Acute Renal Failure in Falciparum Malaria

Saroj K Mishra*, Shradhanand Mohapatra*, Sanjib Mohanty*, NC Patel*, DN Mohapatra*

Introduction

Malaria has emerged as one of the top 10 killer diseases in the world. It is the major cause of mortality in tropical and subtropical regions. Nearly half of world population is vulnerable to malaria. About 500 million people suffer from malaria leading to death in 2 to 3.0 million cases. Majority of the cases as well as deaths occur in sub-Saharan Africa. Outside Africa, the disease is seen in about 100 countries–Indian subcontinent and Brazil contributing two thirds of these cases.

Acute renal failure (ARF) occurs as a complication of *P. falciparum* malaria in less than 1% of cases, but the mortality in these cases may be upto 45%. It is more common in adults than children. Malarial acute renal failure is diagnosed when serum creatinine level rises above 3 mg/dL (265 mol/L) and/or when urinary output is less than 400 ml in 24 hours. Renal involvement varies from mild proteinuria to severe azotaemia associated with metabolic acidosis.

Pathology and pathogenesis

In mild cases of renal failure, there is hardly any change in the renal parenchyma. There may be minimal tubular degeneration, mild swelling of renal parenchyma, and presence of vacuoles. However, in severe cases, tubular degeneration is present with distal tubular necrosis. Some proximal and collecting tubules are also involved. Casts loaded with malarial pigments are often seen in the proximal tubules. Haemoglobin granules may be found in the tubular cells. Casts and malaria pigments are often seen in proximal convoluted tubules (PCT) and haemoglobin granules may be observed in the tubular cells.

In a study from our hospital in 1982, evidence of acute tubular necrosis was detected in most of the cases, except in a few with features of glomerulonephritis in light microscopy. A later study from Patna (1996) also observed that the clinical course of malaria ARF was consistent with acute tubular necrosis in majority of the patients. Only one case out of six revealed histological features of necrotising glomerulonephritis alongwith acute tubulointerstitial nephritis. The biopsies in the other five patients showed features of acute tubular necrosis in three cases, and acute interstitial oedema with patchy tubular necrosis in two.

Acute renal failure is mediated through several mechanisms. These may be due to the effect of the parasitised RBC (pRBC) on the microcirculation, hypovolaemic shock, or non-specific effects of inflammation.

a. Effect of pRBC on the microcirculation

The entry of parasite into the RBC produces changes in the surface of the pRBC causing formation of knob-like processes, which helps in anchoring the endothelium and adhesion between RBCs. This tight pack of RBCs impedes the microcirculation to various vital organs.

There occurs cytoadherence due to thrombospondin formation from vascular endothelium. This is specifically seen in *P. falciparum* and not in *P. vivax* or *P. malariae*. Hence, acute renal failure is seen in falciparum malaria cases.

Inability of pRBCs to deform according to the need of microcirculation leads to sluggish blood flow and consequently to renal ischaemia.

b. Hypovolaemia : Hypovolaemia may occur due to fever (hyperpyrexia), sweating, or decreased intake of fluid.
c. Non-specific effects of inflammation: There may be leakage of fluid from intravenous compartment due to increased vascular permeability.

d. Intravascular coagulation (DIC)

e. Increased plasma viscosity due to infection.

f. Release of chemical mediators (TNF, etc.): which produce vasoconstrictor effect, increased catecholamine release, and increased vascular permeability.

g. Hyperbilirubinemia: High levels of bilirubin has also a contributory effect in the pathogenesis of acute renal failure. Haemolysis is invariably present in cases of P. falciparum malaria. It can cause alteration in renal haemodynamics in addition to depression in cardiac function. Hyperuricaemia induced by severe jaundice may further compromise renal function in the presence of decreased acid urine flow.

Black water fever is occasionally associated with acute renal failure, and is caused by G6PD deficiency in these patients.

g. Release of chemical mediators leading to vasoconstrictor effect, catecholamine release, and increased vascular permeability.

h. Bacterial endotoxaemia may potentiate ischaemic renal injury (Cytokinsins, cachectins, TNF etc.) Cachectin can cause haemoconcentration, shock, and tubular necrosis. The angioes studies depict decreased blood flow to the cortical areas of kidney in the acute stage. But glomerulonephritis is very rare.

Clinical features

Acute renal failure in severe malaria is common in adults, and rare in children.

There are two subsets of presentation (a) patients with multiple organ dysfunction including acute renal failure (b) patients with acute renal failure alone (where other complications have subsided with treatment but still they go on to develop renal failure, usually at the end of first week). The former is associated with poor prognosis. In about a third of patients with cerebral malaria, serum creatinine was above 2 mg% . These patients have higher incidence of anaemia, jaundice, hypoglycaemia, and prolonged coma. Acidosis appears early and may be associated with clouding of sensorium, convulsions, and coma. In a few patients, the patient is fully conscious, oriented, without evidence of acidosis. This group of patients have better prognosis.

The patient may be oliguric or anuric or even with normal urination or polyuric. Frequent monitoring of biochemical tests like blood urea nitrogen, electrolytes, blood sugar should be carried out.

<table>
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<th>The vulnerable group of patients are:</th>
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<td>pregnant women,</td>
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<td>with high parasitaemia,</td>
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<tr>
<td>with deep jaundice,</td>
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<tr>
<td>with prolonged dehydration, or</td>
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<td>patients receiving NSAIDs.</td>
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Patients with peripheral parasitaemia should be monitored for the presence of renal failure (oliguric or non-oliguric). However, there may be another group of patients. These patients may be seen at a time, when the parasites are no longer present in the peripheral blood, making it difficult to establish the diagnosis of malaria. High index of suspicion, and use of dipstick method for detection of P. falciparum (viz., paracheck, ICT, etc.) or other alternative diagnostic tools are of paramount importance.

Isolated presence of acute renal failure in falciparum malaria is usually rare, but they carry a good prognosis. Presence of acute renal failure alongwith multiple complications is associated with poor prognosis, but onset of acute renal failure in the latter part of the disease, when other complications are subsiding, the outcome is invariably good with dialysis.
Critical determinants:
- hypovolaemia and hypervolaemia,
- hyperparasitaemia,
- haemoconcentration,
- hyperbilirubinaemia,
- hyperpyrexia

Lab. investigations and monitoring

In addition to the peripheral blood smear examination to establish the diagnosis and parasite clearance, the following tests are needed for the management of the cases.

Blood: Urea, creatinine, bilirubin, SGPT, Na⁺, K⁺, HCO₃⁻, pH
Urine: Specific gravity, renal failure index, fractional excretion of Na⁺
ECG, Chest X-Ray when indicated

Treatment

The treatment guidelines include institution of appropriate antimalarials, at the earliest, and maintenance of fluid and electrolytes: recording of intake and output chart, prevention of fluid overload, and secondary infection including pneumonia. Treatment of acquired infection should be done at the earliest.

Fluid and electrolytes: a meticulous record of fluid requirement and urinary output is needed. It helps to guide the administration of fluid, monitoring the improvement, and most of all preventing fluid overload. This simple, albeit most important factor, is left to the nursing staff or the ignorant attendants of the patient, thus getting a confused or inadequate information. To prevent fluid overload a CVP line can be established.

Fluid challenge: If any patient is dehydrated, he should be given a fluid challenge of up to 20 ml/kg of 0.9% saline infused over 60 minutes. In order to prevent fluid overload, auscultation of lungs and JVP measurements (and if possible, CVP measurements) should be performed after every 200 ml of fluid. The CVP should always be kept between 0 and +5. If there is no urine output after fluid replacement, an intravenous diuretic challenge may be given.

Diuretic challenge: The loop diuretic (furosemide or bumetanide) 40 mg is given initially and then in incremental dose of 100, 200, and 400 mg at half hourly intervals. If there is still no urine flow, dopamine 2.5 - 5 µg/kg/min may be tried.

Dopamine challenge: The use of dopamine for the prevention and treatment of acute renal failure is not yet established. Its use is based on the understanding that selective renal vasodilatation will occur when it is infused at low dose. A recent article compared the effects of dopamine and epinephrine in various doses on renal haemodynamics and oxygen transport in patients with severe malaria and severe sepsis[19]. In a prospective, controlled, crossover trial in an intensive care unit of an infectious diseases hospital in Vietnam, dopamine at a "renal" dose (2.5 µg/kg/min) was associated with a mean (95% confidence interval) fractional increase in the absolute renal blood flow index (RBFI) of 37% (13% to 61%) and in RBF as a fraction of cardiac output (RBF/CO) of 35% (10% to 59%; \( p = .007 \) and \( p = .014 \), respectively). At higher doses (10 µg/kg/min), both RBF and RBF/CO were not significantly different from baseline values and decreased further as the dose was reduced again. Neither epinephrine, nor dopamine significantly affected creatinine clearance or urine output. There was no evidence that either drug produced any beneficial effect on renal oxygen metabolism or function. A review article analysed the available data on the clinical use of dopamine. When used to prevent acute renal failure in high-risk treatments there is no evidence of benefit of dopamine. In treatment of acute renal failure, the quality of the data is poor. Except one small randomised trial of moderate acute renal failure in patients with malaria showing clinically significant benefits by use of dopamine, rest of the data, in the form of case series, showed either minor or no benefit of clinical significance. Hence, its use
cannot be advised until trials examining clinically important endpoints in large numbers of patients have been performed.

Similarly, with use of diuretics, urinary output increases in 75% of the oliguric patients and only in 5% anuric patients. However, there may not be associated improvement in the renal parameters. Rather it may lead to delay in initiating dialysis. So use of diuretic challenge should be considered with utmost caution.

If fluid replacement with or without the above procedures are ineffective, it is critical that further fluid should be restricted to keep the CVP between 0 to +5 of H₂O, and monitored for need of dialysis.

Antimalarials: Quinine, chloroquin, and artemisinin are the mainstay of therapy. Even in the presence of pregnancy and acute renal failure, quinine should not be withheld for fear of toxicity. Quinine should be given in a dose of 10 mg/kg 8 hourly during the first 48 hours of treatment. However, when it needs to be given beyond this period, the dose should be reduced to 2/3rd or ½. The dose should not be reduced in the initial 48 hours.

Cardiotoxicity of quinine must be of concern in malaria patients with ARF after 3 days of quinine therapy, and ECG monitoring during quinine infusion is recommended in all severe malaria patients with persistent ARF. If there is any arrhythmia, the infusion should be discontinued. However, in some hospitals where ECG facilities are not available, reduction in quinine dosage in persistent ARF patients should be considered after the third day of therapy. The appropriate dosage reduction should be further studied. Monitoring of free rather than total plasma quinine concentrations is of value for predicting the cardiotoxicity in ARF patients. However, ECG seems to be the practical procedure to monitor cardiotoxicity. It may be possible to use the QTc interval for this purpose. Artemisinin drugs do not require any dose modification in the presence of acute renal failure. However, care should be taken to monitor cardiotoxicity as artemisinins are also known to cause prolongation of QT interval.

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<th>Drugs to be avoided in malaria patients as they may impair renal function:</th>
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<td>• NSAID should not be given as they may precipitate pre-renal azotaemia to ischaemic ARF.</td>
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<td>• ACE inhibitors and cyclo-oxygenase inhibitors.</td>
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<td>• Nephrotoxic drugs should be avoided where ARF is suspected or anticipated, such as, cephalosporins, aminoglycosides.</td>
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Assessment of renal function using measurement of urine volume should not be done in patients receiving diuretics.

Exchange transfusion: it is of use in patients with severe haemolysis and hyperbilirubinaemia. However, in other conditions it is of doubtful value.

Dialysis: Dialysis has improved the survival of the cases when instituted early in the course.

Indications for dialysis include:

a) Clinical indications:
   1. Uraemic symptoms
   2. Symptomatic volume overload, e.g., pulmonary oedema, congestive heart failure
   3. Pericardial rub

b) Laboratory indications:
   1. Severe metabolic acidosis (HCO₃ < 15 mEq/1)
   2. Hyperkalaemia (K⁺ > 6.5 mEq/1)

Clearance of urea and other molecular waste products is much faster with haemodialysis (HD) as compared to peritoneal dialysis (PD). However, PD has certain advantages such as: PD does not need a special set up, it can be started immediately, it may prove to be life saving. Thus, in the absence of facilities for HD whenever indicated, PD should be started as early as possible.
### Table I: Dosage and use of antimalarial drugs in severe malaria.

<table>
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<tr>
<th>Agent</th>
<th>Route of administration</th>
<th>Dosage</th>
<th>Duration of therapy</th>
<th>Dose modification in renal failure</th>
<th>Special precaution</th>
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<tr>
<td>Quinine dihydrochloride</td>
<td>Intravenous infusion</td>
<td>10 mg salt/kg body weight, diluted in 10 ml/kg body weight of 5% dextrose or dextrose saline infused over a period of 4 hours and repeated every 8 hrs.</td>
<td>7 days</td>
<td>No modification of IV quinine for first 48 hrs even if renal (or hepatic) insufficiency is present.* If the drug is continued intravenously beyond 48 hours, the dose is halved in presence of renal failure.*</td>
<td>Pulmonary oedema Hypotension Hypoglycaemia Prolonged QT interval</td>
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<tr>
<td>Artesunate</td>
<td>Intravenous</td>
<td>2.4 mg/kg (loading dose) IV, followed by 1.2 mg/kg at 12 hours, then 1.2 mg/kg daily for 6 days, if the patient is able to swallow, the daily dose can be given orally.</td>
<td>6 days</td>
<td>No dose modification</td>
<td>Safe drug. It can be used in patients with fluid overload, hypotension, or shock. Does not cause hypoglycaemia</td>
</tr>
<tr>
<td>Artemether</td>
<td>Intramuscular</td>
<td>3.2 mg/kg body wt stat, followed by 1.6 mg/kg daily</td>
<td>5 days</td>
<td>No dose modification</td>
<td>Artemisinin drugs are not yet approved (by Govt of India) for use in pregnant women and children</td>
</tr>
<tr>
<td>Arteether</td>
<td>Intramuscular</td>
<td>2.4 mg/kg or 150 mg</td>
<td>3 days</td>
<td>No dose modification</td>
<td></td>
</tr>
<tr>
<td>Chloroquine**</td>
<td>Intramuscular</td>
<td>10 mg base/kg bwt on day 1, day 2, and 5mg/kg bwt on day 3</td>
<td>3 days</td>
<td>No dose modification</td>
<td>Daily dose must not exceed 15 mg/kg bwt. Total dose not to exceed 25 mg/kg bwt</td>
</tr>
<tr>
<td>Mefloquin Halofantrine</td>
<td>Oral</td>
<td>No role in patients of severe malaria as parenteral preparation is not available.</td>
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* If there is no clinical improvement after 48 hours of parenteral therapy, the maintenance dose of parenteral quinine should be reduced as follows (even without any renal or hepatic involvement):
First 48 hours (two days) of treatment: 30 mg salt/kg of body weight per 24 hours.
Subsequently: 15-21 mg salt/kg of body weight per 24 hours.

** Widespread chloroquine resistance is reported from South-East Asia. It is therefore recommended to treat all patients of severe malaria with quinine or appropriate artemisinin derivatives.

Conservative treatment in patients of acute renal failure in severe malaria needs careful monitoring. A patient may develop signs as mentioned above and at any odd hours without giving a scope for initiation of dialysis. Many lives have been lost as dialysis is decided but institution was delayed. Sudden cardiac death may ensue in a patient who is improving due to development of pulmonary oedema or hyperkalaemia.

Adequacy of dialysis is considered when the post-dialysis creatinine and urea decrease to 50% or less of the pre-dialysis values.

**Antimalarial drugs during dialysis:** There were no significant changes in plasma quinine levels during dialysis.
concentrations in patients with ARF during haemodialysis. No quinine was detectable in haemodialysate fluids. This suggests that dosage adjustment of quinine during haemodialysis is unnecessary\textsuperscript{21}. No data is yet available for the artemisinin drugs for modification during dialysis.

Associated conditions requiring attention:
- Hypervolaemia
- Hyperkalaemia
- Metabolic acidosis
- Anaemia
- Infection

Prognosis

Overall mortality among those with renal failure was 45\%, compared with 10\% in those without\textsuperscript{1,15}. The mortality is reported between 15 to 54\% from different countries (15.8\% from Pakistan\textsuperscript{16}, 30.8\% from Patna\textsuperscript{6}, 45\% from Yemen\textsuperscript{24}, and 54\% from Ethiopia\textsuperscript{17}). The survival with PD is lower than that of HD\textsuperscript{23,24}. In our hospital the mortality decreased significantly when HD was instituted early. It is pertinent to mention that acute renal failure in malaria needs urgent recognition and management. Multiple complications need urgent management in a tertiary care hospital with multidisciplinary approach.

Prognostic importance of acute renal failure in severe malaria:
- Death increases three-fold in presence of acute renal failure.
- Very high mortality in presence of multiple organ failure.
- Mortality can be reduced to 10\% if early and frequent dialysis is instituted.

Acknowledgement

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Reference


