crude mortality of 46.5% observed by Rivers and colleagues (7). So what of the effect of alternative resuscitation strategies on AKI in septic shock? Given the absence of difference in outcome in the main analysis, it is perhaps unsurprising that no difference is noted with regard to the primary endpoint of development of new AKI when protocolized care is used compared with usual care.

However, despite any obvious benefit from EGDT, several lessons can be learned from this excellently performed study that may well inform future treatment goals in this patient group. Clearly, the observed incidence of AKI is in keeping with other studies in the critically ill, with more than 50% of patients having AKI at presentation, increasing to almost 70% throughout admission (1, 8, 9). Therefore, this cohort accurately reflects the case mix commonly seen in intensive care practice. The patients with, or who develop, AKI have the usual risk factors, including older age, diabetes, and heart failure, and in particular, those who present with AKI have a degree of chronic kidney disease and are more likely to develop positive blood cultures. The severity of illness of those presenting with AKI on admission appears to be worse. Do these results then support a nihilistic view with regard to volume resuscitation in these patients? Clearly not, as the authors themselves concede. However, the results do suggest that overall care may have improved with time, and that by the time of presentation, one is faced with damage limitation with regard to further organ failure, including AKI, rather than a reversal of the fundamental pathological processes. Indeed, of those who develop AKI, most do within a few days of admission, which probably reflects events occurring prehospital; hence, intervention may not be as fruitful.

A major criticism of many interventional studies on AKI is the fact that both creatinine and urine output criteria are rarely

employed, given the perceived difficulties in achieving accurate urine output. This is not the case in this study, where data are robust and almost complete, with only seven patients excluded from enrollment. Interestingly, patients who developed AKI after admission were classified predominantly on the basis of urine output criteria, rather than change in serum creatinine. This is of note, as it may reflect an inadequacy to excrete the solute load in individuals who one assumes are catabolic, and despite the fact that there is no observed creatinine rise, this still translates into a worse outcome. Herein lies one of the confounders of AKI diagnosis, in that creatinine, a robust marker of chronic kidney disease in relatively stable patients, performs poorly in the acute arena. Thus, a "rise" in creatinine may be masked by a reduction in creatinine production that can fall by up to 50% in sepsis (10). This study highlights the observation that functional change in urine output may herald significant risk, which may have been overlooked previously and may not be identified in terms of renal recovery. Indeed, this study provides further insights into recovery from sepsis-associated AKI, in that individuals who survive to resolution of AKI (as defined by a serum creatinine of <1.5 baseline) appear to approach the same long-term outcomes as those who did not suffer AKI. It would be interest to see whether individuals classified as having AKI by urine output criteria alone have a similar or different longer-term risk profile.

So where does that leave the treatment of AKI complicating septic shock? Clearly initial resuscitation and prompt use of antibiotic therapy remain the mainstay in treating sepsis, and it is doubtful that EGDT, even if the protocols are changed slightly, will result in significant improvements. We should consider fluid therapy as a drug therapy, with more attention given to the different phases of fluid therapy during the patient's course of illness. This includes lifesaving fluid resuscitation in the rescue phase, titration of fluids to tissue perfusion in the optimization and stabilization phases, and mobilization of accumulated fluid in the deescalation phase (11, 12). In addition, the choice of fluids deserves further study, as cohort studies suggest worse outcomes for patients resuscitated with unbalanced crystalloid solutions (13–15). In addition, therapies aimed at restoring function to near baseline may be the future. This may, of course, be as simple as avoiding episodes of hypotension, restricting volume, and avoiding nephrotoxins. Such attention to detail should be mandatory to avoid the scenario in which renal function is killed, as perhaps the most sobering statistic from this study is the appalling outlook for those who do not recover, given a mortality rate approaching 80% at 28 days. So fluids remain in the armamentarium of those charged with treating AKI, but protocolized goal-directed therapy does not seem to be a magic bullet. ■

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ORIGINAL ARTICLE

The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock

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Abstract

Rationale: Septic shock is a common cause of acute kidney injury (AKI), and fluid resuscitation is a major part of therapy.

Objectives: To determine if structured resuscitation designed to alter fluid, blood, and vasopressor use affects the development or severity of AKI or outcomes.

Methods: Ancillary study to the ProCESS (Protocolized Care for Early Septic Shock) trial of alternative resuscitation strategies (two protocols vs. usual care) for septic shock.

Measurements and Main Results: We studied 1,243 patients and classified AKI using serum creatinine and urine output. We determined recovery status at hospital discharge, examined rates of renal replacement therapy and fluid overload, and measured biomarkers of kidney damage. Among patients without evidence of AKI at enrollment, 37.6% of protocolized care and 38.1% of usual care patients developed kidney injury ($P = 0.90$). AKI duration ($P = 0.59$) and rates of renal replacement therapy did not differ between study arms (6.9% for protocolized care and 4.3% for usual care; $P = 0.08$). Fluid overload occurred in 8.3% of protocolized care and 6.3% of usual care patients ($P = 0.26$). Among patients with severe AKI, complete and partial recovery was 50.7 and 13.2% for protocolized patients and 49.1 and 13.4% for usual care patients ($P = 0.93$). Sixty-day hospital mortality was 6.2% for patients without AKI, 16.8% for those with stage 1, and 27.7% for stages 2 to 3.

Conclusions: In patients with septic shock, AKI is common and associated with adverse outcomes, but it is not influenced by protocolized resuscitation compared with usual care.

Key words: sepsis; septic shock; resuscitation; early goal-directed therapy; acute kidney injury

Acute kidney injury (AKI) is a common complication of critical illness, affecting nearly two-thirds of patients admitted to intensive care units (ICU) (1–3). Two of the most commonly identified etiologies for AKI are sepsis and shock (4); when these conditions occur together, the rate of AKI approaches 80% (1). Fluid resuscitation followed by vasopressor medications are the mainstays of initial treatment for shock. Protocolization of resuscitation aims to limit variation and improve deployment of these treatments. However, fluid overload may lead to congestion in the kidney and worsen injury (5, 6). Therefore, it is important to understand whether protocols that alter fluid therapy and pressor use during resuscitation provide benefit or harm to the kidney as manifested by differences in rates and severity of AKI, need for renal replacement therapy (RRT), or recovery of kidney function.

To address these questions, we conducted an ancillary study to the ProCESS

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*A complete list of ProCESS and ProGReSS-AKI Investigators is available at https://crisma.upmc.com/progressakistudy.

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At a Glance Commentary

Scientific Knowledge on the Subject: Protocolized resuscitation may reduce acute kidney injury and improve recovery and reduce need for renal replacement therapy.

What This Study Adds to the Field: In patients with septic shock, neither the development nor the course of acute kidney injury is influenced by protocolized resuscitation compared with current usual care. Because most sepsis-associated acute kidney injury is present at or soon after presentation, effective strategies should focus on improving resolution.

(Protocolized Care for Early Septic Shock) study, a 31-site, randomized controlled trial of alternative resuscitation strategies (two experimental protocols vs. usual care) for septic shock (7). Specifically, we examined the occurrence of AKI on presentation, the development of new AKI, and the course of all AKI across treatment arms by clinical criteria and by novel kidney injury biomarkers. We also studied the use of RRT both during the hospitalization and out to 1 year. Our hypothesis was that protocolized resuscitation would reduce new AKI, improve recovery from new or existing AKI, and result in less short- and long-term dialysis use.

Methods

Study Design

Details of the ProCESS trial have been published previously (7). Briefly, ProCESS was a multicenter, randomized clinical trial that tested alternative resuscitation strategies for patients who presented to emergency departments with septic shock. Eligible patients had suspected infection plus hypotension, hyperlactemia, or both after an initial fluid bolus. One strategy, known as early goal-directed therapy (EGDT) (8), targeted fluids, vasoactive medication, and blood transfusions to central venous oxygen saturation (as a measure of oxygen delivery to the tissues.) Another strategy, termed protocol-based standard care (PSC), used a simpler structured approach based on blood pressure and heart rate, and the clinical assessment by the study team. The third arm of the trial was "usual care," in which the clinical providers, not the study team, directed all care, with the study coordinator collecting data but not prompting any actions (Table 1). Lead investigators at a site could not serve as the bedside treating physician for patients in the usual care group.

Patients and Study Procedures

In ProCESS, we randomized 1,351 patients 1:1:1 to either EGDT, PSC, or usual care within 2 hours of meeting entry criteria. All patients or their legally authorized representatives provided written informed consent. We randomized subjects using a centralized Web-based program in variable block sizes of 3, 6, or 9, with stratification according to site and race. After excluding patients with end-stage renal disease (n = 83) or baseline serum creatinine values >4 mg/dl (n = 8), or with missing enrollment serum creatinine values (n = 7), 1,243 patients remained in the analysis (Figure 1).

Outcome Measures

Our primary outcome was the development of new onset AKI (any stage) over the first 28 days after enrollment. Secondary outcomes included duration of AKI, recovery status at hospital discharge, development of fluid overload in the first 72 hours, and use of RRT. For the primary analysis, we restricted our sample to patients without AKI at enrollment, but for the secondary analyses, we included all patients. We also examined outcomes associated with AKI, including mortality (in-hospital to 60 d), 1-year survival, and death or use of dialysis at 60 days and 1 year.

We classified AKI according to Kidney Disease: Improving Global Outcomes criteria (9) using both serum creatinine and urine output. Patients with evidence of AKI based on serum creatinine at the time of enrollment were classified as having AKI at enrollment. We recorded hourly urine output for the first 72 hours or until ICU discharge if before 72 hours. We obtained daily serum creatinine values for 28 days for all subjects who

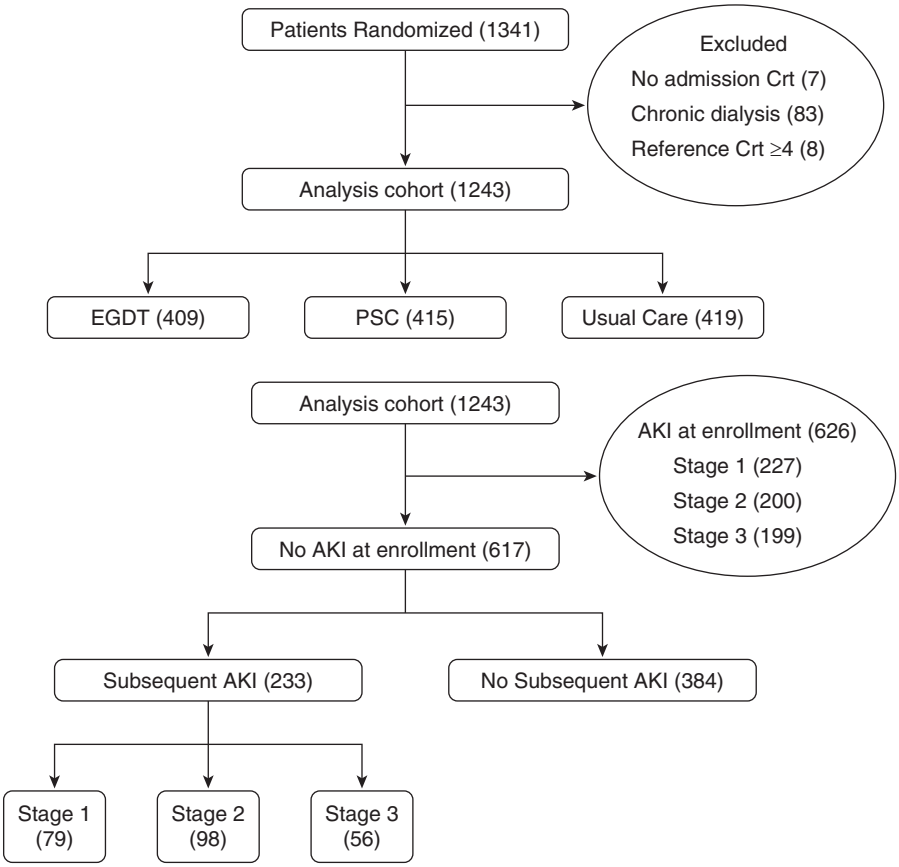

Figure 1. Study cohort. The *top panel* displays the analysis cohort by treatment arm. The *bottom panel* shows acute kidney injury (AKI) status at enrollment and subsequently, as well as AKI stages. Crt = creatinine; EGDT = early goal-directed therapy; PSC = protocol-based standard care.

Table 1. Differences in Interventions by Treatment Arm

Intervention*	EGDT (*n* = 439)	PSC (*n* = 446)	Usual Care (*n* = 456)	*P* Value†
Resuscitation				
Central venous catheterization	411 (94%)	252 (57%)	264 (58%)	<0.0001
Central venous oximeter catheterization	409 (93%)	18 (4%)	16 (4%)	<0.0001
Intravenous fluids, L, mean	2.8	3.3	2.3	<0.0001
Vasopressor use	241 (55%)	233 (52%)	201 (44%)	0.003
Dobutamine use	35 (8%)	5 (1%)	4 (1%)	<0.0001
Blood transfusion	63 (14%)	37 (8%)	34 (8%)	0.001
Ancillary care				
Mechanical ventilation	116 (26%)	110 (25%)	99 (22%)	0.25
Intravenous antibiotics	428 (98%)	433 (97%)	442 (97%)	0.90
Corticosteroids	54 (12%)	48 (11%)	37 (8%)	0.16
Activated protein C	1 (0.2%)	1 (0.2%)	0 (0%)	0.55

Definition of abbreviations: EGDT = early goal-directed therapy; PSC = protocol-based standard care.
Mechanical ventilation, central venous catheterization, and ancillary care (antibiotics, corticosteroids, and activated protein C) were counted from arrival at the emergency department to 6 hours. Resuscitation therapies (intravenous fluids, vasopressor, and dobutamine infusions, and blood product administration) were counted from randomization to 6 hours.
*Values are n (%) unless otherwise indicated.
†*P* values are shown for three-way comparison (Fisher's exact test).

remained hospitalized. We determined the stage of AKI each day based on maximum severity by either creatinine or urine output criteria (until ICU discharge or 72 h). We determined baseline (preadmission), admission, and reference (the lower of baseline and admission) serum creatinine as previously described (1, 10, 11). We only assigned an AKI stage by urine output criteria if the urine output values were recorded. Missing urine output was not imputed and did not contribute to staging for patients.

We determined duration of AKI and stage 2 to 3 AKI as previously described (1) using the first episode of AKI only and using a 72-hour criterion for sustained recovery off RRT and alive. We determined recovery status at hospital discharge truncated at 28 days, defining complete recovery as alive, free of RRT, and with a last known serum creatinine <1.5 times the reference creatinine. For recovery from stage 2 to 3 AKI, we considered partial recovery as alive, free of RRT, and improvement by at least one AKI stage but without return to <1.5 times reference creatinine as previously described (12, 13). We examined rates and duration of RRT across treatment arms. We considered inpatient RRT to end when the last treatment occurred as long as the patient was still in hospital for at least 96 hours. For patients who were discharged (alive or dead) before 96 hours, the last day of inpatient RRT was considered to be the date of discharge. We calculated fluid balance from all fluid in and out over the first 72 hours after enrollment, and expressed it as a percent based on body mass using 10% as the threshold that defined fluid overload (5). We determined postdischarge outcomes by linking to National Death Index and United States Renal Data System. An honest broker obtained the data from these sources and merged these results with the study data.

Biomarkers of Kidney Damage

In a subgroup of 270 patients, we measured urinary biomarkers at 0, 6, 24, and 72 hours after enrollment. Our panel included five urinary biomarkers: neutrophil gelatinase-associated lipocalin (NGAL); kidney injury molecule-1 (KIM-1); liver-fatty acid binding protein (L-FABP); pi glutathione S-transferase (πGST); and α glutathione S-transferase (αGST). Assays were performed using ELISA kits obtained from EKF diagnostics (Cardiff, UK) and performed according to the manufacturer's specifications. Urine creatinine assessment used an enzymatic assay (EKF diagnostics) performed according to the manufacturer's specifications.

Statistical Analysis

We analyzed data by intention to treat, testing the primary outcome for differences across all three arms using Fisher's exact test. We also sequentially tested if protocolized resuscitation (EGDT or PSC) was superior to usual care, and if so, whether EGDT was superior to PSC. For this latter analysis, we detected a 12% absolute difference between protocolized treatment and usual care, assuming an α of 0.05 and a power of 80%. We used the Kruskal-Wallis test to determine whether duration of AKI varied by treatment arm due to a right skew in the distribution of duration of AKI. The distribution of values for percent positive fluid balance over 72 hours was normal, which allowed for use of analysis of variance. We performed sensitivity analyses by restricting to stage 2 to 3 AKI and including patients with stage 1 AKI at enrollment. We varied the criteria for AKI (serum creatinine, urine output, or both) and time for ascertainment of RRT. Subgroup analyses for patients who were enrolled on the basis of lactate only criterion fitted an interaction term between the treatment arm and entry method, and were assessed using the Wald test. We used Stata 13 (StataCorp LP, College Station, TX) for Kaplan-Meier curves and SAS 9.4 (SAS Institute Inc., Cary, NC) for all other statistical analyses.

Results

Baseline Patient Characteristics by AKI Status

At enrollment, 626 patients (50.4%) had AKI, with 399 (32.1%) having stage 2 to 3 AKI. Of the 617 patients without AKI at enrollment, 233 (37.8%) subsequently manifested AKI. Baseline characteristics for patients stratified by enrollment and subsequent AKI status are shown in Table 2.

Table 2. Baseline Characteristics of Patients According to Acute Kidney Injury Status

Characteristic	AKI at Enrollment (*n* = 626)	AKI after Enrollment (*n* = 233)	No AKI (*n* = 384)	*P* Value*
Age, yr[†]	60.7 ± 15.9	66.1 ± 15.8	59.2 ± 16.4	<0.0001[a]
Male sex	394 (62.9%)	111 (47.6%)	183 (47.7%)	<0.001
Race				<0.001
White	395 (63.6%)	183 (78.%)	289 (75.3%)	
Black or African American	184 (29.6%)	41 (17.6%)	62 (16.2%)	
Other	42 (6.7%)	9 (3.9%)	33 (8.6%)	
Ethnicity[‡]				0.01
Hispanic	54 (8.6%)	23 (9.9%)	55 (14.4%)	
Non-Hispanic	571 (91.4%)	210 (90.1%)	328 (85.6%)	
Comorbid conditions[§]				
Charlson comorbidity score	2 (1–4)	2 (1–4)	1 (1–3)	0.03[b]
Hypertension	369 (59.4%)	142 (60.9%)	204 (53.1%)	0.08
Diabetes mellitus	221 (35.6%)	80 (34.3%)	103 (26.9%)	0.02
Chronic respiratory disease	126 (20.3%)	63 (27%)	91 (23.7%)	0.10
Cancer	103 (16.6%)	46 (19.7%)	78 (20.3%)	0.28
Renal impairment	92 (14.8%)	20 (8.6%)	14 (3.7%)	<0.001
Acute congestive heart failure	58 (9.3%)	40 (17.2%)	41 (10.7%)	0.005
Prior myocardial infarction	58 (9.3%)	27 (11.6%)	46 (12%)	0.37
Cerebral vascular disease	68 (10.9%)	31 (13.3%)	20 (5.2%)	0.001
Peripheral vascular disease	46 (7.4%)	22 (9.4%)	24 (6.3%)	0.35
Chronic dementia	45 (7.3%)	30 (12.9%)	22 (5.7%)	0.004
Hepatic cirrhosis	44 (7.1%)	17 (7.3%)	16 (4.2%)	0.13
Peptic ulcer disease	38 (6.1%)	9 (3.9%)	21 (5.4%)	0.45
AIDS and related syndromes	19 (3.1%)	6 (2.6%)	9 (2.3%)	0.82
Source of sepsis				0.06
After review judged not infected	11 (1.8%)	6 (2.6%)	12 (3.1%)	0.34
Pneumonia	188 (30.3%)	91 (39.1%)	136 (35.4%)	0.03
Intra-abdominal infection	89 (14.3%)	25 (10.7%)	44 (11.5%)	0.26
Urosepsis	144 (23.2%)	44 (18.9%)	84 (21.8%)	0.40
Skin and soft-tissue infections	45 (7.3%)	16 (6.9%)	29 (7.6%)	0.97
Central nervous system	3 (0.5%)	3 (1.3%)	4 (1%)	0.43
Endocarditis	2 (0.3%)	3 (1.3%)	2 (0.5%)	0.19
Catheter-related infection	10 (1.6%)	7 (3%)	8 (2.1%)	0.42
Unknown	81 (13.0%)	33 (14.2%)	37 (9.7%)	0.16
Other	48 (7.7%)	5 (2.2%)	28 (7.3%)	0.005
Blood culture positive	211 (34%)	66 (28.3%)	93 (24.2%)	0.006
APACHE II score	21 (17–27)	20 (16–24)	16 (13–20)	<0.001[b]
Entry criteria				
Refractory hypotension	325 (52.3%)	121 (51.9%)	224 (58.3%)	0.14
Hyperlactatemia	404 (65.1%)	132 (56.7%)	188 (49%)	<0.001
Physiologic variables				
Systolic blood pressure, mm Hg	95 ± 27	106 ± 28	107 ± 29	<0.0001[b]
Serum lactate, mmol/L	2.6 (1.3–4.5)	2.0 (1.3–3.4)	1.6 (0.9 – 3.0)	<0.001[b]
Anemia[‖]	108 (17.6%)	38 (16.5%)	40 (10.6%)	0.008
Time to randomization				
From ED arrival,[¶] min	162 (118–210)	162 (120–212)	179 (131–243)	<0.001[b]
From meeting entry criteria, min	69 (39–102)	66 (38–91)	60 (34–94)	0.14[b]

Definition of abbreviations: AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; ED = emergency department.
Values are number of subjects (%), median (95% confidence interval), or mean ± SD.
**P* values are shown for 3-way comparison (Fisher's exact test unless otherwise noted: [a]analysis of variance; [b]Kruskal-Wallis).
[†]Excludes one subject with missing age.
[‡]Excludes two subjects with missing ethnicity.
[§]Chronic conditions defined as per Charlson comorbidity index (19).
[‖]Anemia was defined by hemoglobin <10 for males, <8 for females.
[¶]Not all subjects were eligible at time of ED arrival.

Treatments Received

Treatments received by patients in each study arm are described in detail elsewhere (7) and are listed in Table 1. Total cumulative fluid balance by treatment arm over the 6-hour resuscitation period is shown in Figure 2, and was greatest with PSC and least with usual care (mean difference 1.0 L; $P < 0.001$). Ninety-four percent of the fluids given across all three arms was isotonic (0.9%) saline. Other differences in resuscitation can seen in Table 1, whereas ancillary care was similar in all three groups.

Development of AKI by Treatment Arm

Development and duration of AKI, fluid overload, and use of RRT by treatment are shown in Table 3. There were no differences across treatment arms for presence of AKI on enrollment ($P = 0.79$), development of AKI after enrollment ($P = 0.52$), or

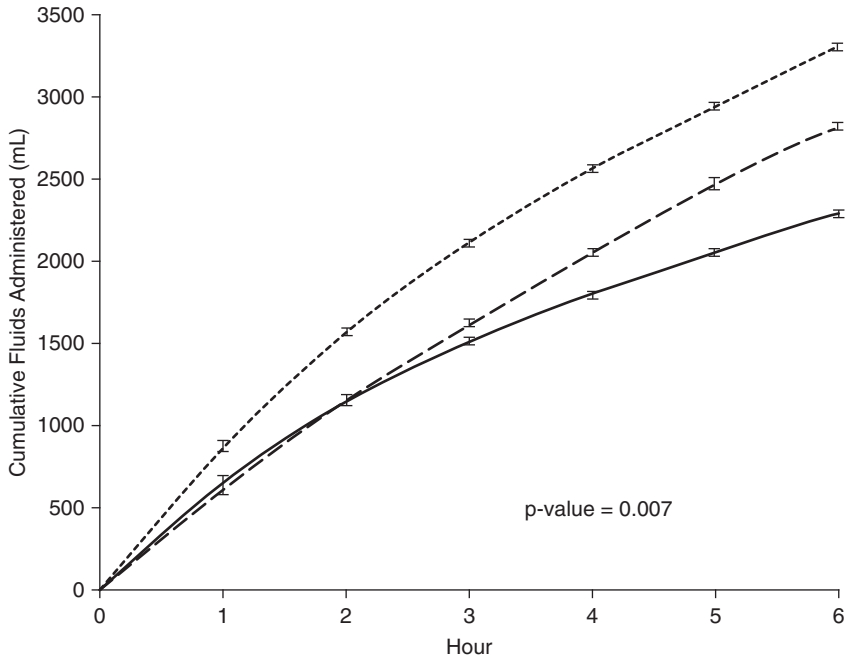

Figure 2. Cumulative fluid use by study arm. Total fluid received over the first 6 hours. *Solid line*, usual care; *long dashes*, early goal-directed therapy; *short dashes*, protocol-based standard care.

development of stage 2 to 3 AKI after enrollment ($P = 0.59$). Analysis by EGDT+PSC versus usual care similarly showed no significant differences. In sensitivity analyses, when the criteria for AKI was restricted to only serum creatinine or only urine output criteria, there were no differences in AKI by treatment arm (*see* Table E1 in the online supplement). Similarly, the results were unchanged when we restricted analysis to patients enrolled on lactate criteria versus hypotension criteria versus both (*see* Figure E1). Additional sensitivity analyses are provided in Table E2. In the subgroup of 270 patients with urine biomarkers (KIM-1, NGAL, L-FABP), the three intervention groups did not differ in terms of biomarker trends over time (*see* Figure E2).

Use of RRT and presence of fluid overload are also shown by treatment arm in Table 3. Receipt of RRT on day 7 was greater with PSC ($P = 0.04$) compared with the other arms as previously reported (7). However, we found no differences for RRT at 48 hours after enrollment or over the entire course of hospitalization. Neither did we find any differences for RRT when comparing analysis by EGDT+PSC versus usual care at any time point.

Survival and Renal Replacement Therapy by AKI Status

Hospital mortality truncated at 60 days was 6.2% for patients without AKI, 16.8% for patients with maximum AKI stage 1, and 27.7% for stage 2 to 3 AKI ($P < 0.0001$). Outcomes were not different for patients who manifested AKI at enrollment versus afterwards: hospital mortality (to 60 d)

Table 3. Acute Kidney Injury by Treatment Arm

Outcome	EGDT (*n* = 409)	PSC (*n* = 415)	Usual Care (*n* = 419)	*P* Value*
AKI				
AKI at enrollment	203/409 (49.6%)	206/415 (49.6%)	217/419 (51.9%)	0.79
Stage 2–3 AKI at enrollment	134/409 (32.8%)	130/415 (31.3%)	135/419 (32.2%)	0.91
AKI after enrollment	83/206 (40.3%)	73/209 (34.9%)	77/202 (38.1%)	0.52
Stage 2–3 AKI after enrollment	58/206 (28.2%)	47/209 (22.5%)	49/202 (24.3%)	0.39
Development of stage 2–3 AKI†	90/275 (32.7%)	86/285 (30.2%)	97/284 (34.2%)	0.59
Median (95% CI) duration of AKI,‡ d				
Any AKI	2 (2–3)	2 (2–3)	2 (2–3)	0.45
Stage 2–3	2 (1–3)	2 (1–3)	2 (1–3)	0.79
Recovery from AKI‡				0.89§
Complete	164/286 (57.3%)	154/279 (55.2%)	159/294 (54.1%)	
Partial	31/286 (10.8%)	27/279 (9.7%)	31/294 (10.5%)	
None	91/286 (31.8%)	98/279 (35.1%)	104/294 (35.4%)	
Renal replacement therapy use‡				
Any time during hospitalization	25/407 (6.1%)	32/414 (7.7%)	18/419 (4.3%)	0.11
At 1 wk	12/382 (3.1%)	24/399 (6.0%)	11/397 (2.8%)	0.04
At 48 h	13/405 (3.2%)	16/411 (3.9%)	10/417 (2.4%)	0.48
Fluid overload				
>10% over first 72 h	40/408 (9.8%)	28/414 (6.8%)	26/415 (6.3%)	0.13
% positive fluid balance over 72 h, mean (SD)	1.6% (6.4%)	1.7% (5.3%)	1.2% (5.6%)	0.40‖

Definition of abbreviations: AKI = acute kidney injury; CI = confidence interval; EGDT= early goal-directed therapy; PSC = protocol-based standard care.
**P* values are shown for three-way comparison (Fisher's exact test unless otherwise specified), analysis by EGDT+PSC versus usual care showed no significant differences.
†Includes patients with stage 1 AKI on enrollment.
‡Includes patients with AKI (any stage) on enrollment.
§*P* value is shown for comparison across all categories and groups (Fisher's exact).
‖Analysis of variance.

23.5% versus 28.3% ($P = 0.16$). One-year survival for patients with and without AKI, and with AKI stratified by degree of recovery of kidney function is shown in Figure 3. Dialysis at day 60 or in-hospital death by 60 days occurred in 22.1% for EGDT, 18.0% for PSC, and 20.7% for usual care groups ($P = 0.35$, three-way; $P = 0.85$, two-way). Death or dialysis at 1 year occurred in 38.9% for EGDT, 37.0% for PSC, and 38.6% for usual care groups ($P = 0.84$, three-way; $P = 0.90$ two-way).

Discussion

In this preplanned ancillary analysis of a large randomized trial of protocol-based fluid resuscitation for septic shock, we found no benefit for protocolized management in terms of development or severity of AKI or for renal outcomes, including severity of fluid overload, use of RRT, and recovery of kidney function. Our results were consistent across subgroups defined by patient characteristics (lactate vs. hypotension criteria), or AKI criteria (creatinine, urine output, novel biomarkers). Our results are important clinically because fluid resuscitation is a mainstay of treatment for septic shock, and protocolized fluid resuscitation is often recommended to prevent kidney damage. Protocolized hemodynamic management for patients with septic shock is recommend by the Kidney Disease: Improving Global Outcomes clinical practice guideline (9) based on a previous metaanalysis (14). Our results do not support the adoption of either of the protocols studied to prevent new AKI or alter the course of existing AKI in patients presenting with septic shock.

Our results should not be interpreted to imply that fluid therapy is unimportant in the management of septic shock or that alternative protocols for resuscitation might be better than current practice. Although volume overload can result in respiratory compromise and venous congestion in the kidney and other organs (5, 6, 15), all our patients received aggressive fluid therapy, and rates of fluid overload and RRT were rather low (both <10%). Nevertheless, the lack of benefit with protocolized resuscitation for AKI despite more mean fluid use should temper enthusiasm for systematic approaches that simply increase fluid use in resuscitation in the setting of septic shock. Similarly, the use of central venous oxygen saturation to titrate vasoactive medication and blood product use (as per the EGDT arm) was not effective in altering the course of AKI.

These results also shed light on the epidemiology of AKI in patients with septic shock by demonstrating several key aspects. First, AKI is extremely common with more than two-thirds of patients developing AKI within the first 7 days. Almost three-quarters of episodes of AKI manifested at or soon after presentation to the emergency department. Although progression of AKI was still common after admission, the substantial burden of kidney injury evident on presentation combined with the well-known delay in clinical manifestations of AKI using functional criteria (creatinine and urine output) (16) means that for sepsis, primary AKI prevention will be nearly impossible. Second, AKI is often transient (median duration was only 2 days, and RRT was used in only 4–8%), but is nevertheless severe (25% of all patients have stage 2 to 3 AKI within the first week) and was strongly associated with increased mortality at 60 days. Third, patients who fail to recover renal function have a dismal survival, and the hazard for this association manifests in the first 30 days (Figure 3). Conversely, when patients with sepsis-associated AKI recover renal function, even incompletely, their survival seems to be similar to patients without AKI. To our knowledge, this relationship has not been reported previously. Together these findings imply that for treatments for AKI in the setting of sepsis to be successful, they will need to be effective after initiation of kidney injury. However, should they result in increased recovery, the prognosis, out to a year at least, may be considerably improved.

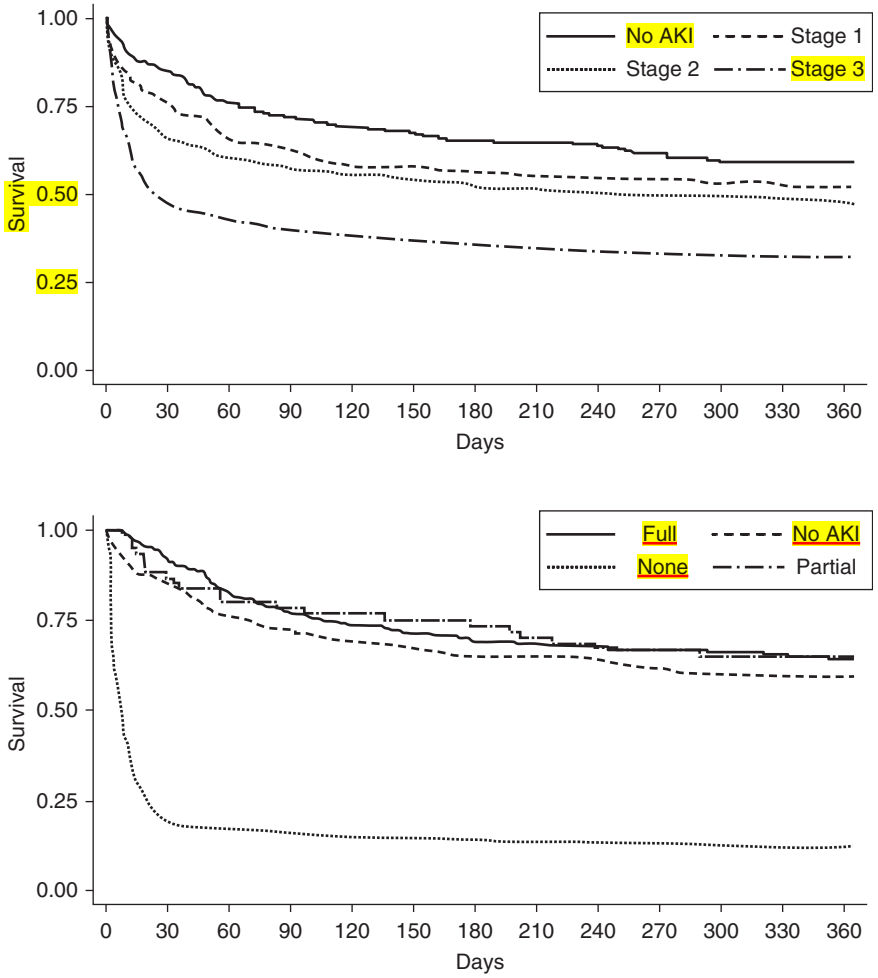

Figure 3. Survival by acute kidney injury (AKI) and recovery status. (*Top panel*) One-year survival by AKI status (no AKI, stage 1, 2, or 3). (*Bottom panel*) One-year survival for stage 2 to 3 AKI by recovery status (complete, partial, none).

Among the strengths of this study are a large protocolized cohort conducted in 31 sites (7), prompt enrollment (patients were enrolled with 2 h of meeting criteria), availability of baseline and postintervention fluid and renal specific endpoints, assessment of long-term outcomes, and AKI biomarkers. Nonetheless, there are important limitations. First, we did not examine fluid type because 0.9% saline was the predominant fluid used. Second, our study did not address the initial fluid resuscitation that was given to qualify for entry into ProCESS; typically, this was 2 L before enrollment. It is possible that even earlier or greater volumes of fluid at this stage could have been beneficial. However, because additional fluids given to patients with evidence of ongoing shock (hypotension and/or hyperlactatemia) did not improve outcome, it is reasonable to hypothesize that less fluids might have been better in the initial resuscitation. There is some evidence that this initial bolus therapy could be deleterious in some situations. For example, in the FEAST (Fluid Expansion as Supportive Therapy) trial, bolus fluids resulted in worse outcome in children with sepsis in Africa (17). However, we did not observe harm with protocolized resuscitation, and although not significantly different, rates of stage 2 to 3 AKI developing at anytime after enrollment were actually highest with usual care. Meanwhile, although the rate of RRT use did not differ over the entire course of hospitalization or at 48 hours after enrollment across treatment groups, at 7 days, RRT use was highest in the PSC arm, the arm receiving the most fluid. This contradictory signal, in which AKI rates and RRT rates move in opposite directions, has been seen with other fluid trials—most notably, the CHEST trial (Crystalloid versus Hydroxyethyl Starch Trial) (18), in which AKI rates were lowest with starch, but dialysis rates were increased. We speculate that apart from any direct toxicity of fluids, early reversal of shock is beneficial, but excess fluids are harmful and strategies that provide more rapid resolution of shock might pay a price in greater fluid overload and use of RRT. Third, although we used the latest consensus criteria for AKI and recovery, and examined biomarkers of kidney damage, we cannot exclude that some patients may have had "subclinical AKI" or may have been missed, particularly if AKI occurred late. Finally, our protocols dictated a "pattern of management" rather than specific amounts of fluid, blood, or vasopressor; we did not study the relationship between individual fluid volumes or vasopressor doses and outcomes. Some subbjects in each arm may have received far more or less than the mean amounts. Therefore, we are best able to comment on the effect of systematic resuscitation targets, not specific amounts of therapy *per se*.

In conclusion, in patients with septic shock, AKI is common and associated with adverse outcomes, but it was not influenced by the use of either EGDT or an alternative resuscitation protocol compared with usual care. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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