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ORIGINAL

Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy

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Abstract *Objective:* To describe the incidence and outcomes associated with early acute kidney injury (AKI) in septic shock and explore the association between duration from hypotension onset to effective antimicrobial therapy and AKI. *Design:* Retrospective cohort study. *Subjects:* A total of 4,532 adult patients with septic shock from 1989 to 2005. *Setting:* Intensive care units of 22 academic and community hospitals in Canada, the United States and Saudi Arabia. *Measurements and main results:* In total, 64.4% of patients with septic shock developed early AKI (i.e., within 24 h after onset of hypotension). By RIFLE criteria, 16.3% had risk, 29.4% had injury and 18.7% had failure. AKI patients were older, more likely female, with more co-morbid disease and greater severity of illness. Of 3,373 patients (74.4%) with hypotension prior to receiving effective antimicrobial therapy, the median (IQR) time from hypotension onset to antimicrobial therapy was 5.5 h (2.0–13.3). Patients with AKI were more likely to have longer delays to receiving antimicrobial therapy compared to those with no AKI [6.0 (2.3–15.3) h for AKI vs. 4.3 (1.5–10.8) h for no AKI, $P < 0.0001$). A longer duration to antimicrobial therapy was also associated an increase in odds of AKI [odds ratio (OR) 1.14, 95% CI 1.10–1.20, $P < 0.001$, per hour (log-transformed) delay]. AKI was associated with significantly higher odds of death in both ICU (OR 1.73, 95% CI 1.60–1.9, $P < 0.0001$) and hospital (OR 1.62, 95% CI, 1.5–1.7, $P < 0.0001$). By Cox proportional hazards analysis, including propensity score-adjustment, each RIFLE category was independently associated

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with a greater hazard ratio for death (risk 1.31; injury 1.45; failure 1.56). *Conclusion:* Early AKI is common in septic shock. Delays to appropriate antimicrobial therapy may contribute to significant increases in the incidence of AKI. Survival was considerably lower for septic shock associated with early AKI, with increasing severity of AKI, and with increasing delays to appropriate antimicrobial therapy.

Keywords Acute kidney injury · Acute renal failure · Critically ill · Sepsis · Septic shock · Mortality · Incidence · Multi-center

Introduction

Acute kidney injury (AKI) is commonly encountered in critically ill patients and independently predicts poor outcome [1–4]. Two recent large multi-center cohort studies reported AKI occurred in an estimated 36% of all patients admitted to ICU [5, 6]. Additional observational data suggest the incidence of AKI is rising [7, 8].

Sepsis has consistently been found a predisposing factor for AKI [9–17]. The distinction of AKI of septic compared with non-septic origin may have clinical relevance [18]. Emerging data indicate septic AKI may be characterized by a distinct pathophysiology [19–22]. For that reason, septic AKI may show important differences in patient characteristics, response to interventions and clinical outcomes when compared to AKI of non-septic origin. Relatively few studies to date have focused on describing the epidemiology of septic AKI in critically ill patients [10–17].

Early goal-directed resuscitation in septic shock has been shown to improve survival [23]. This approach is now widely endorsed and integrated into consensus guidelines [24]. While early hemodynamic optimization and restoration of global tissue perfusion are a clear priority, recent data have found that the early administration of antimicrobial therapy also has an important impact on survival [25]. Kumar et al. found that delays in effective antimicrobial therapy exhibited a strong association with mortality and that fewer than 50% received their therapy within 6 h of documented hypotension. To date, no study has evaluated the impact of delay in effective antimicrobial therapy (a potential modifiable factor in sepsis management) and secondary organ dysfunction, such as AKI.

Accordingly, we interrogated a large multi-center database of patients with septic shock from 22 ICUs in Canada, the United States and Saudi Arabia covering cases over a 16-year period [25]. The objectives were to describe in patients with septic shock: (1) the incidence of early AKI, (2) the clinical characteristics and severity of early AKI, (3) the association between duration from hypotension onset to effective antimicrobial therapy and the occurrence and severity of early AKI, and (4) the survival in relation to early AKI.

Methods

Study population

This was a retrospective analysis of data from adult (age $\geq$ 18 years) cases of septic shock occurring between 1st January 1989 to 31st December 2005. The final study population comprised of data generated from the ICUs of 22 hospitals (14 tertiary/academic, eight metropolitan/community) in Canada, the United States and Saudi Arabia. This study was approved by the Health Ethics Board of the University of Manitoba and at each individual participating center.

Identification of cases

Each case of septic shock was defined by use of consensus criteria as previously described [25–27]. All included cases were required to have no other obvious etiology of shock. Those cases without serum creatinine at baseline (i.e., within 3 h of shock identification) and at 20–28 h following identification of shock were excluded (n = 1,183). Patients with pre-existing end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) were also excluded (n = 458). Evidence for AKI was assessed at the time of diagnosis of septic shock and at 24 h after presentation (early AKI). AKI was classified according to the RIFLE criteria [28]. The RIFLE criteria (acronym indicating risk of renal dysfunction; injury to the kidney; failure of kidney function; loss of kidney function; and ESKD) classifies AKI into three categories of severity (risk, injury, and failure) and two categories of clinical outcome (loss and ESKD). For this study, the outcome RIFLE categories Loss and ESKD were not evaluated. As urine output data were not available, only changes in serum creatinine were used to define the presence of early AKI by RIFLE category. Baseline serum creatinine values were estimated by the modification of diet in renal disease (MDRD) equation as recommended by the ADQI Working Group (assuming a lower limit of normal baseline GFR of 75 mL/min) [5, 6]. For analysis, patients were assigned to their worst RIFLE category according to serum creatinine criteria at 24 h after presentation and we use the term "early" to describe septic AKI occurring within this interval.

Study definitions

Hypotension was defined as a mean arterial pressure <65 mmHg, a systolic pressure <90 mmHg, or a decrease in systolic pressures >40 mmHg from baseline [26, 27]. An episode of hypotension was considered to represent the initial onset of septic shock when (a) hypotension persisted from onset despite fluid (>2 L of 0.9% normal saline or equivalent) was administered (persistent hypotension); or (b) hypotension was only transiently improved (hypotension resolution <1 h) with fluid resuscitation (recurrent hypotension). Hypotension that resolved in the absence of therapy or following administration of <2 L of 0.9% normal saline or equivalent without subsequent clinical deterioration was not considered to represent initial onset of septic shock-related hypotension. Nosocomial infection-related septic shock was defined as septic shock caused by any infection developing >48 h after hospital admission. Cases not meeting this definition were considered to be septic shock associated with community-acquired infections. Documented infections were those in which a plausible microbial pathogen were identified from the clinical infection site or blood in the context of a compatible clinical syndrome or in which infection was supported by a definitive radiological, surgical or pathologic diagnosis (biopsy or autopsy). All other infections were considered suspected. Effective antimicrobial therapy was considered to have been initiated when antimicrobials with in vitro activity appropriate for the isolated pathogen or pathogens (or in the case of culture-negative septic shock, antimicrobial therapy matching accepted national guidelines modified to local flora) were received either before onset of recurrent or persistent hypotension or within 6 h of administration of the first new antimicrobial following onset of hypotension [25].

Data collection

A detailed description of data collection has been previously published [25]. Comprehensive clinical, physiologic, laboratory, microbiological and therapeutic data were retrieved. Demographic information included age, sex, ethnicity, body mass index and dates and sources of ICU admission. Clinical data encompassed the presence of co-morbidities, surgical status, and need for mechanical ventilation. Physiologic data included details of hemodynamics, vasopressor use, and severity of illness [acute physiology and chronic health evaluation (APACHE) II] [29]. Laboratory data collected included standard hematology and electrolyte parameters. Microbiologic data included sources of septic shock and details of causative pathogen if isolated, as previously described [25]. The time from initial documentation of persistent or recurrent hypotension to administration of effective antimicrobial therapy was calculated for all cases.

Statistical analysis

Analysis was performed using Intercooled Stata (Stata Corp, College Station, TX). In the event of missing data values, data were not replaced. The incidence of early AKI was described as the cumulative proportion of patients developing AKI defined by the RIFLE criteria. Severity of AKI was presented as the cumulative proportion of patients fulfilling RIFLE categories for risk, injury, and failure. The incidence and severity of AKI were also determined from time (hours) to initiation of effective antimicrobial therapy relative to the first occurrence of recurrent or persistent hypotension (independent variable) (restricted to those cases where effective antimicrobial initiation followed onset of hypotension). Clinical factors associated with the development of AKI were evaluated by univariate analysis. Those covariates deemed clinically important and/or associated with $P < 0.25$ by univariate analysis were considered for multi-variable logistic regression analysis to evaluate factors independently associated with risk of AKI. Initial model variables considered included: age, sex, co-morbid disease, body mass index, surgical status, admission source, source of sepsis, APACHE II score, clinical variables (vital signs), laboratory variables (lactate, bilirubin, platelets, INR) and therapies (mechanical ventilation, vasopressors, fluid therapy). Sequential elimination of variables was performed by the likelihood ratio method to develop a final model and propensity score model with all remaining covariates having a $P < 0.25$. The final model was used to calculate a propensity score for the probability of development of AKI [30]. Multi-collinearity in the model was evaluated by generation of a matrix of correlation coefficients for included covariates. Model calibration and discrimination were assessed using the goodness-of-fit test and the area under the receiver operator characteristic (AuROC) curve, respectively.

Mortality at ICU and hospital discharge and 90 days are also described for both the presence and severity of AKI. Estimates of annual percent change in mortality for the study period were determined by fitting a straight line regression of the natural logarithm of the rates with calendar year used as an independent variable as previously described [7]. Normally or near normally distributed variables are reported as mean with standard deviations (SD) and compared by Student's t test, analysis-of-variance or simple linear regression. Non-normally distributed continuous data are reported as medians with inter-quartile ranges (IQR) and compared by Mann Whitney U test or Kruskal–Wallis test. Categorical data were reported as proportions and compared using Fisher's exact test. Crude survival stratified by severity of AKI was assessed graphically by the Kaplan–Meier product limit estimator and compared with the log-rank test. Survival was measured from the date of

documentation of sepsis-associated hypotension. Cox proportional hazards analysis was used to evaluate the association severity of early AKI and other covariates, including time to initiation of effective antimicrobial therapy. Data are presented as crude, covariate-adjusted and propensity score and covariate-adjusted mortality. A priori selected variables for multivariable analysis included propensity score, age, sex, co-morbidity, source of infection, surgical status, need for mechanical ventilation, need for vasopressors, APACHE II score, hospital site and study year. Plots of log [-log(survival)] versus log (survival time) were performed to evaluate the assumption of proportionality. Data are presented as hazard ratios and 95% confidence intervals (CI). A P value of <0.05 was considered statistically significant for all comparisons.

Results

In total, 5,715 patients with septic shock were admitted to the study ICUs during the 16-year study period. These patients had a mean (SD) age of 62.5 (16.2) years, 44% were female, 71.5% had at least one co-morbid illness and the mean (SD) APACHE II scores were 25.2 (9.7). After exclusion of those with ESKD and those lacking serum creatinine values within 3 h and between 20 and 28 h of initial documentation of hypotension, 4,532 patients (79.3% of total) were available for analysis.

Study cohort

The demographic, clinical characteristics, and acute physiology of the study cohort are shown in Tables 1 and 2. These patients had a mean (SD) age of 62.5 (16.6) years, 43% were female, and 70.6% had co-morbid illness with 36.4% having ≥ 2 or more. The majority of admissions were referred from the emergency department (36.1%) and for non-surgical indications (76.9%). Community-acquired infections accounted for 56.3% of cases, whereas 43.7% where classified as nosocomial. Documented culture positive infections were present in 71.1% with 34.1% having positive blood cultures (Table 3).

Early AKI

Acute kidney injury was present in 64.4% at 24 h after onset of hypotension. When classified according to the RIFLE criteria, 16.3% had risk, 29.4% had injury and

Table 1 Baseline demographics and clinical characteristics of septic shock patients stratified by early acute kidney injury

Variable	Total ($n = 4,532$)	No AKI ($n = 1,615$)	AKI ($n = 2,917$)	P value
Age [mean (SD)] (years)	62.5 (16.6)	58.2 (17.6)	64.9 (15.5)	<0.001
Female sex # (%)	1,948 (43)	634 (39.3)	1,314 (45.1)	<0.001
Body mass index [mean (SD)] ($n = 2,410$)	27.6 (7.6)	26 (7.3)	28.5 (7.6)	<0.001
Surgical # (%)	1,045 (23.1)	414 (25.6)	631 (21.6)	0.003
Elective # (%)	739 (16.3)	280 (17.3)	459 (15.7)	0.17
Emergency surgery/trauma # (%)	351 (7.7)	153 (6.8)	198 (9.5)	0.001
Admission source				
Emergency department # (%)	1,638 (36.1)	569 (35.2)	1,069 (36.7)	0.005
Medical ward # (%)	1,338 (29.5)	472 (29.2)	866 (29.7)	
Surgical ward # (%)	877 (19.4)	355 (22)	522 (17.9)	
Transfer from another hospital # (%)	679 (15)	219 (13.6)	460 (15.8)	
Co-morbid disease				
Any disease # (%)	3,200 (70.6)	1,054 (65.3)	2,146 (73.6)	<0.001
≥ 2 disease # (%)	1,649 (36.4)	523 (32.4)	1,126 (38.6)	<0.001
Specific co-morbid diseases				
Coronary artery disease # (%)	389 (8.6)	118 (7.3)	271 (9.3)	0.02
Congestive heart failure (NYHA Class IV) # (%)	426 (9.4)	101 (6.3)	325 (11.1)	<0.001
Liver failure # (%)	404 (8.9)	114 (7.1)	290 (9.9)	0.001
Diabetes mellitus # (%)	1,146 (25.3)	317 (19.6)	829 (28.4)	<0.001
Insulin-dependent diabetes mellitus # (%)	389 (8.6)	104 (6.4)	285 (9.8)	<0.001
COPD (medication or oxygen requiring) # (%)	638 (14.1)	255 (15.8)	383 (13.1)	0.01
Acute/chronic hematologic malignancy # (%)	261 (5.8)	77 (4.8)	184 (6.3)	0.03
Metastatic solid organ cancer # (%)	411 (9.1)	149 (9.2)	262 (9.0)	0.79
Solid organ transplant # (%)	147 (3.2)	31 (1.9)	116 (4.0)	<0.001
Ethanol abuse # (%)	630 (13.9)	254 (15.7)	376 (12.9)	0.009
HIV/AIDS (1993 CDC Criteria) # (%)	105 (2.3)	55 (3.4)	50 (1.7)	<0.001
Immunosuppressive chemotherapy or long-term steroid therapy (>10 mg prednisone equivalent daily) # (%)	688 (15.2)	266 (14)	462 (15.8)	0.10

COPD chronic obstructive pulmonary disease, *CDC* Centers for Disease Control, *NYHA* New York Heart Association

Table 2 Summary of physiologic and laboratory details of septic shock patients stratified by early acute kidney injury

Variable	Total	No AKI	AKI	*P* value
APACHE II score [mean (SD)] (n = 4,532)	24.3 (9.3)	20.6 (20.2)	26.3 (9.4)	<0.001
APACHE II score ≥25 # (%)	2,164 (47.8)	457 (28.3)	1,707 (58.2)	<0.001
Temperature (°C) [mean (SD)] (n = 4,481)	37.6 (1.7)	37.9 (1.6)	37.5 (1.8)	<0.001
≥38°C # (%)	2,222 (49.6)	893 (56.0)	1,329 (46.1)	<0.001
Heart rate (beats/min) [mean (SD)] (n = 4,495)	116 (29)	119 (28)	115 (30)	<0.001
Cardiac output (L/min) [mean (SD)] (n = 1990)	7.3 (3.3)	7.2 (3.0)	7.3 (3.4)	0.43
≥2 Vasopressors # (%)	2257 (49.8)	628 (38.9)	1629 (55.9)	<0.001
Mechanical ventilation # (%)	3771 (83.2)	1308 (81)	2463 (84.4)	0.003
Sodium (mmol/L) [mean (SD)] (n = 1,601)	137 (6.9)	137 (6.8)	137 (7)	0.38
Chloride (mmol/L) [mean (SD)] (n = 1,589)	105 (8.5)	105 (8.1)	105 (8.7)	0.39
Bicarbonate (mmol/L) [mean (SD)] (n = 3,488)	19.3 (6.4)	21.9 (6.2)	17.9 (6.1)	<0.001
Bilirubin (mmol/L) [median (IQR)] (n = 3,841)	17 (10–36)	15 (9–27)	19 (10–42)	<0.001
Platelets (10^9 cells/L) [mean (SD)] (n = 2,424)	225 (154)	247 (163)	211 (146)	<0.001
CK (U/L) [median (IQR)] (n = 1,966)	157 (56–521)	95 (42–289)	196 (73–672)	<0.001
Troponin >0.5 μg/L (n = 1,394) # (%)	247 (17.7)	64 (14.3)	183 (19.3)	0.02
Lactate (mmol/L) [mean (SD)] (n = 2,847)	4.4 (4.0)	3.3 (3.0)	4.8 (4.3)	<0.001
Fluid therapy (L) [mean(SD)]				
Initial 6 h (n = 2,404)	3.3 (2.8)	3.3 (2.8)	3.2 (2.2)	0.19
Initial 24 h (n = 2,399)	6.6 (4.3)	6.2 (3.7)	6.9 (4.3)	<0.001

APACHE acute physiology and chronic health evaluation, *MAP* mean arterial pressure, *CK* creatine kinase

Table 3 Summary of details of source of septic shock stratified by early acute kidney injury

Variable	Total (n = 4,532)	No AKI (n = 1,615)	AKI (n = 2,917)	*P* value
Acquired				
Community # (%)	2,552 (56.3)	895 (55.4)	1,657 (56.8)	0.38
Nosocomial # (%)	1,980 (43.7)	720 (44.6)	1,260 (43.2)	
Culture positive # (%)	3,222 (71.1)	1,156 (71.6)	2,066 (70.8)	0.61
Positive blood cultures # (%)	1,545 (34.1)	465 (28.8)	1,080 (37.0)	<0.001
Infection site				
Chest # (%)	1,777 (39.2)	743 (46.0)	1,034 (35.5)	<0.001
Abdominal # (%)	1,323 (29.1)	396 (24.5)	927 (31.8)	<0.001
Genitourinary # (%)	506 (11.2)	142 (8.8)	364 (12.5)	<0.001
Skin/soft tissue/joint # (%)	382 (8.4)	131 (8.1)	251 (8.6)	0.58
Bloodstream infection # (%)	341 (7.5)	125 (7.7)	216 (7.4)	0.68
Systemic-disseminated # (%)	132 (2.9)	45 (2.8)	87 (3.0)	0.78
Central nervous system # (%)	42 (0.9)	21 (1.3)	21 (0.7)	0.07
Surgical wound # (%)	29 (0.6)	12 (0.7)	17 (0.6)	0.65

AKI acute kidney injury

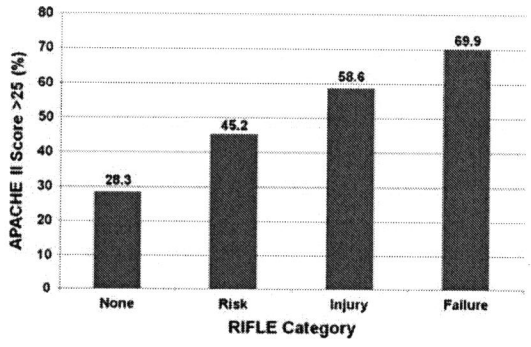

Fig. 1 Severity of illness (APACHE II score ≥25) stratified by RIFLE category

18.7% had failure. Clinical variables significantly associated with development of AKI by univariate analysis are shown in Tables 1, 2, 3. In general, these patients were older with a higher burden of co-morbid illness, and had greater aberrancies in acute physiology and laboratory parameters. These patients were also more likely to receive vasopressors, mechanical ventilation, greater total fluid therapy, and have greater severity of illness (as indicated by the fraction of patients in each category with APACHE II >25) (Table 2; Fig. 1). Greater absolute changes to serum creatinine within the first 24 h were also associated with a higher incidence of AKI. (Table 4) By multi-variable analysis, several clinical covariates were found to be independently associated with development of AKI (Table 5).

Table 4 Incidence of AKI stratified by quartiles of changes in serum creatinine at 24 h and associated duration from hypotension onset to effective antimicrobial therapy and 90-day mortality ($n = 3,373$)

	Change in serum creatinine in first 24 h (μmol)			
	>−20	−20 to 0	0–20	>20
Incidence AKI (%)	63.7	43.4	57.6	94.9
Duration of hypotension[a] (hours)	4.5 (1.7–9.5)	5.2 (1.8–12.6)	6.0 (2.3–15.9)	7.0 (2.9–19)
APACHE II score [mean (SD)]	24.5 (9.3)	22.4 (8.6)	24.0 (9.1)	27.6 (10.0)
ICU mortality (%)	30.7	38.5	46.6	65.8
90-Day mortality (%)	37.2	43.3	52.8	69.8

AKI acute kidney injury, *ICU* intensive care unit, *APACHE* acute physiology and chronic health evaluation
[a] Median (IQR)

Duration from hypotension onset prior to effective antimicrobial therapy and AKI

In total, 3,373 septic shock patients (74.4%) had recurrent or persistent hypotension prior to receiving effective antimicrobial therapy. In these patients, the median (IQR) time from hypotension onset to antimicrobial therapy was 5.5 (2.0–13.3) h. Patients with AKI had significantly longer duration from hypotension onset to antimicrobial therapy when compared to those with no AKI [6.0 (2.3–15.3) h for AKI vs. 4.3 (1.5–10.8) h for no AKI, $P < 0.0001$). Greater declines in kidney function (measured by change in serum creatinine) and higher severity of AKI in the first 24 h were both associated with longer duration from hypotension onset to antimicrobial therapy ($P = 0.0001$ for each) (Tables 4, 6). A longer duration from hypotension onset to antimicrobial therapy was also associated an increase in crude and covariate-adjusted odds of AKI [crude: OR 1.14, 95% CI 1.10–1.20, $P < 0.001$; covariate-adjusted: OR 1.42, 95% CI 1.06–1.92, $P < 0.02$, per hour [log-transformed] delay) (Table 5; Fig. 2).

Table 5 Multi-variable logistic regression and propensity score analysis for factors associated with AKI in critically ill patients with septic shock (goodness-of-fit, $P = 0.39$, AuROC 0.84)

Covariate	OR (95% CI)	*P* value
Duration of hypotension[a] (per log-transformed hour)	1.45 (1.06–1.99)	0.02
Age (per year)	1.04 (1.02–1.05)	<0.001
Body mass index (per point)	1.08 (1.04–1.12)	<0.001
APACHE II score (per point)	1.10 (1.07–1.13)	<0.001
Surgical admission (present)	1.72 (0.95–3.12)	0.07
Co-mordid illness		
Hypertension	2.65 (1.08–6.53)	0.03
Chronic obstructive pulmonary disease	0.40 (0.21–0.75)	0.004
Chronic kidney disease	6.00 (1.97–18.3)	0.002
Lymphoma/lymphoma	3.19 (0.98–10.4)	0.06
Nosocomial Infection (present)	0.61 (0.36–1.04)	0.07
Culture-positive infection (present)	0.62 (0.33–1.15)	0.14
Blood cultures positive (present)	1.54 (0.88–2.66)	0.12
Infection site[b]		
Gastrointestinal/intra-abdominal	2.44 (1.35–4.42)	0.003
Genitourinary	3.79 (1.61–8.95)	0.002
Heart rate (per beat/min)	0.99 (0.98–0.99)	0.03
Serum lactate (per mmol/L)	1.04 (0.98–1.11)	0.23
Total fluid resuscitation in first 24 h (per litre)	1.03 (0.99–1.06)	0.11
≥2 Vasopressors needed (present)	1.44 (0.89–2.33)	0.14

OR odds ratio, *CI* confidence interval
[a] Log transformed
[b] Reference variable: chest infection

Clinical outcomes

Crude ICU, hospital and 90-day mortality were 45.2, 51.4 and 50.1%, respectively. Over the study period, 90-day mortality decreased by 2.1% per year (95% CI, 1–3%, $P = 0.005$). A diagnosis of AKI was associated with significantly higher odds of crude death in both ICU (OR 1.73, 95% CI 1.60–1.9, $P < 0.0001$) and hospital (OR 1.62, 95% CI, 1.5–1.7, $P < 0.0001$) compared to those with no AKI. Crude mortality was also significantly association with decline in kidney function in the first 24 hours and severity of AKI (Tables 4, 6; Fig. 3) Crude, covariate-adjusted, and propensity score and covariate adjusted hazards analyses for death are shown in Table 7. Each RIFLE category and duration of hypotension was independently associated with a greater hazard ratio for death after covariate-adjustment alone and after covariate and propensity score-adjusted analysis. In addition, durations of stay in both ICU and hospital were significantly longer for survivors with AKI compared with no AKI.

Discussion

We performed a multi-center analysis of prospectively collected data on critically ill patients with septic shock over a 16-year period to evaluate the incidence, association between time from hypotension onset from effective antimicrobial therapy and clinical outcomes for those with early AKI.

Table 6 Association between duration from hypotension onset to antimicrobial therapy, severity of early acute kidney injury and outcome ($n = 3{,}373$)

	Any AKI	RIFLE category			
		None	Risk	Injury	Failure
Duration of hypotension[a] (hours)	6.0 (2.3–15.3)	4.3 (1.5–10.8)	5.3 (2.0–12.0)	5.8 (2.3–15.3)	7.3 (2.7–18.1)
ICU mortality (%)	53.4	30.7	45.1	53.7	59.7
Hospital mortality (%)	59.5	36.7	50.6	60.2	66.2
90-Day mortality (%)	58.4	35.2	49.7	59.1	64.9
ICU length of stay[a] (days)	8 (5–17)	7 (4–14)	8 (5–16)	9 (5–16)	9 (5–18)
Hospital length of stay[a] (days)	30 (16–55)	26 (14–50)	28 (15–55)	31 (16–57)	31 (18–53)

AKI acute kidney injury, *ICU* intensive care unit
[a] Median (IQR) for survivors

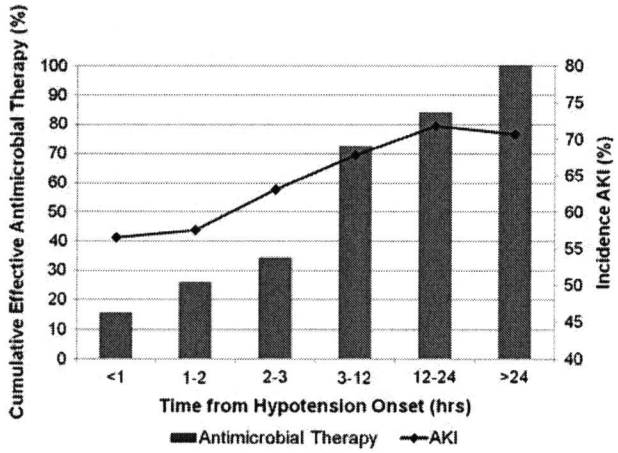

Fig. 2 Cumulative effective antimicrobial therapy following onset of hypotension and associated incidence of AKI

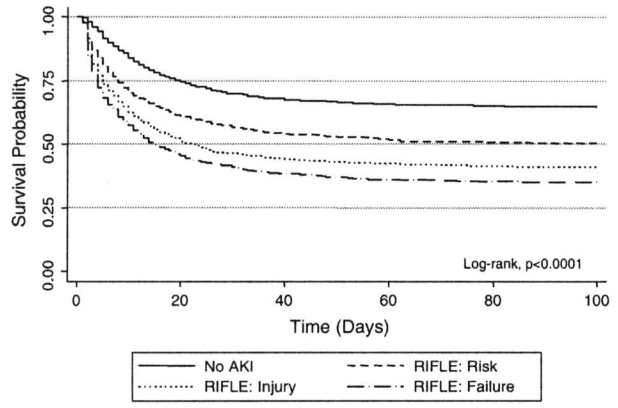

Fig. 3 Crude survival for septic shock patients stratified by severity of AKI (truncated at 100 days)

An important and novel finding of our study was that the incidence of early AKI appeared to increase with delays to appropriate antimicrobial therapy from the time of onset of hypotension. In addition, crude, covariate and covariate plus propensity score-adjusted mortality were significantly higher for those with early AKI and with greater durations from onset of hypotension to appropriate antimicrobial therapy. When stratified by the RIFLE criteria, there was an associated increase in crude, covariate and covariate plus propensity score-adjusted mortality with increasing severity of early AKI. Our data also show that worsening of kidney function within the first 24 h (by increases in serum creatinine) was associated with higher mortality. The early administration of effective antimicrobial therapy after documentation of hypotension in septic shock has been shown in both experimental and clinical studies to improve survival [25, 31]. This is the first study to identify the potential impact of delays in antimicrobial therapy on secondary organ dysfunction, specifically an increase in incidence of early AKI. This finding has clinical implications, suggesting the rapid identification and delivery of appropriate antimicrobial therapy in septic shock may be a critical determinant for not only survival, but also for prevention of secondary organ dysfunction. Kumar et al. have suggested there exist a critical window whereby the delivery of antimicrobial therapy may alter and/or interrupt the biologic response to widespread systemic inflammatory injury and improve clinical outcome [25, 31].

Prior studies of septic AKI have consistently reported that septic AKI contributes to markedly higher mortality than either non-septic AKI or sepsis alone [10–14, 16, 17]. These studies are in general agreement with our findings. Furthermore, our study extends the findings of these prior investigations by showing a clear "dose-response" increase in crude and adjusted mortality with greater severity of AKI when stratified by RIFLE criteria. Again, our cohort focused primary on patients with septic shock, and those fulfilling the RIFLE category failure where shown to have the highest mortality. Neveu et al. [13] have similarly documented a considerable increment in mortality between severe sepsis and septic shock when associated with AKI. The findings of this study, along with prior investigations, imply that septic AKI may be distinct clinical entity and independently portends a worse

Table 7 A summary of the impact of AKI and duration of hypotension prior to appropriate antimicrobial therapy on survival by crude, covariate-adjusted and propensity and covariate-adjusted Cox proportional hazards models

RIFLE category[a]	Crude HR (95% CI)	Covariate-adjusted HR (95% CI)[b]	Propensity and covariate-adjusted HR[c]
Risk	1.60 (1.37–1.85)	1.31 (1.12–1.52)	1.31 (1.12–1.52)
Injury	1.91 (1.68–2.17)	1.44 (1.26–1.64)	1.45 (1.27–1.66)
Failure	2.20 (1.92–2.51)	1.54 (1.33–1.78)	1.56 (1.35–1.80)
Duration of hypotension[d]	1.53 (1.48–1.58)	1.46 (1.41–1.51)	1.46 (1.41–1.52)

HR hazards ratio, *CI* confidence interval

[a] Reference variable: no AKI

[b] Adjustment for: age, sex, co-morbid disease, surgical status, APACHE II score, mechanical ventilation, ≥2 vasopressors needed, infection source, hospital site, study year

[c] Adjustment as above plus propensity score. Propensity score derived from multi-variable logistic regression model shown in Table 5

[d] Log transformed

prognosis. Accordingly, a diagnosis of septic AKI may require separate stratification and/or a priori identification for subgroup analysis in future studies evaluating therapeutic strategies for AKI in critically ill patients.

This study has generated several other important observations including the fact that early AKI was observed in almost two of every three patients admitted with septic shock. In addition, those developing early AKI were more likely older, had a higher body mass index, had more pre-existing co-morbid illness (specifically systemic hypertension, chronic kidney disease and hematologic malignancies), admitted with surgical disease, and had significantly greater overall illness severity. Patients with early AKI were also more likely to have primary intra-abdominal or genitourinary sources of infection and positive blood cultures. Further, deterioration in kidney function in the first 24 h and severity of AKI both correlated with overall illness severity and risk of death.

These findings confirm and broaden the data from prior investigations describing septic AKI. Observational data have indicated the incidence of both sepsis and AKI are increasing [7, 8, 32–34]. More specifically, small single center studies have found that 11–37% of all septic patients had AKI [11, 12, 16], while, two recent multi-center European studies estimated 41–51% develop concomitant AKI [14, 15]. Likewise, two large multi-center observational studies found that sepsis was a key contributing factor in 32–48% of critically ill patients with AKI [10, 13, 17]. While our study primarily focused on patients fulfilling criteria for septic shock, our findings clearly illustrate the remarkable high burden of early AKI (64.4%) in this cohort. This observation is similar to data from a prospective multi-center observational study of hospitalized patients, where Rangel-Frausto et al. [9] found that 89% of patients fulfilling criteria for septic shock develop AKI (defined as need for RRT). Other studies also support the observation that severity of illness at ICU admission is closely correlated with the occurrence of early AKI [11, 13].

Few studies have described the association of AKI and the primary infectious source and/or microbiologic diagnosis [10, 11, 14]. Both intra-abdominal and urogenital sources of infection, along with positive blood cultures, were independently associated with higher risk of early AKI in our cohort. Oppert et al. [14], in a multi-center point prevalence study of septic AKI, found similar but non-significant trends for primary abdominal and urogenital sources. Primary chest infections, however, were associated with a lower risk of early AKI in our study. Interestingly, in two prior observational studies of septic AKI, primary chest infections were the most commonly described in association with AKI [10, 11]. Whether the primary source of infection imparts an important contribution to the pathophysiology of AKI in septic shock remains uncertain and clearly warrants further investigation.

There are limitations to our study. First, the primary weakness is that our study is observational and is potentially susceptible to several forms of bias. In addition, approximately 20% of the initial cohort was excluded due to omitted or missing kidney function data. This may also potentially contribute to selection bias and impact incidence and outcome estimates. However, this issue may, at least in part, be obviated by our large cohort and by the fact our data appear largely consistent with previous studies on this topic. Second, the incidence of AKI was estimated only within the initial 24 h after presentation. Consequently, the incidence and outcomes for ICU-acquired AKI are unknown [35]. This may contribute to an under-estimate of the true incidence of septic AKI; however, we contend our data provide a global approximation of the disease burden of AKI associated with septic shock. Third, we calculated an estimate of baseline serum creatinine by use of the MDRD equation as recommended by the ADQI Working Group. Fourth, we did not have urine output data to integrate into the worst RIFLE categories. These factors may have contributed to a misclassification of some patients and may have influenced incidence estimates of AKI. Finally, the inability to

describe the association of initial RIFLE category to additional clinical outcomes such as the proportion of patients receiving RRT, long-term survival or renal recovery may also be of concern. The contribution of septic AKI, along with the duration from onset of hypotension to antimicrobial therapy to latent morbidity and mortality conditional on hospital survival remains uncertain.

In summary, we have conducted a multi-center observational study of AKI incidence, association of early AKI with delays to antimicrobial therapy and outcomes for a large heterogeneous cohort of critically ill patients with septic shock. The study demonstrates that AKI is common and frequently occurs early in septic shock. Further, our data suggest delays to appropriate antimicrobial therapy may contribute to increases in the incidence of AKI. Survival is considerably lower for septic shock associated with early AKI, with increasing severity of AKI, and with delays to appropriate antimicrobial therapy.

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References

1. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T (2005) Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 9:R700–R709
2. Korkeila M, Ruokonen E, Takala J (2000) Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Med 26:1824–1831
3. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30:2051–2058
4. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
5. Bagshaw SM, George C, Dinu I, Bellomo R (2008) A multi-centre evaluation of the Rifle criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant 23:1203–1210
6. Ostermann M, Chang RW (2007) Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 35:1837–1843
7. Bagshaw SM, George C, Bellomo R (2007) Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 11:R68
8. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, Himmelfarb J, Collins AJ (2006) Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 17:1135–1142
9. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP (1995) The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 273:117–123
10. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA (2007) Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2:431–439
11. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA (2003) Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol 14:1022–1030
12. Lopes JA, Jorge S, Resina C, Santos C, Pereira A, Neves J, Antunes F, Prata MM (2007) Acute renal failure in patients with sepsis. Crit Care 11:411
13. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P (1996) Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. Nephrol Dial Transplant 11:293–299
14. Oppert M, Engel C, Brunkhorst FM, Bogatsch H, Reinhart K, Frei U, Eckardt KU, Loeffler M, John S (2008) Acute renal failure in patients with severe sepsis and septic shock a significant independent risk factor for mortality: results from the German Prevalence Study. Nephrol Dial Transplant 23:904–909
15. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D (2006) Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 34:344–353
16. Yegenaga I, Hoste E, Van Biesen W, Vanholder R, Benoit D, Kantarci G, Dhondt A, Colardyn F, Lameire N (2004) Clinical characteristics of patients developing ARF due to sepsis/systemic inflammatory response syndrome: results of a prospective study. Am J Kidney Dis 43:817–824
17. Bagshaw SM, George C, Bellomo R (2008) Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 12:R47
18. Wan L, Bellomo R, Di Giantomasso D, Ronco C (2003) The pathogenesis of septic acute renal failure. Curr Opin Crit Care 9:496–502
19. Bellomo R, Bagshaw S, Langenberg C, Ronco C (2007) Pre-renal azotemia: a flawed paradigm in critically ill septic patients? Contrib Nephrol 156:1–9
20. Langenberg C, Wan L, Bagshaw SM, Egi M, May CN, Bellomo R (2006) Urinary biochemistry in experimental septic acute renal failure. Nephrol Dial Transplant 21:3389–3397

21. Langenberg C, Wan L, Egi M, May CN, Bellomo R (2006) Renal blood flow in experimental septic acute renal failure. Kidney Int 69:1996–2002
22. Licari E, Calzavacca P, Ronco C, Bellomo R (2007) Fluid resuscitation and the septic kidney: the evidence. Contrib Nephrol 156:167–177
23. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
24. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL (2008) Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34:17–60
25. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
26. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. Chest 101:1644–1655
27. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31:1250–1256
28. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
29. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
30. Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacedo E, Gibney N, Tolwani A, Ronco C, Kellum JA (2004) Diuretics and mortality in acute renal failure. Crit Care Med 32:1669–1677
31. Kumar A, Haery C, Paladugu B, Kumar A, Symeoneides S, Taiberg L, Osman J, Trenholme G, Opal SM, Goldfarb R, Parrillo JE (2006) The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli* septic shock: association with serum lactate and inflammatory cytokine levels. J Infect Dis 193:251–258
32. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310
33. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554
34. Brun-Buisson C, Meshaka P, Pinton P, Vallet B (2004) EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 30:580–588
35. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ (1996) Acute renal failure in intensive care units–causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. Crit Care Med 24:192–198