

Malaria Requiring Intensive Care

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Abstract

We studied 24 consecutive adult patients with malaria who required intensive care between 1 January 1994 and 31 December 1997. This was out of a total of 256 patients hospitalised at the Singapore General Hospital with malaria during these 4 years. Our aim was to characterise the type and severity, clinical features, complications, treatment and outcome of adult patients with malaria who required intensive care. In addition, we compared the actual and predicted mortality based on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

The travel history, prophylaxis, duration of fever before receiving treatment, type of malaria and severity, clinical data, complications, APACHE II score, treatment and outcome were analysed.

Most cases were imported by locals travelling overseas or foreigners infected with the parasite elsewhere. Four patients had vivax malaria and 20 patients had severe falciparum malaria. All but 1 patient received transfusion with blood products and 6 patients with severe falciparum malaria had exchange transfusions. Complications were restricted to infection with *P. falciparum*: 9 patients required acute dialysis and 8 required mechanical ventilation. Three patients died giving a mortality of 15% for severe falciparum malaria. The overall mortality of patients with malaria was 1.2%. The mortality of patients with malaria requiring intensive care was 12.5% as compared with a predicted mortality of 18.7% based on the APACHE II prognostication system.

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Introduction

Malaria is an important and common infectious parasitic disease globally. It is associated with significant morbidity and mortality, especially in endemic areas. Non-endemic areas are not totally without risks as malaria is frequently imported into non-malarious areas in the blood of travellers. Four pathogenic species of *Plasmodium* cause disease in humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. The severity and clinical features of the disease are determined by the infecting species, parasite load and the pathophysiologic effects of the parasite and cytokines released as a result of the infection. *P. falciparum* is the most lethal parasite and accounts for nearly all malaria mortality, killing an estimated 2 million persons yearly.¹ Untreated, this disease may be devastating but even the deadliest of malarias remains eminently treatable with modern intensive care.

P. falciparum is endemic in Southeast Asia, Africa and

South America. The major cities here (including Singapore) are however, nearly malaria free. During the 4-year period between 1 January 1994 and 31 December 1997, there were 256 adult patients admitted to our 1600-bedded acute tertiary care hospital (Singapore General Hospital) with malaria. Of these, 24 (9.4%) required admission to our 8-bedded medical intensive care unit (ICU), and the admission criteria include patients who require or potentially require intubation and mechanical ventilation, and those who require haemodynamic manipulation. We found that these cases were mainly imported from malarious areas by travellers and foreign workers.

The aim of our study was to characterise the type and severity, clinical features, complications, treatment and outcome of adult patients with malaria who required intensive care unit admission. Our ICU database is based on the Acute Physiology and Chronic Health

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Evaluation II (APACHE II) score, which is a widely used system for prognostically stratifying acutely ill patients in intensive care units. Besides providing a measure of severity of illness, the APACHE II score is also useful in studies of therapeutic efficacy. In addition, an expected death rate based on APACHE II can be compared to actual death rate as a test of therapeutic efficacy, thus we also compared the mortality of patients with malaria requiring intensive care with the predicted mortality based on the APACHE II prognostication system.

Patients and Methods

The records of 24 consecutive patients with malaria requiring admission to the medical intensive care unit from 1 January 1994 to 31 December 1997 were reviewed retrospectively. The travel history, use of prophylaxis, duration of fever before receiving anti-malarial treatment, clinical data, presence of any of the features of severe malaria as defined below within 24 hours of admission to hospital were recorded.

Patients with severe malaria were identified according to the 1990 World Health Organization (WHO) criteria² as infection with *P. falciparum* plus the presence of one or more of the following features:

- 1) cerebral malaria defined as unrousable coma³ [Glasgow Coma Scale (GCS) ≤ 8] with the exclusion of other causes;
- 2) hypoglycaemia (serum glucose < 2.2 mmol/L);
- 3) temperature $> 40^{\circ}\text{C}$;
- 4) hypotension with systolic blood pressure < 90 mmHg;
- 5) severe anaemia (haemoglobin < 5 g/dL or haematocrit $< 20\%$);
- 6) acute renal failure (serum creatinine > 265 mmol/L);
- 7) metabolic acidosis (plasma bicarbonate < 15 mmol/L);
- 8) parasitaemia $> 5\%$;
- 9) spontaneous bleeding; and
- 10) jaundice with a serum bilirubin > 50 $\mu\text{mol/L}$.

Other information abstracted from the medical records were the maximum parasite load, treatment, complications and outcome. In addition, the APACHE II score (scored within 24 hours of admission to the ICU) was retrieved from the medical ICU database.

Univariate analyses were conducted using unpaired t-tests and Chi-squared tests for categorical data, to determine potentially significant risk factors for mortality ($P < 0.2$), for inclusion into the multiple logistic model. Using multiple logistic regression with a stepwise variable selection method, only age was found to be a significant risk factor for mortality. The statistical analyses were done using SPSS 7.5 for Windows.

Results

There was a total of 256 patients with malaria (37 had *falciparum* malaria) that were admitted to our hospital during the 4-year study period. Twenty-four (9.2%) of these patients were admitted to the medical intensive care unit (ICU) (Table I). The commonest source country of imported infection was Indonesia ($n = 13$). Only 1 patient gave a history of prophylaxis with chloroquine for travel to Zimbabwe. Twenty had *P. falciparum* infection (patient no. 3 had mixed *P. falciparum* and *P. vivax* infection) and 4 had *P. vivax* infection. The parasite load ranged from $< 0.1\%$ to 45%. The mean age was 37 ± 13.9 years. The male to female ratio was 5:1. The mean duration of ICU stay was 4.7 ± 4.1 days and the mean duration of hospital stay was 14.2 ± 10.2 days. The mean duration of fever before anti-malarial treatment was initiated was 6.7 ± 4.3 days.

All patients with *P. vivax* malaria had hypotension that required haemodynamic manipulation. All of the 20 patients with *P. falciparum* infection had severe malaria at presentation based on the WHO criteria defined above (Table II). The commonest defining criteria for severe malaria were jaundice ($n = 15$), parasitaemia $> 5\%$ ($n = 9$) and renal failure ($n = 9$). Three patients (nos. 1, 13 and 14) had altered mental status (with seizures in 2 of them), but none had unrousable coma with GCS ≤ 8 , or hypoglycaemia.

Table III shows the maximum parasite load, APACHE II score (within 24 hours of admission to the ICU), presence of hepatic dysfunction (as defined by serum AST or ALT > 50 u/L) and coagulation abnormalities (as defined by a elevated prothrombin time and partial thromboplastin time); blood products transfusion requirement and inotropes used; and the development of acute renal failure requiring dialysis and respiratory distress requiring intubation plus mechanical ventilation (including the duration of mechanical ventilation); and the outcome. The mean APACHE II score was 13.25 ± 6.0 (range 3 to 30). All but 2 patients (91.7%) had evidence of biochemical hepatitis. Eighteen (75%) had an abnormal coagulation profile and 23 (95.8%) had received blood products transfusion.

Acute dialysis and mechanical ventilation were however restricted to patients with *falciparum* malaria. Eight patients received haemodialysis and 1 received peritoneal dialysis. Of the 8 who received mechanical ventilation (duration between 1 to 10 days), only 1 patient (no. 3) had acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) as defined by the new international criteria (ALI defined as the acute onset of bilateral pulmonary infiltrates with a $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg regardless of positive end-expiratory pressure (PEEP) and a pulmonary artery occlusion pressure ≤ 18 mmHg or no clinical evidence of left atrial hypertension, and ARDS defined as ALI with a $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg).⁴

TABLE I: PATIENTS, TRAVEL HISTORY AND TYPES OF MALARIA

	Sex	Age	Origin	Travel	Malaria type
1	M	32	New Zealand	Zimbabwe (Africa)*	<i>Falciparum</i>
2	M	54	Singapore	Bintan (Indonesia)	<i>Falciparum</i>
3	M	38	Singapore	Tanjong Pinang (Indonesia)	<i>Falciparum</i>
4	M	43	Thailand	Mauritius, Madagascar (Africa)	<i>Falciparum</i>
5	F	24	Singapore	Namibia, Zimbabwe, Botswana (Africa)	<i>Falciparum</i>
6	F	25	New Zealand	India, Nepal, Thailand, Indonesia	<i>Vivax</i>
7	M	49	Singapore	Batam (Indonesia)	<i>Falciparum</i>
8	M	17	Malaysia	Malaysia	<i>Falciparum</i>
9	F	31	Singapore	Java (Indonesia)	<i>Falciparum</i>
10	M	29	Singapore r.	South Africa	<i>Falciparum</i>
11	M	30	Singapore	Bintan (Indonesia)	<i>Falciparum</i>
12	M	47	Singapore r.	Tanjong Pinang (Indonesia)	<i>Falciparum</i>
13	M	28	Thailand	Thailand	<i>Falciparum</i>
14	M	21	Korea	Bangladesh (India)	<i>Falciparum</i>
15	M	58	Singapore	Batam (Indonesia)	<i>Falciparum</i>
16	M	51	Singapore	Bintan (Indonesia)	<i>Falciparum</i>
17	M	50	Malaysia	Johore (Malaysia)	<i>Falciparum</i>
18	M	25	Bangladesh	New Delhi (India)	<i>Vivax</i>
19	M	54	Indonesia	Surabaya, Pulau Lembak (Indonesia)	<i>Falciparum</i>
20	M	26	Indonesia	Bintan (Indonesia)	<i>Falciparum</i>
21	F	26	Singapore	Batam (Indonesia)	<i>Vivax</i>
22	M	31	Singapore	Kusu Island (Singapore)	<i>Falciparum</i>
23	M	30	Burma	Burma	<i>Vivax</i>
24	M	70	Singapore	Tanjong Pinang (Indonesia)	<i>Falciparum</i>

M: Male, F: Female; r.: resident

* Took chloroquine prophylaxis

TABLE II: SEVERE *FALCIPARUM* MALARIA AT PRESENTATION AND THE DEFINING CRITERIA

Severe malaria: 1 + one or more of 2 to 11	Number	%
1. <i>P. falciparum</i>	20	100
2. Cerebral malaria (GCS $\leq$ 8)	0	0
3. Hypoglycaemia (glucose $<$ 2.2 mmol/L)	0	0
4. Temperature $>$ 40°C	1	
5. Hypotension with SBP $<$ 90 mmHg	7	30
6. Severe anaemia (Hgb $<$ 5 g/dL or Hct $<$ 20%)	4	20
7. Acute renal failure (Cr $>$ 265 mmol/L)	9	45
8. Acidosis (HCO ₃ ⁻ $<$ 15 mmol/L)	7	35
9. Parasitaemia $>$ 5% on admission	9	45
10. Spontaneous bleeding	6	30
11. Jaundice (Serum bilirubin $>$ 50 μ mol/L)	15	75

GCS: Glasgow Coma Scale; SBP: systolic blood pressure;
Hgb: haemoglobin; Hct: haematocrit; Cr: serum creatinine;
HCO₃⁻: serum bicarbonate

Two patients (nos. 2 and 12) had pulmonary oedema with a pulmonary artery occlusion pressure of $>$ 18 mmHg.

All patients with *falciparum* malaria and 2 of the 4 patients with *vivax* malaria received intravenous quinine. Patient no. 21 received intravenous chloroquine and patient no. 23 was treated with oral chloroquine. Six patients with severe *falciparum* malaria (patient nos. 1, 4, 13, 14, 15 and 22), with parasite counts ranging from 7%

to 45%, received exchange transfusion without any immediate adverse effect.

Patient nos. 2, 12 and 15 died (all had severe *falciparum* malaria), giving an overall mortality of 1.2% for malaria. The mortality of patients with malaria requiring intensive care was 12.5% as compared with a predicted mortality of 18.7% based on the APACHE II score. When severe *falciparum* malaria was considered by itself, the mortality was 15%, while the mortality of patients hospitalised with *falciparum* malaria was 8.1%. The only risk factor for mortality in our study was age. There was no correlation between duration of fever before treatment, parasite load, APACHE II score, need for dialysis and mechanical ventilation, and mortality.

Discussion

Less than 10% of patients with malaria admitted to our hospital during the 4-year study period required admission to the ICU. Many Singaporeans travel to Indonesia due to its close proximity and as a result, Indonesia was the commonest source of imported malaria requiring intensive care. In fact, 11 of the 13 (84.6%) who gave travel history to Indonesia were locals. The only patient (a New Zealander) who gave a history of prophylaxis took chloroquine for travel to Zimbabwe and this was inappropriate for that region, according to the current recommendations.⁵

Fifty-four per cent of patients with *falciparum* malaria

TABLE III: MAXIMUM PARASITE LOAD, APACHE II SCORE, COMPLICATIONS, TREATMENT AND OUTCOME

	Max Load	Fever to Rx	APACHE II score	Hepatitis	Coagulopathy	Transfusion requirement	Inotropic support	Acute dialysis	MV (days)	Outcome
1	13		14	yes	yes	plt, pct	dp	hd	0	cured
2	+++	3	14	yes	yes	plt, ffp	dp, db	no	1	died
3	20	4	8	yes	yes	plt, pct	dp	no	10	cured
4	45	10	21	yes	yes	plt, pct	dp	pd	0	cured
5	9.5	4	6	yes	yes	plt	no	no	0	cured
6*	15	10	18	yes	yes	plt, pct	no	no	0	cured
7	4.6	7	13	yes	yes	plt, ffp	no	hd	0	cured
8	<0.1	21	13	no	no	pct	no	no	0	cured
9	3	7	9	yes	no	plt, pct	no	no	0	cured
10	6.8	4	3	yes	no	nil	no	no	0	cured
11	11.1	7	13	yes	yes	plt, ffp, pct	no	hd	5	cured
12	0.6	7	25	yes	yes	plt, ffp, pct	dp, na, a	hd	9	died
13	15		22	yes	yes	plt, pct	dp, na	hd	4	cured
14	15	5	30	yes	yes	plt, ffp, pct	no	hd	6	cured
15	7	3	15	yes	yes	plt, ffp, pct	dp	no	3	died
16	1	2	16	yes	no	plt	no	hd	0	cured
17	9.7	7	9	yes	yes	plt	no	no	0	cured
18*	1.8	3	5	yes	yes	plt, ffp	no	no	0	cured
19	0.2	14	20	yes	yes	plt, ffp, pct	no	hd	7	cured
20	0.3	3	11	yes	no	plt	no	no	0	cured
21"	0.7	9	10	yes	no	nil	dp	no	0	cured
22	17	7	5	yes	yes	plt, pct	no	no	0	cured
23"	0.6	7	9	no	yes	plt	no	no	0	cured
24	22	4	19	yes	yes	plt, pct	no	no	0	cured

*: *vivax* malaria; +++: 3 plus on qualitative smear

Fever to Rx: duration of fever before receiving treatment (- = not elicited in history); Max Load: maximum parasite load; plt: platelets; ffp: fresh frozen plasma; pct: packed cells/whole blood; dp: dopamine; db: dobutamine; na: noradrenaline; a: adrenaline; MV: duration of mechanical ventilation in days

that were admitted to our hospital during the study period required intensive care, and all of them had severe *falciparum* malaria at presentation. Jaundice was seen commonly (75%) in these patients and this is usually due to intravascular haemolysis as the hepatic dysfunction is usually mild. Although hypoglycaemia is reported to be common in *falciparum* malaria, none of the patients in our study had documented hypoglycaemia within 24 hours of admission probably because dextrose infusions were routinely started upon admission.

P. falciparum can invade red cells of any age thus producing unrestricted parasitaemias and fatality. In contrast, *P. vivax* invades only young red cells, limiting the resultant parasitaemia and is therefore considered relatively benign. In our study, there was no significant morbidity or mortality associated with *P. vivax* infection that required intensive care. *P. falciparum* has the ability to sequester in the capillaries and postcapillary venules of vital organs such as the brain and kidney. The more mature forms are able to adhere to vascular endothelium causing organ dysfunction. Severe malaria is also associated with high levels of tumour necrosis factor and interleukins but whether this represents cause or effect remains unclear.⁶

Pulmonary oedema and ARDS are severe and often

fatal manifestation of *P. falciparum* malaria in adults and this syndrome is associated with a mortality of about 80%.^{7,8} When ALI was defined according to the criteria above, only 1 of 20 patients (5%) had ALI complicating *falciparum* malaria. This is in contrast to Gachot et al's study⁹ whereby when similar criteria for severe *falciparum* malaria and ALI were used, 12 of 40 patients (30%) had ALI. This patient survived as did 1 of the 2 patients with pulmonary oedema.

Cerebral malaria is the most feared complication of *P. falciparum* infection and also accounts for about 80% of the fatality.¹⁰ Despite intensive care management, the mortality of severe malaria remains around 20% in developed countries.¹¹ Although we had no patients with cerebral malaria according to the strict definition used above (unrousable coma with GCS ≤ 8), we had 3 patients diagnosed to have cerebral malaria based on presence of altered mental status (without hypoglycaemia) and seizures. All of them survived, and from a practical point of view, any alteration in mental status or sign of cerebral dysfunction e.g. seizures should be treated with utmost urgency as cerebral malaria.⁷

The mortality of our patients with severe *falciparum* malaria was 15%. Mortality in *falciparum* malaria increased with age in United States civilian travellers¹² and

this was consistent with our study where the mean age of non-survivors was significantly higher than survivors (56 ± 2.8 years versus 35.3 ± 13.1 years). The mortality of all patients admitted to the medical intensive care unit with malaria in our study was low as compared with the predicted mortality based on the APACHE II score. This comparison has only been made by Lichtman et al¹³ in their series of 26 patients with severe *falciparum* malaria where their predicted mortality was 34% compared with an actual mortality of 38%.

Whilst prompt administration of the appropriate schizonticide is essential (intravenous quinine remains the drug of choice for severe malaria where chloroquine-resistance is endemic and is usually administered until parasitaemia is absent and markers of severe malaria have normalised) in the treatment of severe malaria, aggressive supportive intensive care including careful fluid management, blood products support, acute dialysis and mechanical ventilation when necessary, remain crucial for a favourable outcome.

The use of exchange transfusion is controversial in severe malaria and has been recommended as an adjunct to drug therapy.¹⁴⁻¹⁶ The rationale for exchange blood transfusion in severe malaria is to reduce the parasitaemia and circulating "toxic" factors, as well as to rapidly correct the anaemia and coagulopathy whilst avoiding fluid overload. Parasitaemia does decrease rapidly during exchange transfusions but it also drops rapidly with appropriate drug therapy alone. The potential problems with exchange transfusion (besides transmission of infection) include inappropriate fluid management and the theoretical likelihood that serum levels of antimalarials might decrease somewhat. The indications for exchange transfusion and total volume of exchange required remain uncertain and frequently depend on the clinician's subjective impression. So far, there has been only one small randomised controlled clinical trial¹⁷ on the outcome after exchange transfusion and in this Zimbabwean study, 3 of 4 patients not receiving exchange transfusion died, whereas none of the 4 who received the procedure died. In our experience, this form of treatment was not associated with any short-term complications but clearly, larger prospective randomised trials are needed to determine whether exchange transfusions improve outcome.

The clinician must recognise severe malaria as this is an eminently treatable condition, and when appropriate

measures (including intensive unit monitoring and support) are taken, and prompt treatment is administered, the mortality remains low. The institution of preventive measures and appropriate prophylaxis for travel into endemic areas might further enhance control of this potentially deadly disease.

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