Septic Acute Kidney Injury in Critically Ill Patients: Clinical Characteristics and Outcomes

Sean M. Bagshaw,*† Shigehiko Uchino,*¶¶ Rinaldo Bellomo,* Hiroshi Morimatsu,‡ Stanislao Morgera,§ Miet Schetz,‖ Ian Tan,¶ Catherine Bouman,** Ettiene Macedo,†† Noel Gibney,† Ashita Tolwani,‡‡ Heleen M. Oudemans-van Straaten,§§ Claudio Ronco,‖‖ and John A. Kellum;*** for the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators

**Department of Intensive Care and Department of Medicine, Austin & Repatriation Medical Centre, Melbourne, Australia; †Division of Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada; ‡Department of Anesthesiology and Resuscitology, Okayama University Medical School, Okayama, Japan; §Department of Nephrology, University Hospital Charité, Berlin, Germany; ‖Dienst Intensieve Geneeskunde, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; ¶Intensive Care Unit, Department of Anaesthesia, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China; **Adult Intensive Care Unit, Academic Medical Center, Amsterdam, The Netherlands; ††Nephrology Division, University of São Paulo School of Medicine, São Paulo, Brazil; ‡‡Department of Medicine, Division of Nephrology, University of Alabama at Birmingham, Alabama, Alabama; §§Department of Intensive Care, Onze Lieve Vrouwe Gasthius, Amsterdam, The Netherlands; ‖‖Department of Nephrology, Intensive Care, St. Bortolo Hospital, Vicenza, Italy; ¶¶Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan; and ***Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania*

Sepsis is the most common cause of acute kidney injury (AKI) in critical illness, but there is limited information on septic AKI. A prospective, observational study of critically ill patients with septic and nonseptic AKI was performed from September 2000 to December 2001 at 54 hospitals in 23 countries. A total of 1753 patients were enrolled. Sepsis was considered the cause in 833 (47.5%); the predominant sources of sepsis were chest and abdominal (54.3%). Septic AKI was associated with greater aberrations in hemodynamics and laboratory parameters, greater severity of illness, and higher need for mechanical ventilation and vasoactive therapy. There was no difference in enrollment kidney function or in the proportion who received renal replacement therapy (RRT; 72 *versus* 71%; $P = 0.83$). Oliguria was more common in septic AKI (67 *versus* 57%; $P < 0.001$). Septic AKI had a higher in-hospital case-fatality rate compared with nonseptic AKI (70.2 *versus* 51.8%; $P < 0.001$). After adjustment for covariates, septic AKI remained associated with higher odds for death (1.48; 95% confidence interval 1.17 to 1.89; $P = 0.001$). Median (IQR) duration of hospital stay for survivors (37 [19 to 59] *versus* 21 [12 to 42] d; $P < 0.0001$) was longer for septic AKI. There was a trend to lower serum creatinine (106 [73 to 158] *versus* 121 [88 to 184] μmol/L; $P = 0.01$) and RRT dependence (9 *versus* 14%; $P = 0.052$) at hospital discharge for septic AKI. Patients with septic AKI were sicker and had a higher burden of illness and greater abnormalities in acute physiology. Patients with septic AKI had an increased risk for death and longer duration of hospitalization yet showed trends toward greater renal recovery and independence from RRT.

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Acute kidney injury (AKI) is a common complication of critical illness (1,2). The development of AKI increases patient morbidity, predicts higher mortality, and consumes considerable health resources (3–7). The cause of AKI in critically ill patients is often multifactorial. Sepsis, a highly prevalent syndrome that prompts admission to intensive care, is a leading precipitant of AKI (1,8–11). Between 45 and 70% of all AKI is considered associated with sepsis (1,9–11).

The discrimination of septic and nonseptic AKI may have clinical relevance for clinicians. For example, recent evidence suggested that septic AKI may be characterized by a distinct pathophysiology (12–14). Thus, septic AKI may be unique and, as such, may have differences in clinical outcomes and responses to interventions when compared with nonseptic AKI.

Regrettably, only a few clinical studies have focused on the presentation, profile, and outcome of septic AKI (11,15,16). Two small, single-center studies found that AKI occurred in 11 to 16% of critically ill patients who presented with sepsis (15,16). Neveu *et al.* (11), however, reported that AKI was of septic origin in 46% of cases and associated with a significantly higher

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Address correspondence to: Dr. Sean M Bagshaw, Division of Critical Care Medicine, University of Alberta Hospital, 3C1.16 Walter C Mackenzie Centre, 8440-122 Street, Edmonton, Alberta T6G2B7, Canada. Phone: 780-407-6755; Fax: 780-407-1228; E-mail: bagshaw.sean@gmail.com

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hospital mortality than nonseptic AKI. A recent large, multicenter, epidemiologic investigation of severe AKI in critically ill patients, called the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Study, collected information that offers a unique opportunity to expand our understanding of the combined syndromes of sepsis and AKI (1).

Accordingly, in view of the limited data on septic AKI and its likely importance, we sought to describe the clinical characteristics of critically ill patients with septic compared with nonseptic AKI. In addition, we investigated whether the presence of sepsis as a major contributing factor to AKI portends a different clinical course and overall prognosis.

Materials and Methods

Study Protocol

This study used a database from a large, prospective, multinational, multicenter, observational cohort study of critically ill patients with severe AKI. The study was conducted at 54 centers across 23 countries from September 2000 to December 2001, as described previously (1). The research ethics board at each participating center reviewed the study protocol before commencement.

Study Population

All patients who were aged >12 yr (selected intensive care units [ICU] treated adolescents) and admitted to a participating ICU with evidence of AKI were eligible for study inclusion. The operational definition and criteria for AKI were (*1*) oliguria defined as urine output <200 ml over 12 h, (*2*) marked azotemia defined as a serum urea >30 mmol/L (84 mg/dl), and/or (*3*) need for acute renal replacement therapy (RRT). Patients with preexisting ESRD, those who were treated with RRT before admission to ICU or for drug toxicity, and those who did not fulfill at least one predefined criterion for AKI were excluded.

Data Collection

All data were prospectively collected on standardized data forms. Data variables collected included patient age, gender, body weight, presence of premorbid chronic kidney disease (any evidence of abnormal serum creatinine or creatinine clearance before hospital admission), type of admission, and primary diagnosis. Pre-ICU serum creatinine values were used to calculate the proportion of patients who fulfilled the RIFLE (risk–injury–failure–loss–ESRD) categories of injury and failure at the time of ICU admission (17). Numerous clinical and physiologic details were also collected, including those that compose the Simplified Acute Physiology score (SAPS II) and Sequential Organ Failure Assessment score (18,19). Several *a priori* predisposing factors for development of AKI were determined as described elsewhere (1). Sepsis was diagnosed on clinical grounds by the attending clinician using published consensus criteria (20), and the primary source/diagnosis was documented. Surrogates of kidney function (serum creatinine, urea, and urine output) were documented at ICU admission, at study enrollment, and at ICU and hospital discharge. Several details of RRT were documented, including modality, timing from enrollment, and duration. Renal recovery was defined as independence from RRT. Outcome data were documented on ICU and hospital lengths of stay and on ICU and hospital survival.

Statistical Analyses

Analysis was performed using Stata version 8.2 (Stata Corp., College Station, TX). Normally or near normally distributed variables are presented as means and SD and compared using the *t* test. Non-normally distributed continuous data are presented as medians and interquartile ranges (IQR) and compared using the Mann-Whitney *U* test. Categorical data were compared with Fisher exact test. Data were missing for <1% of outcomes and when incomplete were not replaced and a lower denominator (*n*) was reported. Follow-up duration was calculated from study enrollment or diagnosis of AKI to either death or hospital discharge. The survivorship functions of the septic and nonseptic AKI groups are presented as Kaplan-Meier curves. Equality in the estimated survivorship functions was determined by the log-rank test. A multivariate logistic regression model was developed to determine the impact of septic *versus* nonseptic AKI on hospital mortality. Initial model variables included the covariates country, age, gender, baseline kidney function (normal, impaired, or unknown), admission type (surgical *versus* medical), SAPS II score, need for RRT, sepsis AKI, and variables with complete data and a $P \leq 0.20$ in univariate analysis. Backward elimination was performed by the likelihood ratio method to develop a final parsimonious model. Model adequacy was assessed using the area under the receiver operator characteristic curve and the Hosmer-Lemeshow goodness-of-fit test. Data are presented as odds ratios with 95% confidence intervals (CI). $P < 0.05$ was considered statistically significant.

Results

During the study period, 1753 critically ill patients developed AKI at the time of or during admission to ICU. Their mean (±SD) age was 63.2 (16.2) yr, 64% were male, and the mean (±SD) SAPS II score was 50.3 (17.8). Of these, 48% were postsurgical admissions, and AKI developed a median (IQR) of 3 (1 to 7) d after surgery.

Sepsis was a contributing factor to AKI in 833 (47.5%) patients. The primary sources of sepsis are presented in Table 1.

Table 1. Primary source of sepsis in patients with septic AKI[a]

Source of Sepsis	*n* (%)
Thoracic	250 (30.0)
Intra-abdominal	202 (24.3)
Endovascular	56 (6.7)
Hematologic/oncologic/ immunocompromised	48 (5.8)
Urogenital	34 (4.1)
Skin/soft tissue/bone	29 (3.5)
Central nervous system	12 (1.4)
Other	7 (0.8)
Source unknown/not specified	195 (23.4)

[a]Thoracic included pneumonia, lung abscess, mediastinitis, purulent pericarditis epiglottitis, and sinusitis; intra-abdominal included biliary sources, pancreatitis, perforated viscous, spontaneous bacterial peritonitis, and liver abscess; endovascular included bacteremia, infective endocarditis, catheter-associated bloodstream infection, infected vascular grafts, and septic thrombophlebitis; hematologic/oncologic/immunocompromised included febrile neutropenia, post-bone marrow transplant, AIDS-related, and immune suppression; central nervous system included meningitis, ventriculitis, and epidural abscess; skin/soft tissue/bone included cellulitis, necrotizing fasciitis, osteomyelitis, and septic arthritis; other included malaria, dengue fever, and leptospirosis.

Sepsis was the sole contributing factor for AKI in 356 (43%) patients, whereas 320 (38%) had one additional factor and 157 (19%) had two or more additional factors. These additional factors in those with septic AKI included postsurgical status in 204 (24.5%), hypovolemia in 175 (21%), drug-induced toxicity in 155 (19%), and concomitant cardiogenic shock in 127 (15%).

A comparison of the baseline characteristics and physiologic variables between patients with septic and nonseptic AKI are presented in Tables 2 and 3. Patients with septic AKI were more likely to be medical admissions, had greater severity of illness, and a higher proportion of them required mechanical ventilation and administration of vasoactive medications (Table 2).

Abnormalities in several hemodynamic and laboratory parameters were greater in septic AKI compared with nonseptic AKI (Table 3). Septic AKI was associated with higher mean heart rates, respiratory rates, and central venous pressures and lower mean arterial pressures and Glasgow Coma Scale scores. Septic AKI was also associated with greater acidemia and higher serum lactate levels. Likewise, median white blood cell counts were higher.

Details of kidney function and outcomes are summarized in Table 4. Data on pre-ICU serum creatinine were available for 1326 patients (75.6% of total cohort). Of those with normal premorbid kidney function ($n = 840$), 34.5% had a RIFLE category of injury and 19.9% had failure at the time of ICU admission. There was a trend for a higher proportion of patients with *versus* without sepsis to have injury (37.4 *versus* 31.3%; $P = 0.07$) but no difference in those with failure. In those with impaired premorbid function ($n = 486$), 19.4% had a RIFLE category of injury and 7.8% had failure at the time of ICU admission. In these patients, sepsis was associated with a higher proportion of both injury (25.1 *versus* 15.8%; $P = 0.01$) and failure (10.9 *versus* 5.9%; $P = 0.05$) at ICU admission.

Although there was no significant difference in serum creatinine or urea at the time of enrollment, patients with sepsis had greater changes in serum creatinine from baseline, and a higher proportion fulfilled RIFLE categories for both injury and failure (Table 4). These findings were similar at the time of initiation of RRT between septic and nonseptic AKI. Oliguria was more common in septic AKI, with fewer patients having received loop diuretics.

Overall, 71% of the entire cohort received RRT with no difference between patients with septic and nonseptic AKI (Table 4, Supplementary Tables 1 and 2). Patients with septic AKI were in the ICU longer before initiation of RRT compared with those with nonseptic AKI (2 [0 to 6] for septic *versus* 1 [1 to 3] d for nonseptic; $P = 0.004$). This delay in initiation of RRT was independently associated with hospital mortality (Supplementary Table 3). A higher proportion of patients with septic AKI received continuous RRT rather than intermittent hemodialysis (IHD), whereas patients with nonseptic AKI were more likely to receive IHD (Table 4). There was no significant difference in the median duration of RRT; however, there was a trend for fewer surviving patients with septic AKI to be dependent on RRT at hospital discharge. The serum creatinine levels at hospital discharge were lower in those with septic AKI; however, this difference seemed to be because a greater proportion of patients with nonseptic AKI had premorbid impaired kidney function compared with patients with septic AKI. Similarly, there was no significant difference in RRT dependence at hospital discharge between patients with septic and nonseptic AKI when stratified by premorbid kidney function. For example, for those with normal premorbid function, the rates of RRT dependence at hospital discharge were 5.7% in patients with septic AKI and 7.8% in patients with nonseptic AKI ($P = 0.52$). For those with impaired premorbid function, 16.7% of patients with septic AKI and 24.7% of patients with nonseptic AKI were dependent on RRT ($P = 0.28$). Overall, however, for both patients with septic and nonseptic AKI, those with impaired premorbid function had higher rates of RRT dependence compared with those with normal premorbid function (22.6 *versus* 6.9%; $P < 0.001$).

Septic AKI was associated with a higher crude in-hospital case-fatality rate compared with nonseptic AKI (70.2 *versus* 51.8%; relative risk 1.35; 95% CI 1.3 to 1.5; $P < 0.001$). Crude Kaplan-Meier survival curves demonstrated reduced survival in patients with septic compared with nonseptic AKI (Figure 1). The median (95% CI) survival for patients with septic AKI compared with nonseptic AKI was 14 (11 to 17) *versus* 31 (25 to 36) d ($P < 0.001$). After adjustment for covariates, septic AKI remained independently associated with a higher odds for death (odds ratio 1.48; 95% CI 1.17 to 1.89; $P = 0.001$; Table 5). Total ICU length of stay was significantly longer for septic AKI (16 [7 to 33] *versus* 9 [5 to 19] d; $P < 0.0001$). For those who survived to hospital discharge, length of stay from time of

Table 2. Baseline characteristics between septic and nonseptic AKI at time of study enrollment[a]

Characteristic	Total ($n = 1753$)	Septic ($n = 833$)	Nonseptic ($n = 920$)	P
Age (yr; mean [SD])	63.2 (16.2)	63.5 (15.7)	62.9 (16.6)	0.49
Male gender (%)	64	64.6	64.4	0.77
Weight (kg; mean [SD])	75 (18.3)	75.6 (18.9)	74.5 (17.6)	0.26
Surgical admission (%)	48	40.8	54.5	<0.001
SAPS II score (mean [SD])	50.3 (17.8)	54.1 (17.9)	46.9 (17)	<0.001
SOFA score mean [SD])	10.5 (3.5)	11.5 (3.4)	9.5 (3.4)	<0.001
Mechanical ventilation (%)	76.1	85.4	67.6	<0.001
Vasoactive drugs (%)	69.1	78.3	60.7	<0.001

[a]SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Table 3. Baseline physiologic data at time of study enrollment[a]

Variable	Total (n = 1753)	Septic (n = 833)	Nonseptic (n = 920)	P
Heart rate (per min; mean [SD])	98 (21)	101 (22)	96 (20)	<0.001
Respiratory rate (per min; mean [SD])	19.5 (6.5)	20.2 (6.5)	18.9 (6.4)	<0.001
SBP (mmHg; mean [SD])	116 (27)	112 (24)	119 (29)	<0.001
MAP (mmHg; mean [SD])	76.8 (17.3)	74.1 (15.6)	79.4 (18.3)	<0.001
CVP (cmH_2O; mean [SD])	14.2 (6.1)	14.8 (6.3)	13.6 (5.9)	<0.001
GCS (median [IQR])	14 (10 to 15)	13 (8 to 15)	15 (11 to 15)	<0.001
WBC (10^9 cells/ml; median [IQR])	13.4 (9 to 19.4)	14.6 (9.2 to 22)	12.4 (9 to 18)	<0.001
Platelets (10^9 cells/ml; median [IQR])	127 (69 to 209)	126 (62 to 214)	130 (77 to 203)	0.16
Bilirubin (mmol/L; median [IQR])	19 (11 to 51)	22.2 (11 to 66)	17 (10 to 39)	<0.001
Serum sodium (mmol/L; median [IQR])	139 (7.6)	139 (7.1)	139 (7.9)	0.95
Serum potassium (mmol/L; median [IQR])	4.7 (1.1)	4.7 (1.1)	4.7 (1.1)	0.32
pH (mean [SD])	7.31 (0.1)	7.28 (0.1)	7.34 (0.1)	<0.001
Bicarbonate (mmol/L; mean [SD])	19.8 (6.3)	18.9 (6.2)	20.7 (6.3)	<0.001
Lactate (mmol/L; median [IQR])]	2.1 (1.2 to 4.8)	2.3 (1.3 to 5.3)	2.0 (1.1 to 4.2)	<0.001
Pao_2/Fio_2 ratio (mean [SD])	210 (141 to 303)	196 (130 to 287)	230 (150 to 315)	<0.001
SIRS criteria at enrollment (%)[b]	57.7	64.8	51.3	<0.001

[a]CVP, central venous pressure; Fio_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; MAP, mean arterial pressure; SBP, systolic BP; SIRS, systemic inflammatory response syndrome; WBC, white blood cell count.
[b]Scores for temperature not available.

enrollment was also significantly longer for septic AKI (37 [19 to 59] *versus* 21 [12 to 42] d; $P < 0.0001$).

A sensitivity analysis was performed to determine whether there were any important differences in those with isolated septic AKI (n = 356) compared with those with septic AKI mixed with other contributing factors (n = 477; Supplementary Tables 4 through 6). Overall, there were few clinically important differences between these groups. However, patients with isolated septic AKI were more likely to be medical admissions (23.6 *versus* 53.6%; $P < 0.0001$) and had a higher illness severity score (SAPS II score 55.7 *versus* 52.9; $P = 0.03$). Furthermore, patients with isolated septic AKI had a lower enrollment urea (25 *versus* 30 mmol/L; $P < 0.001$) but more oliguria (71.5 *versus* 64.2%; $P = 0.03$). Although statistically significant, there was no clinically meaningful differentiation in age, baseline respiratory rate, Glasgow Coma Scale score, or serum pH. There were no differences in the proportion who required RRT, the duration of RRT, RRT modality, or rate of recovery to RRT independence at hospital discharge. Patients with isolated septic AKI had slightly higher median serum creatinine (123 *versus* 100 μmol/L; $P = 0.001$) and urea (11 *versus* 9 mmol/L; $P = 0.03$) values at hospital discharge. In-hospital case-fatality rates were similar for isolated septic and mixed septic AKI (68 *versus* 72%; relative risk 0.94; 95% CI 0.86 to 1.03; $P = 0.17$).

Discussion

We conducted a large, multicenter, observational study to describe the characteristics and investigate the clinical outcomes that are associated with septic compared with nonseptic AKI in critically ill patients. We found that patients with septic AKI are clinically distinct and have numerous distinguishing features when compared with those with nonseptic AKI. First, septic AKI was associated with a higher acuity and greater burden of illness as demonstrated by severity-of-illness scores, concomitant nonrenal organ dysfunction, need for mechanical ventilation, and proportion of patients who required vasoactive therapy. Second, septic AKI was associated with greater aberrations in vital signs, markers of inflammation, and blood chemistry. Third, patients with septic AKI were less likely to have impaired premorbid kidney disease, despite no differences in kidney function at study enrollment or in the proportion who received RRT. Fourth, the initiation of RRT in septic AKI generally occurred later after ICU admission compared with nonseptic AKI. Fifth, these distinctive features of septic AKI translated into clinically relevant differences in patient outcomes when compared with nonseptic AKI. For example, septic AKI was coupled with a higher risk for hospital death, even after adjustment for relevant covariates. Furthermore, septic AKI contributed to longer stays in both the ICU and the hospital. Finally, our data suggested a trend toward greater recovery of kidney function to independence from RRT by hospital discharge in those with septic compared with nonseptic AKI.

The findings of our study support and greatly extend those of previous investigations. Sepsis has emerged as the most important and prevalent predictor of AKI in critically ill patients (11,15,16,21). Two small, single-center, epidemiologic studies found that AKI occurred in 11 to 16% of all critically ill patients with sepsis (15,16). However, these studies are limited by their inclusion of only patients with sepsis and, therefore, their inability to compare septic and nonseptic AKI. However, both of these studies found that development of AKI after a diagnosis of sepsis was associated with older age, greater severity of illness, higher central venous filling pressures, greater need for vasoactive support, and lower urine output when compared

Table 4. Characteristics of renal function associated with septic and nonseptic AKI[a]

Characteristic	Total (n = 1753)	Septic (n = 833)	Nonseptic (n = 920)	P
Baseline kidney function				
normal (%; n = 980)	56	61	51	<0.001
impaired (%; n = 520)	30	24	35	
unknown (%; n = 253)	14	15	14	
Baseline serum creatinine (median [IQR]; n = 1326)				
normal function (μmol/L; n = 840)	83 (70 to 96)	80 (66 to 93)	87 (71 to 97)	0.002
impaired function (μmol/L; n = 486)	178 (141 to 246)	180 (141 to 246)	177 (141 to 244)	0.83
Enrollment kidney function (median [IQR])				
SCr (μmol/L)	290 (191 to 424)	283 (188 to 419)	293 (192 to 432)	0.27
ΔSCr (μmol/L)[b]	150 (72 to 256)	159 (82 to 264)	144 (65 to 248)	0.05
urea (mmol/L)	28 (16 to 35)	28 (17 to 35)	26 (15 to 35)	0.28
RIFLE, injury (%)	60.5	65.8	55.7	<0.001
RIFLE, failure (%)	36	41.4	31.2	<0.001
Enrollment urine output (median [IQR])				
6 h pre (mL/h)	20 (6 to 60)	17 (5 to 53)	25 (8 to 67)	<0.001
24 h pre (mL/h)	27 (10 to 63)	23 (9 to 58)	33 (12 to 66)	<0.001
RRT initiation kidney function (median [IQR])				
SCr (μmol/L)	309 (203 to 442)	309 (208 to 440)	309 (202 to 449)	0.99
ΔSCr (μmol/L)[b]	163 (78 to 269)	180 (90 to 285)	151 (67 to 255)	0.003
urea (mmol/L)	24 (15 to 35)	26 (17 to 36)	23 (14 to 34)	0.02
Oliguria (%)[b]	63	67	59	<0.001
Loop diuretic therapy (%)	66	60	72	<0.001
Required RRT (%)	71	72	71	0.83
Modality of RRT (%)				
CRRT	82	85.4	78.4	0.004
IHD	15	11.2	18.4	
SLED	1.6	1.9	1.4	
PD	1.7	1.5	1.8	

[a]ΔSCr, change in serum creatinine from baseline; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SLED, slow low-efficiency dialysis.
[b]Oliguria defined as <0.5 ml/kg per h output over 6 h.

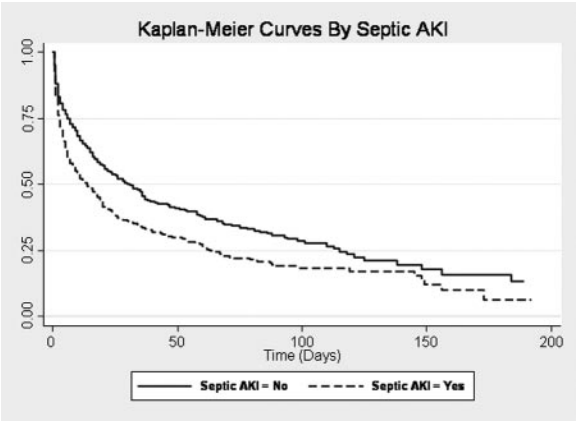

Figure 1. Kaplan-Meier survival estimates by septic acute kidney injury (AKI; log rank, $P < 0.0001$).

with those who did not develop AKI. Furthermore, Hoste *et al.* (15) found that the presence of an elevated serum creatinine or pH <7.3 at the time when sepsis was diagnosed was associated with an increased risk for AKI (defined as a rise in serum creatinine >177 μmol/L).

In the only other multicenter, epidemiologic study to compare septic with nonseptic AKI, Neveu *et al.* (11) found that AKI had a septic origin in 46% of patients. This is similar to our findings: Nearly half of all patients with AKI had sepsis. Moreover, in our study, sepsis was found to be the sole contributing factor in 43%. Neveu *et al.* showed that those with septic AKI were generally older and had greater burden of illness and nonrenal organ failure compared with those with nonseptic AKI. Although these findings are consistent with our data, there are a few notable differences. In particular, despite evidence of more severe AKI at enrollment, only 47% of patients with septic AKI (49% overall) received RRT (11). Of these, approximately 80% received conventional IHD (83% overall). In addition, many of these patients underwent dialysis against cuprophane membranes, a factor that is recognized to potentially to influence outcome (22). Whether these differences, specifically the proportion who received RRT, timing to initiate RRT, or chosen modality, are what account for the disparity in

Table 5. Multivariate logistic analysis assessing the impact of septic AKI on hospital mortality[a]

Factor[b]	OR	95% CI	*P*
Age (per year)	1.02	1.01 to 1.03	<0.001
Premorbid kidney function[c]			
impaired	0.81	0.62 to 1.05	0.11
unknown	0.72	0.51 to 1.01	0.06
SAPS II (per point)	1.02	1.01 to 1.03	<0.001
Vasoactive drugs (present)	1.66	1.28 to 2.16	<0.001
Mechanical ventilation (present)	2.49	1.88 to 3.30	<0.001
Oliguria (present)	1.52	1.20 to 1.92	<0.001
Sepsis (present)	1.48	1.17 to 1.89	0.001

[a]Hosmer-Lemeshow goodness-of-fit, $P = 0.98$, area under the receiver operator characteristic curve 0.75. CI, confidence interval; OR, odds ratio.
[b]Multivariate analysis also adjusted for country, but data not shown.
[c]Reference variable: Normal premorbid kidney function.

survival remains speculative and controversial (23–26). Nevertheless, Neveu *et al.* (11) described an in-hospital mortality of 75% for patients with septic AKI, only modestly higher than the 70% shown in our cohort. In the end, however, both studies were consistent in illustrating that septic AKI was an independent predictor of hospital death (11,27).

Another finding was that patients with septic AKI were more oliguric in the 24 h preceding enrollment and that use of loop diuretics was less common. This was evident despite higher central venous filling pressures. Oliguria in this cohort seemed to exert an independent effect on hospital mortality as was previously shown (11). Although diuretics may potentially improve urine output, their impact on clinical outcome remains controversial (28–30). Previous studies documented high rates of loop diuretic use in patients with septic AKI (16). Van Biesen *et al.* (31) also showed patients with that septic AKI experienced greater oliguria despite having received more diuretics and greater fluid resuscitation and having evidence of higher central venous pressures. We unfortunately are unable to comment on concomitant fluid therapy in our study. However, if central venous pressure were considered a surrogate for fluid resuscitation, then these findings raise important questions about the role of diuretics, fluid therapy, and oliguria in septic AKI.

The findings of our study support the notion that the discrimination of septic and nonseptic AKI may have clinical relevance. They suggest that septic AKI may differ from AKI that is induced by other factors (32). This concept is supported by recent experimental evidence that septic AKI may have a distinct pathophysiology (12,13,33). This notion is also supported by small clinical studies of septic shock (14,34,35). Furthermore, although septic AKI may be unique, our study also highlights that AKI in critically ill patients is frequently multifactorial in cause, whereby septic AKI is further complicated by additional insults as a result of operative procedures, diagnostic investigations, concomitant drug toxicity, or impaired myocardial function. Regardless of the potential limitations of previous studies of septic AKI (small sample size, retrospective, single center, or surgical only), all consistently found that septic AKI contributed to considerably higher hospital mortality with rates in excess of 70% when compared with nonseptic AKI (11,15,16). Similar to our findings, septic AKI independently portended a worse prognosis. It is interesting that our study also found that RRT was commenced later after ICU admission for septic compared with nonseptic AKI. This was evident despite similarities in serum creatinine and greater oliguria in septic compared with nonseptic AKI at the time of study enrollment and before initiation of RRT. By multivariate analysis, later initiation of RRT after ICU admission was found to be independently associated with hospital mortality. However, we note that the later initiation of RRT may also in part correspond to the subgroup of patients who developed AKI later after admission to ICU and thereby act as a surrogate for ICU-acquired AKI. Both later initiation of RRT and delayed occurrence of AKI have been shown to have an adverse impact on hospital mortality (27,36–38). These findings have relevance for treatment of the patient with sepsis and AKI. In particular, they raise several considerations on understanding the role of timing, modality, dosage, and pattern of prescription of extracorporeal blood purification therapies specifically in septic compared with nonseptic AKI and how each of these may have an impact on outcome (23,39–42).

Finally, we found a trend to suggest that patients with septic compared with nonseptic AKI were more likely to recover renal function to RRT independence by hospital discharge. Overall, there are limited data on renal recovery after septic AKI; however, higher rates of recovery to independence from RRT have been reported (9,43). The particular pathophysiologic features of septic AKI compared with nonseptic AKI that may portend an improved rate of recovery remain unknown. However, this trend again suggests that septic AKI may be distinct and that therapeutic strategies in the future may need to be tailored as such.

There are limitations to our study. First, the diagnosis of sepsis was made at the discretion of individual investigators supported by consensus criteria. The accuracy of such an approach is unknown. However, it mimics clinical practice, and this cohort was composed of patients with a clear primary diagnostic condition of septic type (*e.g.*, pneumonia, peritonitis,

endocarditis). Second, the definition of AKI in this study was likely biased toward the more severe spectrum of AKI that is encountered in critically ill patients as evidenced by high rates of RRT. It would be consistent with the failure category in the proposed RIFLE classification for AKI (2,17). Third, our study was not able to estimate the prevalence of AKI among all patients with sepsis. Fourth, centers opted to participate and contribute data, and this study is observational in design. Although both of these factors may predispose to selection bias, this study represents the largest prospective, multicenter study of septic AKI conducted to date. Finally, no data on long-term follow-up were available beyond hospital discharge. Therefore, whether septic AKI contributes to downstream morbidity and mortality conditional on hospital survival remains unknown.

Conclusion

We conducted a large, multicenter, observational study to document the clinical profile and outcomes of septic AKI in critically ill patients. We showed that septic AKI is associated with a high burden of illness, greater abnormalities in acute physiology and laboratory findings, and greater nonrenal organ failure and need for support when compared with nonseptic AKI. We further showed that septic AKI exerts an important and independent increase in the risk for hospital death. In survivors, septic AKI is associated with prolonged ICU and hospital stays but also a trend toward greater recovery of kidney function. These findings support the concept that septic AKI may represent a unique pathophysiologic condition.

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Participating centers and investigators: Australia: Intensive Care Unit, Austin and Repatriation Medical Center (S.M.B., R.B., H.M.), Department of Intensive Care, Western Hospital (Craig French), Intensive Care Unit, Epworth Foundation (John Mulder), Department of Intensive Care, Sir Charles Gairdner Hospital (Mary Pinder, Brigit Roberts), Intensive Care, Frankston Hospital (John Botha, Pradeen Mudholkar), Critical Care Unit, Flinders Medical Centre (Andrew Holt, Tamara Hunt); Belgium: Service de Soins Intensifs, Clinique Saint-Pierre (Patrick Maurice Honoré, Gaetan Clerbaux), Dienst Intensieve Geneeskunde, Universitair Ziekenhuis Gasthuisberg (M.S., Alexander Wilmer); Brazil: Nephrology Division, University of São Paulo School of Medicine (Luis Yu, E.M.), Nephrology Division, Hospital do Servidor Público Estadual (Sandra Maria Laranja, Cassio José Rodrigues), Nephrology Unit, Casa de Saúde São José/CDR Serviços Hospitalares (José Hermógenes Rocco Suassuna, Frederico Ruzany), Lutheran University of Brasil (Bruno Campos); Canada: Intensive Care, Maisonneuve-Rosemont Hospital (Martine Leblanc, Lynne Senécal), Division of Critical Care Medicine, University of Alberta, Edmonton (N.G., Curtis Johnston, Peter Brindley); China: Intensive Care Unit, Department of Anesthesia, Pamela Youde Nethersole Eastern Hospital (I.T.), Surgical Intensive Care Unit, Beijing Chao Yang Hospital (Hui De Chen, Li Wan); Czech Republic: ICU, Department of Internal Medicine I, Charles University Hospital Plzen (Richard Rokyta, Ales Krouzecky); Germany: Department of Nephrology, University Hospital Charité, CCM (S.M., Hans-Helmut Neumayer), Klinik für Anaesthesiologie, Universitätsklinikum Duesseldorf (Kindgen-Milles Detlef, Eckhard Mueller); Greece: Intensive Care Unit, General Regional Hospital, "G. Papanikolau" (Vicky Tsiora, Kostas Sombolos); Indonesia: ICU, National Cardiovascular Center and Mitra Keluarga Hospital (Iqbal Mustafa, Iwayan Suranadi); Israel: Intermediate Intensive Care Unit, Rambam Medical Center (Yaron Bar-Lavie, Farid Nakhoul); Italy: Anesthesia and Intensive Care Unit, Cliniche Humanitas-Gavazzeni (Roberto Ceriani, Franco Bortone), Nephrology, Intensive Care, St. Bortolo Hospital (C.R., Nereo Zamperetti), Istituto di Anestesia e Rianimazione Servizio di Anestesia e Rianimazione per la Cardiochirurgia, Ospedale San Raffaele IRCCS Università Vita e Salute (Federico Pappalardo, Giovanni Marino), Unità Operativa di Rianimazione, Ospedale Vittorio Emanuele (Prospero Calabrese, Francesco Monaco), Anestesia e Rianimazione, City Hospital of Sesto San Giovanni (Chiara Liverani, Stefano Clementi), Intensive Care Unit, Surgical and Medical Emergencies Institute (Rosanna Coltrinari, Benedetto Marini); Japan: Intensive Care Center, Tiekyo University School of Medicine Ichihara Hospital (Nobuo Fuke, Masaaki Miyazawa), Intensive Care Unit, Okayama University Hospital (Hiroshi Katayama, Toshiaki Kurasako), Department of Emergency and Critical Care Medicine, Graduate School of Medicine, Chiba University (Hiroyuki Hirasawa, Shigeto Oda), Emergency and Critical Care Medicine, Fukuoka Univeristy Hospital (Koichi Tanigawa, Keiichi Tanaka); Netherlands: Intensive Care Unit, Onze Lieve Vrouwe Gasthuis (H.M.O.-V.S.), Adult Intensive Care Unit, Academic Medical Center (C.B., Anne-Cornelie J.M. de Pont); Norway: Department of Anesthesia, Rikshospitalet (Jan Frederik Bugge, Fridtjov Riddervold), Department of Anaestesiology, University and Regional Hospital in Tromsø (Paul Åge Nilsen, Joar Julsrud); Portugal: Unidade de Cuidados Intensivos (ICU), Hospital de Curry Cabral (Fernando Teixeira e Costa, Paulo Marcelino), Unidade De Cuidados Intensivos Polivalente, Hospital Fernando Fonseca (Isabel Maria Serra); Russia: Unit for Exrtacorporeal Blood Purification, Bakoulev Scientific Center for Cardiovascular Surgery (Mike Yaroustovsky, Rachik Grigoriyanc); Singapore: Medicine Department, National University of Singapore (Kang Hoe Lee), Surgical Intensive Care Unit, Tan Tock Seng Hospital (Shi Loo, Kulgit Singh); Spain: Anaesthesiology and Critical Care Department, Hospital Comarcal De Viaros (Ferran Barrachina, Julio Llorens), Department of Intensive Care Medicine, Section of Severe Trauma, Hospital Universitario "12 de Octubre" (Jose Angel Sanchez-Izquierdo-Riera, Darío Toral-Vazquez); Sweden: Department of Anesthesia and Intensive Care, Sunderby Hospital (Ivar Wizelius, Dan Hermansson); Switzerland: Department of Surgery, Surgery Intensive Care Unit and Department of Medicine, Medical Intensive Care Unit, University Hospital Zürich (Tomislav Gaspert, Marco Maggiorini); United Kingdom: Center for Nephrology, Royal Free Hospital (Andrew Davenport); Uruguay: Department of Critical Care Medicine, Impasa (Raúl Lombardi, Teresita Llopart); United States: Department of Critical Care Medicine, University of Pittsburgh Medical Center (Ramesh Venkataraman, J.K.), Department of Medicine, Section of Nephrology, University of Chicago (Patrick Murray, Sharon Trevino), Surgical Intensive Care Unit, Mount Sinai Medical Center (Ernest Benjamin, Jerry Hufanda), Nephrology & Hypertension, M82, Cleveland Clinic Foundation (Emil Paganini), Department of Medicine, Division of Nephrology, University of Alabama at Birmingham (A.T., David Warnock), Internal Medicine/Nephrology, University of Nebraska Medical Center (Nabil Guirguis).

Disclosures

None.

References

1. 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: Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA.* 294: 813–818, 2005
2. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care* 10: R73, 2006
3. Ahlstrom A, Tallgren M, Peltonen S, Rasanen P, Pettila V: Survival and quality of life of patients requiring acute renal replacement therapy. *Intensive Care Med* 31: 1222–1228, 2005
4. Bagshaw SM, Mortis G, Doig CJ, Godinez-Luna T, Fick GH, Laupland KB: One-year mortality in critically ill patients by severity of kidney dysfunction: A population-based assessment. *Am J Kidney Dis.* 48: 402–409, 2006
5. Korkeila M, Ruokonen E, Takala J: 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, 2000
6. Manns B, Doig CJ, Lee H, Dean S, Tonelli M, Johnson D, Donaldson C: Cost of acute renal failure requiring dialysis in the intensive care unit: Clinical and resource implications of renal recovery. *Crit Care Med* 31: 449–455, 2003
7. Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH: Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. *Am J Kidney Dis* 40: 275–279, 2002
8. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303–1310, 2001
9. Bagshaw SM, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T: 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, 2005
10. Silvester W, Bellomo R, Cole L: Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. *Crit Care Med* 29: 1910–1915, 2001
11. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P: 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, 1996
12. Langenberg C, Wan L, Egi M, May CN, Bellomo R: Renal blood flow in experimental septic acute renal failure. *Kidney Int* 69: 1996–2002, 2006
13. Langenberg C, Wan L, Bagshaw SM, Egi M, May CN, Bellomo R: Urinary biochemistry in experimental septic acute renal failure. *Nephrol Dial Transplant* 21: 3389–3397, 2006
14. Brenner M, Schaer GL, Mallory DL, Suffredini AF, Parrillo JE: Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. *Chest* 98: 170–179, 1990
15. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA: Acute renal failure in patients with sepsis in a surgical ICU: Predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol* 14: 1022–1030, 2003
16. Yegenaga I, Hoste E, Van Biesen W, Vanholder R, Benoit D, Kantarci G, Dhondt A, Colardyn F, Lameire N: 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, 2004
17. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: 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, 2004
18. Le Gall JR, Lemenshow S, Saulnier F: A new simplified acute physiology score (SAPS-II) based on a European/North American multicenter study. *JAMA* 270: 2957–2963, 1993
19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart K, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 22: 707–710, 1996
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31: 1250–1256, 2003
21. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 273: 117–123, 1995
22. Vanholder R, Lameire N: Does biocompatibility of dialysis membranes affect recovery of renal function and survival? *Lancet* 354: 1316–1318, 1999
23. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 368: 379–385, 2006
24. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, Kaplan RM: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 60: 1154–1163, 2001
25. Uehlinger DE, Jakob SM, Ferrari P, Eichelberger M, Huynh-Do U, Marti HP, Mohaupt MG, Vogt B, Rothen HU, Regli B, Takala J, Frey FJ: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 20: 1630–1637, 2005
26. Augustine JJ, Sandy D, Seifert TH, Paganini EP: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 44: 1000–1007, 2004
27. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ: 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, 1996
28. Ho KM, Sheridan DJ: Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ* 333: 420, 2006

29. Mehta RL, Pascual MT, Soroko S, Chertow GM: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 288: 2547–2553, 2002
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: Diuretics and mortality in acute renal failure. *Crit Care Med* 32: 1669–1677, 2004
31. Van Biesen W, Yegenaga I, Vanholder R, Verbeke F, Hoste E, Colardyn F, Lameire N: Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: A prospective analysis. *J Nephrol* 18: 54–60, 2005
32. Wan L, Bellomo R, Di Giantomasso D, Ronco C: The pathogenesis of septic acute renal failure. *Curr Opin Crit Care* 9: 496–502, 2003
33. Wan L, Bellomo R, May CN: The effect of normal saline resuscitation on vital organ blood flow in septic sheep. *Intensive Care Med* 32: 1238–1242, 2006
34. Lucas CE, Rector FE, Werner M, Rosenberg IK: Altered renal homeostasis with acute sepsis. Clinical significance. *Arch Surg* 106: 444–449, 1973
35. Rector F, Goyal S, Rosenberg IK, Lucas CE: Renal hyperemia in associated with clinical sepsis. *Surg Forum* 23: 51–53, 1972
36. Gettings LG, Reynolds HN, Scalea T: Outcome in posttraumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. *Intensive Care Med* 25: 805–813, 1999
37. Guerin C, Girard R, Selli JM, Perdrix JP, Ayzac L: Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhone-Alpes Area Study Group on Acute Renal Failure. *Am J Respir Crit Care Med* 161: 872–879, 2000
38. Cosentino F, Chaff C, Piedmonte M: Risk factors influencing survival in ICU acute renal failure. *Nephrol Dial Transplant* 9[Suppl 4]: 179–182, 1994
39. Bouman CSC, Oudemans-van Straaten HM, Tijssen JGP, Zandstra DF, Kesecioglu J: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 30: 2205–2211, 2002
40. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C: A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med* 30: 100–106, 2002
41. Ratanarat R, Brendolan A, Piccinni P, Dan M, Salvatori G, Ricci Z, Ronco C: Pulse high-volume haemofiltration for treatment of severe sepsis: Effects on hemodynamics and survival. *Crit Care* 9: R294–R302, 2005
42. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 356: 26–30, 2000
43. Oudemans-van Straaten HM, Bosman RJ, van der Spoel JI, Zandstra DF: Outcome of critically ill patients treated with intermittent high-volume haemofiltration: A prospective cohort analysis. *Intensive Care Med* 25: 814–821, 1999

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