Review Articles

Renal failure in malaria

B.S. Das

Emeritus Medical Scientist (ICMR), Institute of Life Sciences, Bhubaneswar, India

Abstract

Acute renal failure (ARF) is seen mostly in *Plasmodium falciparum* infection, but *P. vivax* and *P. malariae* can occasionally contribute for renal impairment. Malarial ARF is commonly found in non-immune adults and older children with falciparum malaria. Occurance of ARF in severe falciparum malaria is quite common in southeast Asia and Indian subcontinent where intensity of malaria transmission is usually low with occasional microfoci of intense transmission. Since precise mechanism of malarial ARF is not known, several hypotheses including mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation, etc, have been proposed. Increased fluid administration, oxygen toxicity, and yet unidentified factors may contribute to pulmonary edema, acute respiratory distress syndrome (ARDS), multiorgan failure and death. Mainstay of treatment consists of appropriate antimalarial drug therapy, fluid replacement, and renal replacement therapy. Loop diuretics can convert an oliguric renal failure to non-oliguric renal failure without affecting outcome of the disease though the conversion reduces the risk of volume overload. There is little evidence on beneficial effect of vasoactive drugs. Nephrotoxic drugs such as ACE inhibitors, NSAIDs, aminoglycosides, cephalosporins should be avoided. Currently, high quality intensive care, early institution of renal replacement therapy, and avoidance of nephrotoxic drugs are standard practice of the prevention and management of ARF.

Key words Acute renal failure – malaria – *Plasmodium falciparum* – *P. malariae* – *P. vivax*

Introduction

Malaria is caused by four species of the genus *Plasmodium* namely, *Plasmodium vivax*, *P. falciparum*, *P. malariae* and *P. ovale*. Common clinical presentations of infection with all four Plasmodia species are periodic paroxysm, chills, rigors, sweating, body aches, headache, nausea, general weakness and prostration. Severe life-threatening complications such as cerebral malaria (CM), severe anemia, acidosis, respiratory distress, jaundice, acute renal failure (ARF), acute respiratory distress syndrome (ARDS), etc occur mostly with *P. falciparum* infection. A few reports have appeared indicating association of severe complications of malaria with *P. vivax* infection[1–3]. Recently, life threatening complications with *P. knowlesi* infection has been reported in humans[4]. Renal involvement has been reported in *P. falciparum*, *P. malariae*, and recently in *P. vivax* infections. *P. malariae* associated nephropathy was reported mainly from Africa, that too before 1980. Publications on *P. vivax* renal failure are too few and inconclusive to merit a detailed review. Therefore, renal failure related to *P. falciparum* malaria will be reviewed in detail while renal involvement in *P. malariae* and *P. vivax* will be mentioned briefly.

Renal involvement in P. malariae infection: Incidence of progressive glomerulonephritis was significantly higher in malaria-endemic areas of Africa. *P. malariae* was considered an important cause of chronic malarial nephropathy (quartan malarial nephropathy)[5]. The incidence of glomerulonephritis gradually declined along with eradication of malaria in many parts of Africa[6,7]. The disease affected mostly children and presented as steroid-resistant nephrotic syndrome. The pathogenesis of renal involvement is possibly mediated through immune complex deposition. Histopathologic observations include features of mesangiocapillary glomerular, and subendothelial immune complex deposits containing IgG, C3, and malarial antigens. The disease progresses to renal failure even after successful eradication of the infection. Quartan malarial nephropathy was reported mainly from Africa[6–12]. However, most evidences in favour of quartan malaria nephropathy have been circumstantially linked with *P. malariae* infection. A recent study in children from Ghana could not notice any evidence for a dominant role of steroid-resistant tropical glomerulopathies. Histological findings consisted of focal and segmental glomerulosclerosis and minimal change disease. Membrano-proliferative glomerulonephritis was absent in almost all the cases. It was concluded that a uniform pattern is not seen throughout Africa[13]. Another recent review on nephrotic syndrome in quartan malaria inferred that the association between renal involvement and *P. malariae* infection was only coincidental and reported mostly before 1975. Currently, there is no evidence of chronic malarial glomerulopathy in African children with nephrotic syndrome[14].

Renal involvement in P. vivax malaria: Renal involvement in *P. vivax* malaria has been reported mostly from Indian subcontinent. In one of the earlier studies, Mehta *et al*[15] observed that out of 24 patients of malarial ARF, 16 were infected with *P. falciparum*, 3 with *P. vivax,* and 5 with mixed infection of *P. falciparum* and *P. vivax*. In a retrospective analysis, 13 of the 93 patients of malarial ARF had *P. vivax* infection, while another 6 had mixed infection with *P. falciparum* and *P. vivax*. Renal ischemia resulting in acute tubular necrosis was considered responsible for the renal failure[16]. Evidence of renal involvement was noticed in 2 cases of *P. vivax* malaria from a total of 81 cases of malarial ARF in another study[17]. In a study from Karachi, Pakistan, 3 out of 124 cases of malarial ARF had *P. vivax* infection while the remaining 121 had *P. falciparum* infection[18]. Rare manifestations such as renal failure, uremic encephalopathy, and thrombocytopenia were reported in an 8-year-old boy with *P. vivax* malaria[19]. Clinical pictures of toxic shock showing disseminated intravascular coagulation (DIC) with marked thrombocytopenia, oliguric renal failure, and pulmonary edema were found in patients with *P. vivax* malaria from Republic of Korea[20].

Epidemiology

Since malarial ARF is almost always caused by *P. falciparum* infection, the discussions mentioned below relates exclusively to ARF induced by *P. falciparum* infection. ARF is a frequent and serious complication of falciparum malaria in non-immune adults and older children[21–23]. Proportion of ARF in complicated falciparum malaria is several fold higher in patients from non-malarious regions than those from high malaria transmission areas. Malarial ARF has been reported from several European countries, where malaria transmission is virtually non-existent[24,25]. The incidence of ARF according to one report is as high as that of CM[26]. In contrast, incidence of ARF in falciparum malaria is absent or very low in sub-Saharan Africa, particularly, from the areas of intense malarial transmission, where younger children are worst affected[27,28]. A large proportion of malarial ARF patients admitted to a hospital in Ethiopia consisted of non-immune visitors[29]. However, in recent years, malarial ARF with associated morbidity and mortality is reported more frequently in semi-immune African children[30,31].

Occurrence of ARF in severe falciparum malaria is quite common in southeast Asia and Indian subcontinent where intensity of malaria transmission is usually low with occasional microfoci of intense transmission. High incidence of malarial ARF has been reported from Vietnam[32]. Subsequent studies have proved the incidence to be even higher than that reported earlier. Severe malaria in Vietnamese adults is usually a multisystem disease where more than 40% of severe malaria patients had ARF, and more than 55% of fatal cases had ARF on admission that rose to 70% by the time they died[33]. Similarly, a significant proportion of severe malaria patients in Thailand had ARF[34]. High incidence of ARF has also been reported from other southeast Asian countries as well. Hypercatabolic ARF associated with CM, heavy parasitemia, and hyperbilirubinemia was noticed in Malaysian patients[35]. ARF constituted 23.3% of severe malaria patients in a hospitalized study from Kampuchea. Coma stage III and multiorgan failure were the most common causes of death[36]. Significant proportion of severe malaria patients in Singapore had ARF[37].

In India, complications of *P. falciparum* malaria occur in all age groups but frequency of different complications differs in children and adults. CM occurs in equal frequency in children and adults and was the common cause of mortality. Severe anemia and convulsions were more common, jaundice less common, ARF and ARDS rarely occurred in young children[38]. There is a perceptible change in the clinical presentation of severe malaria in India in last 10–15 years; a gradual shift from single to multiple complications. CM alone was the predominant complication in adults earlier, where as currently, multiple complications are the usual presentation of severe malaria. Mortality in CM patients with associated complications such as jaundice and ARF is twice as high as that with CM alone. A significant increase in the incidence of malarial ARF has been reported from several centres across India. In 1982, a study from southern part of Orissa state in eastern India indicated CM

as the predominant presentation of severe malaria. Out of 173 cases of CM, renal involvement was observed in 6% and hepatic involvement in 1%[39]. Twenty years later a study from the same area and same hospital showed 35% cases of severe *P. falciparum* malaria having ARF. The study also indicated an increase in incidence of malarial ARF, from 95 cases in 1994 to 215 cases in 1998[40]. In another large series published in 1989 Mehta *et al*[41] did not find a single case of renal failure in 425 cases of falciparum malaria. Malaria transmission in south India is relatively less in comparison to eastern and central India. Accordingly, malarial ARF was found only occasionally in south India. However, in the recent past, a significant change has been noticed in the trend of ARF admissions. While ARF due to leptospiral infection is on the decline, malaria has become the emerging cause of ARF[42]. High incidence of malarial ARF, both in children and adults has been reported from several centres across the country[15–17, 43–48]. A common inference from these studies is that the incidence of ARF and jaundice is in the rise, and development of multiple complications result in increased mortality. A similar report from an intensive care unit of a tertiary care university hospital also found malaria as an important cause of multiorgan failure in India and regardless of the organ system involved mortality was significantly higher with multiple organ failure than with one or no organ failure[49]. Studies from Pakistan also report malarial ARF contributing significantly to total ARF burden[50].

Pathogenesis

Precise mechanism of renal failure in falciparum malaria is not clearly known. Several hypotheses including mechanical obstruction by infected erythrocytes, immune mediated glomerular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation, etc have been proposed[21,22,51]. Cytoadherence of *P. falciparum* infected red blood cells (IRBCs) to the vascular endothelial cells of different host organs along with rosette for-

mation is considered as a most important mechanism of severe malaria. IRBCs preferentially sequester in the deep vascular beds of vital organs, including the brain, liver, lung, spleen, intestine, and kidney[52–54]. Parasite proteins referred to as variant surface antigens (VSA) expressed on the IRBC surface mediate adhesion of infected erythrocytes to host vascular endothelial receptors[55,56]. Significantly more IRBCs were seen in renal vasculature of malaria patients with ARF than those without ARF. However, the extent of IRBC sequestration in glomerular and tubulointerstitial capillaries was far less than the cerebral vessels[57]. Thus, contribution of IRBC cytoadherence and clogging of the capillaries towards pathogenesis of malarial ARF appears at best only marginal.

Mononuclear cell infiltration in glomeruli and tubulointerstitium has been reported in renal tissues in severe falciparum malaria[58-61]. Other recent studies have also showed mononuclear cells in glomerular and peritubular capillaries though the number of leukocytes was not significantly different between the ARF group and the non-ARF group[62,63]. Margination of mononuclear cell to the brain capillary endothelium has been demonstrated earlier in a significant proportion of patients[64]. Activation of locally marginated mononuclear cells within glomerular and peritubular capillaries is likely to induce host immune reactions by releasing cytokines, reactive oxygen intermediates (ROI) and nitric oxide (NO) locally. Further studies on the mechanism and effect of mononuclear cell margination in the glomerular and peritubular capillaries with special reference to local release of soluble mediators will help in understanding the pathogenesis of malarial ARF.

Exaggerated host immune response is considered an important mechanism for several complications of malaria. Host-parasite interaction may result in mechanical, immunologic and humoral responses, which while eliminating parasite also injures host tissues. Cytokines, ROI, and NO play an important role in elimination of the parasite, though an unbalanced response may be responsible for pathogenesis of severe malaria. Levels of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukins 1-alpha, 6, and 8 (IL-1α, IL-6, and IL-8) are elevated in malaria patients[65]. Higher concentrations of proinflammatory cytokines are observed in severe complications of malaria[66–69]. Anti-TNF-α and anti-IFN-γ antibodies prevented occurrence of CM in experimental malaria[70]. However, these effects could not be replicated in human malaria except for amelioration of fever[71].

Increased production of ROI and NO is commonly found in malaria infection, but evidence on their role in protection and pathogenesis of the disease has remained inconclusive. ROI is considered to play a significant role both in protection and pathogenesis of malaria[72,73]. Higher blood concentrations of ROI and depleted antioxidant defense system have been observed in malaria patients[74–76]. The effect of NO depends on its time of release and the type of isoform released. While early increase of NO stimulates Th1 response to control parasitemia[77], late increase of NO production in the liver and spleen appear to have pathological consequences[78]. Regulatory functions of NO are dependent on the presence of various isoforms of the enzyme nitric oxide synthase (NOS). Constitutive NOS (cNOS) is responsible for continuous synthesis of NO in low concentrations for imparting its physiological functions. In contrast, inducible NOS (iNOS) synthesize high levels of NO, which plays a crucial role in pathological consequences. Increased iNOS activity and production of NO was observed in severe malaria[79]. During the blood stage of malaria TNF-α upregulates NO synthesis either alone or in combination with other cytokines[80].

Restricted local blood flow in the kidneys is considered a major contributor for malarial ARF. Low intake of fluids, loss of fluids because of vomiting and pyrexial sweating may be responsible for dehydration and renal ischemia. Depending on the degree of re-

nal hypoperfusion, the spectrum of manifestations varies from milder forms like pre-renal azotemia to more severe forms of ischemic ARF. Pre-renal azotemia is the most common form of renal impairment resulting from mild to moderate renal hypoperfusion. It is rapidly reversible upon restoration of renal blood flow. However, administration of intravenous fluids often worsens the general condition of the patient by inducing pulmonary edema, a situation similar to shock like syndrome. A generalized vasodilatation with an associated decrease in systemic vascular resistance is considered an important contributor for septic shock as well as malarial ARF. Vasodilatation leads to activation of sympathetic nervous system, rennin-angiotensin-aldosterone axis (RAAA), and release of vasopressin for maintaining the falling blood pressure. Unfortunately, these compensatory mechanisms may worsen the renal pathology leading to overt ARF[81,82] while efficacy of these pressor hormones to raise blood pressure through development of generalized vascular resistance is attenuated by higher hydrogen ion and lactic acid concentrations. Hyperlactataemia is considered a marker for poor prognosis in sepsis[83] as well as in malaria[84,85].

Malarial ARF can occur as an isolated complication or as a component of multiorgan involvement. Shock and multiorgan failure is a common association in malarial ARF as also in ARF of sepsis. In fact, extensive similarities have been observed between the sepsis and severe malaria in clinical presentation and cytokine profile indicating that the two diseases operate through very similar mechanisms[86]. Arterial vasodilatation that accompanies sepsis is mediated, at least in part by, cytokines that up-regulate the expression of iNOS in vasculature[87,88]. Plasma concentration of several small and middle molecular weight proteins is reduced in severe malaria because of extravasations from vascular compartment to interstitial space[89,90]. Even, the respiratory distress noticed in severe malarial anemia may have been caused by hypovolemia induced by vasodilatation rather than

volume overload biventricular failure[91]. In patients of severe anemia administration of albumin for volume expansion reduces mortality[92]. However, others did not notice severe volume depletion or hypotension in severe malaria[93,94].

Low intake of fluids, loss of fluids because of vomiting and pyrexial sweating, cytokine and NO mediated arterial vasodilatation specifically organ specific release of NO, resistance to vasoactive hormones, cytopathic hypoxia leading to decreased ATP synthesis, cytoadherence of PRBCs, etc all may contribute singly or in combination towards malarial ARF. Increased fluid administration, oxygen toxicity, and yet unidentified factors may contribute to pulmonary edema, acute respiratory distress syndrome (ARDS), multiorgan failure and death (Fig. 1).

Histology

Various histologic pictures including glomerulonephritis, acute tubular necrosis (ATN), and interstitial nephritis have been described in malarial ARF either alone or in combination. Ultrastructural examination of kidney of mice infected with *P. berghei* demonstrated extensive cytoplasmic vacuolation in proximal tubular cells, thickened endothelial wall on peritubular capillary, and swollen rough endoplasmic reticulum and mitochondria. The lumen of vessels contained parasitized erythrocytes and an inflammatory infiltrate of macrophages[95].

Contribution of glomerular pathology towards malarial ARF is not clearly defined. Several studies have reported histological evidence of glomerular lesions in patients dying of falciparum malaria[23,96,97]. The lesions were characterized by prominent mesangial proliferation with modest matrix expansion, and occasional basement membrane thickening. Deposition of an eosinophilic granular material has been noticed along the capillary walls, within the mesangium, and in the Bowman's capsule. The glomerular capillaries may contain occasional IRBCs. Immunofluorescence
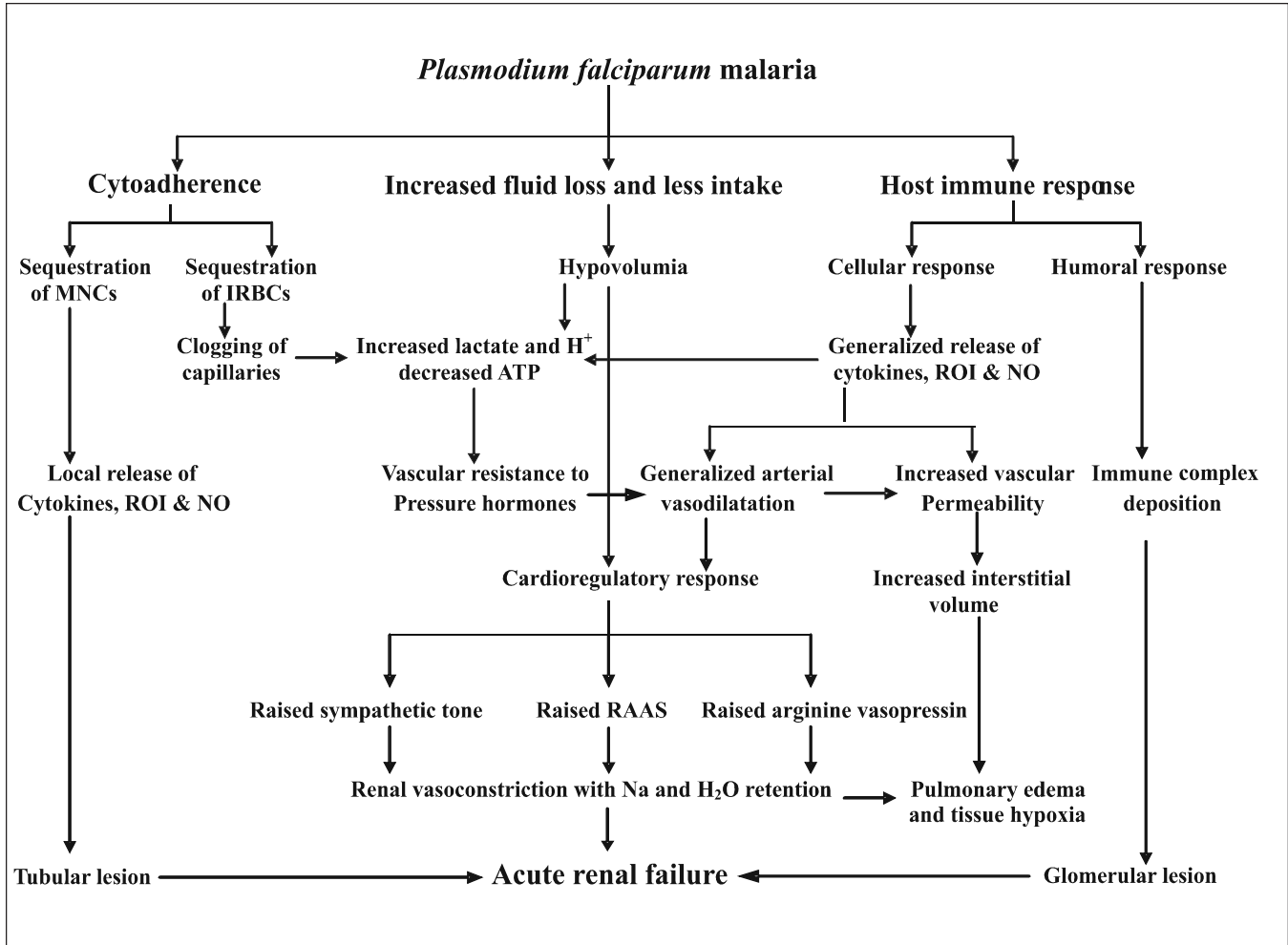
Fig. 1: Mechanism of malarial acute renal failure (MNCs–Mononuclear cells; IRBCs–Infected red blood cells; RAAS– Renin-angiotensin-aldosterone system; ROI–Reactive oxygen intermediates; NO– Nitric oxide; H^{+}– Hydrogen ion)

examination showed presence of IgM and C3 deposits in the capillary walls and in the mesangium. Electron microscopy showed subendothelial and mesangial electron-dense deposits along with granular, fibrillar, and amorphous material[5,98]. Presence of immune complexes of *P. falciparum* antigen in the glomerular basement membrane and mesangium has also been observed[60]. In *P. falciparum* infection high circulating load of parasite antigens are observed because of cyclical rupture of IRBCs. An active host immune response generating specific antiplasmodial antibodies is likely to promote immune complex formation and deposition in the capillary wall. However, clinical presentation and urine examination findings do not

support presence of such deposits in malarial ARF. In a recent study, deposition of immune complex was not seen either in the basement membrane or mesangium of glomeruli[63]. One important contributor for discrepancy in the observations could be short duration of disease process. Though enough plasmodial antigen circulate in the blood during acute stage of the disease, short duration of the disease process may not allow enough time for the development of appropriate antibodies for formation of circulating immune complexes of the right structure to be deposited in the kidney.

ATN has been found as the most consistent histological finding. Variable degrees of altered tubular cell

morphology, beginning from cloudy swelling to cellular necrosis are seen. Tubular changes include deposits of hemosiderin granular deposits, presence of hemoglobin casts in the tubular lumen, and edematous interstitium with mononuclear cellular infiltration. The venules may contain IRBCs and rosettes. A recent study from Vietnam and Thailand found that most patients showed mononuclear cells in glomerular and peritubular capillaries. Phagocytosed malarial pigment was seen in the cytoplasm of mononuclear cells in some patients[63].

Acute interstitial inflammation is a well-recognized pattern of malarial nephritis in experimental models and after vaccination with *P. falciparum* antigens in monkeys. It is considered a consequence of potent host immune response. Though interstitial inflammation is a common histopathologic association in malarial ATN, isolated interstitial nephritis is uncommon.

Clinical presentation

Renal involvement in falciparum malaria can present as electrolyte abnormality, abnormal urinary sediments and increased urinary protein excretion, ARF, etc[17]. ARF is usually associated with oliguria and in severe cases even anuria. Occasionally ARF may be non-oliguric, which makes the diagnosis difficult unless serum creatinine is estimated. Pre-renal azotemia usually presents with clinical signs of severe dehydration. However, prolonged anuria or oliguria may lead to inevitable expansion of extracellular fluid volume because of diminished salt and water excretion. Oliguric phase usually lasts about a week but may vary from few days to few weeks. Malarial ARF is catabolic in type characterized by rapid rise of plasma urea and creatinine due to increased catabolism. Subclinical impairment of renal function is also observed in a significant proportion of malaria patients. Glomerular filtration rate (GFR) assessed using cystatin C, was found elevated in 17% children with falciparum malaria[99].

The common predisposing factors for malarial ARF are volume depletion, gastrointestinal bleed, sepsis, nephrotoxic drugs (aminoglycosides and NSAID), etc. Prognosis of malarial ARF depends on several factors including other associated complications such as CM, jaundice, shock, ARDS, severe anemia, high plasma creatinine concentration, duration of ARF, etc. Mortality is higher when plasma creatinine at presentation is high, urine output is low, delayed referral to the hospital, and when associated with other complications[100].

Hyperbilirubinemia in falciparum malaria possibly predisposes for ARF, which may remain unnoticed[101]. In an another study, nine patients of acute falciparum malaria with severe hyperbilirubinemia developed ARF, though interestingly, referral diagnosis did not include malaria as a cause of ARF in 8 out of 9 patients[47]. Simultaneously, malarial ARF was significantly associated with liver dysfunction as well[32]. The association between renal failure and jaundice is a recurrent finding in studies on severe malaria[102–104]. Other studies have also indicated that almost all patients of ARF with jaundice had conjugated hyperbilirubinemia with cholestasis. This well described association may contribute to the reduction of GFR or development of ATN[18,22]. ARF associated with jaundice had high mortality in comparison to non-jaundiced ARF patients[45,99].

Similarly, association of ARF with CM has been reported from southeast Asia and Indian subcontinent where malarial ARF is a common in *P. falciparum* malaria. Out of 526 cases of CM reported from Rourkela, in Sundargarh district of Orissa state, more than 62% had associated severe complications including 28.9% with ARF and 47.5% with jaundice. Mortality in this series was particularly high (59%) specifically in those with multiorgan failure[105]. The effect of associated ARF on mortality in CM patients indicated, mortality was as high as 39.5% when associated with ARF, while it was only 13.9% when unassociated with ARF. For each one log unit increase of creatinine at admission, odds of death in-

creased by a factor of 10.8[106]. The association was even higher in studies from Vietnam and Thailand. About half of all adult patients with CM had biochemical evidence of renal impairment (raised blood urea and serum creatinine)[32,107].

Management

Malarial ARF is suspected when urinary output falls to less than 400 ml in 24 h or 20 ml/h, which fails to improve after adequate rehydration. Occasionally malarial ARF may be non-oliguric in which case diagnosis can only be made from biochemical investigations. The diagnosis is confirmed when the serum creatinine exceeds 3 mg/dL (260 μmol/L) in adults and 1.5 mg/dL (130 μmol/L) in children. It is essential to distinguish between pre-renal azotemia and established ARF for appropriate management. A simple test to distinguish between the two is measurement of urine specific gravity; while in pre-renal azotemia it is more than 1.02, in established ARF it is less than 1.01. The mainstay of treatment in malarial ARF revolves around: (i) appropriate antimalarial therapy; (ii) fluid replacement; (iii) renal replacement therapy; (iv) supportive therapy; and (v) avoidance of nephrotoxic drugs.

Chloroquine is cheap, safe, and effective in chloroquine sensitive parasites, therefore, the preferred drug of choice. However, chloroquine is no longer used for treatment of severe falciparum malaria because of widespread resistance of *P. falciparum* parasites to the drug. The current practice is to treat all patients of severe malaria including ARF with quinine or appropriate artemisinin derivatives. The patients should receive antimalarial drugs preferably through parenteral route. Therapeutic window of quinine is very small and higher blood concentration may lead to severe cardiac toxicity[108] and hypoglycemia by inducing hyperinsulinimia[109]. Monitoring blood quinine concentration and ECG changes can detect quinine toxicity. Parenteral quinine dose should therefore, be reduced to half after 48 h if ARF is present.

Plasma concentration of 3-hydroxyquinine(3OHQn), the main metabolite of quinine, may go up to 45% of the plasma quinine level in malaria patients with ARF. The metabolite possibly contributes to a significant proportion of the antimalarial activity as well as adverse effects of the parent compound, although this metabolite is not quantitated routinely by current high-performance liquid chromatography quinine assays[110]. Quinine is not significantly removed by continuous venovenous hemofiltration. The filter clearance accounted for less than 1.5% of the total body clearance[111]. Quinine was not detectable in haemodialysate fluids and no significant change in plasma quinine concentrations was noticed in ARF patients during hemodialysis[112]. Malarial ARF significantly modifies the pharmacokinetics of intramuscular artemether. The changes could be attributed to improved absorption, bioavailability, a reduction of systemic clearance, or a change in plasma protein binding of the drug. However, response of treatment in relation to the parasite and fever clearance time, recrudescence, and recovery of consciousness in comatose patients were not different in patients with malarial ARF than those without ARF[113].

Preservation of renal blood flow and perfusion pressure prevents deterioration of renal function. The first step to achieve this is by infusion of fluids. The patient should be carefully examined for clinical features of hypovolemia. Fluids should be administered slowly and titrated against jugular venous pressure and urine output, because of the vulnerability of ARF patients for post-transfusional volume overload. Composition of replacement fluids for treatment of pre-renal azotemia due to hypovolemia must be tailored according to the composition of the lost fluid. Close monitoring for signs of volume overload during transfusion of blood or fluids is essential.

Because of the hypercatabolic state of malarial ARF, hemodialysis or peritoneal dialysis should be immediately performed in conditions of rapid increase in creatinine concentration. Continuous removal of

fluid and waste products minimizes problem of fluid overload and may prevent the progression of respiratory failure. More than half of malarial patients in different series required dialysis. Early dialysis is often indicated to take care of hypercatabolic state. Although peritoneal dialysis is less effective because of the complicating circulatory disturbances, it is often the only available dialysis modality in areas where malaria is endemic. Continuous arteriovenous hemofiltration or continuous peritoneal dialysis is considered superior. Beneficial effects of continuous peritoneal dialysis have been observed in patients of malarial ARF[114]. A comparative study to evaluate efficacy of hemofiltration versus peritoneal dialysis showed significant lower mortality with hemofiltration (15 vs 47%). The rates of resolution of acidosis and decline in the serum creatinine concentration with hemofiltration were more than twice than with peritoneal dialysis. Renal-replacement therapy was required for a significantly shorter period with hemofiltration[115]. A systematic search of peer-reviewed publications studying dialysis support in adults with ARF (of all causes) indicated intermittent hemodialysis and continuous renal replacement therapy appear to lead to similar clinical outcomes in ARF patients. If continuous venovenous hemofiltration is used, a dose of 35 ml/kg per hour should be provided[116]. Apheresis has been reported to successfully support anuric patients with cerebral and pulmonary complications[117].

Oliguria being a bad prognostic sign, diuretics are often used to increase urine output in patients with or at risk of ARF. Addition of vasoactive agents to boost the efficacy of diuretics to restore renal blood flow and perfusion pressure has yielded conflicting results. Vasoactive drugs are often administered to improve either cardiac output or mean arterial pressure in the hope that renal blood flow will also be improved and, thereby, renal protection achieved. While many of these pharmacological approaches appear theoretically reasonable, their efficacy is uncertain. Furosemide in large doses along with dopamine at both low and high doses has been tried with inconsistent results. One study did not notice any beneficial effect with intravenous furosemide at the dosage of 200 mg 6 hourly for a period of 4 days, but addition of dopamine (1 μg/kg/min) increased creatinine clearance and arrested the progress of renal failure when the serum creatinine was less than 400 μmol/L, but failed to alter the course of renal failure when the serum creatinine exceeded 600 μmol/L[118]. Although dopamine increased and epinephrine decreased fractional renal blood flow, there was no evidence that these drugs produced either a beneficial or a deleterious effect on renal oxygen metabolism or function at any of the doses investigated[119]. Others have opined that there is no evidence in favour of low-dose dopamine preventing renal failure or improving renal function. The addition of norepinephrine can be of value if high doses of dopamine fail to restore perfusion pressure[120]. A review of vasoactive drugs and their effects on the kidney has inferred that none have been demonstrated to achieve clinically important benefits in terms of renal protection[121]. The review concluded that there have been no randomized controlled trials of sufficient statistical power to detect differences in clinically meaningful outcomes except for low-dose dopamine and there is a great need for large randomized controlled trials to test the clinical, instead of physiological, effects of vasoactive drugs in critical illness.

Similarly, from a pathophysiological point of view there are sound reasons to believe that loop diuretics also could have a beneficial effect on renal function. However, clinical trials on the prophylactic use of loop diuretics rather point to a deleterious effect on parameters of kidney function. In patients with established ARF loop diuretics have been shown to increase urine output, but a beneficial effect on renal function has not been demonstrated[122]. Although mannitol can flush out intratubular casts and increases tubular flow, so far no well-designed clinical studies have demonstrated its efficacy in ARF[120]. Another systematic review comparing loop diuretics

with control in the management of ARF did not notice any association of diuretic use with reduction in mortality or requirement for renal replacement therapy. However, use of diuretics was associated with shorter duration of renal replacement therapy and increased urine output[123].

In summary, appropriate antimalarial drug therapy, fluid replacement, and renal replacement therapy remains mainstay of treatment. Loop diuretics can convert an oliguric renal failure to non-oliguric renal failure. In spite of adequate urine volume, diuretics do not usually affect outcome of the disease and serum creatinine may continue to rise. However, conversion of oliguric to non-oliguric renal failure reduces the risk of volume overload. There is little evidence on beneficial effect of vasoactive drugs. Nephrotoxic drugs such as ACE inhibitors, NSAIDs, aminoglycosides, cephalosporins should be avoided. Currently, high quality intensive care, early institution of renal replacement therapy, and avoidance of nephrotoxic drugs are standard practices of the prevention and management of ARF.

In spite of several research publications, mechanism of malarial ARF and its effective management has remained unclear. In addition, the literature is almost silent on the mechanism of recent increase in incidence of ARF and a shift towards multiple complications specifically in India. Though development of chloroquine resistance has been suggested as possible mechanism in a few publications, it has not been substantiated by hard data. Other possible important contributors could be rampant and indiscriminate use of antibiotics and NSAID, indiscriminate use of antimalarials for every fever, inadequate dosage of antimalarials, use of spurious antimalarials, and other parasite and host factors that have not been looked into. While answer for these questions should be looked into, of immediate concern is to understand antimalarial drug metabolism and pharmacokinetics in malaria patients with multiple complications, specifically those having both liver and kidney impairment. Majority of antimalarial drugs are metabolized in liver and excreted through kidneys. What happen to their metabolism and excretion when both the organs are involved needs to be clearly understood for effective management and prevention of adverse drug reactions.

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Correspondence: Dr B.S. Das, M.D., Emeritus Medical Scientist, Institute of Life Sciences, Nalco Square, Chandrasekharpur, Bhubaneswar–756 023, India.
E-mail: bhabanisankar@gmail.com