Peer reviewed article

Acute kidney injury in an infectious disease intensive care unit – an assessment of prognostic factors

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Summary

Background: Acute kidney injury (AKI) is a common complication in many infectious diseases. There are few studies to investigate risk factors for death in infectious diseases-associated AKI.

Methods: This is a retrospective study including all patients with acute kidney injury (AKI) admitted to an infectious diseases intensive care unit (ICU) in Brazil between October 2003 and September 2006.

Results: A total of 722 patients were admitted to the infectious disease ICU in the study period. AKI occurred in 147 cases (17.7%). The mean age was 45 ± 15.6 years, and 77% were male. The mean length of hospital stay was 11.5 ± 10.3 days. The main causes of ICU hospitalization were acquired immunodeficiency syndrome (AIDS)-related diseases (28.6%), pneumonia (13%), leptospirosis (11.6%), meningitis (8.2%), disseminated histoplasmosis (6.8%) and tetanus (5.4%). The main cause of AKI was sepsis (41.5%). Patients were classified according to RIFLE as "Risk" (5.6%), "Injury" (21.7%) and "Failure" (72.7%). Patients in "Failure" showed a higher mortality (p = 0.007). Multivariate analysis showed that dependent risk factors for death were oliguria (OR = 5.59, P = 0.002), metabolic acidosis (OR = 5.13, P = 0.01), sepsis (OR = 4.79, P = 0.001), hypovolaemia (OR = 4.11, P = 0.01), use of vasoactive drugs (OR = 3.34, P = 0.02), use of mechanical ventilation (OR = 2.94, P = 0.03) and high APACHE II score (OR = 1.14, P = 0.001).

Conclusion: There are important risk factors for death among critically ill patients with infectious diseases associated with AKI.

Key words: acute kidney injury; intensive care units; infectious diseases; sepsis; prognosis; RIFLE

Introduction

Acute kidney injury (AKI) is defined as an abrupt decline in renal function resulting in the inability to excrete metabolic wastes and maintain proper fluid and electrolyte balance. Pre-renal azotaemia and ischaemic tubular necrosis occur in a continuum of the same pathophysiological process. These two conditions account for 75% of AKI cases [1]. The main cause of in-hospital AKI is acute tubular necrosis resulting from multiple nephrotoxic insults such as sepsis, hypotension and the use of nephrotoxic drugs or radiocontrast media [2].

The incidence of AKI is almost 500 per million per year [3, 4] and in Scotland the incidence of AKI requiring dialysis is more than 200 per million per year [5], placing high demands on the public health system.

AKI is common, occurring in 5% of all in-hospital patients and in from 6% to 23% of ICU patients [6, 7]. The mortality of patients with multiple organ failure receiving renal replacement therapy is high, exceeding 70% in intensive care units (ICU) [8, 9]. Mortality rates have changed little over the past decades despite significant advances in supportive care. This lack of improvement may be more apparent than real as patients have become older and have more pre-existing chronic health problems [9, 10].

The risk factors for death and the outcome of critically ill patients with AKI in ICU have been studied for several groups [11–14]. The main risk factors identified were advanced age, male gender, prolonged hospital stay, hepatic, biliary tract and

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haematological diseases, hypotension, coma, use of vasoactive drugs, respiratory distress or the need for mechanical ventilation, sepsis, need for dialysis treatment, high levels of creatinine, oliguria and delayed nephrology consultation [11, 15–17].

AKI is an important complication seen in many infectious diseases. There are few studies to investigate prognostic factors in infectious disease-associated AKI.

Material and methods

Study design and definitions

The study was conducted at the Hospital São José de Doenças Infecciosas, in Fortaleza, Northeast Brazil. The records of all patients admitted to the Intensive Care Unit (ICU) from October 2003 to September 2006 were retrospectively evaluated. All patients who developed AKI during their ICU stay were included in the study. The protocol of this study was approved by the Ethical Committee of the Institution. Patients were classified according to RIFLE criteria [18].

Clinical and laboratory features at admission and during ICU stay were studied. Hypotension was defined as mean arterial blood pressure (MAP) <60 mm Hg, and therapy with vasoactive medication was initiated when the MAP remained <60 mm Hg despite fluid administration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at admission, measured with a sphygmomanometer. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, as "the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38 ºC or <36 ºC; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and white blood cell count >12 000/mm^3, <4000/mm^3, or >10% immature (band) forms" [19]. Hypovolaemic shock was differentiated from septic shock when a patient without sepsis, ie, those who did not fill the criteria for sepsis by ACCP/SCCM developed hypotension. Metabolic acidosis was defined as pH <7.35 and arterial bicarbonate <20 mEq/L. Oliguria was considered to be present when the urinary volume was less than 400 mL/day despite appropriate fluid replacement. Other laboratory data evaluated were serum urea and creatinine, total blood count, aspartate amino transaminase (AST), alanine amino transaminase (ALT), serum albumin, prothrombin time, serum sodium and potassium. Dialysis was indicated in those patients who remained oliguric after effective hydration, in those cases where uraemia was present and when there was hyperkalaemia and/or hypovolaemia non-responsive to medical treatment.

Patient population

The patients were divided into two groups, survivors and non-survivors, in order to investigate if there were differences in relation to all the studied parameters. We hypothesized and recorded the possible risk factors for death. The presence of hypotension, sepsis, use of vasoactive drugs (epinephrine, norepinephrine, dopamine), loop diuretics, aminoglycosides, angiotensin converting enzyme (ACE) inhibitors required during ICU stay, need for mechanical ventilation, hypertension, diabetes mellitus, hepatic failure, cardiovascular diseases, surgery, neoplasm, need for dialysis treatment, time to initiate dialysis, oliguria, high levels of creatinine (>3 mg/dL), coagulation abnormalities, metabolic acidosis, anaemia (haemoglobin >10 g/dL), thrombocytopenia and severe hypoalbuminaemia (serum albumin <2 g/dL), were investigated in all patients included in the study at ICU admission. The medical records of all patients were reviewed until the day of hospital discharge or the occurrence of death (in-hospital mortality). Non-survivors were included when death occurred after ICU discharge but before hospital discharge.

The APACHE (acute physiology and chronic health evaluation) II score [20] and the Glasgow Coma Scale [21] were calculated for the first 24 h of admission.

Statistical analysis

Results were expressed mean ± SD or median (range) for quantitative variables. Univariate and multivariate analysis of clinical and laboratory data was conducted with SPSS version 10.0 (SPSS Inc. Chicago, IL) and Epi Info version 6.04b (Centers for Disease Control and Prevention) software. Comparison of parameters of the two groups (survivors and non-survivors) was done with Student's t-test and Fischer's exact test. Analysis of associations between death and categorized risk factors was done with Fischer's exact test and Pearson's chi-square test. A logistic regression model was used for quantitative variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A multivariate logistic regression was performed to analyze the possible risk factors for death. The factors included in the multivariate model were those that showed a significance level <20% in the univariate analysis (Mann-Whitney test and chi-square test). P values <0.05) were statistically significant.

Results

Characteristics of patients

A total of 722 patients were admitted to the infectious disease ICU in the study period. AKI occurred in 147 cases (20.3%). The median age was 45 years (43 years for men, range 17 to 88 years; and 53 years for women, range 24 to 91) (p = 0.001); 113 (77%) were male.

Clinical course

The median length of hospital stay was 11 days (range 2 to 54 days). There was no significant correlation between mortality and days of hospitalization. Ninety-six patients (65%) were in AKI at admission (ie the diagnosis of AKI was confirmed within the first 24 hours of ICU stay), and

Table 1

Characteristics of critically ill patients with infectious disease-associated acute kidney injury.

Parameter		Survivors (n = 49)	Non-survivors (n = 98)	P
Gender	Male	38 (77%)	75 (76%)	NS
	Female	11 (23%)	23 (24%)	
Age (years)		44 ± 16	45 ± 15	NS
AKI (initial/delayed)		37/12	59/39	NS
Time to develop AKI (days after admission)		4.6 ± 4.5	4.2 ± 3.9	NS
Time to start dialysis (days)		5.0 ± 1.5	3.8 ± 0.7	NS
Length of hospital stay (days)		16 ± 1.4	9.3 ± 0.9	<0.0001
SBP_{min} (mm Hg) at admission		121 ± 4.1	108 ± 2.1	0.007
DBP_{min} (mm Hg) at admission		72 ± 2.5	65 ± 1.5	0.009
Primary diagnosis at admission				
HIV infection		8 (16.3%)	34 (34.7%)	0.02
Leptospirosis		11 (22.4%)	6 (6.1%)	0.006
Medications during ICU stay				
Nephrotoxic Drugs		15 (30.6%)	39 (39.8%)	NS
Vasoactive drugs		15 (30.6%)	79 (80.6%)	<0.0001
Loop diuretics		18 (36.7%)	47 (48%)	NS
ACE inhibitors		14 (28.6%)	4 (4.1%)	<0.0001
Co-morbidities				
Hypertension		12 (24.5%)	9 (9.2%)	0.02
Clinical manifestation during ICU stay				
Sepsis		19 (38.8%)	80 (81.6%)	<0.0001
Hypotension		10 (20.4%)	64 (65.3%)	<0.0001
Hyperbilirubinaemia		18 (94.7%)	23 (63.9%)	0.02
Metabolic acidosis		19 (38.8%)	79 (80.6%)	<0.0001
Mechanical ventilation		24 (49%)	84 (85.7%)	<0.0001
Oliguria		9 (18.4%)	42 (42.9%)	0.003
Dialysis		14 (28.6%)	38 (38.8%)	NS
Glasgow Coma Scale		11 ± 0.6	8.5 ± 0.5	<0.0001
APACHE II score		19 ± 0.9	28 ± 0.9	<0.0001

AKI = acute kidney injury; SBP_{min} = minimum systolic blood pressure; DBP_{min} = minimum diastolic blood pressure; ICU = intensive care unit; ACE inhibitors = angiotensin converting enzyme inhibitors; APACHE = acute physiology and chronic health evaluation; NS = not significant. Values expressed as mean ± SD and %. Significant P <0.05.

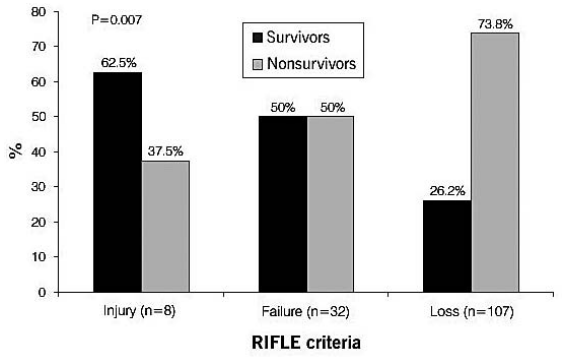

Figure 1

Mortality associated with RIFLE criteria for acute kidney injury in patients admitted to an infectious diseases intensive care unit in Brazil. Scores in patients with acute kidney injury admitted to an infectious diseases ICU.

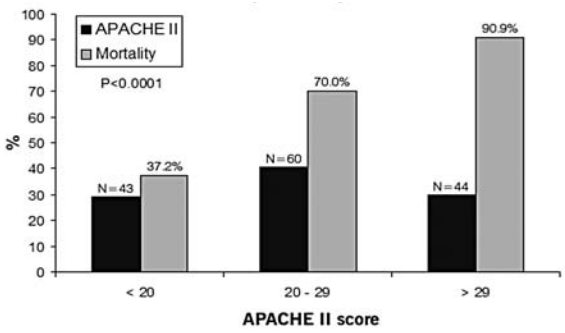

Figure 2

Mortality associated with APACHE II scores in patients with acute kidney injury admitted to an infectious diseases ICU. Dark bars represent the percentage of patients with an APACHE II in the indicated range and light bars represent the percentage of mortality in each group of patients.

51 (35%) developed AKI during hospitalization. The median time to the development of AKI, after ICU admission, was 4 days (range 1 to 20 days). Intermittent dialysis was administered in 52 (35%) patients. No continuous procedure was used. Oliguria was present in 51 (34%) cases.

Causes of ICU admission

The main causes of ICU hospitalization were AIDS-related diseases (28.6%), pneumonia (13%), leptospirosis (11.6%), meningitis (8.2%), histoplasmosis (6.8%), tetanus (5.4%), visceral leishmaniasis (4.1%) and hepatitis (4.1%). The main causes of AKI were sepsis (41.5%), hypovolaemia (28.6%), hypotension (11.6%) and nephrotoxic drugs (10.2%).

Clinical and laboratory findings during hospitalization

The comorbidities found among these patients were respiratory insufficiency (19%), hypertension (13%), liver disease (10%), diabetes mellitus (8.8%) and cardiovascular diseases (3.4%). The main cause of death was septic shock (72%). A comparison of clinical and laboratory data from survivors and non-survivors is shown in tables 1 and 2.

RIFLE criteria and outcome

Patients were also classified according to RIFLE as in "Risk" (5.6%), "Injury" (21.7%) and "Failure" (72.7%), as can be seen in table 3. Patients classified in "Failure" suffered a higher mortality (p = 0.007), as demonstrated in figure 1.

Table 2

Laboratory data at ICU admission from critically ill patients with infectious disease-associated acute kidney injury – comparison of survivors and non-survivors.

Parameter	Survivors (n = 49)	Non-survivors (n = 98)	P
Serum Creatinine (mg/dL)	2.5 ± 0.2	2.3 ± 0.2	NS
Serum Urea (mg/dL)	93 ± 8.0	83 ± 5.3	NS
ASL (IU/L)	256 ± 81	328 ± 102	NS
ALT (IU/L)	147 ± 36	213 ± 55	NS
Prothrombin time (%)	67 ± 2.9	49 ± 2.7	<0.0001
Serum Potassium (mEq/L)	4.0 ± 0.1	4.4 ± 0.1	0.03
Blood pH	7.36 ± 0.01	7.25 ± 0.01	<0.0001
Blood HCO_3 (mEq/L)	18 ± 0.8	15 ± 0.5	0.001

ASL = aspartate amino transaminase, ALT = alanine amino transaminase, NS = not statistically significant. Values expressed as mean ± SD. Significant P <0.05.

Table 3

Classification of critically ill patients with infectious disease-associated acute kidney injury according to RIFLE criteria in survivors and non-survivors.

	Survivors (n = 49)	Non-survivors (n = 98)
"Injury", n = 8 (5.4%)	5 (62.5%)	3 (37.5%)
"Failure", n = 32 (21.8%)	16 (50.0%)	16 (50.0%)
"Loss", n = 107 (72.6%)	28 (26.2%)	79 (73.8%)

Fischer Exact Test. P = 0.007.

Table 4

Univariate analysis for risk factors for death in critically ill patients with infectious disease-associated acute kidney injury.

Parameter	OR	95% CI	P
Use of vasoactive drugs	9.42	4.28–20.7	<0.0001
Oliguria	8.44	3.29–21.65	<0.0001
Hypotension	7.34	3.26–16.49	<0.0001
Metabolic acidosis	7.12	2.82–17.94	<0.0001
Sepsis	7.01	3.52–15.14	<0.0001
Mechanical ventilation	6.25	2.81–13.85	<0.0001
Hyperkalaemia	5.20	1.71–15.75	0.002
Use of sulfamethoxazole	3.80	1.54–9.32	0.002
HIV infection	2.72	1.14–6.46	0.02
APACHE II score	1.18	1.11–1.26	<0.0001
Prothrombin time >60%	0.96	0.94–0.98	<0.0001
Glasgow Coma Scale	0.86	0.79–0.93	<0.0001
Hypertension	0.31	0.12–0.80	0.02
Use of ACE inhibitors	0.10	0.03–0.34	<0.0001
RIFLE			
Injury	1.00	–	
Failure	1.66	0.34–817	0.01
Loss	4.702	1.05–20.9	

OR, odds ratio; CI, confidence interval. Significant P <0.05.

The overall mortality among patients studied was 66.6% (98 out of 147 patients). Mortality associated with APACHE II score is shown in figure 2. Out of the 43 patients with APACHE II score <20, 16 (37.2%) died, compared with 41 (68.3%) of the 60 patients with APACHE II score between 20 and 29, and 40 (90.9%) out of the 44 patients with APACHE II score >29 (P <0.001). The causes of death were septic shock (88%), multiple organ dysfunction (5%), respiratory insufficiency (2%), hypovolaemic shock (2%), cardiogenic shock (1.5%) and hepatic insufficiency (1.5%).

Factors associated with death

The univariate analysis found the following factors to be associated with death: use of vasoactive drugs, oliguria, hypotension, metabolic acidosis, sepsis, use of mechanical ventilation, hyperkalaemia, use of sulfamethoxazole, HIV infection, APACHE score and RIFLE classification. Protective factors were: elevated prothrombin time, length of hospital stay, high Glasgow Coma Scale, hypertension and use of ACE inhibitors. All data are shown in table 4.

The multivariate analysis found the following to be independent risk factors for death: oliguria, metabolic acidosis, sepsis, hypovolaemia, need for vasoactive drugs, need for mechanical ventilation and APACHE II score. RIFLE classification was not an independent predictor of mortality in this special ICU population. All data are summarized in table 5.

Table 5

Independent risk factors for death in critically ill patients with infectious disease-associated acute kidney injury.

Parameter	OR	95% CI	P
Oliguria	5.59	1.83–17.07	0.002
Metabolic acidosis	5.13	1.96–13.4	0.01
Sepsis	4.79	1.88–12.17	0.001
Hypotension	4.11	1.34–12.6	0.01
Use of vasoactive drugs	3.34	1.22–9.10	0.02
Mechanical ventilation	2.94	1.09–7.90	0.03
APACHE II score	1.14	1.05–1.23	0.001

OR, odds ratio; CI, confidence interval. Significant P <0.05.

Discussion

This is the first study to investigate prognostic factors among patients with infectious disease-associated AKI in Brazil, especially using the RIFLE criteria. We found associations between many factors and death in this population, which need to be identified earlier in order to improve the effectiveness of treatment. Moreover, our data demonstrated the need to use validated RIFLE criteria in more specific situations to determine its real accuracy in predicting mortality.

This study has some limitations. It is a retrospective study that in itself causes some difficulties in statistical analysis. The so-called "multiple exposure" problem faced by statisticians may lead to false results. This problem arises when there are few events to concurrently estimate the number of

potential risk factors of interest. This can cause bias in the results. However the results achieved seem to have significance when we compare them with other studies and when we try to correlate them with clinical practice.

In the present study, the mean age was 43 years for men, and 53 years for women, and there was no significant difference of ages among survivors and non-survivors. Many studies have demonstrated the importance of age and male gender as risk factors for death in AKI. Mataloun et al. [21] found that men were at higher risk for development of AKI. Male gender could be related to the more frequent pre-existent vascular diseases [11, 23–27]. The high incidence rate of AKI in males was more pronounced for those over 65 years old ($p < 0.0001$) [28].

A study that involved 826 patients admitted to an ICU found AKI in 15% [29]. In our study, AKI occurred in 147 cases (20.3%). The main cause of AKI was sepsis (41.5%), followed by hypovolaemia (28.6%). Brivet et al. [24] similarly found sepsis (48%), other haemodynamic mechanisms (32%) and nephrotoxicity (20%) to be the main causes of AKI. Silva Jr et al. [30], in one of the few studies performed in our region, found hypotension (48.4%) and sepsis (40.6%) to be related to AKI. Balbi et al. [31], found that AKI was due to ischaemia (51.5%), nephrotoxicity (22.3%) or multifactorial causes (26.2%).

In the present study the mean length of ICU stay was 11 days (range 2 to 54), 16 days in survivors and 9 days in non-survivors. Non-survivor group included patients in a worse clinical condition, such as pulmonary bleeding due to leptospirosis and had an early mortality. Illness severity is one of the major factors that determine short time of hospitalization. In our study, the short length of ICU stay in non-survivors was mainly due to leptospirosis associated with pulmonary bleeding. Brivet et al. [24] found a similar median length of ICU stay of 11 days (range 1 to 54) in a general ICU population. Uchino et al. [7] reported a mean stay of 10 days (range 5 to 22 days). Otherwise, Silva Jr et al. [30] found median length of ICU stay of 18 days in non-survivors and 16 days in survivors.

Isolated severe AKI is uncommon in the ICU. More than 80% of patients with severe AKI of critical illness have associated respiratory and circulatory failure. Chronic diseases such as liver cirrhosis [32], cardiovascular disease [32, 33] and previous renal insufficiency [33] have been found to be risk factors. Brivet et al. [24] found that none of these diseases alone represent independent predictors of death. The main comorbidities found in our study were respiratory insufficiency (19%) hypertension (13%), liver disease (10%), diabetes mellitus (8.8%) and cardiovascular diseases (3.4%). Respiratory insufficiency (28.9%) and cardiovascular diseases (25.8%) were the main comorbidities found in another study [30].

Mortality rate in AKI remains high, despite all the advances in critical care in the last decades, and varies according to the place of admission: ICUs 69.9%, medical wards 42.8%, surgical wards 36.3% and nephrology wards 18.1% [27]. Sepsis, especially septic shock, is one of the main causes of AKI [7, 23, 24, 30, 34–38]. AKI occurs in approximately 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock, when blood cultures are positive [36, 39]. The combination of AKI and sepsis is associated with 70% mortality, as compared with a 45% mortality among patients with AKI alone [40]. In our study, death occurred in 98 cases (66.6%). The main cause of death was septic shock (88%).

The majority of patients included in the present study were classified as "Failure", according to RIFLE criteria, and higher mortality was observed. Other studies have found an association between RIFLE criteria and mortality in patients with AKI [18]. This criterion should then be used in every patient with AKI and patients with the worst classification should receive a more intensive approach, although in our data the RIFLE criterion was not an independent predictor of mortality. This fact may be due the specific systemic conditions in infectious disease that override renal lesions in determining mortality.

Several studies [30, 34, 37, 38] have showed that hypotension and the need for mechanical ventilation were found to be predictors of a worse prognosis in multivariate analysis. We also demonstrated that the use of mechanical ventilation and hypotension increase the risk of death. Requirement for mechanical ventilation has been identified as predictive of a poor prognosis on admission or during the subsequent ICU course, a prognostic factor which suggests the role of multiple organ failure [33].

The risk factors for death in patients with infectious disease-associated AKI admitted to the ICU must be identified early. Prognostic score indices used in the prediction of outcomes in AKI patients are useful tools for the standardization and comparison of the effectiveness of treatment [22, 24, 32].

In conclusion, there are important risk factors for death among critically ill patients with infectious disease-associated AKI that must be identified early in order to decrease mortality. Our findings support the view that oliguria, metabolic acidosis, sepsis, hypovolaemia, use of vasopressors, mechanical ventilation and high APACHE II score are factors associated with death. The increased prothrombin time, high Glasgow Coma Scale and previous use of ACE inhibitors, were protective factors for development of death. Identification of these factors might lead to more intensive monitoring and early specific treatments. Further studies must be performed to consolidate the predictive factors in critically ill patients with infectious disease-associated AKI and to guide physicians towards more effective treatments, especially focused on the RIFLE criteria.

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