

A Case Series of Falciparum Malaria-induced Acute Renal Failure

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Abstract

Falciparum malaria is a disease of tropical climates which affects 270 million people annually and has an overall mortality of 1%. While the incidence of acute renal failure in malaria is less than 1%, mortality is reported to be as high as 45% in those with renal failure. We report the clinical course and outcome in 5 patients with falciparum malaria-induced acute renal failure treated at the Singapore General Hospital between June and July 1997. All 5 males, with mean age of 35.2 ± 13.1 years, were admitted with history of fever and reported travel to a known malarious zone. Mean laboratory parameters upon admission included serum creatinine $725 \pm 515 \mu\text{mol/L}$ and serum urea $47 \pm 31 \text{ mmol/L}$. Three patients with hypotension on admission were started on haemodiafiltration, of whom 2 were subsequently converted to haemodialysis as their haemodynamics improved. Two remaining patients were started on intermittent bicarbonate haemodialysis. The overall mortality in our series was 20%, with 1 patient having died of complications of adult respiratory distress syndrome, disseminated intravascular coagulation and multiorgan failure. The remaining 4 survived and recovered their renal function. The single patient mortality occurred in the patient with admission serum creatinine of $1632 \mu\text{mol/L}$, a value significantly higher than that of the 4 patients who survived (mean serum creatinine, $499 \pm 106 \mu\text{mol/L}$, $P < 0.002$). These results suggest that falciparum malaria associated with acute renal failure is associated with a high morbidity, but early presentation and intervention with appropriate antimalarial and renal replacement therapy is associated with improved survival and recovery of renal function.

Ann Acad Med Singapore 1999; 28:578-82

Key words: Cytoadherence, Haemodiafiltration, Haemodialysis, Parasitised-erythrocytes, Survival rate

Introduction

Predominantly a disease of hot and humid climates, malaria affects 270 million people worldwide annually, and has a mortality rate of 1%.¹ The increasing morbidity and mortality attributable to malaria in recent years follows the loss, in the early 1970s, of the impetus and impact of the initial WHO eradication programme. Increasing chloroquine and insecticide resistance has further compounded the problem.¹ Falciparum malaria is the most severe form of the 4 malaria-causing *Plasmodium* species. Acute renal failure is diagnosed in less than 1% of all falciparum cases, but in over 60% of complicated cases.^{2,3} Mortality in those with renal impairment is reported to be 45%.⁴

The pathophysiology of acute renal failure in falciparum malaria is multifactorial. Renal cortical ischaemia due to sludging of erythrocytes in the renal microcirculation has been suggested to be the primary abnormality.⁵ Kelejian et al have shown that the membranes of erythrocytes infected with the malarial parasite are altered to form electron-dense protrusions or knobs.^{6,7} These knobs have been suggested to adhere to

the vascular endothelial cells and to knobs of other infected erythrocytes through an erythrocyte receptor, thrombospondin.^{8,9} The resulting cytoadherence interferes with blood flow in the renal microcirculation. Other factors suggested to contribute to reduced renal blood flow are hypovolaemia, vascular endothelial damage due to anoxia or generation of free oxygen radicals released during the inflammatory process, increased catecholamine activity, and activation of the renin-angiotensin system.^{5,10,11} There is also evidence to suggest an important role for cachectin and other monokines in contributing to renal ischaemia.^{11,12}

As acute renal failure is associated with a high mortality, the present study examines the clinical course and outcome in 5 patients with falciparum malaria-induced acute renal failure who were admitted to the Singapore General Hospital within a 5-week period from June to July 1997.

Case Reports

A retrospective review was made of case records of 5 patients who were treated for malarial acute renal fail-

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ure at the Singapore General Hospital between June and July 1997, and is presented below. Renal replacement-dependency was defined as the duration of renal replacement therapy, either haemodialysis or haemodiafiltration. Recovering renal function was defined as a declining trend in the serum creatinine following cessation of renal replacement therapy. Unpaired t-tests assuming equal variances were performed to assess statistical significance in differences between the survivors and the single mortality.

The study population consisted of 5 males with an age range of 21 to 51 years (mean 35.2 ± 13.05 years). Prior to hospitalisation, each had either visited or come from a known malarious zone, and they gave history of fever ranging from 4 to 7 days (mean 5.8 ± 1.5 days) (Table I).

Patient A

A 29-year-old Chinese male presented in early June 1997, having been to the Indonesian island of Bintan just off the coast of Singapore two weeks prior to presentation. He gave a one week's history of intermittent fever, jaundice and myalgia, though he denied oliguria. He was conscious and well orientated, not fluid overloaded,

but was deeply jaundiced. He was uraemic (serum creatinine $501 \mu\text{mol/L}$), and 10% per cent of his erythrocytes had parasitaemia (Tables I and II). He was transferred to the Intensive Care Unit and commenced on intravenous quinine. Intermittent bicarbonate haemodialysis was started the day after admission via a femoral vein catheter. Subsequent complications included progressive hypoxaemia requiring intubation and ventilation, nosocomial pneumonia (multiple organisms) and septic arthritis of the elbow requiring drainage. After having received seven sessions of intermittent haemodialysis over a period of 13 days, his urine output gradually improved and he did not require further dialysis. After a full month in the ward, he was discharged with a serum creatinine of $215 \mu\text{mol/L}$ and recovering liver function. When he was reviewed in the second week of July 1997, his serum creatinine was found to be $133 \mu\text{mol/L}$, and he was discharged from further follow-up.

Patient B

A 47-year-old male Eurasian was admitted in early June 1997 with fever and a provisional diagnosis of falciparum malaria. Five days prior to admission, while in Tanjong Pinang, an Indonesian island near Singapore, he had been seen by a doctor for fever, epistaxis and bleeding per rectum, and given medicine of unknown nature. On admission, he was mentally alert but was tachypnoeic and had a blood pressure of $141/60 \text{ mmHg}$. He was jaundiced, had hepatosplenomegaly and evidence of gastrointestinal bleeding. The serum creatinine was $1632 \mu\text{mol/L}$, serum urea 100 mmol/L , and he was hyperkalaemic and acidotic (Table I). Other parameters included 0.4% *Plasmodium falciparum* parasitised erythrocytes, haemoglobin of 5.7 G/dL , prolonged prothrombin and activated partial prothrombin times, normal platelet counts and serum total bilirubin 39 mmol/L (Table II). The chest X-ray showed bilateral infiltrates. The urine output on day of admission was 454 cc .

A diagnosis of malaria with adult respiratory syndrome and disseminated intravascular coagulation was made. Mechanical ventilation was commenced and intravenous quinine was given. Within hours of his admission, he was commenced on haemodiafiltration with a polyacrylonitrile dialyser via a catheter in the internal jugular vein. The blood pressure was difficult to maintain despite administration of inotropes and blood transfusions. On the tenth day of admission he began having intermittent bouts of generalised convulsions. He had received a hundred hours of haemodiafiltration over this period. He became progressively hypotensive and more haemodynamically unstable, and could not tolerate haemodiafiltration preterminally for the subsequent two days after which he "collapsed" and did not respond to further resuscitation.

TABLE I: ADMISSION (RENAL) PARAMETERS

	Cr ($\mu\text{mol/L}$)	Urea (mmol/L)	Na ⁺ (mmol/L)	K (mmol/L)	HCO ₃ (mmol/L)	UOP (cc)
Patient A	501	30	120	4.6	19.8	63
Patient B ²	1632	100	130	6.0	11.3	454
Patient C	413	40	136	4.1	10.6	850
Patient D	648	45	129	3.0	N	80
Patient E	433	21	129	3.4	19.6	150
All ¹	725 ± 515	47 ± 31	129 ± 6	4.2 ± 1.2	15.3 ± 5	319 ± 336

¹ Mean $\pm$ standard deviation is reported for the 5 patients.

² The level of serum creatinine at presentation in Patient B was significantly different from that of the remaining 4 patients ($P < 0.002$).

Cr: serum creatinine; Urea: serum urea; Na⁺: serum sodium;

K: serum potassium; HCO₃: serum bicarbonate;

UOP: urine output on day of admission; N: no record

TABLE II: OTHER LABORATORY PARAMETERS

	Parasitised RBC (%)	Hb (G/dL)	SAP (U/L)	AST (U/L)	ALT (U/L)	T Bili (mmol/L)
Patient A	10	14	145	315	250	447
Patient B	0.4	5.7	79	60	45	39
Patient C	16	10	91	52	20	76
Patient D	15	4.5	N	N	N	283
Patient E	1	6.2	106	49	64	50
All ¹	8.5 ± 7.5	8.1 ± 3.9	105 ± 29	119 ± 131	95 ± 105	179 ± 180

¹ Mean $\pm$ standard deviation is reported for the 5 patients.

RBC: red blood corpuscles; Hb: haemoglobin; SAP: serum alkaline phosphatase; AST: serum alanine aspartate; ALT: serum alanine transaminase; T Bili: serum total bilirubin; N: no record

Patient C

A 21-year-old Thai national was admitted in the second week of June 1997 with fever of undetermined duration. He was jaundiced, hypotensive and there was clinical evidence of cerebral malaria. On admission, he was not oliguric; his serum creatinine was 413 $\mu\text{mol/L}$ and he had metabolic acidosis (Tables I and II). Sixteen per cent of his erythrocytes were parasitised with *P. falciparum*. Computed tomography scan showed cerebral oedema. Ventilatory and inotrope support, and concomitant intravenous quinine were started. Because of the high parasitised erythrocyte load, he received two exchange blood transfusions. He required only three sessions of intermittent bicarbonate haemodialysis as his urine output improved, and after twenty-two days in the ward he was discharged, with a serum creatinine of 189 $\mu\text{mol/L}$ (Table III). He presumably returned to Thailand soon after discharge and therefore could not be reviewed.

Patient D

A 28-year-old South Korean, living in Singapore, went to Bangladesh in early June 1997 where he did jungle trekking. He returned to Singapore and, in the third week of June 1997, was admitted with a one-week's history of fever with chills. He was deeply jaundiced, hypotensive, had hepatomegaly and there was clinical evidence of cerebral malaria. He was oliguric on the day of admission and had a serum creatinine of 648 $\mu\text{mol/L}$ with 15% parasitaemia (Tables I and II). He was managed in the intensive care unit where he was intubated and mechanically ventilated. Intravenous quinine was given, and haemodiafiltration instituted using a polyacrylonitrile dialyser. As the blood pressure improved after Day 4, renal replacement therapy was changed to intermittent bicarbonate haemodialysis, of which he received a total of seven sessions (Table III). In view of the high parasitised erythrocyte load, he was

given exchange blood transfusion. By the end of the first week he was extubated, by the end of the second week the urine output had improved, and he was discharged by the end of the third week. When reviewed 5 days after discharge, the serum creatinine was 139 $\mu\text{mol/L}$.

Patient E

A 51-year-old Malay Singaporean man had visited the Indonesian island of Bintan near the end of June 1997. He was admitted in early July 1997 with a 4-day history of fever. He was oliguric, had fluid overload, jaundiced, and hypotensive. He was in acute renal failure with a serum creatinine of 433 $\mu\text{mol/L}$. The *P. falciparum* parasitised erythrocyte load was 1%. He did not require ventilatory support. Haemodiafiltration was commenced, as was intravenous quinine. As the blood pressure soon stabilised, he was converted to intermittent standard bicarbonate haemodialysis. After three sessions of intermittent haemodialysis, and with a serum creatinine of 645 $\mu\text{mol/L}$, he went home against medical advice. He returned for review in September 1997, at which time he was well with a serum creatinine of 106 $\mu\text{mol/L}$ and was discharged from further follow-up.

The overall mortality in our series was 20%. The single mortality occurred in Patient B who presented with an admission serum creatinine of 1632 $\mu\text{mol/L}$, a value significantly higher than the mean value for the other 4 patients (mean $499 \pm 106 \mu\text{mol/L}$, $P < 0.002$ assuming equal variances; Tables I and II tabulate the admission and other laboratory parameters, and Table III tabulates renal replacement therapy provided and renal function at discharge). There were no significant differences in the other parameters tested between the survivors and the non-survivor, namely in the serum urea, acidosis, presence of oliguria on admission (defined by urine output of $<400 \text{ cc/day}$), level of parasitaemia, the haemoglobin and bilirubin levels, or the interval to presentation. Though there was a trend towards longer duration

TABLE III: RENAL REPLACEMENT THERAPY AND RECOVERY OF RENAL FUNCTION

	Day RRT started	No. of RRT sessions	RRT duration (hours)	RRT dependency (days)	Total UF (L)	Discharge Cr ($\mu\text{mol/L}$)
Patient A	2	IHD-7	26	13	13.5	215
Patient B	1	CVVHDF - 5	100	8	21.0	Died
Patient C	3	IHD-2	6	4	1.0	189
Patient D	1	CVVHDF - 1				
		IHD-7	42	15	23.5	N
Patient E	3	CVVHDF - 1				
		IHD-3	13	7	4.0	@
All ¹	2 ± 1	5 ± 2	37 ± 38	9 ± 4	12.6 ± 10	-

¹ Mean $\pm$ standard deviation is reported where relevant.

RRT: renal replacement therapy including intermittent haemodialysis (IHD) and continuous veno-venous haemodiafiltration using polyacrylonitrile dialysers (CVVHDF);

UF: ultrafiltration volume during RRT; Cr: serum creatinine; N: not available

@ This patient went home against medical advice with a serum Cr of 645 $\mu\text{mol/L}$.

of renal replacement therapy in patients with higher bilirubin levels (patients A and D), there was no correlation between these two parameters (Tables I and II, Pearson's Linear Correlation, $P = \text{ns}$). Likewise, though there was a trend towards more significant hyponatraemia in patients with higher density parasitaemia, this did not reach statistical significance ($P = \text{ns}$).

Discussion

Though malaria was prevalent in the early years of this century, Singapore has recently been relatively free of malaria, with cases seen sporadically being those imported by travellers coming to Singapore from malaria endemic zones. In fact, malarial acute renal failure has not been reported in Singapore in either of the two previous series of acute renal failure analysed—one series was between 1985 and 1989,¹³ and the other series was between 1991 and 1993.¹⁴ The present series, is therefore, the first on malarial acute renal failure to be reported in Singapore.

Acute renal failure complicating any illness is a serious disorder, with overall mortality rates ranging from 36% to 72% in those requiring dialysis.¹⁵ These figures have not changed significantly since the introduction of dialysis.¹⁶ Overall mortality in acute renal failure in Singapore as reported in a recent series was 52%.¹³ In our series of 5 patients with acute renal failure complicating *P. falciparum* infection, the overall mortality was 20%. The overall mortality among patients with malarial renal impairment was reported by the World Health Organisation to be 45% in 1990.⁴ In a series from Papua New Guinea of 16 adults with malarial renal failure treated within a two-year period, 6 died, giving a mortality of 37.5%.¹⁷ A larger series of 104 malaria-associated renal failure patients, seen in Vietnam during a 26-month period and managed with peritoneal dialysis, returned a mortality rate of 26%.¹⁸ The single death in the present series was noted in the patient whose admission serum creatinine was $>650 \mu\text{mol/L}$, while the admission serum creatinine levels of the patients who survived was $<650 \mu\text{mol/L}$ ($P < 0.002$). Thus severity of renal dysfunction upon admission was an important predictor of outcome in our series, a finding not previously reported from the other series.^{17,18} A delay in presentation and thus definitive treatment for malaria due to its apparent partial treatment at Tanjong Pinang may have led to more severe complications of malaria in Patient B.

Hyperbilirubinaemia and jaundice, which are consistent features of malarial renal failure, is multifactorial in its aetiology; haemolysis has been implicated in those with unconjugated hyperbilirubinaemia while hepatocyte dysfunction has been implicated in those with very high total bilirubin.^{4,5} Though the severity of jaundice is known to impact adversely on renal function, its presence did not correlate with an adverse outcome in our

series. Nevertheless, longer periods of renal replacement therapy were required by the patients with higher admission serum bilirubin levels (Tables I, II and III)—an observation found statistically not significant, probably because of our small numbers.^{5,18}

Other biochemical abnormalities noted in our patients were hypoglycaemia and hyponatraemia. Four of the patients had varying periods of mild hypoglycaemia, likely due to the hyperinsulinic effect of quinine. Hyponatraemia, a common finding of multifactorial aetiology, was found in 4 of our patients at presentation.¹⁹ There was a trend towards a greater degree of hyponatraemia in patients with higher parasite density in our series of patients (Tables I & II), a finding also reported by Miller et al though not found in other series.^{19,20} The correlation did not reach statistical significance in our series likely because of our small numbers.

Traditionally, heavy parasitaemia is considered a correlate of more severe disease and fatal outcome and an indication for exchange transfusion.^{17,18} However, Aikawa et al²¹ have suggested that infected erythrocytes retreat from the peripheral circulation to the visceral circulation once knobs appear on the membrane surface. This retreat may be the reason for the absence of a correlation between the level of renal dysfunction at presentation and the percentage of parasitised erythrocyte loads in our series of patients (Tables I & II). In fact, the lowest level of parasitaemia was recorded in the non-survivor. Thus, apart from the serum creatinine, no other biochemical or clinical parameter correlated with mortality in patients with falciparum malaria-associated acute renal failure in our series.

In managing patients with malarial acute renal failure, reduction in quinine dosage, especially during the first 48 hours of therapy, is not recommended despite the oculotoxic and cardiotoxic effects of quinine.²² It has been suggested that reducing the dosage, even in severe acute renal failure, will result in a suboptimal antimalarial effect and may thus be associated with a high mortality.²³ Because of its cardiotoxicity, however, intensive ECG monitoring is recommended, and significant QT-c prolongation ($>25\%$) may be an indication for a reduction in quinine dosage.²⁴ Quinine is not cleared during haemodialysis and requires no supplementation post-dialysis.²⁴ All the 5 patients presented in this series were treated with adequate doses of intravenous quinine under intensive care monitoring.

The survival rate of 80% as reported in our series may be attributed to several factors. Early commencement of renal replacement therapy may certainly be one contributing factor. Debate continues about the value of early commencement of renal replacement therapy in acute renal failure and its impact on morbidity and mortality. Nevertheless, early and frequent renal replacement

therapy is necessary to control the hypercatabolic state. Thus in our series, renal replacement therapy was commenced at a mean serum creatinine of 561 $\mu\text{mol/L}$ in those of our patients who had a subsequent recovery of renal function. The newer modalities of renal replacement therapy as utilised in our present series such as haemodiafiltration also permitted salvage of critically ill, ventilated patients in whom conventional haemodialysis would not have been otherwise possible. There is a potential benefit with the use of polyacrylonitrile membrane dialysers which are more biocompatible, as they are associated with a very low degree of complement activation, and thus hypotension and hypoxaemia during dialysis are not exacerbated.²⁵ An alternative modality of renal replacement therapy, that of peritoneal dialysis, has been suggested to be less effective in malarial acute renal failure as parasitised erythrocytes on the microcirculation interfere with solute transport across the peritoneal membrane.²⁶ With the modalities of renal replacement therapy utilised in the present series of patients, successful renal recovery was eventually achieved in 4 patients.

In conclusion, falciparum malaria with acute renal failure remains a serious disorder, but early commencement of anti-malarial treatment and early, appropriate, and adequate renal replacement therapy is associated with a better prognosis. Expectations for the future for the control of malaria lie in the development of a malaria vaccine.²⁷ Another possibility would appear to be to inhibit anophiline vectorial ability by altering the mosquito's genetic make-up, and releasing into the mosquito population viable mosquitoes that are no longer able to support the sexual cycle of *P. falciparum*.²⁷

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