Malaria and Acute Kidney Injury

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Summary: Malaria is a major public health problem in tropical countries. About 500 million people suffer from malaria, leading to death in 1 to 3 million cases. Acute kidney injury (AKI) is one of the most dreaded complications of severe malaria. As per World Health Organization criteria, acute renal failure (serum creatinine level, ≥3 mg/dL or ≥265 μmol/L) occurs as a complication of *Plasmodium falciparum* malaria in less than 1% of cases, but the mortality rate in these cases may be up to 45%. It is more common in adults than children. Renal involvement varies from mild proteinuria to severe azotemia associated with metabolic acidosis. It may be oliguric or nonoliguric. AKI may be present as a component of multi-organ dysfunction or as a lone complication. The prognosis in the latter is generally better. Several pathogenic mechanisms interplay for the clinical manifestation. The predominant lesions are acute tubular necrosis and mild proliferative glomerulonephropathy. These patients do not progress to chronic kidney disease. The management of malaria-induced AKI includes appropriate antimalarials (parenteral artesunate or quinine), fluid electrolyte management, and renal replacement therapy at the earliest. The use of diuretics should be avoided.
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Approximately 40% of the world's population lives in regions where malaria transmission is endemic, mainly tropical and subtropical regions. About 300 to 400 million clinical cases of malaria are reported annually,[1] and mortality estimates range between 0.7 and 2.7 million. Most of these deaths are in young children. In sub-Saharan Africa, where malaria mortality is highest, 90% of reported malaria-related deaths are children younger than the age of 5. However, the actual figures of illness, morbidity, and mortality may be very different from those cited because of poor surveillance, misdiagnosis, and underreporting of malarial deaths for various reasons. Malarial deaths occur mostly at home and rarely are reported.[2] Unfortunately, the disease burden is on the rise. By using a combination of epidemiologic, geographic, and demographic data, Snow et al[3] estimated that there were 515 (range, 300-600) million episodes of clinical *Plasmodium falciparum* malaria in 2002. These global estimates were up to 50% higher than those reported by the World Health Organization and 200% higher for areas outside Africa.

Malaria is caused by 4 species of the genus *Plasmodium*, namely *Plasmodium vivax, P falciparum, Plasmodium malariae*, and *Plasmodium ovale*. Malaria parasites (sporozoites) enter the circulation and subsequently the liver after being bitten by an infective mosquito. In the liver sporozoites invade hepatocytes, multiply, and produce merozoites that are capable of invading the red blood cells. The hepatic cycle usually lasts for about a week. Merozoites released from hepatocytes enter the blood stream and within a very short period invade the erythrocytes. Within the infected erythrocytes, merozoites consume host cell proteins, specifically hemoglobin for their growth and multiplication. The parasite grows through ring, trophozoite, schizont, and merozoite stages. Eventually the infected erythrocyte ruptures, releasing an asexual form of merozoites, which invades fresh erythrocytes and the cycle is repeated. For appearance of clinical manifesta-

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tions at least 3 to 4 such cycles are necessary to reach a critical level of parasitemia. A small proportion of parasites grow to sexual forms (gametocytes). Circulating gametocytes are taken up by the mosquitoes during their blood meal. In the mosquito gut, gametocytes differentiate into male gametocytes (microgametocytes) and female gametocytes (macrogametocytes). Microgametes and macrogametes fuse to form a zygote. Developing zygotes transform into spindle-shaped ookinetes, cross the inner wall of the abdomen, and, finally, transform into sporozoites. Thousands of sporozoites lodge in the salivary glands, ready to be injected into human beings through the bite of a female anopheles mosquito.

Common clinical characteristics of *Plasmodia* infection of all 4 species are periodic paroxysm, chills, rigors, sweating, body aches, headache, nausea, general weakness, and prostration. Chronic anemia and splenomegaly are observed in a majority of malaria patients residing in high malaria transmission areas. Severe life-threatening complications such as severe anemia, cerebral malaria (CM), acute kidney injury (AKI), acidosis, jaundice, respiratory distress, acute respiratory distress syndrome, and so forth occur only with *P falciparum* infection. However, recently a few reports have appeared indicating association of severe complications of malaria with *P vivax* infection as well,[4–6] including AKI.[7,8]

EPIDEMIOLOGY

The contribution of malaria to the overall hospital admissions for AKI varies from 2% to 39%[9–11] in different populations. The wide variation is because of its dependence on the age and antimalarial immunity, which in turn are influenced by malaria transmission intensity. Malarial AKI (MAKI) is considered a disease predominantly of adults and older children,[11–13] specifically in nonimmune adults from areas of low intensity of malaria transmission. Thus, a large number of reports on MAKI have appeared from southeast Asia and the Indian subcontinent where malaria transmission generally is low, with occasional microfoci of intense transmission. The occurrence of AKI in patients from endemic areas with severe malaria is less than 1% to 4.8%, whereas in nonimmune Europeans it is 25% to 30%. The incidence of AKI in severe *P falciparum* malaria is as common as cerebral malaria in nonimmune European adults.[14] AKI was a frequent accompaniment in patients with severe falciparum malaria reported from Austria and The Netherlands.[15,16] Almost all patients with fatal cases had AKI and reported a history of recent travel to malaria-endemic areas.

Only a few reports of MAKI are available from Africa, particularly from areas with intense malaria transmission, where malaria affects mostly young children. In contrast to severe malaria in adults, none of the 180 Gambian children with severe malaria had AKI.[17] However, malaria transmission intensity is not uniform in Africa and a higher incidence of AKI with associated morbidity and mortality has been reported in semi-immune African children.[18] An earlier study from Ghana found massive intravascular hemolysis; and black water fever was the most common cause of AKI. However, only 1 patient had *P falciparum* malaria whereas 26 patients had various bacterial and viral infections.[19] One third of severe malaria patients admitted to a University Hospital in Ethiopia had AKI, but the majority of these patients were nonimmune visitors coming to malaria-endemic regions.[20] Another study from the Renal Unit of Tikur Anbessa Hospital in Addis Ababa found 29 (21%) of 136 consecutively treated adult AKI patients had falciparum malaria. The contribution of malaria to AKI was only second to septic abortion, and mortality rates in MAKI were as high as 37.9%.[21] In a recent prospective study from 1994 to 2003 in Nigerian children, 123 cases of AKI caused by *P falciparum* malaria were detected (mean age, 6.28 ± 4.0 y).[22] The occurrence of AKI in severe falciparum malaria is quite common in southeast Asia, including India. A significant increase in the incidence of AKI has been reported from several centers across India. In 1982 a study from Orissa indicated cerebral malaria as the predominant presentation of severe malaria. Associated complications of 173 cases of cerebral malaria were AKI (6%) and hepatic failure (1%).[23] Twenty years later, another study from the same area and the same

hospital showed 35% of cases with severe *P falciparum* malaria had AKI. There was a consistent increase in incidence of AKI (from 95 cases in 1994 to 215 cases in 1998).[24] A high incidence of AKI in falciparum malaria has been reported from eastern,[25–27] western,[28] northern,[29] southern,[30] and central India.[31,32] The majority of the studies had a common inference that the incidence of AKI and jaundice is increasing, and the development of multiple complications result in increased mortality.[33] Studies from Pakistan also reported MAKI contributing significantly to the total AKI burden.[34] A high incidence of AKI in severe *P falciparum* malaria was observed from southeast Asian countries. Hypercatabolic AKI was noted in Malaysia in patients with cerebral malaria with heavy parasitemia and hyperbilirubinemia.[35] AKI constituted 23.3% of severe malaria patients hospitalized in Kampuchea. Coma and multi-organ failure were the most common causes of death.[36] A high incidence of MAKI also has been reported from Singapore,[37] Vietnam,[38] and Thailand.[39]

PATHOPHYSIOLOGY

The pathogenesis of AKI in falciparum malaria is not clearly known. Malarial complications possibly are caused by the interaction of the parasite with the host, resulting in mechanical, immunologic, and humoral responses. These responses, while attempting to eliminate the parasites, may also injure the host tissues. Different hypotheses proposed for MAKI include mechanical obstruction by infected erythrocytes, exaggerated host immune response mediated through cytokines and reactive oxygen and nitrogen species, immune complex deposition, hypovolemia, disturbances in the renal microcirculation, and so forth. No explanation, however, is available for the consistent increase in the incidence of MAKI in some areas.

Cytoadherence

The pathogenesis of severe *P falciparum* malaria is attributed in part to the cytoadherence of parasitized red blood cells (PRBCs) to the vascular endothelial cells in different host organs.[40–42] Parasite proteins referred to as *variant surface antigens* expressed on the PRBC surface mediate the adhesion of infected erythrocytes to host vascular endothelial receptors.[43,44] PRBCs preferentially sequester in the deep vascular beds of vital organs, including the brain, liver, lung, spleen, intestine, and kidney.[41,45] Sequestration of PRBCs in glomerular and tubulointerstitial capillaries has been shown, although at a lesser degree than the cerebral vessels.[45] Studies on southeast Asian adults dying from severe falciparum malaria indicated that the frequency of PRBC sequestration in renal vessels of patients dying from AKI were significantly higher than those without AKI. Significantly more PRBCs were seen in vessels in malarial AKI patients than in non-AKI patients. However, the ultrastructural examination of renal microvascular sequestration showed much less PRBC sequestration than of brain tissue of the same patients. The majority of patients showed mononuclear cells in glomerular and peritubular capillaries, although the number of leukocytes was not significantly different between the AKI group and the non-AKI group.[46,47] Margination of mononuclear cells to the brain capillary endothelium was shown earlier in a significant proportion of patients.[48] Thus, contribution of PRBC cytoadherence and clogging of the capillaries toward pathogenesis of MAKI appears at best only marginal.

Cytokines, Reactive Oxygen Species, and Nitrogen Species

Literature on the influence of cytokine concentrations on renal pathology in malaria is scanty although cytokines, reactive oxygen intermediates, and nitrogen intermediates (ROI and NO) play an important role in both protection against malaria and pathogenesis of severe malaria. Levels of inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interferon-γ, and interleukins 1-α, -6, and -8 are increased in malaria.[49] Higher blood concentrations of proinflammatory cytokines have been observed in severe complications of malaria.[50–53] Anti–TNF-α and anti–interferon-γ antibodies are reported to abolish the onset of cerebral malaria.[54] However, in contrast to observations in the murine model, monoclonal antibodies to

TNF-α ameliorate fever but not the manifestations of human cerebral malaria.[55]

Increased production of ROI and NO have been reported in malaria infection. The involvement of ROI and NO in the protection and pathogenesis of malaria has been studied extensively. An early increase in NO stimulates the helper T-cell-1 (Th_1) response to control parasitemia similar to natural immunization during malaria infection,[56] whereas a late increase in NO production in the liver and spleen appear to have pathologic consequences.[57] During the blood stage of malaria TNF-α up-regulates NO synthesis either alone or in combination with other cytokines.[58] Regulatory functions of NO are dependent on the presence of various isoforms of the enzyme nitric oxide synthase (NOS). Physiologic function of NO is regulated by low basal concentrations synthesized by constitutive NOS isoforms. A high concentration of NO usually is produced by inducible NOS isoforms (iNOS), which play a crucial role in pathologic consequences. Increased iNOS activity and production of NO have been observed in severe malaria.[57] Lipopolysaccharide is reported to be a potent stimulator of iNOS messenger RNA.[59] Similarly, ROI also plays a significant role in the protection and pathogenesis of malaria.[60,61] Higher blood concentrations of ROI and a depleted antioxidant defense system have been observed in patients with malaria.[62–64]

Sepsis Model for MAKI

Extensive parallels exist between sepsis and severe malaria in the clinical presentation and cytokine profile, indicating that the 2 diseases operate through very similar mechanisms.[65] Shock and multi-organ failure, a common association in sepsis, frequently are observed in MAKI as well[66] (Mishra et al, unpublished data). Contrary to the common belief that respiratory distress complicating severe malarial anemia is a consequence of biventricular failure, observations from the clinical picture in African children indicate characteristic features of hypovolemia[67] and the administration of albumin for volume expansion reduces mortality rates.[68] Plasma concentrations of several small- and middle-molecular-weight proteins are reduced in severe malaria because of extravasations from the vascular compartment to the interstitial space.[69,70] Arterial vasodilatation that accompanies sepsis is mediated, at least in part, by cytokines that up-regulate the expression of iNOS in vasculature.[71] NO thus released has a potent vasodilatory effect.[72] However, several other studies did not notice severe volume depletion or hypotension in severe malaria.[73,74]

Restricted local blood flow in the kidneys is considered a major contributor for MAKI. A similar pathology is observed in AKI of sepsis. Generalized vasodilatation with an associated decrease in systemic vascular resistance is the most important hemodynamic abnormality observed in sepsis. Vasodilatation leads to activation of the sympathetic nervous system, renin-angiotensin-aldosterone axis, and release of vasopressin for maintaining the decreasing blood pressure. Unfortunately, these compensatory mechanisms predispose to AKI.[75,76] Simultaneously, the vasoconstriction effects of norepinephrine and angiotensin II are dependent on open calcium channels, which are not available when associated with increased hydrogen ion and lactic acid concentrations. Increased plasma concentrations of lactate and hydrogen ions, and a decrease in adenosine triphosphate (ATP) generation in vascular smooth muscle cells, activate the ATP-sensitive potassium channels,[77,78] resulting in potassium efflux and closure of the voltage gated calcium channels in the membrane. Therefore, vascular resistance to these pressor hormones occurs in conditions of lactic acidosis. Hypoxia in severe falciparum malaria is brought about possibly by a combination of volume depletion, hypotension, pulmonary edema, and clogging of the capillaries by cytoadhered PRBCs and mononuclear cells, resulting in lactic acidosis. Cytopathic hypoxia caused by inflammation-induced mitochondrial dysfunction is now considered a major contributor to the pathogenesis of sepsis.[79] Proinflammatory cytokines, higher concentrations of which are present in both sepsis and malaria,[51,52] are considered responsible for mitochondrial shutdown, leading to reduced ATP synthesis and increased lactate accumulation. Hyperlactatemia is considered a marker

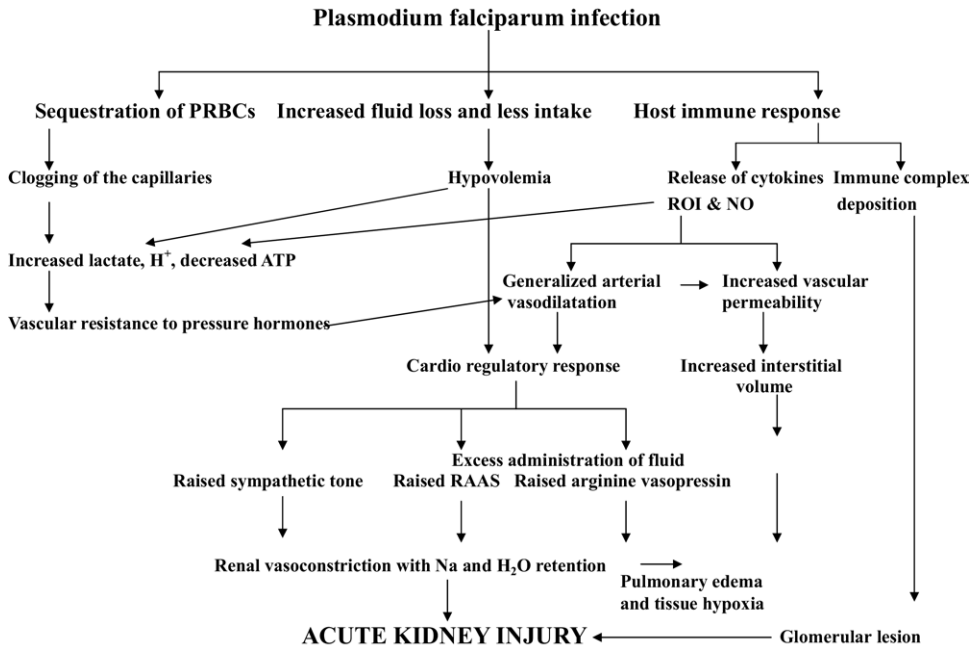

Figure 1. Pathogenesis of AKI in malaria.

for poor prognosis in sepsis,[80] as well as in malaria.[81,82]

MAKI can occur as an isolated complication or as a component of multi-organ involvement. A 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, and cytoadherence of PRBCs all may contribute singly or in combination toward MAKI (Fig. 1). Increased fluid administration, oxygen toxicity, and as yet unidentified factors may contribute to pulmonary edema, acute respiratory distress syndrome, multi-organ failure, and death.

Histology

The histopathology of MAKI is a combination of various pathogenetic mechanisms such as acute tubular necrosis, interstitial nephritis, and glomerulonephritis. However, tubular changes are the most common and consistent findings.[11,12,83] Tubular changes include cell necrosis, tubular swelling, and deposits of hemosiderin granules. The tubular lumens often contain hemoglobin casts. Acute interstitial inflammation is associated commonly with acute glomerulosclerosis. In glomerulonephritis, the glomeruli are swollen with expansion of the mesangial area and proliferation of mesangial cells. Periodic acid-Schiff staining reveals widening of the mesangial stalk and irregular thickening of the glomerular basement membrane (Fig. 2).

In a recent report on an ultrastructural study of renal pathology in fatal falciparum malaria, there was sequestration of PRBCs in glomerular and tubulointerstitial vessels, and acute tubular damage. However, there was no evidence of immunomediated glomerulonephritis. There

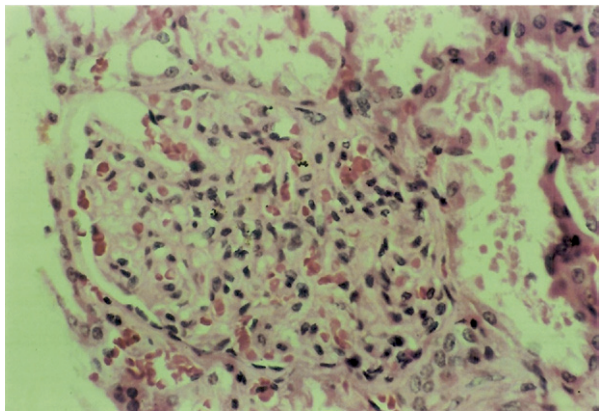

Figure 2. Kidney biopsy from an Indian adult male who died from cerebral malaria with acute renal failure.

was mild glomerular hypercellularity with host monocytes in the glomerular capillaries.[47]

CLINICAL PRESENTATION

Malaria-related AKI invariably is caused by falciparum malaria. It is defined as an abrupt (within 48 hours) reduction in kidney function that may be characterized by the following: (1) an absolute increase in serum creatinine level of 0.3 mg/dL or more (≥26.4 μmol/L), (2) a percentage increase in serum creatinine level of 50% or more (1.5-fold from baseline), or (3) a reduction in urine output (documented oliguria of <0.5 mL/kg/h for >6 hours). However, to categorize a patient as having severe malaria on the basis of renal function as per World Health Organization criteria,[11] the serum creatinine level has to be 3 mg/dL or more (≥265 μmol/L). It is common in adults, and rare in children.[11–13] In a study from Orissa consisting of 1,857 patients, although both children and adults were vulnerable for severe malaria, almost all the MAKI cases were observed in adult patients.[26] It is encountered more often in male patients than in female patients.[26,34]

The incidence ranges from 0.5% to 15% in different series because it depends on the cohort of patients and the criteria used for the definition of MAKI. Malaria may be a major cause of renal failure in a hospital, although it may be encountered occasionally in another hospital. In a study of 500 adults in Vietnam, 30% of the patients had MAKI, with a higher incidence of jaundice and hypoglycemia,[11] whereas the incidence was 4% in a series from Orissa (India).[26]

A history of recent travel to malaria-endemic areas must always be sought. Although some of the complications can be identified easily on clinical examination, recognition of renal failure needs a high index of suspicion and early biochemical investigations.

MAKI may present in 2 different ways: (1) as a component of multi-organ dysfunction, and (2) as AKI alone.

When MAKI is a part of multi-organ failure, it often is present at the time of presentation and invariably carries a poor prognosis. It has been reported that about a third of patients with cerebral malaria have renal impairment (serum creatinine level, >2 mg/dL).[15] These patients have a higher incidence of anemia, jaundice, hypoglycemia, and prolonged coma. Acidosis appears early and may be associated with clouding of sensorium, convulsions, and coma.

In the other subset, renal impairment occurs as a sole complication. This group of patients has a better prognosis. It invariably occurs when other complications have subsided, and the patient is fully conscious, oriented, and often afebrile. These patients develop oliguria, encephalopathy, hyperkalemia, and signs of acidosis. It has to be noted that this group of patients is encountered at a time when the parasites are no longer present in the peripheral blood, making it difficult to establish the diagnosis of malaria. A high index of suspicion and the use of a dipstick method for detecting *P falciparum* (eg, rapid diagnostic kits, immuno-chromatographic test [ICT], and so forth) or other alternative diagnostic tools are of paramount importance.

Urine output usually is decreased (<400 mL/d).[11] Although Prakash et al[32] observed oliguria in 70% of patients in India, Manan et al[34] observed it in 76% of patients from Pakistan. Oliguria usually persists for 3 to 10 days. However, urine output may be normal or increased in a few patients. Hence, oliguria alone should not be relied on for a diagnosis of AKI in malaria. A daily estimation of biochemical tests such as blood urea nitrogen and creatinine levels must be performed.

The complications usually appear 3 to 7 days after onset of the fever, and may last for a few days to several weeks. Patients with peripheral parasitemia should be screened regularly for the presence of renal failure. In a clinical setting with a high index of suspicion of malaria, patients even without peripheral parasitemia or oliguria should be screened for renal impairment.

Of 402 detected smear-positive malaria cases in a hospital from Mumbai, Western India, 24 had malarial AKI. Eighteen were age 21 to 40 years. *P falciparum* was detected in 16, *P vivax* in 3, and mixed infection in 5. Nonoliguric AKI was seen in 14 patients (58%).[28]

Dehydration, volume depletion, hypotension, and shock also are encountered. Volume

depletion was detected in more than half of the patients and hypotension was detected in a third of the patients.[32] Hypotension occurs as a result of several factors: low intake of fluids, loss of fluids because of vomiting and pyrexial sweating, arterial vasodilatation, and the effect of cytokines. Peripheral blood pooling has been implicated in a number of cases. The effective arterial blood volume is reduced, and hypotension occurs on presentation. Few patients may present with shock syndrome (Mishra et al, unpublished data). These patients need urgent attention for fluid replenishment including vasopressin (vide supra).

Associated Complications

Cerebral malaria

Cerebral malaria often is associated with AKI, but frank renal failure occurs in about 30%. In a series from Thailand, 30% of adult patients with CM had associated AKI (serum creatinine level, >2 mg/dL [2 mg%]). These patients had a higher incidence of jaundice, hypoglycemia, and pulmonary edema.[84] A large series from India reported the incidence as 29% among cerebral malaria patients versus 4% among non-cerebral malaria patients.[85] An important predictor in the survival of patients with cerebral malaria is the presence of MAKI. The presence of AKI in CM makes the prognosis worse.[86]

Jaundice

Jaundice is an invariable accompaniment in MAKI. It occurs in more than half of patients with renal failure.[11,87] Conversely, renal impairment is observed in 10% of patients with hyperbilirubinemia. The hyperbilirubinemia predominantly is unconjugated in nature owing to hemolysis.[11,27] However, a few reports described the presence of malaria hepatitis with MAKI. It is important to be aware of the simultaneous presence of renal and hepatic dysfunction in certain situations, namely, leptospirosis, dengue, hepatorenal syndrome, and so forth.

Anemia

Although anemia (hemoglobin level <10 g/dL) is associated in about 60% of patients with malarial renal failure, severe anemia (hemoglobin level, <5 g/dL) is reported in 10% to 20% of cases. Thrombocytopenia occurs in 70% of patients, half of whom develop an overt bleeding tendency. In the majority of patients, this is part of a disseminated intravascular coagulation initiated by the gross rheologic abnormality in severe malaria.

Proteinuria usually is insignificant, but it may be as high as 1 g/24 h in about a third of patients with MAKI. It usually resolves completely with recovery from renal impairment. However, persistent proteinuria may be encountered in the presence of significant interstitial or glomerular involvement.[10,12]

Electrolyte abnormality

An electrolyte imbalance occurs invariably in all patients. Hyponatremia is reported in 25% to 60% of patients.[12,32,34] The mechanisms include hemodilution and sodium wasting before the onset of oliguria. However, an increase of serum antidiuretic hormone is unlikely to play a major role.[10,12] Hyperkalemia is the most important electrolytic parameter for renal replacement therapy. However, the incidence is as low as 4%.[34] But unless it is identified and promptly managed it may be fatal. Hyperkalemia also may result from hemolysis and rhabdomyolysis. Hypokalemia also has been encountered. Electrocardiographic recordings are often helpful.

The serum calcium level often is reduced out of proportion to phosphate retention, which may be owing to hypoparathyroidism of unknown cause.[88] Lactic acidosis has been documented and is a life-threatening condition, often among children. As described before, hypoxia in severe malaria is multifactorial: a combination of volume depletion, hypotension, pulmonary edema, and clogging of the capillaries by cytoadhered PRBCs and mononuclear cells, resulting in lactic acidosis. High blood or cerebrospinal fluid lactate levels are predictors of poor outcome.[81,82]

The vulnerable groups to develop M AKI are the following patients: pregnant, with high parasitemia, deeply jaundiced, with prolonged dehydration, and those receiving nonsteroidal anti-inflammatory drugs.

The critical determinants for MAKI are as follows: hypovolemia and hypervolemia, hyper-

parasitemia, hemoconcentration, hyperbilirubinemia, and hyperpyrexia.

PROGNOSIS

Renal failure associated with malaria resolves in days to weeks, and almost always completely. It does not progress into chronic kidney disease. It is not associated with hypertension. The overall mortality rate among those with renal failure ranges from 15% to 50% in different series.[11,20,34,89–93] Similarly, the simultaneous presence of MAKI in cerebral malaria is associated with a poor prognosis.[86] In a study of 110 patients with cerebral malaria from India, 38 had evidence of AKI. Associated complications as well as mortality rates were significantly higher in the presence of AKI. The mortality rate of patients with cerebral malaria increased from 14% to 40% in the presence of AKI. For each 1 log unit increase of serum creatinine at admission, the odds of death increased by a factor of 10.8 (95% confidence interval, 3.0-39.4).[86]

The survival rate with peritoneal dialysis was lower than that of hemodialysis or hemofiltration.[94] At Rourkela, the mortality rate decreased significantly when hemodialysis was initiated early. It is pertinent to mention that AKI in malaria needs urgent recognition and management. Multiple complications need urgent management in a tertiary care hospital with a multidisciplinary approach.[89]

Several risk factors had been proposed to be responsible for the high mortality rate: late referral, short acute illness, high parasitemia, oliguria, hypotension, severe anemia, or significant jaundice. Patients with severe diarrhea, multisystem involvement, hepatitis, or acute respiratory distress also have a poor prognosis. Co-existing viral or bacterial infections may be encountered in patients with MAKI, increasing the risk of mortality. The presence of multiorgan failures results in a poor prognosis. A simple bedside survival scoring system has been devised that gives relative weighted importance to each complication.[95]

TREATMENT

The management of MAKI needs careful and meticulous management of several problems. Early and prompt decisions and institutions are the hallmark of a better prognosis.

The outlines of treatment guidelines include the following: (1) institution of appropriate antimalarials, (2) maintenance of fluid and electrolyte levels, (3) renal replacement therapy as indicated, (4) treatment of associated complications, and (5) management of infection including pneumonia.

Drugs to be avoided in malaria patients because they may impair renal function are as follows: nephrotoxic drugs such as aminoglycosides should be avoided if AKI is suspected or anticipated, nonsteroidal anti-inflammatory drugs should not be given because they may precipitate prerenal azotemia to ischemic AKI, and angiotensin-converting enzyme inhibitors and cyclooxygenase inhibitors.

Antimalaria Drugs

The preferred antimalarial is artesunate or quinine given parenterally. Intravenous quinine has remained as the time-tested first-line drug. The dose is 10 mg/kg/body weight. If quinine has not been given in the previous 7 days, a loading dose may be given. But it is very difficult to get a definite history, hence it is advisable to start a maintenance dose of 10 mg/kg of body weight every 8 hours. The dose for the initial 48 hours should never be modified, even in the presence of AKI. If quinine needs to be administered only through a parenteral route beyond 48 hours, the dose of quinine must be reduced to two thirds. Oral therapy should be started as soon as the patient is able to accept it orally. The total duration of therapy is 7 days. The common side effects include dizziness, cinchonism, and hypoglycemia.[11,96,97] Careful attention needs to be given to the rate of infusion, cardiac monitoring, and prevention of fluid overload. Prolonged QT interval, atrial or ventricular ectopic beats, heart block and hypotension may be anticipated in patients treated with quinine. Quinine is metabolized and 80% is excreted through the liver and 20% through the kidneys. However, estimation of blood level is not readily available in most centers and careful clinical assessment at frequent intervals is mandatory.[11]

The introduction of artemisinin derivatives has improved the survival rates of patients with

severe malaria.[98-100] These drugs clear parasitemia rapidly and are practically devoid of side effects.[98,101] In addition, no dosage modification is needed in the presence of renal or hepatic dysfunction. The preferred molecule is artesunate because it can be given intravenously. Intravenous artesunate is given at a dose of 2 mg/kg/body weight at 0, 12, and 24 hours, and then once daily for a total of 7 days.

The use of other drugs, namely chloroquine or sulfadoxine pyrimethamine, should be avoided owing to widespread resistance from areas where CM and AKI are common. Similarly, there are scant data to recommend the use of mefloquine or halofantrine. These oral drugs should not be used in patients with severe malaria.

Fluid and electrolyte therapy are of utmost importance: 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 but most important factor is overlooked at small, busy, and overcrowded hospitals. It often is left to the uninformed attendants/relatives of the patient, thus getting erroneous information. To prevent fluid overload a central venous pressure (CVP) line can be established.

The identification and treatment of co-existing or acquired infection should be managed at the earliest.

Fluid Challenge

Many patients with oligura are dehydrated. They should receive fluid, up to 20 mL/kg of 0.9% saline infused over 60 minutes. To prevent fluid overload, auscultation of the lungs and jugular venous pressure 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.[11]

Diuretic Challenge

The loop diuretic (frusemide 40 mg or bumetanide 1 mg) is given initially. If urination does not occur, further diuretic challenge can be tried at every 30-minute intervals with incremental doses (frusemide 100, 200, and 400 mg or bumetanide 2, 4, and 6 mg). If there is still no urine flow, dopamine 2.5 to 5 μg/kg/min may be tried. However, the use of diuretics in MAKI has not improved the outcome. Rather, it appears to be ineffective in oliguric patients. In a small number of patients it may increase the urine output, but no improvement occurs in the renal status. Rather, it may give a sense of complacency. A systematic review and meta-analysis was conducted to evaluate loop diuretics in the management of AKI in 555 patients from 5 randomized controlled trials. There was no statistical difference in the mortality rates (odds ratio, 1.28; 95% confidence interval, 0.89-1.84; $P = .18$) or renal recovery (odds ratio, 0.88; 95% confidence interval, 0.59-1.31; $P = .5$) with the use of loop diuretics compared with controls.[102] However, the use of loop diuretics may result in a shorter duration of renal replacement therapy and a shorter time for the decline in serum creatinine level. It causes an increase in urine output. There was, however, insufficient data on acid-base status, length of hospital stay, and treatment costs. Four studies reported toxicity, most commonly transient tinnitus and deafness. It was suggested that loop diuretics were not associated with improved survival.[102]

In a prospective, randomized, double-blind, placebo-controlled, multicenter trial, 338 patients with AKI requiring dialysis therapy were administered either furosemide (25 mg/kg/d intravenously or 35 mg/kg/d orally) or matched placebo. The end points were survival, number of dialysis sessions, and time to achieve a serum creatinine level of less than 200 μmol/L and dieresis (urine, >2 L/d). It was observed that there were no differences in survival and renal recovery rates between the 2 groups. The time to achieve a 2-L/d diuresis was shorter with furosemide (5.7 $\pm$ 5.8 d) than placebo (7.8 $\pm$ 6.8 d; $P = .004$). Overall, 148 patients achieved a urine output of at least 2 L/d during the study period (94 of 166 patients; 57%) with furosemide versus 54 of 164 patients (33%) with placebo ($P < .001$). However, there were no significant differences in the number of dialysis sessions and the time on dialysis therapy be-

tween the furosemide and placebo groups. So it was reported that high-dose furosemide maintains urinary output, but does not influence survival or renal recovery rates of patients with established renal impairment.[103]

Dopamine Challenge

The use of dopamine for the prevention and treatment of AKI has not yet been established. Its use is based on the understanding that selective renal vasodilatation will occur when it is infused at a low dose. A recent article compared the effects of dopamine and epinephrine in various doses on renal hemodynamic and oxygen transport in patients with severe malaria and severe sepsis. In a prospective, controlled, cross-over 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 (RBF) index of 37% (13% to 61%) and in RBF as a fraction of cardiac output of 35% (10%-59%; $P = .007$ and $P = .014$, respectively). At higher doses (10 μg/kg/min), both RBF and RBF/cardiac output 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.[104]

Vasopressin Therapy

As discussed in the pathogenesis, there appears to be a future role for the use of vasopressin in the management of malarial shock as well as MAKI. However, sufficient data need to be collected before this agent is accepted to improve the survival.

Albumin Infusion

The administration of albumin for volume expansion reduces mortality rates.[68] Exchange transfusion is of use in patients with severe hemolysis. However, in the presence of severe jaundice and renal failure, no data are available to recommend its use.

Dialysis

Dialysis has improved the survival rates of patients when instituted early in the course of treatment. It can be intermittent hemodialysis (daily or alternate day), continuous venovenous hemofiltration, or continuous arteriovenous hemofiltration. The latter methods cause less hemodynamic instability than conventional hemodialysis. Peritoneal dialysis is less effective in controlling biochemical abnormalities.

Indications for dialysis include the following: (1) clinical indications: uremic symptoms, symptomatic volume overload (eg, pulmonary edema, congestive heart failure), and pericardial rub; (2) laboratory indications: severe metabolic acidosis ($HCO3 < 15$ mEq/L) and hyperkalemia ($K+ > 6.5$ mEq/L).

The clearance of urea and other molecular waste products is much faster with hemodialysis as compared with peritoneal dialysis. However, peritoneal dialysis has certain advantages such as: peritoneal dialysis does not need a special set-up, it can be started immediately, and it may prove to be life-saving. Thus, in the absence of facilities for hemodialysis whenever indicated, peritoneal dialysis should be started as early as possible. Conservative treatment in patients with AKI with severe malaria needs careful monitoring. A patient may develop signs as mentioned earlier and at any odd hours without giving a scope for initiation of dialysis. Many lives have been lost as dialysis was decided but institution was delayed. Sudden cardiac death may ensue in a patient who is improving owing to the development of pulmonary edema or hyperkalemia.

Adequacy of Dialysis

Dialysis is considered adequate when the postdialysis creatinine and urea levels decrease to 50% or less of the predialysis values.

Antimalarial Drugs During Dialysis

Significant changes in plasma quinine concentrations do not occur in patients with AKI during hemodialysis. Quinine was not detectable in hemodialysate fluids. This suggests that dosage adjustment of quinine during hemodialysis is unnecessary. There are no data as yet available

for the artemisinin drugs for modification during dialysis.

Management of the Diuretic Phase

The diuretic phase may return gradually or in a few hours. Careful attention needs to be given toward fluid and electrolyte requirements. In addition, repeated estimation of Na, K, and bicarbonate is essential.

Nutrition

One must not overlook the nutrition aspect of patients with AKI. Attempts should be made to suppress endogenous protein catabolism by providing fat and carbohydrates.

In patients without dialysis, protein restriction is advised, whereas those undergoing daily hemodialysis may require additional proteins.

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