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Severe Malaria

Manifestations, diagnosis, chemotherapy, and management of severe malaria in adults

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INTRODUCTION

The burden of malaria is increasing, especially in sub-Saharan Africa, because of drug and insecticide resistance and social and environmental changes (1). Each year an estimated three to four hundred million people will contract malaria globally, resulting in five hundred thousand to two million deaths. Ninety percent of the world's malaria, and at least 90% of malaria-related mortality, occurs in Sub-Saharan Africa, primarily in young children (2). Malaria occurs in every country in sub-Saharan Africa, with the exception of Lesotho, but transmission rates vary within regions and within countries. In parts of Africa where endemicity of malaria is high and transmission stable, such as Tanzania, Malawi, and Mozambique, severe malaria is mainly a disease of children under 5 years of age and of pregnant women. It is less common in older children and adults because of the partial immunity acquired as a result of repeated infections. In areas of low endemicity severe malaria occurs in both adults and children. Non-immune travellers to malaria areas are always at risk for severe disease (3,4).

The majority of malaria cases in Africa are due to *Plasmodium falciparum*, the major species associated with mortality and morbidity. The development of parasite resistance to chemotherapeutic agents such as chloroquine has resulted in a significant increase in malaria morbidity and mortality. The demise of chloroquine, an affordable option in resource-poor countries, has major implications for malaria management (5). In Africa resources for management of severe malaria are limited and at least 20-30% of patients with complications of disease will die. In a confidential inquiry into malaria deaths in an area of South Africa with

limited tertiary care facilities, major contributing factors were delays in diagnosis and initiation of adequate therapy, failure to administer the correct antimalarial at the correct dosage and frequency, inadequate monitoring of severity indicators in complicated cases, and the sub-optimal management of complications (6).

PATHOGENESIS OF SEVERE MALARIA

Key features of malaria are the adherence of infected red blood cells to the endothelium of small blood vessels compromising blood flow through tissues, and the production of pro-inflammatory cytokines (7). Factors that determine whether a patient develops mild or severe disease are complex and multifactorial and are related to both the parasite and the host. Parasites causing severe malaria have a greater multiplication potential than those causing uncomplicated infections (8). The effect of inoculum dose on severity is unclear and difficult to investigate. Cyto-adherence of parasitised red cells may be influenced by the virulence of different strains of parasite (9).

The development of immunity to the clinical effects of malaria requires several years of continuous exposure. Lack of this protective immunity would be expected to be the major factor determining the severity of a clinical attack of malaria. Differences in HLA antigens may play a role in host predisposition to severe disease. Certain red blood cell abnormalities, including sickle-cell trait, protect against malaria disease. Prevalence rates of these abnormalities are high in some parts of Africa and may provide some protection against severe malaria (9). Plasma interleukin (IL-6, IL-10) and tumour necrosis factor- α and the IL-6 : IL-10 ratio is significantly higher in patients who die than in survivors (10).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms and signs of malaria may present as early as seven days, but more commonly an average of 10-21 days after being bitten by an infected mosquito. Fever is prominent, but may be absent in some cases. Some of the following symptoms may also appear: rigors, headache, myalgia, diarrhoea, vomiting and cough. Physical signs may include fever, anaemia, jaundice, hepatosplenomegaly and a variety of cerebral signs. Malaria should be suspected in any person presenting with any of the

above symptoms or signs with a history of travel to, or residence in a malaria transmission area. Presentation is very variable and may mimic other diseases, including influenza, hepatitis, meningitis, septicaemia, typhoid, tickbite fever, viral haemorrhagic fever, trypanosomiasis, HIV seroconversion illness, and relapsing fever (4).

P. falciparum infections may progress rapidly to a lethal, multi-system disease. The diagnosis of malaria is urgent, and complications can develop rapidly within 48 hours of the onset of disease in any non-immune person but especially in young children and pregnant women (4). The clinical manifestations of severe malaria depend on the age of the patient. In children, hypoglycaemia, convulsions, and severe anaemia are relatively common; acute renal failure, jaundice, and ARDS are more common in adults. Cerebral malaria, shock and acidosis may occur at any age (11). A number of clinical and laboratory criteria are used to define severe malaria, as shown in Table 1 (4,11).

Table 1: Indicators of severe malaria

<p>Clinical Features</p> <ul style="list-style-type: none"> • Impaired consciousness, convulsions • Respiratory distress: acidosis, ARDS, pulmonary oedema • Jaundice • Bleeding • Shock <p>Biochemical Features</p> <ul style="list-style-type: none"> • Renal impairment – serum creatinine >265µmol/L, rapidly rising creatinine or urine output <400 ml/day (adult) • Acidosis (plasma bicarbonate <15 mmol/L) (serum lactate >5 mmol/L) • Hepatic impairment (transaminases >3 times normal) • Hypoglycaemia (blood glucose <2.2 mmol/L) • Hypoxia (PO₂ - <8 Kpa in room air) <p>Haematological Features</p> <ul style="list-style-type: none"> • Parasitaemia ≥5% or ≥3+ • Haemoglobin <6 g/dL or haematocrit <20% • ≥5% neutrophils contain malaria pigment • Presence of schizonts of <i>P.falciparum</i> in peripheral blood smear • Evidence of DIC

Laboratory diagnosis

Patient blood should be examined immediately to confirm or exclude the diagnosis of malaria. In the majority of cases of severe malaria, examination of correctly stained blood smears will reveal malaria

parasites, however, a negative smear does not exclude the diagnosis, and repeat smears are indicated. Some patients with severe malaria may have a negative smear due to sequestration of parasitised red blood cells, and a decision to treat with antimalarial chemotherapy should be considered if the index of suspicion is very high. In these cases it is imperative to continue to look for alternative diagnoses, especially trypanosomiasis, septicaemia and viral haemorrhagic fever.

High levels of parasitaemia ($\geq 5\%$) are generally predictive of severe malaria in nonimmune patients. Importantly, the converse may not be true, with severe disease also occurring with low parasitaemias in the peripheral blood (11,12). Quantification is often inaccurate, peripheral parasitaemia may not reflect the total parasite load and sequestration in the organs, and levels of parasitaemia may vary cyclically. Prognosis worsens considerably if *P. falciparum* schizonts are present in a blood smear, and if more than 5% of peripheral polymorphonuclear leucocytes contain visible malaria pigment (13).

Commercial kits are available that rapidly detect parasite antigen or enzymes. The tests for *P. falciparum* are highly sensitive, but depend on correct usage, interpretation of results, and the quality of the particular test used. These tests can only be used for diagnosis of acute malaria infections, and not for follow-up, as the test may remain positive for several weeks, even after successful treatment (14).

In a febrile patient where there is no obvious cause of fever, and a recent history of visiting or living in a malaria area is not forthcoming, malaria should still be excluded, as infected mosquitoes have been documented to travel long distances in road, rail and air transport. Mortality is high in this group of patients, because of missed diagnosis, but a finding of thrombocytopenia should always stimulate a search for possible malaria parasites (15).

TREATMENT OF SEVERE MALARIA

Patients should be treated urgently with the most effective treatment regimen available, in a facility with the highest level of care. The choice of chemotherapy for malaria is dependent on the severity of disease, the known or suspected resistance pattern of the parasite in the area where the malaria infection was acquired, the species of parasite, and patient profile

(age, pregnancy, comorbidity, allergies, and medications, including any antimalarials recently administered).

Quinine, the drug of choice for the treatment of severe malaria in Africa, is rapidly effective (4,11). In most parts of Africa quinine resistance has not developed. In some parts of West Africa however, foci of low-level resistance have been documented (15). An initial loading dose of quinine to rapidly reach a therapeutic level is critical in the management of severe malaria and has a major impact on favourable outcome. The loading dose should be omitted if the patient has definitely received mefloquine, quinine, quinidine or halofantrine in the previous 24 hours, mefloquine in the previous seven days, or 40mg/kg of quinine in the previous two days. If there is doubt, the loading dose of quinine should be given (4,11,16). The loading dose is given as quinine di-hydrochloride salt, 20mg/kg body weight diluted in 5-10 ml/kg body weight of dextrose water, by slow intravenous infusion over two to four hours. Quinine must never be administered by bolus intravenous injection, as this is associated with cardiotoxicity. The loading dose is given strictly according to body weight. The disposition of quinine in very obese patients is not known. It has been suggested that there is a ceiling dose above which quinine should not be given, but there is no evidence to support this (17).

Six to eight hours after starting the loading dose, a maintenance dose of quinine di-hydrochloride salt, 10mg/kg diluted in 5-10 ml/kg body weight of a dextrose-containing solution should be commenced and infused over 4-6 hours. Intravenous quinine should be administered every eight hours until the patient can take oral medication (usually by 48 hours). For obese patients, the maintenance dose should be calculated according to ideal body weight (17).

Males: $IBW (kg) = 0.9 \times \text{height in cm} - 88$

Females: $IBW (kg) = 0.9 \times \text{height in cm} - 92$.

The dosage of oral quinine is 10mg/kg/dose or 600mg/dose given three times a day. The total duration of quinine therapy is 7-10 days. Additional drugs, tetracycline (usually as doxycycline 100mg twice a day x 7 days), or clindamycin (10mg/kg twice a day x 7 days) are recommended to improve cure rates (4,11,18). These, however, do not add initial therapeutic benefit, may contribute to drug side effects, and should be introduced only once the patient is improving. Quinine can be administered by deep intramuscular injection if intravenous infusion is not possible (4).

Quinine has a narrow therapeutic window, although serious side effects are rare. The pharmacokinetic properties of quinine are altered considerably in malaria with a contraction in the volume of distribution and a reduction in clearance that is proportional to the severity of disease (19). There is significant binding of quinine to acute phase reactants, notably α 1-acid glycoprotein, with reduction in the levels of free quinine. Quinine toxicity is, therefore, relatively uncommon (20). The most frequent side effect of quinine therapy is hypoglycaemia, especially in children and pregnant women (19,21). Although quinine may prolong the QTc-interval, hypotension, heart block, and ventricular arrhythmias are rare (4,19,22). Convulsions and visual disturbances have been reported as idiosyncratic responses or with overdosage (4,19). Doses should be reduced by 30-50% after the third day of treatment to avoid accumulation of the drug in patients who remain seriously ill, especially those with evidence of renal failure (4). The measurement of levels of free (not total) quinine may be helpful in patients with severe malaria and renal failure, but accessibility to this test is very limited. The precise level has not been defined but probably lies between 0.8-2mg/L (11).

Quinidine is more active than quinine, but is also more cardiotoxic and more expensive, is not readily available, and consequently is not used for treating severe malaria in Africa (23).

Artemisinin

In the early 1970's Chinese scientists identified artemisinin, a sesquiterpene lactone peroxide, as the principal active component of the traditional Chinese malaria remedy, qinghaosu. Artemisinin and two derivatives, artesunate and artemether are effective against multi-drug resistant *P falciparum* and clear sensitive parasites from the blood more rapidly than other antimalarial agents due to their broad stage specificity of anti-malarial action. Despite administration to over 3 million people, resistance has not emerged, and only rarely has treatment failure been reported. The drugs are well tolerated and despite neurotoxicity in animal studies, serious adverse reactions have included only a few case reports of anaphylaxis. The chemical structure and mode of action of these drugs distinguish them from other currently available antimalarial agents, and render them less vulnerable to cross-resistance. However, when used alone, unacceptably high recrudescence rates are seen (4,11,24,25).

Combination therapy, which includes an artemisinin, is the recommended malaria treatment policy to delay the emergence of drug resistance to sequential monotherapy, as well as to improve cure rates. Drugs used in

combination with the artemisinins include mefloquine, sulfadoxine pyrimethamine, amodiaquine and lumefantrine, and the choice depends on parasite resistance in the geographical area (26).

There are parenteral preparations of the artemisinins, either intramuscular (artemether, arteether, artesunate) or intravenous (artesunate). Artemether and arteether are oil-based preparations and absorption from the intramuscular site may be compromised in severe malaria, leading to treatment failures (27). Artesunate is water-based, can be given intravenously, or intramuscularly from where it is well absorbed. Although theoretically preferable, there are no large comparative trials to indicate whether artesunate is superior to artemether or quinine (28). The use of parenteral artemisinins is limited by availability and manufacturing practices, which may not adhere to international standards.

A meta-analysis of randomized clinical trials comparing the efficacy of artemether with quinine in the management of severe malaria demonstrated equality, but indicated a trend toward greater effectiveness of artemether in regions where there is recognised quinine resistance. Artemether was superior to quinine in terms of overall serious adverse events (29,30). In patients with hyperparasitaemia there may be an advantage of the artemisinins over quinine. In South-East Asia, where multi-drug-resistant malaria is a major problem and quinine resistance has emerged, the artemisinin drugs are used as first-line therapy for severe malaria (30).

Other drugs

Widespread, high-level chloroquine resistance precludes the use of chloroquine in the treatment of both uncomplicated and severe malaria in most parts of the world, including Africa. Sulfadoxine pyrimethamine, mefloquine and halofantrine are not indicated in the management of severe malaria (4).

COMPLICATIONS OF MALARIA AND THEIR MANAGEMENT

Anaemia

Anaemia may result from haemolysis or dyserythropoiesis (31). Severe anaemia is defined as a haemoglobin of less than 6g/dL, or haematocrit <20%. Severe anaemia is the most important manifestation of severe

malaria in areas of high stable transmission and occurs predominantly in children. Pregnant women may also present with profound degrees of anaemia. Anaemia may manifest as shock, cardiac failure, hypoxia, or confusion and the rate at which anaemia develops is an important determinant of compensatory mechanisms. Blood transfusion using packed cells should be considered in patients in whom the haemoglobin is 6g/dL or less, especially those with cardiovascular decompensation. Fluid overload must be avoided. Transfused blood has a reduced lifespan in malaria patients (4).

Cerebral malaria

In many parts of the world cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. The term cerebral malaria in many published studies is restricted to the syndrome in which altered consciousness associated with a malaria infection could not be attributed to convulsions, sedative drugs or hypoglycaemia alone or to a non-malarial cause. Cerebral malaria may be part of multi-system pathology, in which case the outlook is much poorer than if disease was localised only to the central nervous system.

Clinically, the commonest neurological picture is of a symmetrical upper motor neuron lesion, mild neck stiffness is not uncommon, and muscle tone and tendon reflexes are variable. Cerebral malaria can resemble bacterial or viral meningitis and a lumbar puncture should be considered in patients where the diagnosis is not clear. Hypoglycaemia, metabolic disturbances, severe anaemia and hypoxia as a result of malaria can all present with signs of central nervous system dysfunction. Generalised or focal convulsions may occur as a result of cerebral malaria, or in association with hypoglycaemia (4).

Imaging of the brain commonly shows evidence of mild cerebral swelling. Oedema is very unusual, and may be an agonal phenomenon (32,33). Studies to date with dexamethasone or mannitol have not shown benefit and have been associated with prolongation of coma and gastro-intestinal haemorrhage (34). Anticonvulsants should only be used once convulsions occur, and should not be used prophylactically (35). The use of iron-chelating agents has not been shown to impact on mortality (36). In adult patients who recover, neurological sequelae are uncommon.

Renal failure

Renal failure is an early complication of severe malaria in adults. Hypovolaemia, sequestration of parasitised red cell in the renal

vasculature, intravascular haemolysis and haemoglobinuria are implicated and may lead to acute tubular necrosis. Renal failure is generally oligaemic and hypercatabolic. A serum creatinine of greater than 256 $\mu\text{mol/L}$ or a rapidly rising creatinine and/or a urine output of < 400 ml/day in an adult should be regarded as renal failure. A central venous catheter (CVP) should be inserted and dehydration should be corrected. The CVP should not be above 5cm of water. The indications for dialysis are the same as for patients with other diseases, but since renal failure in malaria occurs against a background of a hypercatabolic state and non-renal causes of acidosis frequently co-exist, early dialysis is recommended (37). Venovenous haemofiltration is the recommended mode of dialysis and is significantly more efficient than peritoneal dialysis (38).

Quinine is not removed by dialysis and in patients with severe malaria and renal failure, the dosage of quinine should be reduced by half to one-third after 2 days of full dosage administration. If the patient survives the acute phase of the disease and has no pre-existing underlying disease, recovery of renal function generally occurs within three weeks (4).

Respiratory failure

This is a grave complication of severe falciparum malaria in adults, and may present several days after commencing malaria chemotherapy. The cause of this often lethal complication is unknown in falciparum malaria. Some cases show evidence of pulmonary oedema while others resemble acute respiratory distress syndrome. Pregnant women are particularly at risk. Iatrogenic overadministration of fluids may contribute to the development of ARDS or pulmonary oedema and should be avoided. Some patients may require ventilatory support (4,11,39,40).

Hepatic dysfunction

Although a raised indirect bilirubin due to haemolysis is a frequent finding in malaria, the clinical presence of jaundice or the finding of raised hepatic transaminases (≥ 3 x normal) should alert the clinician to the probability of severe malaria. The presence of jaundice combined with renal failure and acidosis may indicate a grave prognosis (4).

Disseminated intravascular coagulation (DIC)

DIC is rare in patients with severe malaria although laboratory evidence of haemostatic abnormalities may be present without bleeding. Moderate degrees of thrombocytopenia are noted in the majority of cases of uncomplicated malaria unassociated with other coagulation abnormalities and bleeding is uncommon. Possible mechanisms of thrombocytopenia

include sequestration in the spleen, decreased production, or reduced survival from intravascular lysis. Platelet transfusion should be considered if the platelet count is less than 20,000/mm³, or if there is evidence of bleeding. Platelet counts should return to normal within a few days with effective malaria treatment. Continuing thrombocytopenia may indicate failed antimalarial therapy, sepsis, or a drug reaction to quinine (4)

Secondary infection

Secondary bacterial infections may complicate malaria: aspiration pneumonia, urinary tract infections or nosocomial septicaemia. In a significant number of patients, especially children, septicaemia may complicate severe malaria very early. Salmonella species and staphylococci are common causes of septicaemia. The syndrome is associated with high mortality. Since the features of bacterial sepsis and malaria overlap, empiric treatment using a broad-spectrum antibiotic for Gram-positive and Gram-negative organisms is recommended (4).

Acidosis

Metabolic acidosis is a consistent feature of severe malaria. Lactic acidosis is a major cause of death from severe falciparum malaria. The pathophysiology of acidosis is multifactorial and results from tissue hypoxia and anaerobic glycolysis, liver dysfunction and impaired renal handling of bicarbonate. The presence of acidosis is an important predictor of poor outcome (41). The management of acidosis includes correction of fluid balance, improvement in haemodynamic status, and haemodialysis (4). The use of dichloracetate has been shown to be beneficial in animal models.

Haemoglobinuria and Blackwater fever

The pathogenesis of this rare condition is unknown, and is seen in patients with G-6-PD deficiency who receive oxidant drugs. It may also occur in patients without apparent G-6-PD deficiency but who have severe malaria and are treated with quinine or artemisinin derivatives. Intravascular haemolysis results in anaemia, and the passage of haemoglobinuria. A small minority will develop renal failure, the cause of which is unknown. In patients with malarial haemoglobinuria, quinine chemotherapy should be continued. Supportive therapy includes blood transfusions for severe anaemia, maintaining adequate hydration, and renal dialysis where indicated (4,42).

Hypoglycaemia

Hypoglycaemia may result from impaired glycolysis or gluconeogenesis, or as a result of quinine-induced hyperinsulinaemia. It is a particular problem in pregnant women and patients on intravenous quinine. Blood glucose should be monitored, as the signs may be very subtle. Hypoglycaemia must be excluded in all patients with an altered mental state and in those who present with convulsions (4).

Shock

Shock may occur as a result of hypovolaemia, massive blood loss from splenic rupture or gastrointestinal haemorrhage, bacterial septicaemia, hypoxia and severe metabolic acidosis. Myocardial function is remarkably good in severe falciparum malaria and most patients have an elevated cardiac index (43). Hypovolaemia should be corrected with an appropriate intravenous infusion, usually 0.9% saline initially, followed by a plasma expander. The central venous pressure should not be allowed to exceed 5cm. If hypotension persists, inotropes should be administered (4).

Pregnancy

The placenta acts as a haven for parasites due to upregulation of adhesion receptors. The course of malaria in pregnancy is rapidly progressive and common complications are anaemia, hypoglycaemia and ARDS. The risk of severe disease extends into the immediate postpartum period. Malaria may cause abortion, premature delivery and low birth-weight. The management remains the same as in non-pregnant patients, with emphasis on preventing and managing the complications mentioned. In particular, fluid restriction is important to prevent ARDS. Quinine is the drug of choice but may be associated with intractable hypoglycaemia. The use of the artemisinin drugs is currently not indicated due to a lack of safety data, unless there is evidence of quinine resistance. There is no indication to terminate pregnancy. In areas of high malaria transmission, anaemia is the most common manifestation of severe disease and placental parasitaemia is associated with low birth-weight infants (4).

Non-falciparum malaria

The non-falciparum malarias are not generally associated with severe disease due to a lack of sequestration of parasitised red cells. Rarely *Plasmodium vivax* has been associated with the development of ARDS and cerebral malaria (44,45). Mixed infections with falciparum malaria occur occasionally and should be managed as for falciparum malaria.

HIV and severe malaria

Malaria and human immunodeficiency virus (HIV) infections are common, widespread and overlapping problems in Africa. Any interaction between these two pandemics would be of great importance. This interaction could be in either direction, with malaria causing more rapid progression of HIV, and HIV-associated immunosuppression leading to an impaired immune response to malaria. Greater parasite densities and rates of clinical malaria have been demonstrated in HIV-positive patients from Uganda, an area of high malaria endemicity, where the majority of people would be expected to have developed some malaria immunity (46,47). In a cohort study of non-immune patients with malaria in South Africa, HIV-positive patients had an increased rate of severe malaria compared to HIV-negative patients, and the rate increased as CD4+ cell count decreased. HIV-positive patients had significantly increased rates of renal failure, severe anaemia and DIC (48).

Exchange transfusion

The efficacy of exchange transfusion as adjunctive therapy for severe malaria is controversial. No sufficiently powered, randomized, controlled study has been reported, although anecdotal case reports in the literature indicate benefits in selected groups of patients with hyperparasitaemia and organ failure (49,50). A meta-analysis of eight studies comparing survival rates associated with exchange transfusion to survival rates with antimalarial chemotherapy alone did not show improved survival rates in the former groups of patients. There were significant problems with the comparability of treatment groups in the studies reviewed, with higher levels of parasitaemia and more severe malaria in the group who received transfusions (51). Recent studies suggest that the benefits associated with exchange transfusion result from replacing the rigid, non-deformable parasitised and unparasitised red cells with fresh blood, and not from reducing parasite load or removal of toxins or cytokines (52).

Requirements for exchange transfusion include the availability of pathogen-free compatible blood, facilities for adequate clinical monitoring, and a haemodynamically stable patient. Exchange transfusion may be considered in a patient who is seriously ill and the parasitaemia exceeds 15%. Exchange should still be considered with parasitaemia in the range of 5-15%, if there are other signs of poor prognosis. There is no consensus of the volume of blood to be exchanged for a given parasitaemia and the volumes have varied from 4 litres to 20 litres. Blood may be exchanged using a double-lumen catheter or alternatively via

haemodialysis (4,11). Successful red blood cell exchange using a cell separator has been reported (52).

PREDICTORS OF MORTALITY

In a study conducted in a well-established intensive-care unit in South Africa, despite appropriate chemotherapy with quinine, and standard intensive-care support including inotropic agents, ventilatory support and haemodialysis where appropriate, mortality was 28.5% in a group of 28 patients (24 adults and 4 children). Pregnancy was a major cause of unfavourable outcome. ARDS was the most important cause of death. High Apache II scores, high arterial lactate, and negative base excess in the first 24 hours of admission correlated with mortality. Admission haemoglobin, platelet count, level of parasitaemia and level of Glasgow Coma Scores in the first 24 hours were shown not be predictors of mortality. These parameters may be useful in the assessment of disease severity and in patient triage for ICU admission (53).

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