46. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008; 73: 538–546
47. Haynes BE, Freeman C, Rubin JL *et al*. Medical response to catastrophic events: California's planning and the Loma Prieta earthquake. *Ann Emerg Med* 1992; 21: 368–374
48. Kuwagata Y, Oda J, Tanaka H *et al*. Analysis of 2, 702 traumatized patients in the 1995 Hanshin-Awaji earthquake. *J Trauma* 1997; 43: 427–432

Received for publication: 1.3.10; Accepted in revised form: 28.6.10

Nephrol Dial Transplant (2011) 26: 524–531
doi: 10.1093/ndt/gfq477
Advance Access publication 11 August 2010

Acute kidney injury in tropical acute febrile illness in a tertiary care centre—RIFLE criteria validation

Gopal Basu[1], Anugrah Chrispal[2], Harikishan Boorugu[2], Kango G. Gopinath[2], Sara Chandy[3], John Anthony Jude Prakash[4], Kurien Thomas[2], Asha M. Abraham[3] and George T. John[1]

[1]Department of Nephrology, [2]Department of Medicine, [3]Department of Virology and [4]Department of Microbiology, Christian Medical College, Vellore, India

Correspondence and offprint requests to: George T. John; E-mail: George_John@health.qld.gov.au

Abstract

Background. Acute febrile illnesses are a common cause of tropical acute kidney injury (AKI). The incidence and severity of AKI in tropical febrile illnesses and validity of RIFLE classification are unclear.

Methods. Consecutive adult inpatients of a tertiary hospital in southern India with tropical acute febrile illness between January 2007 and January 2008 were prospectively studied for the incidence and severity of AKI based on RIFLE classification and its association with mortality and dialysis requirement.

Results. The 367 patients (mean age 39.7 ± 16.9 years; 60% males) with tropical acute febrile illness due to scrub typhus (51.2%), falciparum malaria (10.4%), enteric fever (8.7%), dengue (7.6%), mixed malaria (6.5%), leptospirosis (3.3%), undifferentiated acute febrile illness (8.4%) and others (3.8%) (spotted fever, vivax malaria and Hantaan virus infection) had an overall mortality rate of 12.3%. The incidence of AKI was 41.1%; of which, 17.4%, 9.3% and 14.4% were in the Risk, Injury and Failure classes, respectively. Of the patients, 7.9% required dialysis. Among the Risk, Injury and Failure groups, there was an incremental risk of mortality (OR 6.9, 20.2 and 25.6; $P < 0.001$) and dialysis requirement (OR 3.4, 28.8 and 178.8; $P < 0.001$).

Conclusions. The incidence of AKI in the common tropical acute febrile illnesses in our study such as scrub typhus, falciparum malaria, enteric fever, dengue and leptospirosis is 41.1%. RIFLE classification is valid and applicable in AKI related to tropical acute febrile illnesses, with an incremental risk of mortality and dialysis requirement.

Keywords: acute kidney injury/acute renal failure; dengue; malaria; RIFLE; scrub typhus

Introduction

Worldwide incidence of acute kidney injury (AKI) is variable [1,2], and even more among the developed and the developing countries [3]. Tropical acute febrile illnesses such as malaria, typhoid, leptospirosis, dengue and others are a major cause of AKI in the tropics [4,5]. There is renewal of interest with the emergence of such diseases in the developed nations and non-tropical regions [6,7] due to global warming [8,9] and travel to tropics [10,11]. Incidence of AKI with these infections has been unclear due to varying definitions of AKI [12,13], and overestimation due to referral bias in tertiary care centre reports. The Risk, Injury, Failure, Loss of function and End stage (RIFLE) criteria unified the definition and classification of AKI [14], and were originally validated for ischaemic AKI [15]. There are limited data on validity of RIFLE classification for AKI in tropical acute febrile illnesses. We evaluate the incidence of AKI and validity of the RIFLE classification in tropical acute febrile illnesses.

Materials and methods

The study was permitted by the institutional review board and ethics committee. From January 2007 to January 2008, consecutive medical ward

inpatients (aged ≥18 years) of Christian Medical College, Vellore, India, who had fever for 5–21 days without an obvious focus of infection (such as lower respiratory tract infection or urinary tract infection) were prospectively enrolled after informed consent. Patients who had chronic infections (e.g. tuberculosis), or non-infective causes of fever (e.g. systemic lupus erythematosus or lymphoma) and immunocompromised individuals (HIV infection or with immunosuppressive drug use) were excluded. All patients had a detailed clinical history and examination, a standard set of investigations including complete blood counts, liver function tests, serum creatinine, urea, electrolytes, chest radiograph, three peripheral blood smears for malaria, urinalysis, and two blood cultures, and a standard set of febrile serological investigations including leptospiral IgM ELISA (Virion\Serion GmbH, Germany), scrub typhus ELISA (PanBio Ltd, Brisbane, Australia), dengue IgM–IgG ELISA (Dengue Duo Cassette, PanBio Ltd, Brisbane, Australia), typhidot (Malaysia Bio-Diagnostics Research Sdn., Malaysia) and spotted fever ELISA (PanBio Ltd, Brisbane, Australia) on patients with rash. In patients whose preliminary tests were non-contributory to the diagnosis, further diagnostics including convalescent serological testing were undertaken. All patients were monitored till the end of their hospital stay.

Serum creatinine was measured using the modified Jaffe's kinetic alkaline picrate method (colorimetry) without deproteinization using an automated chemistry analyzer Olympus AU 2700 (Japan). AKI was classified based on RIFLE classification. When baseline creatinine was not available, it was derived using the four-variable MDRD equation by assuming a baseline glomerular filtration rate (GFR) of 90 mL/min/1.73 m^2. The RIFLE class was determined based on the worst of either the serum creatinine or GFR criteria or urine output criteria. Renal replacement therapy (RRT) (intermittent haemodialysis and slow low-efficiency haemodialysis) was initiated for standard indications. The primary outcomes studied were in-hospital mortality and requirement of RRT. Statistical analysis was performed using SPSS software version 11.0. The statistical significance of the associations between AKI based on RIFLE classification and mortality or dialysis requirement was assessed by chi-square test (with Yates continuity correction wherever appropriate) or Fisher's exact test. The degree of association was estimated using odds ratio with 95% confidence intervals.

Results

Of the 6132 admissions in the medical wards, 396 patients met the inclusion criteria. Twenty-nine (7.3%) patients who had fever due to chronic infections like tuberculosis, non-infective causes like systemic lupus erythematosus, vasculitis, and ubiquitous infections such as urinary tract infection, focal abscesses, meningoencephalitis, pneumonitis, drug rash and infectious mononucleosis were excluded. Of the 367 patients (with mean age of 39.7 ± 16.9 years) included for the final analysis, 219 (59.7%) were males, and 148 (40.3%) were females. Patients had fever for a mean duration of 9.3 ± 3.8 days prior to admission. The other baseline characteristics are detailed in Table 1.

The overall incidence of AKI among the tropical acute febrile illnesses was 41.1% (n = 151/367); of which, 17.4, 9.3 and 14.4% were in the Risk, Injury and Failure classes, respectively. Of the 151 (41.1%) patients who developed AKI, 131 (35.7%) were detected to have AKI at the time of admission [RIFLE: R, 53 (14.4%); I, 28 (7.6%); and F, 50 (13.6%)], and 20 (5.4%) developed AKI after admission. RRT in the form of intermittent haemodialysis or slow low-efficiency dialysis was initiated in 19.2% of patients with AKI (n = 29/151) for medically unresponsive severe metabolic acidosis (51.7%, n = 15), hyperkalaemia (31.0%, n = 9) and pulmonary oedema (17.3% n = 5). The overall mortality rate was 12.3% (n = 45/367).

Among the 37 (10.1%) elderly patients (age ≥65 years), AKI occurred at a rate (73.0%, n = 27) significantly higher than the rest (37.6%, n = 124; $P < 0.001$). Diabetes mellitus was present in 20 (6.0%) patients. Though the incidence of AKI was higher among diabetic patients (not statistically significant), mortality was not. Pre-existing chronic kidney disease (CKD) was documented in three (0.8%) patients, while none had chronic liver disease. Though all three patients with CKD developed AKI (one in the Risk and two in the Failure classes; with one requiring RRT), none died. Apart from the elderly age group, shorter duration of fever, presence of icterus, oliguria, breathlessness, tachycardia, tachypnoea and shock at presentation predicted the occurrence of AKI (Table 1) and mortality (except icterus). The mean serum creatinine at admission (Cr_{adm}) was significantly higher among the patients who had AKI, across all the three classes of RIFLE classification compared with the non-AKI patients. In addition, patients who suffered in-hospital mortality had higher mean Cr_{adm}. A GFR at admission (GFR_{adm}) <60 mL/min/1.73 m^2 was predictive of both AKI and in-hospital mortality.

AKI developed after hospital admission only in 20 (5.4%) patients: Risk—11 (17.2%), Injury—6 (17.6%) and Failure—3 (5.7%). Patients who developed AKI before admission and after admission had similar baseline characteristics (with the obvious exception of Cr_{adm} and GFR_{adm}), RRT requirement (19.8% vs. 15.0%) and mortality (24.4% vs. 40.0%).

Analysis after excluding the subgroup of 131 (35.7%) patients, who developed AKI before admission, revealed that the Cr_{adm} differed from the estimated baseline creatinine by a median of 0.0 mg/dL (IQR from −0.2 to +0.1). In this selected subgroup of 236 patients (who did not develop AKI before admission), RIFLE classification with Cr_{adm} as baseline misclassified 8.9% (n = 21/236) of patients compared with the RIFLE classification with the estimated baseline creatinine.

AKI developed during their hospital stay in 5.4% patients. Among the rest (35.7%), RIFLE class worsened during their hospital stay in 5.4% (n = 20): Risk to Injury—5 (1.4%), Risk to Failure—4 (1.1%) and Injury to Failure—11 (3.0%). Patients with AKI had prolonged in-hospital stay (mean difference: 1.5 days), a higher serum creatinine (Cr_{dis}) and a lower eGFR at discharge (GFR_{dis}), with 69 (45.7%) having a GFR_{dis} <60 mL/min/1.73 m^2.

The final diagnosis of the acute febrile illness is listed in Table 2. The common tropical acute febrile illness in this study was scrub typhus (51.2%), followed by falciparum malaria, mixed malaria (*Plasmodium falciparum* and *Plasmodium vivax*), enteric fever (typhoid and paratyphoid fevers), dengue (dengue fever, dengue haemorrhagic fever and dengue shock syndrome), leptospirosis, vivax malaria, other rickettsial spotted fevers and Hantaan virus infection. In 8.4% patients, the aetiology could not be ascertained. Most patients with AKI (n = 80/151) were among those with scrub typhus. However, the incidence of AKI was highest with falciparum malaria (63.2%), followed by mixed malaria (54.2%), leptospirosis (50.0%) and least with enteric fever (6.3%). AKI was observed at an average rate of 35–40% among other acute febrile illnesses (Table 2). In general, 15–20% belonged to the Risk class (due to increased sensitivity of the criteria), but the proportion in the Failure class was quite variable. Falciparum

Table 1. Baseline characteristics and its effect on AKI, RIFLE classification and mortality

Characteristic	Total	No AKI	AKI	P[#]	Risk	Injury	Failure	Dialysis	Alive	Death	P[$]
Number (%)	367 (100)	216 (58.9)	151 (41.1)		64 (17.4)	34 (9.3)	53 (14.4)	29 (7.9)	322 (87.7)	45 (12.3)	
Female *n* (%)	148 (40.3)	94 (43.5)	54 (35.8)	0.136	26 (40.6)	13 (38.2)	15 (28.3)	10 (34.5)	124 (38.5)	24 (53.3)	0.058
Age in years mean ± SD	39.7 ± 16.7	34.5 ± 14.6	47.1 ± 17.2	<0.001	47.4 ± 17.8	46.6 ± 16.1	47.1 ± 17.5	45.3 ± 19.2	38.6 ± 16.5	47.4 ± 17.9	0.001
Elderly (>65 years) *n* (%)	37 (10.1)	10 (4.6)	27 (17.9)	<0.001	13 (18.3)	5 (13.5)	11 (19.0)	6 (20.0)	28 (8.0)	11.0 (22.9)	0.001
Co-morbidities											
Diabetes *n* (%)	22 (6.0)	9 (4.2)	13 (8.6)	0.078	4 (6.3)	4 (11.8)	5 (9.4)	1 (3.4)	21 (6.5)	1 (2.2)	0.225
CKD *n* (%)	3 (0.8)	0	3 (2.0)	0.136*	1 (1.6)	0	2 (3.8)	1 (3.4)	3 (0.9)	0	1.000*
CLD *n* (%)	0	0	0		0	0	0	0	0	0	
Clinical features											
Duration of fever in days mean ± SD	9.3 ± 3.8	9.7 ± 4.1	8.8 ± 3.3	0.028	9.3 ± 3.4	9.0 ± 2.9	8.0 ± 3.5	7.8 ± 2.2	9.3 ± 3.9	9.3 ± 3.3	0.942
Oliguria *n* (%)	44 (12.0)	12 (5.6)	32 (21.2)	<0.001	7 (10.9)	7 (20.6)	18 (34.0)	10 (34.5)	33 (10.2)	11 (24.4)	0.006
Breathlessness *n* (%)	99 (27.0)	47 (21.8)	52 (34.4)	0.007	17 (26.6)	17 (50.0)	18 (34.4)	13 (44.8)	72 (22.4)	27 (60.0)	<0.001
Oedema *n* (%)	28 (7.6)	12 (5.6)	16 (10.6)	0.073	7 (10.9)	3 (8.8)	6 (11.3)	3 (10.3)	20 (6.2)	8 (17.8)	0.006
Icterus *n* (%)	79 (21.5)	31 (14.4)	48 (31.8)	<0.001	14 (21.9)	10 (29.4)	24 (45.3)	13 (44.8)	67 (20.8)	12 (26.7)	0.370
Pulse/min mean ± SD	100.5 ± 16.4	97.5 ± 15.5	104.9 ± 16.7	<0.001	102.4 ± 15.4	111.0 ± 15.0	104.0 ± 18.4	108.2 ± 16.1	98.5 ± 15.7	114.9 ± 14.5	<0.001
RR/min mean ± SD	25.5 ± 9.8	22.9 ± 8.8	28.5 ± 10.2	<0.001	25.5 ± 10.1	32.2 ± 11.1	29.9 ± 8.8	30.8 ± 6.6	23.7 ± 8.8	35.6 ± 10.4	<0.001
MAP mmHg mean ± SD	82.2 ± 16.8	85.3 ± 11.3	77.8 ± 21.8	<0.001	81.2 ± 18.6	68.8 ± 22.5	79.6 ± 23.6	79.4 ± 23.3	84.6 ± 14.0	65.3 ± 24.5	<0.001
Shock *n* (%)	66 (18.0)	12 (5.6)	54 (35.8)	<0.001	15 (23.4)	18 (52.9)	21 (39.6)	12 (41.4)	32 (9.9)	34 (75.6)	<0.001
In-hospital stay in days mean ± SD	6.9 ± 5.0	6.3 ± 4.0	7.8 ± 6.0	0.011	6.8 ± 3.8	6.9 ± 5.2	9.5 ± 8.1	11.0 ± 9.9	6.9 ± 4.2	7.0 ± 8.9	0.964
Creatinine and eGFR											
Cr_{adm} in mg/dL mean ± SD	1.5 ± 1.5	0.9 ± 0.2	2.3 ± 2.0	<0.001	1.2 ± 0.3	1.8 ± 0.6	4.0 ± 2.7	3.9 ± 3.1	1.4 ± 1.5	2.1 ± 1.6	0.003
GFR_{adm} in mL/min/1.73 m^2 mean ± SD	78.8 ± 38.0	101.8 ± 27.4	45.9 ± 24.6	<0.001	62.6 ± 13.6	46.2 ± 21.0	25.5 ± 21.6	30.0 ± 25.5	83.1 ± 37.3	47.9 ± 28.0	<0.001
GFR_{adm} <60 mL/min/1.73 m^2 *n* (%)	108 (29.4)	0	108 (71.5)	<0.001*	31 (48.4)	27 (79.4)	50 (94.3)	26 (89.7)	77 (23.9)	31 (68.9)	<0.001
Cr_{hi} in mg/dL mean ± SD	1.7 ± 1.9	0.9 ± 0.2	2.9 ± 2.6	<0.001	1.3 ± 0.3	2.0 ± 0.6	5.3 ± 3.0	5.3 ± 3.2	1.5 ± 1.8	2.9 ± 2.1	<0.001
GFR_{low} in mL/min/1.73 m^2, mean ± SD	74.4 ± 38.6	98.3 ± 23.5	40.3 ± 28.9	<0.001	59.2 ± 10.6	41.0 ± 40.5	17.0 ± 15.5	17.4 ± 11.2	79.9 ± 37.1	35.3 ± 23.4	<0.001
Cr_{dis} in mg/dL mean ± SD	1.2 ± 1.1	0.8 ± 0.2	1.8 ± 1.5	<0.001	1.0 ± 0.3	1.4 ± 0.6	3.0 ± 2.0	3.3 ± 2.1	1.1 ± 0.9	2.3 ± 1.5	<0.001
GFR_{dis} in mL/min/1.73 m^2 mean ± SD	88.7 ± 37.1	106.0 ± 25.7	63.9 ± 36.8	<0.001	84.0 ± 29.7	63.2 ± 29.4	40.1 ± 34.8	30.3 ± 20.8	94.4 ± 33.3	47.7 ± 37.4	<0.001
GFR_{dis} <60 mL/min/1.73 m^2 *n* (%)	69 (18.8)	0	69 (45.7)	<0.001*	11 (17.2)	17 (50.0)	41 (77.4)	27 (93.1)	36 (11.2)	33 (73.3)	<0.001

*With continuity correction. [#]Comparison between No AKI and AKI groups. [$]Comparison between Alive and Death groups.
SD, standard deviation; CKD, chronic kidney disease; CLD, chronic liver disease; RR, respiratory rate; MAP, mean arterial pressure; Cr, serum creatinine; GFR, estimated glomerular filtration rate by four-variable MDRD equation, $_{adm}$, at the time of admission; $_{dis}$, at discharge/last in-hospital value; hi, highest value in hospital; low, lowest value in hospital.

Table 2. Diagnosis of tropical acute febrile illness and the incidence of acute kidney injury, dialysis therapy and mortality by RIFLE criteria

Diagnosis	Total *n* (%)	Total AKI	Risk	Injury	Failure	Dialysis	Mortality
Scrub typhus *n* (%)	188 (51.2)	80 (42.6)	38 (20.2)	21 (11.2)	21 (11.2)	11 (5.9)	25 (13.3)
Falciparum malaria *n* (%)	38 (10.4)	24 (63.2)	7 (18.4)	3 (7.9)	14 (36.8)	9 (23.7)	5 (13.2)
Enteric fever *n* (%)	32 (8.7)	2 (6.3)	0	1 (3.1)	1 (3.1)	0	0
Dengue *n* (%)	28 (7.6)	10 (35.7)	4 (14.3)	1 (3.6)	5 (17.9)	2 (7.1)	7 (25)
Mixed malaria *n* (%)	24 (6.5)	13 (54.2)	6 (25.0)	2 (8.3)	5 (20.8)	4 (16.7)	1 (4.2)
Leptospirosis *n* (%)	12 (3.3)	6 (50.0)	3 (25.0)	1 (8.3)	2 (16.7)	0	0
Spotted fever *n* (%)	7 (1.9)	2 (28.6)	1 (14.3)	0	1 (14.3)	1 (14.3)	1 (14.3)
Vivax malaria *n* (%)	6 (1.6)	2 (33.3)	2 (33.3)	0	0	0	0
Hantaan virus infection *n* (%)	1 (0.3)	1 (100.0)	0	0	1 (100.0)	0	0
Undifferentiated *n* (%)	31 (8.4)	11 (35.5)	3 (9.7)	6 (19.4)	2 (6.5)	2 (6.5)	6 (19.4)
Total *n* (%)	367	151 (41.1)	64 (17.4)	34 (9.3)	53 (14.4)	29 (7.9)	45 (12.3)

malaria had the highest incidence of AKI in the Failure class (36.8%) double that observed in other conditions such as dengue (17.9%) and leptospirosis (16.7%). RRT requirement was also highest in patients with falciparum malaria (23.7%). Mortality was highest among patients with dengue and undifferentiated fever (25.0% and 19.4%, respectively).

AKI was more common among patients who died (27.5% vs. 2.7%). Overall, AKI was a significant risk factor for mortality with an odds ratio of 15.2 (95% CI 5.8–39.6, $P < 0.001$). This association persisted for each of the individual infections (Table 3). The mortality rate increased from 2.3% in the no AKI class to 14.1%, 32.4% and 37.7% in the Risk, Injury and Failure classes, respectively (Figure 1), demonstrating a significant stepwise incremental risk of mortality (Table 4) from Risk to Injury to Failure classes (OR 6.9, 20.2 and 25.6, respectively, $P < 0.001$). RRT requirement also increased from Risk to Injury to Failure classes (1.6%, 11.8% and 45.3%, respectively) following a similar stepwise incremental risk (OR 3.4, 28.8 and 178.8, respectively).

Among the 151 patients who had AKI, 69 (45.7%) had a GFR_{dis} <60 mL/min/1.73 m^2, compared with none in the non-AKI group. Two of the three patients with pre-existing CKD had a GFR_{dis} <60 mL/min/1.73 m^2. Overall, 76 (20.7%) patients (40 of those had AKI) had a follow-up visit after their discharge. Of this, only 31 (8.4%) patients had a follow-up beyond 3 months (14 had AKI and two with GFR_{dis} <60 mL/min/1.73 m^2.). This limited data showed that most patients had improvement in GFR with time.

Table 3. AKI and mortality among tropical acute febrile illnesses

	Mortality		Odds ratio		
Disease	AKI group *n* (%)	No AKI group *n* (%)	Mean	95% CI	P-value
Scrub typhus	22 (27.5)	3 (2.7)	13.3	3.8–46.3	<0.0001
Falciparum malaria	5 (20.8)	0			0.182*
Dengue	6 (60.0)	1 (5.6)	25.5	2.4–275.7	0.003
Mixed malaria	1 (7.7)	0			1.000*
Spotted fever	1 (50.0)	0			0.608*
Undifferentiated	5 (45.5)	1 (5.0)	15.8	1.5–163.5	0.013
Total	40 (26.5)	5 (2.3)	15.2	5.8–39.6	<0.0001

*With continuity correction. Enteric fever, Leptospirosis, Vivax malaria and Hantaan virus infections were not included in this analysis as these patients did not suffer any mortality.

Discussion

Tropical acute febrile illnesses are a common cause of AKI in the developing countries. In this prospective study from a tertiary care centre in southern India, the common tropical acute febrile illness among hospitalized patients included malaria, typhoid, scrub typhus, dengue, leptospirosis, spotted fever and others. Scrub typhus accounted for the majority of tropical acute febrile illnesses in our study. Factors such as prospective inclusion of consequent patients, use of uniform standardized clinical observations and laboratory investigations, standard criteria for diagnosis of febrile illness including analysis of convalescent sera wherever necessary, and a study period extending for a full year annulling the possible seasonal variations [16] strengthen the reliability and validity of the observed incidence of the various infections.

The incidence of AKI (41.1%) in this study is among the highest of reports among tropical infections. However, nearly half of these patients were found to be in the Risk class, characterized by a mild degree of renal dysfunction that is often under-recognized.

We have used an estimated baseline creatinine derived by back-calculating a normalized eGFR of 90 mL/min/1.73 m^2 using the four-variable MDRD equation. The predominant population was from the rural and the suburban regions of the four neighbouring states, people having to travel long distances to reach our hospital. Patients usually do not have health insurance coverage or check-up, and hospital visits are usually for major illnesses. Therefore, most patients do not have a pre-admission baseline serum creatinine. Patients with AKI had a significantly higher Cr_{adm}, as most patients developed AKI prior to admission (35.7%). Among the rest (64.3%), only 5.4% had AKI (after admission). Therefore, Cr_{adm} could not be used as a uniform marker of baseline renal function, being valid only for a small group of patients.

The patient population is predominantly young (mean age of 39.7 ± 16.9 years) with a minority being elderly (10.1%), suffering from diabetes (6.0%) or pre-existing CKD (0.8%). Our (Basu *et al.* 2007, unpublished) experience with renal allograft donors and existing literature sug-

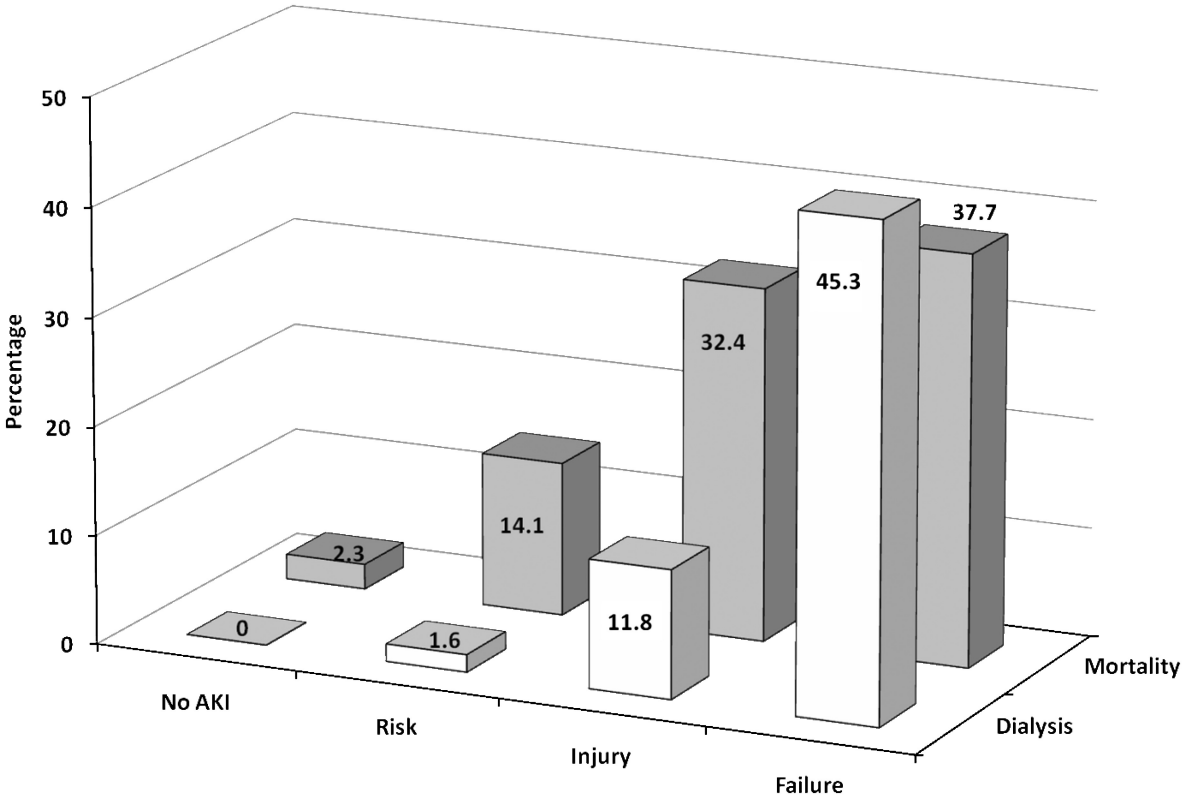

Fig. 1. AKI based on RIFLE classification and percentage of patients with mortality and requirement of renal replacement therapy.

gest that the average south Indian adult GFR (with a mean age of 37.4 ± 11.0 years) is around 95.5 ± 11.6 mL/min/1.73 m^2. [17]. This is in contrast with the literature on RIFLE validation from the developed countries, especially in the ICU settings, where the average age is usually ≥60 years, and a GFR of 75 mL/min/1.73 m^2 was used to calculate baseline creatinine for RIFLE classification [18,19]. In a relatively younger population with minimal pre-existing co-morbidities, we considered a baseline GFR of 90 mL/min/1.73 m^2 to be closer to reality than 75 mL/min/1.73 m^2. This estimated baseline creatinine was not different from the admission creatinine among patients who did not develop AKI prior to admission. In addition, RIFLE classification based on an estimated baseline creatinine is unlikely to misclassify the Injury and Failure groups but may increase the number included in the Risk group [19]. An advantage of availability of pre-calculated baseline serum creatinine and cut-off values for the RIFLE classes for a patient sensitizes the doctor for timely diagnosis and institution of appropriate preventive/therapeutic measures to avoid progression of AKI in hospital.

A majority of the patients had developed AKI prior to admission, with only 5% of the total population developing AKI after admission and another 5% having worsening of their RIFLE status after admission. Measures to prevent AKI are best initiated at the community and primary healthcare level rather than at a tertiary hospital.

AKI was associated with higher age group, the elderly and patients with a severe illness characterized by shorter duration of fever, presenting with shock, tachycardia, tachypnoea, breathlessness, oliguria and icterus. Diabetics had a relatively higher incidence of AKI, though not statistically significant with small numbers. These associations would help in selecting patients for initiating effective therapeutic/preventive strategies against AKI at the primary

Table 4. AKI based on RIFLE classification and incremental risk for mortality and renal replacement therapy

	Mortality				Dialysis			
RIFLE *n* = 367	Alive *n* (%)	Dead *n* (%)	Odds ratio Mean (95% CI)	P-value	No RRT *n* (%)	RRT *n* (%)	Odds ratio Mean (95% CI)	P-value
No ARF	211 (97.7)	5 (2.3)	Reference group		216 (100)	0 (0)	Reference group	
Risk	55 (85.9)	9 (14.1)	6.9 (2.3–20.4)	0.001	63 (98.4)	1 (1.6)	3.4 (0.3–33.3)	0.517*
Injury	23 (67.6)	11 (32.4)	20.2 (6.7–60.7)	<0.001	30 (88.2)	4 (11.8)	28.8 (4.1–196.7)	<0.001*
Failure	33 (62.3)	20 (37.7)	25.6 (9.3–70.3)	<0.001	29 (54.7)	24 (45.3)	178.8 (29.3–1071.3)	<0.001*

*With continuity correction.

care level. It is not possible to derive conclusions regarding other predisposing factors such as CKD, chronic liver disease and drug exposure.

Scrub typhus, a rickettsial infection (*Orientia tsutsugamushi*), is transmitted by trombiculid chigger mites (especially *Leptotrombidium deliense*), found in semi-arid regions of heavy scrub vegetation. Its distribution was initially limited to a triangular area (the tsutsugamushi triangle) bordered by Japan, eastern Australia and eastern Russia, which includes India (sub-Himalayan and southern India), China and the Far East [20,21]. This infection often presents with fever, maculopapular rash with an eschar at mite-bite site, myalgia, hepatosplenomegaly and, in severe cases, with acute lung injury, AKI, and multi-organ dysfunction [22]. The case fatality rate ranges from 3% to 50% [23]. It is diagnosed by a scrub typhus ELISA [24] and treated with drugs such as doxycycline, chloramphenicol, ciprofloxacin and azithromycin [20]. It is grossly under-reported and under-diagnosed [25], due to lack of awareness, non-availability of the diagnostic test at peripheral centres and widespread use of empirical broad-spectrum antibiotics for acute febrile illnesses. In our study, AKI was observed in 40% of patients with scrub typhus, more than half of them being in the Injury or Failure classes and about 13.7% (6% of total) requiring RRT. Though overall mortality was only 13.3%, it was up to 27.5% among patients with AKI. AKI was a definite risk factor for mortality among scrub typhus patients ($P < 0.001$, OR = 13.2, 95% CI 3.8–46.2). The disease was not limited to the people of the low socioeconomic status and was observed across the rural–urban divisions. There is a paucity of literature on the nature and aetiological factors in the evolution of AKI in this infection. The putative mechanisms include pre-renal failure [26], septic shock [27], rhabdomyolysis [28], direct renal invasion of *O. tsutsugamushi* [29], use of non-steroidal anti-inflammatory drugs (NSAIDs) and acute interstitial nephritis secondary to empirical use of antibiotics (e.g. ciprofloxacin).

Falciparum malaria, the next common tropical infection in our study either alone (I = 10.4%) or in combination with vivax (mixed malaria, I = 6.5%), is caused by *P. falciparum* and transmitted by *Anopheles* mosquito. It manifests with fever, haemolysis and systemic inflammatory response with microvascular plugging due to aggregation of infected as well as uninfected erythrocytes [30]. In our study, falciparum malaria (pure and mixed, respectively) had the highest incidence of AKI (63.2% and 54.2%), most of them in Failure class (36.8% and 20.8%) and requiring RRT (23.7% and 16.7%). AKI in malaria is due to renal ischaemia (microvascular plugging), tubular toxicity (haemolysis) and widespread inflammation secondary to sepsis syndrome. Probably due to early diagnosis and effective treatment, the mortality is much lower (13.2% and 4.2%) compared with the other acute febrile illnesses. However, all patients who died had AKI, making it an important risk factor for mortality.

Dengue, a day-biting mosquito-borne (*Aedes aegypti*) infection caused by various strains of *Dengue* flavivirus, places 2.5 billion population at risk worldwide, and results in 50 million confirmed cases in annual, often urban epidemics in numerous tropical countries and developed nations [31]. Exposure to another viral strain again can cause dengue haemorrhagic fever. In this study, of the 7.6% patients with dengue, more than a third had AKI, with half of them in the Failure class. AKI is predominantly due to reduced renal blood flow as in dengue shock syndrome [32], sepsis syndrome [33], rhabdomyolysis [34], empirical use of NSAIDs for analgesic–antipyretic effects, and other rare causes [35]. In keeping with the severity of the disease, this acute febrile illness had the highest mortality rate (25%), AKI being a significant risk factor (OR 25.5).

The incidence of leptospirosis in our study was lower than that observed in centres with humid, marshy environment and higher rainfall [36,37]. Half of the patients suffered AKI, though none of them died or required RRT. AKI is predominantly a non-oliguric acute interstitial nephritis, often associated with hyponatraemia and hypokalaemia [38]. The incidence of other acute febrile illnesses such as vivax malaria and spotted fevers was comparatively lower and had similar rates of AKI, RRT requirement, and mortality.

Despite the use of a standard battery of tests for tropical acute febrile illness, the aetiology of fever could not be ascertained in ~8.4% of the patients, who had comparable AKI but higher (19.4%) mortality without specific disease-directed therapy.

Our study demonstrates that the incidence of AKI (I = 41.1%) is higher than what was widely reported prior to RIFLE classification [39,40]. AKI is a significant risk factor for mortality in these patients (OR = 15.2, $P < 0.001$). There are several disease-specific scoring systems that predict mortality in AKI, such as the Liano [41], SHARF [42], Mehta [43], and the Vellore model derived from the tropics [44]. Stratification based on the RIFLE classification clearly demonstrates an incremental risk of primary end points such as mortality and RRT requirement. The odds ratios for mortality in the Risk, Injury and Failure classes were 6.9, 20.2 and 25.6, respectively ($P \leq 0.001$). This is one of the first reports demonstrating that the RIFLE criteria, initially framed for ischaemic AKI and validated in the western world among critically ill hospitalized patients [45], are equally valid and applicable to AKI of the tropical acute febrile illnesses. This information would help improvise the disease-specific predictive models for mortality in tropical AKI.

Considering there is a high incidence of AKI, a significant risk factor for death among the large number of patients admitted with acute febrile illness in a tropical hospital, validation of RIFLE criteria assumes great importance. Apart from increased mortality, longer duration of hospital stay and the requirement of renal replacement therapy, the loss of the young workforce adds to the economic burden. It is now possible to identify patients at an early stage of AKI using these criteria and study effective therapeutic or preventive measures that can contain and prevent AKI reducing morbidity and mortality, saving money and lives.

This tertiary hospital data, with its inherent referral bias arising from more ill patients reaching a tertiary care centre, may overestimate the incidence of AKI. Though patients who are ill get referred to larger centres, a large but undefined number of patients with AKI in febrile illnesses in tropics have no access to medical attention or

reside far away from large hospitals and will succumb to complications, making this a major public health concern. In addition, as this relatively young population is studied only at hospitalization and the renal dysfunction is thought to be acute, the possibility of a small proportion having an acute on chronic renal failure cannot be excluded.

Conclusions

Scrub typhus, falciparum malaria, enteric fever, dengue and leptospirosis were the most common tropical acute febrile illnesses in this study. The incidence of AKI among these patients is 40%. AKI is a significant risk factor for mortality. RIFLE criteria are valid and applicable in AKI related to tropical acute febrile illnesses showing both an incremental risk of in-hospital mortality and RRT requirement.

Conflict of interest statement. None declared.

References

1. Lameire N, van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. *Nat Clin Pract Nephrol* 2006; 2: 364–377
2. Lameire N, van Biesen W, Vanholder R. The rise of prevalence and the fall of mortality of patients with acute renal failure: what the analysis of two databases does and does not tell us. *J Am Soc Nephrol* 2006; 17: 923–925
3. Cerda J, Bagga A, Kher V *et al*. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol* 2008; 4: 138–153
4. Jha V, Chugh KS. Community-acquired acute kidney injury in Asia. *Semin Nephrol* 2008; 28: 330–347
5. Naicker S, Aboud O, Gharbi MB. Epidemiology of acute kidney injury in Africa. *Semin Nephrol* 2008; 28: 348–353
6. Desai S, van Treeck U, Lierz M *et al*. Resurgence of field fever in a temperate country: an epidemic of leptospirosis among seasonal strawberry harvesters in Germany in 2007. *Clin Infect Dis* 2009; 48: 691–697
7. Rezza G, Nicoletti L, Angelini R *et al*. Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet* 2007; 370: 1840–1846
8. Semenza JC, Menne B. Climate change and infectious diseases in Europe. *Lancet Infect Dis* 2009; 9: 365–375
9. Zell R. Global climate change and the emergence/re-emergence of infectious diseases. *Int J Med Microbiol* 2004; 293: 16–26
10. Nachega JB, Bottieau E, Zech F *et al*. Travel-acquired scrub typhus: emphasis on the differential diagnosis, treatment, and prevention strategies. *J Travel Med* 2007; 14: 352–355
11. Wilson ME, Freedman DO. Etiology of travel-related fever. *Curr Opin Infect Dis* 2007; 20: 449–453
12. Lameire N, van Biesen W, Vanholder R. Acute renal failure. *Lancet* 2005; 365: 417–430
13. Lombardi R, Yu L, Younes-Ibrahim M *et al*. Epidemiology of acute kidney injury in Latin America. *Semin Nephrol* 2008; 28: : 320–329
14. Bellomo R, Ronco C, Kellum JA *et al*. 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* 2004; 8: R204–R212
15. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008; 73: 538–546
16. Mathai E, Rolain JM, Verghese GM *et al*. Outbreak of scrub typhus in southern India during the cooler months. *Ann NY Acad Sci* 2003; 990: 359–364
17. Srinivas S, Annigeri RA, Mani MK *et al*. Estimation of glomerular filtration rate in South Asian healthy adult kidney donors. *Nephrology (Carlton)* 2008; 13: 440–446
18. Hoste EA, Clermont G, Kersten A *et al*. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006; 10: R73
19. Zavada J, Hoste E, Cartin-Ceba R *et al*. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant* 2010; 25: 107–118
20. Raoult D. Scrub Typhus. In: GL Mandell, RG Douglas, JE Bennett, R Dolin (eds). *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 6th ed. Philadelphia, Pa.: Elsevier/Churchill Livingstone, 2005; 2309–10
21. Kamarasu K, Malathi M, Rajagopal V *et al*. Serological evidence for wide distribution of spotted fevers & typhus fever in Tamil Nadu. *Indian J Med Res* 2007; 126: 128–130
22. Varghese GM, Abraham OC, Mathai D *et al*. Scrub typhus among hospitalised patients with febrile illness in South India: magnitude and clinical predictors. *J Infect* 2006; 52: 56–60
23. Kawamura A, Tanaka H, Tamura A. *Tsutsugamushi Disease: An Overview*. Tokyo: University of Tokyo Press, 1995
24. Prakash JA, Abraham OC, Mathai E. Evaluation of tests for serological diagnosis of scrub typhus. *Trop Doct* 2006; 36: 212–213
25. Isaac R, Varghese GM, Mathai EJM *et al*. Scrub typhus: prevalence and diagnostic issues in rural Southern India. *Clin Infect Dis* 2004; 39: 1395–1396
26. Hsu GJ, Young T, Peng MY *et al*. Acute renal failure associated with scrub typhus: report of a case. *J Formos Med Assoc* 1993; 92: 475–477
27. Thap LC, Supanaranond W, Treeprasertsuk S *et al*. Septic shock secondary to scrub typhus: characteristics and complications. *Southeast Asian J Trop Med Public Health* 2002; 33: 780–786
28. Young PC, Hae CC, Lee KH *et al*. Tsutsugamushi infection-associated acute rhabdomyolysis and acute renal failure. *Korean J Intern Med* 2003; 18: 248–250
29. Kim DM, Kang DW, Kim JO *et al*. Acute renal failure due to acute tubular necrosis caused by direct invasion of *Orientia tsutsugamushi*. *J Clin Microbiol* 2008; 46: 1548–1550
30. Eiam-Ong S. Malarial nephropathy. *Semin Nephrol* 2003; 23: 21–33
31. DengueNet—WHO's Internet-based system for the global surveillance of dengue fever and dengue haemorrhagic fever (dengue/DHF) http://www.who.int/denguenet. Dengue/DHF—global public health burden. *Wkly Epidemiol Rec* 2002; 77: 300–304
32. Lee IK, Liu JW, Yang KD. Clinical characteristics, risk factors, and outcomes in adults experiencing dengue hemorrhagic fever complicated with acute renal failure. *Am J Trop Med Hyg* 2009; 80: 651–655
33. Lima EQ, Nogueira ML. Viral hemorrhagic fever-induced acute kidney injury. *Semin Nephrol* 2008; 28: 409–415
34. Karakus A, Banga N, Voorn GP *et al*. Dengue shock syndrome and rhabdomyolysis. *Neth J Med* 2007; 65: 78–81
35. Lima EQ, Gorayeb FS, Zanon JR *et al*. Dengue haemorrhagic fever-induced acute kidney injury without hypotension, haemolysis or rhabdomyolysis. *Nephrol Dial Transplant* 2007; 22: 3322–3326
36. Pappachan MJ, Sheela M, Aravindan KP. Relation of rainfall pattern and epidemic leptospirosis in the Indian state of Kerala. *J Epidemiol Community Health* 2004; 58: 1054
37. Shivakumar S. Leptospirosis in Chennai—changing clinical profile. *J Assoc Physicians India* 2006; 54: 964–965
38. Abdulkader RC, Seguro AC, Malheiro PS *et al*. Peculiar electrolytic and hormonal abnormalities in acute renal failure due to leptospirosis. *Am J Trop Med Hyg* 1996; 54: 1–6
39. Barsoum RS. Tropical acute renal failure. *Contrib Nephrol* 2004; 144: 44–52
40. Sakhuja V, Sud K. Acute renal failure in the tropics. *Saudi J Kidney Dis Transpl* 1998; 9: 247–260
41. Liano F, Gallego A, Pascual J *et al*. Prognosis of acute tubular necrosis: an extended prospectively contrasted study. *Nephron* 1993; 63: 21–31

42. Lins RL, Elseviers MM, Daelemans R *et al*. Re-evaluation and modification of the Stuivenberg Hospital Acute Renal Failure (SHARF) scoring system for the prognosis of acute renal failure: an independent multicentre, prospective study. *Nephrol Dial Transplant* 2004; 19: 2282–2288
43. Mehta RL, Pascual MT, Gruta CG *et al*. Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 2002; 13: 1350–1357
44. Dharan KS, John GT, Antonisamy B *et al*. Prediction of mortality in acute renal failure in the tropics. *Ren Fail* 2005; 27: 289–296
45. Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; 23: 1569–1574

Received for publication: 5.10.09; Accepted in revised form: 12.7.10

Nephrol Dial Transplant (2011) 26: 531–537
doi: 10.1093/ndt/gfq498
Advance Access publication 23 August 2010

Osteopontin predicts survival in critically ill patients with acute kidney injury

Johan M. Lorenzen[1,*], Carsten Hafer[1,*], Robert Faulhaber-Walter[1], Philipp Kümpers[1], Jan T. Kielstein[1], Hermann Haller[1] and Danilo Fliser[2]

[1]Department of Medicine, Division of Nephrology and Hypertension, Hanover Medical School, Hannover, Germany and [2]Saarland University Medical Centre, Homburg/Saar, Germany

Correspondence and offprint requests to: Johan M. Lorenzen; E-mail: J.M.Lorenzen@gmail.com
[*]These authors contributed equally to the study.

Abstract

Background. The cytokine osteopontin is involved in the pathophysiology of experimental acute kidney injury. We have tested the hypothesis that osteopontin levels might serve as a biomarker predicting outcome in critically ill patients requiring renal replacement therapy after acute kidney injury.

Methods. We measured circulating plasma osteopontin levels in 109 critically ill patients with acute kidney injury at inception of renal replacement therapy and 4 weeks thereafter. Critically ill patients without acute kidney injury served as controls. Osteopontin was measured with ELISA.

Results. Baseline osteopontin levels in patients with acute kidney injury were significantly higher compared with controls ($P < 0.0001$). Baseline osteopontin levels in patients recovering from acute kidney injury were significantly elevated compared with patients with permanent loss of kidney function after acute kidney injury ($P = 0.01$). In addition, in patients recovering from acute kidney injury without further need for renal replacement therapy, osteopontin levels were significantly lower 4 weeks after initiation of renal replacement therapy ($P = 0.0005$). Moreover, multivariate Cox analysis revealed osteopontin levels at renal replacement therapy inception as an independent and powerful predictor of mortality ($P < 0.0001$). In the ROC-curve analysis, an osteopontin cut-off value of 577 ng/mL separated survivors from non-survivors with a sensitivity of 100% and a specificity of 61% (AUC 0.82; 95% confidence interval: 0.74–0.89; $P < 0.0001$).

Conclusions. Osteopontin may serve as a novel biomarker for both, overall survival and renal outcome in critically ill patients with acute kidney injury, that require renal replacement therapy.

Keywords: acute kidney injury; mortality; osteopontin; renal replacement therapy

Introduction

Acute kidney injury (AKI) in critically ill patients has been identified as an independent risk factor for increased mortality [1]. Survival of patients with AKI in the intensive care unit (ICU) is still unacceptably low despite significant advances in supportive care [2]. A recent multinational, multi-centre study of 29 000 critically ill patients including 1700 with AKI revealed that the in-hospital mortality is high, exceeding 60% [3]. Thus, detection of patients at particular risk for both death and prolonged kidney failure after AKI in the setting of intensive care medicine and renal replacement therapy (RRT) remains an area of utmost interest.

Osteopontin (OPN) is a cytokine that is broadly expressed and upregulated during inflammation and various