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Severe Malaria: North American Perspective

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BACKGROUND

Plasmodium falciparum is responsible for essentially all of 1 million deaths annually that occur worldwide due to malaria and is the only one of the four human malaria species (others include *P. vivax*, *P. ovale*, and *P. malariae*) that clearly causes severe malaria.[1] *P. falciparum* is endemic in Africa, the Middle East, Oceania, Southeast Asia and India, and Central and South America. Persons living in highly malarious areas may become partially immune to malaria; however, this immunity is not fully protective and may wane during pregnancy or with time after a person leaves the endemic area.

Widespread drug resistance has complicated the clinical management of *P. falciparum*. The resistance of *P. falciparum* to chloroquine has been confirmed in all areas with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America west and north of the former Panama Canal Zone, Egypt, and some countries in the Middle East. In addition, resistance to sulfadoxine-pyrimethamine is widespread in the Amazon River basin area of South America, much of Southeast Asia, other parts of Asia, and, increasingly, in parts of eastern and southern Africa. Resistance to mefloquine has been confirmed on the borders of Thailand with Burma (Myanmar) and Cambodia, in the western provinces of Cambodia, and in the eastern states of Burma (Myanmar).[2, 3]

EPIDEMIOLOGY OF MALARIA IN U.S. TRAVELERS

Non-immune travelers who visit malaria-endemic areas are highly susceptible to severe disease if they become infected with *P. falciparum*. Most imported *P. falciparum* malaria among American travelers is acquired in sub-Saharan Africa. From 1985 through 2001, 5,015 cases of *P. falciparum* among U.S. civilians were reported to the Centers for Disease Control and Prevention. Of these, 4,310 (85.9%) were acquired in sub-Saharan Africa; 278 (5.5%) in Asia; 300 (6.0%) in the Caribbean and Central or South America; and 127 (2.5%) in other parts of the world.

Among 70 fatal malaria cases that occurred among U.S. civilians between 1985 through 2001, 66 (94%) were caused by *P. falciparum*, of which 47 (71%) were acquired in sub-Saharan Africa.[2] The mortality rate from *P. falciparum* in the United States has been estimated at 4.2% with an age-specific mortality rate increasing from 0% on persons under age 20 to 7.9% in those 50 years and older.[4] Factors associated with increased mortality among north American travelers include older age, failure to take antimalarial chemoprophylaxis, delay in seeking medical care, misdiagnosis, and inadequate therapy.[4, 5]

The successful management of *falciparum* malaria includes recognition of infection by health care providers, rapid and accurate laboratory testing and prompt initiation of effective treatment.

DEFINITION OF SEVERE MALARIA

WHO defines severe malaria as occurring when: a patient with asexual *P. falciparum* parasitemia and no other confirmed cause of their symptoms with one or more of the following clinical or lab features: prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions, circulatory collapse, pulmonary edema (radiological), abnormal bleeding, jaundice, hemoglobinuria, severe anemia.[1]

PATHOGENESIS OF SEVERE MALARIA

Malaria sporozoites are transmitted to humans via the bite of infected female *Anopheles* mosquitoes. Sporozoites invade hepatocytes, undergo exo-erythrocytic development and release asexual forms (called

merozoites) into the bloodstream on average 6 to 14 days later. These parasites then invade susceptible red blood cells, and undergo an erythrocytic development phase—once mature, are released from red blood cells and continue the cycle. Some of the asexual forms will differentiate into female and male gametocytes that are then capable of infecting a mosquito during a blood meal. *P. falciparum* causes the preponderance of malaria mortality because, unlike the other malaria species, it invades red blood cells of all ages, leading to a high proportion of red blood cells infected and destroyed by the parasite and is the only malaria species that sequesters in the deep capillary beds, causing microvascular disease—both of which contribute to severe and complicated malaria. The hemolysis, which may lead to severe anemia, hemoglobinuria, acute tubular necrosis, and acute renal failure.[1]

While *P. falciparum* ring forms are seen in circulating erythrocytes, later stages of the falciparum parasite are found sequestered in internal organs. Sequestration is thought to be caused by cytoadherence, rosette formation, and/or decreased deformability of the erythrocytes. Infected erythrocytes have a propensity for sticking to vascular endothelium through a specific molecular interaction between parasite adhesins (that are located on or under the surface of infected red blood cells) and ligands on endothelial cells.[1] Binding of uninfected erythrocytes to the surface of erythrocytes infected with mature forms of *P. falciparum* (called rosetting) may contribute to venular obstruction.[6]

Because parasite sequestration occurs in deep vascular beds of internal organs during severe falciparum malaria, clinicians should anticipate multiple organ involvement with corresponding symptoms and signs—for example, neurologic (impaired consciousness, seizures); respiratory (pulmonary edema); hematologic (abnormal bleeding, hemolysis with subsequent jaundice and hemoglobinuria); and renal (insufficiency).[1] In patients with cerebral malaria, sequestration was more evident in the brain than in other organs.[7] While sequestration is the essential pathological feature of severe falciparum malaria, the exact pathogenesis of how this phenomenon leads to cerebral malaria and the other complications of malaria is still unclear. Proposed mechanisms include the mechanical obstruction of blood flow, systemic cytokine production, and local production and deposition of cytokines.[1, 8]

CLINICAL MANIFESTATIONS

The usual incubation period for *P. falciparum* is 12-14 days, although symptoms may occur as early as one week after exposure. The incubation period may be prolonged in persons taking chemoprophylaxis or who have received partial treatment. Severe malaria typically develops after 3-7 days of non-specific symptoms in adults,[1] but progression to death can occur as rapidly as 24 hours after onset of symptoms.[9] In addition, non-immune patients may have no signs of severe disease at presentation but can subsequently rapidly deteriorate even when on appropriate therapy.[10]

The presenting signs and symptoms of falciparum malaria are non-specific and may mimic a number of common ailments including gastroenteritis, pyelonephritis, pharyngitis, upper respiratory tract infection, and undifferentiated viral syndromes.[11] Among US citizens infected with falciparum malaria, presenting symptoms included fever and chills (88%), malaise and weakness (50%), gastrointestinal symptoms (nausea, vomiting, diarrhea) 43%, neurological symptoms (dizziness, confusion, disorientation, coma) 37%, myalgias (24%), headache (19%), and shortness of breath (9%). [5] Among persons living in endemic areas, children with severe malaria are more likely than adults to have impaired consciousness, acidotic breathing, multiple convulsions, and severe anemia.[1] Children are more likely to present with vomiting, hypoglycemia, and hyperpyrexia than adults.[12] In contrast, pulmonary edema and acute renal failure are more common in adults, with pregnant women at particular risk for pulmonary edema. [1]

Both adults and children may develop cerebral malaria, which often begins dramatically with a convulsion followed by persisting unconsciousness. The strict definition of cerebral malaria requires the presence of unarousable coma in a patient who has a blood smear demonstrating *P. falciparum* and no other identifiable cause. However, it is recommended that patients with malaria who have any degree of impaired consciousness or evidence of neurological dysfunction be treated aggressively. The Glasgow coma scale in adults and Blantyre coma scale in children is useful for determining the level of impaired consciousness.[1] Other clinical manifestations that may be present in persons with cerebral malaria include retinal hemorrhages, decerebration (hypertonicity, posturing, or opisthotonus), disorders of conjugate gaze, forcible jaw closure and teeth grinding (bruxism), and (uncommonly) absent corneal reflexes.[1, 13]

DIAGNOSIS

The clinical diagnosis of malaria can be challenging, given that there are no signs or symptoms that are pathognomic for malaria.[1, 14] The presence of rash, lymphadenopathy, or any sign of focal infection in a patient with suspected malaria should suggest a different or additional diagnosis. The diagnosis of malaria may be missed in patients whose primary presentation is acute renal failure, a bleeding diathesis, severe hemolysis, pulmonary edema or shock. In addition, heat stroke should be considered in the differential diagnosis of severe fever and altered consciousness, especially in unacclimatized visitors to the tropics or in those with a history of excessive exercise. Some persons with malaria develop diarrhea, which may be mistaken for infectious gastroenteritis.[1] In patients with altered consciousness, lumbar puncture should be performed to rule out bacterial meningitis.[15] During pregnancy and the puerperium, severe malaria must be distinguished from sepsis arising from infection in the uterus, urinary tract or breast. Cerebral malaria can be distinguished from eclampsia, as other features such as hypertension and edema are present with eclampsia but not with malaria.[1]

Malaria must be considered in the differential diagnosis of fever in the returned traveler but is often overlooked in non-malarious areas because the travel history is not investigated. Severe malaria may be mistaken for influenza, hepatitis, encephalitis, enteric fever, or psychosis, among other conditions. National U.S. surveillance data from 1959 through 1987 found that among US citizens infected with falciparum malaria, 37-40% were not diagnosed with malaria during the initial contact with the physician.[4, 5] In a review of *P. falciparum* cases presenting to a large emergency department in Los Angeles, a diagnosis of malaria was considered in only 60%; speciation of falciparum malaria was made in only 10% of the cases.[16] Similar findings have been reported by Kain and colleagues from Canada, where the diagnosis of malaria was missed at initial presentation in 61% of cases and 16% of patients reported seeing 3 or more physicians before the diagnosis of malaria was suspected. Thirty percent of patients with *P. falciparum* in this Canadian series received inappropriate treatment.[17] In addition, patients themselves often delay seeking prompt medical attention, with only 54% of persons infected with *P. falciparum* seeking care within 6 days after the onset of illness.[4]

The diagnosis of malaria is confirmed by the identification of parasites in a Giemsa-stained blood film. While a Wright-Giemsa stain may be used, a Wright's stain alone will not reliably stain malaria parasites. Non-

immune patients can have significant symptoms early in their course when the parasitemia levels are still so low that detection on a blood smear is difficult.[11] Thick blood smears are much more sensitive for the detection of low density parasitemia since 10 times the amount of blood can be examined compared to that examined on a thin film. However, because the red blood cells are lysed, persons inexperienced with the slide diagnosis of malaria may have more difficulty reading thick compared to thin smears.

In non-immune persons with no prior exposure to malaria, initial malaria symptoms may occur even with very low parasite densities. Consequently, serial blood smears should be examined by a person experienced in slide diagnosis of malaria.[11] Smears should be repeated every 6 to 12 hours for a minimum of 3 days to rule out malaria unless an alternative diagnosis becomes clear.[1, 11] Although there is a correlation between parasite density and disease severity, a patient can have severe disease without a high level of peripheral parasitemia because a large number of parasites are sequestered in the deep capillary beds.[1] Every febrile illness in an individual who has been in a malaria endemic area during the preceding 3 months and even up to a year, regardless of reported use of malaria prophylaxis use, requires a malaria smear.[11] Because *P.falciparum* malaria is a medical emergency, it is imperative that clinicians and laboratories process malaria blood smears on an urgent basis. Even in case of suspected uncomplicated malaria, blood smears should be collected and read on the same day that the patient presents.

If malaria is suspected but initial smears are negative, the follow-up smears should be done, as noted above, but other potential causes of fever should be pursued. Negative blood smears have been reported very rarely from patients with severe malaria[1, 18] and are hypothesized to be due to prior antimalarial drug treatment, a highly synchronized infection, or a high degree of sequestration. However, some of the reported cases have been poorly documented[18-20] and most likely have alternative diagnoses.

TREATMENT

Patients with severe malaria should be treated with a loading dose of parenteral antimalarial drugs to assure therapeutic blood levels as quickly as possible; most deaths from severe malaria occur within the first 24-48 hours. Oral antimalarial drugs (such as oral quinine, chloroquine, or

mefloquine) are not recommended for the treatment of severe malaria as their absorption may be impaired in the severely ill patient. If severe malaria is strongly suspected but the first blood smear does not demonstrate parasites, a trial of antimalarial drugs should be given. If there is clinical evidence of severe malaria but the blood smear is reported as *P. vivax*, *P. ovale* or *P. malariae*, the patient should be treated for *falciparum* malaria in case of a mixed infection or misdiagnosis.[1] The treatment for *falciparum* malaria covers the other species.

Since 1991, quinidine gluconate has been the only parenterally administered antimalarial drug available in the United States.[21] The artemisinin derivatives are very efficacious and are used in some other countries for the treatment of severe malaria but are not available in the United States. The CDC is attempting to find a mechanism to make a parenteral artemisinin derivative available for cases of failure to respond to quinidine or severe quinidine intolerance.

Quinidine Gluconate

Quinidine gluconate is recommended for patients infected with *P. falciparum* who are unable to take oral medications, have high-density parasitemia (>5% of red blood cells infected), or have end organ complications such as cerebral malaria or acute renal failure.[14, 22] The recommended dosage is 10mg/kg salt (equivalent to 6.25 mg base/kg) infused intravenously over 1-2 hours followed by a continuous infusion of 0.02 mg salt /kg/min (0.0125 mg/kg/min quinidine base). An alternative regimen is an intravenous loading dose of 24 mg/kg quinidine salt (15mg/kg quinidine base) infused over 4 hours, followed by a 12mg/kg salt (7.5mg/kg base) infused over 4 hours every 8 hours, starting 8 hours after the loading dose.[23] Quinidine levels should be maintained in the range of 3-8 mg/L.[14, 15] At least 24 hours of quinidine infusion are recommended (or 3 intermittent doses).[1] Once the parasite density is < 1% and the patient can take oral medication, they can complete their treatment course with oral quinine at a dosage of 10 mg salt/kg every 8 hours. The treatment course of the quinolone derivative (intravenous quinidine followed by oral quinine) may be 3 days in areas without multidrug resistance but should be extended to 7 days in areas with and multidrug resistance.[14]

A second drug is generally used in combination with quinine. In areas without multidrug resistant malaria, using a second drug allows one to shorten the course of quinine to 3 days (otherwise, if quinine is used alone, a full course of 7 days of quinidine/quinine is recommended). In

areas with multidrug resistance, such as in Southeast Asia where a decrease in sensitivity to quinine has been documented,[24] a second drug is required. Oral tetracycline (250mg every 6 hours), doxycycline (100 mg every 12 hours), or clindamycin (5 mg/kg base orally every 6 hours) for 7 days are options. There should be an overlap of 2 to 3 days for quinine/quinidine and tetracycline.[14] Patients unable to tolerate oral therapy can be given intravenous doxycycline hyclate 100mg every 12 hours for 7 days.

Pregnant women should receive treatment with quinidine/quinine as for non-pregnant patients.[1] Although there have been concerns voiced about adverse effects of quinine/quinidine on the fetus (congenital abnormalities) and on the pregnant uterus (inducing labor), no reports linking the use of quinidine with congenital defects have been identified and many of the reports of malformations with quinine have occurred at very high (abortifacient) doses.[25] Most importantly, this therapy is potentially life-saving for both mother and fetus. Studies in Thailand have not demonstrated an oxytocic effect at therapeutic doses.[26, 27] In addition to quinidine, pregnant women or children less than 8 years old can be treated with clindamycin.[14, 28]

Initial (including loading) doses of parenteral quinine or quinidine need not be reduced in persons with renal failure. If renal failure persists or the patient does not have improvement in their clinical condition, the maintenance dosage should be reduced by one-third to one half on the third treatment day[1] because the pharmacokinetic properties of the cinchona alkaloids are altered in malaria, with a contraction in the volume of distribution and reduction in clearance that is proportional to the severity of disease.[29]

Parenteral quinidine is more cardiotoxic than quinine and should be administered in an intensive care setting with continuous EKG and frequent blood pressure monitoring to avoid cardiotoxicity.[1, 22] At the dosages required for the treatment of falciparum malaria, quinidine may cause ventricular arrhythmia, hypotension, hypoglycemia, and prolongation of the QT interval.[30] The risk for serious ventricular arrhythmia is increased by bradycardia, hypokalemia, and hypomagnesemia.[23] The quinidine infusion should be slowed or stopped for an increase in the QRS complex by > 50%, a QT interval > 0.6 seconds, a QTc interval that is prolonged by more than 25% of the baseline value, or hypotension unresponsive to fluid challenge.[1, 14] Recent use of other drugs that may prolong the QT interval (e.g., quinine,

halofantrine, and mefloquine) should be considered when determining whether a patient should receive a loading dose of quinidine gluconate.[30] Recommendations for administration of a loading dose of quinine, for which there is more experience to base decisions on as compared to quinidine, are to give it unless the patient has received more than 40 mg/kg quinine in the last 2 days or if they have received mefloquine in the last 12 hours.[1] Consulting a cardiologist and a physician with experience in treating malaria is advised when treating malaria patients in the United States with quinidine gluconate.[23] Glucose must be monitored closely as quinidine- (or quinine-) induced hyperinsulinemic hypoglycemia can occur, particularly in pregnant women.[26]

With the advent of newer anti-arrhythmic agents, quinidine gluconate has been removed from many hospital formularies and fewer clinicians have experience with the drug. To ensure the availability of quinidine gluconate in U.S. health care facilities, hospital drug services should consider maintaining or adding quinidine gluconate to formularies or alternatively, be able to immediately locate a nearby health care facility that stocks it. If a local source cannot be located, quinidine gluconate should be requested from the local or regional distributor. In the event that quinidine gluconate is needed acutely, pharmacists and clinicians should contact Eli Lilly Company directly, telephone (800) 821-0538 to arrange a rapid shipment of the drug. If further assistance is needed in obtaining quinidine gluconate or in managing patients with malaria, contact CDC's malaria hotline, (770) 488-7788 Monday-Friday 8am to 4:30pm EST or after hours, weekends and holidays, call CDC's security station at (404) 639-2888 and ask to have the on-call person for malaria questions paged. [30]

Other antimalarial drugs

Mefloquine is not recommended for use in the treatment of severe malaria because there is no parenteral preparation. Intravenous antibiotics such as doxycycline and clindamycin are too slow-acting to be used alone and must be used with quinidine or quinine. Intravenous chloroquine is approved but not marketed in the United States and would have limited usefulness since most *P. falciparum* imported into the United States is acquired in areas with high levels of chloroquine resistance. Although no parenteral preparation of atovaquone/proguanil exists, recently, therapy with intravenous quinine followed by oral atovaquone/proguanil (Malarone™) was shown to be safe and efficacious in children with severe malaria in Kenya (personal communication C. Hedgeley).

ADJUNCTIVE THERAPY

Several ancillary therapies have been attempted in an effort to improve outcomes in severe malaria. A few of these have actually been shown to be detrimental, such as corticosteroids and heparin.[31, 32] Others have not shown benefit (pentoxifylline, cyclosporin A, intravenous immunoglobulin, desferrioxamine) or are unproven (deferiprone, osmotic/diuretic agents for cerebral malaria, dextran, prostacyclin, dichloroacetate for lactic acidosis).[1, 33, 34]

EXCHANGE TRANSFUSION

Exchange transfusion has been used in the treatment of severe malaria since 1974 with apparent benefit in some cases.[22, 35-37] However, there is no clear consensus on the indications, or on specifics such as volume to be exchanged. While it has not been proven beneficial in an adequately powered randomized controlled trial[1] and there have been case series of children in endemic areas with hyperparasitemia managed successfully without exchange transfusion,[38] as well as case reports[39] and series[40] of non-immune patients with severe malaria hyperparasitemia who have been cured without exchange transfusion, there is an increasing impression that exchange transfusion is beneficial in very sick patients.[1] A recent meta-analysis of 8 studies found no evidence for increased survival rate among patients receiving exchange transfusion but was limited in ability to draw conclusions given that, in the studies reviewed patients receiving exchange transfusion had higher levels of parasitemia and more severe malaria. In a sub-group analysis, the authors attempted to control for parasite density and WHO criteria for severe malaria and still did not find a survival difference but that sub-analysis lacked the power to detect a significant difference in survival. These authors estimate, if one assumed a (large) reduction in mortality of 50%, one would need at least 400 participants for a definitive study on the benefit or lack thereof of exchange transfusion.[41]

CDC recommends that exchange transfusion be strongly considered for persons with a parasitemia level of more than 10% or if complications such as cerebral malaria, non-volume overload pulmonary edema, or renal compromise exist.[14] Others have suggested other criteria – for example, > 30% in the absence of clinical complications or > 10% in the presence of complications.[1] Exchange transfusion is thought to have beneficial effects by removing infected red cells, by improving the rheological

properties of blood, and by reducing toxic factors such as parasite derived toxins, harmful metabolites, and cytokines.[42] The risks of exchange transfusion include fluid overload, febrile and allergic reactions, metabolic disturbances (e.g. hypocalcemia), red blood cell alloantibody sensitization, transmissible infection, and line sepsis and thus, the potential benefits of exchange transfusion should be weighed against the risks. The parasite density should be monitored every 12 hours until it falls below 1%, which usually requires the exchange of 8-10 units of blood in adults.[14]

The technical aspects of exchange transfusion have been discussed in an excellent review by Powell and Grima.[42] Since cell separators became available in the mid-1980s, the method of choice for exchange transfusion in the developed world has been automated exchange (as opposed to manual exchange). Automated exchange allows for exchange of a greater volume of blood in a substantially shorter period of time, with more effective reduction in parasitemia and less cardiovascular instability.[43] Since most automated cell separators remove only a single component, a RBC exchange (erythrocytapheresis) is performed and the plasma, leukocytes, and platelets are returned to the patient—favourable outcomes have been documented with this procedure in several cases.[43-47] A reasonable exchange would be 1 volume red cell exchange or approximately 8 to 10 units of red blood cells in adults. Because of the theoretical advantage of also removing cytokines, some authors prefer to follow the RBC exchange with a 1-volume plasma exchange using fresh-frozen plasma as the replacement fluid. An alternative would be to use reconstituted whole blood for the automated exchange, obviating the need to perform 2 exchanges,[42] though this may be technically more complicated.

MANAGEMENT OF SEVERE MALARIA AND ITS COMPLICATIONS

The key principles for the successful management of severe falciparum malaria include: early suspicion of diagnosis; rapid clinical assessment; early treatment with drugs using optimal doses of an efficacious agent administered by the parenteral route; prevention or early detection and treatment of complications (e.g. seizures, hypoglycemia); correct fluid, electrolyte and acid-base disturbances; avoidance of harmful ancillary measures (e.g. corticosteroids).

In addition to the immediate administration of efficacious parenteral antimalarial drugs, other important aspects of patient care in those with severe malaria should be assessed and managed. These include: 1) evaluate for hypoglycemia and treat if necessary 2) assess hydration status and administer fluids accordingly; 3) measure and monitor urine output, inserting a urinary catheter if necessary; 4) run serial laboratory tests, e.g. comprehensive metabolic panel, CBC, PT/PTT, serum lactate, arterial blood gases; 5) consider need for hemodynamic monitoring, such as indwelling arterial line, pulmonary artery catheter, and/or central venous pressure catheter; 6) treat high fever; 7) consider lumbar puncture to exclude meningitis; and 8) evaluate and treat specific complications (see below).[1] The parasite count should be measured at least twice daily in all patients.[15] If the parasite count has not fallen at least 75% by 72 hours[48] after instituting antimalarial therapy, it should be rechecked. Upon repeat testing, if it is confirmed at the parasite count has not fallen appropriately, measures should be taken to investigate the problem (e.g. check quinidine level).

Fluid, electrolyte and acid base disturbances

Patients with severe malaria may present in various states of hydration. Dehydration and hypovolemia may contribute to hypotension, shock, and acute renal failure. However, fluid overload can precipitate non-cardiogenic pulmonary edema, especially in adults. Following rehydration, central venous pressure should be monitored and maintained at approximately 5 cm water (pulmonary-artery occlusion pressure < 15 mmHg).[15]

Hyponatremia,[51] hypocalcemia, hypo- and hyperphosphatemia, hypo- and hypermagnesemia[49] have all been reported in patients with *P. falciparum* malaria. Electrolyte levels should be evaluated and alterations treated accordingly.

Metabolic acidosis occurs frequently in patients with severe malaria. In most cases, even in patients with acute renal failure, the acidosis is attributable to lactic acidosis. Sequential studies have shown that lactate levels fall rapidly after treatment is begun, probably due to rehydration, cooling, and to the antiparasitic effects of the antimalarial drugs employed.[1] Alkali therapy has a limited role in the management of patients with lactic acidosis. Therapy with sodium bicarbonate has limited efficacy in raising the pH, and it produces an undesirable increase in the $p\text{CO}_2$ of the body fluids. Carbicarb (a commercially available buffer solution that is a 1:1 solution of sodium bicarbonate and disodium

carbonate) does not produce the same increase in $p\text{CO}_2$ seen with sodium bicarbonate solutions. Other buffers, such as the amine buffer tromethamine, or THAM, that do not generate $p\text{CO}_2$ are available, but clinical experience with it is much more limited than with bicarbonate. The administration of bicarbonate[50] should be considered if arterial pH falls below 7.10 and the patient is deteriorating. In this case, a trial infusion of bicarbonate can be attempted by administering one-half of the estimate bicarbonate deficit. If cardiovascular improvement occurs, bicarbonate therapy can be continued. If bicarbonate therapy is followed by no improvement or further deterioration, further bicarbonate should not be given.[51] Arterial pH should be corrected slowly over 1-2 hours. Too rapid a correction can precipitate cardiac arrhythmias and paradoxical central nervous system acidosis.[1]

Dichloroacetate activates pyruvate kinase and has been shown to lower lactate levels without improving survival in patients with lactic acidosis.[52] Although it could potentially prove to be beneficial in treating the lactic acidosis associated with severe malaria,[53, 54] its efficacy is currently unproven.

Hypotension/shock

Possible etiologies for hypotension in severe malaria cases include hypovolemia, massive blood loss (gastrointestinal bleed or splenic rupture), pulmonary edema, and septicemia.[1] Fluids should be administered, usually 0.9% saline initially followed by a blood product replacement or colloids. Bacterial infections are common in patients with severe malaria, and include pneumonia (especially in those patients comatose for more than 3 days), urinary tract infections in patient with indwelling catheters, intravenous line sepsis, and spontaneous septicemia, usually gram negative, presumably from the gastrointestinal tract.[15] If a patient's condition suddenly deteriorates, blood glucose should be checked to rule out hypoglycemia, cultures of blood (and urine, sputum, and catheter insertion sites, if indicated) performed, and empirical treatment for sepsis with broad-spectrum antibiotics should be initiated.[1, 15]

Pulmonary edema

Pulmonary edema may occur in adults but is rare in children. It frequently has its onset after 1-2 days of treatment and at times occurs when the patient seemed to be improving. It may be due either to fluid overload or increased capillary permeability as part of the adult respiratory distress syndrome (ARDS).[1] Pulmonary artery occlusion pressure can be

measured to differentiate fluid overload from ARDS. Volume overload should be treated with diuretics, careful fluid management, and oxygen. For volume overload or ARDS, mechanical ventilation with positive end expiratory pressure/ continuous positive airway pressure may be needed.

Renal Failure

Acute renal failure in severe falciparum malaria results from acute tubular necrosis. Tubular necrosis may be seen in persons experiencing multisystem dysfunction in the acute phase of *P. falciparum* malaria; in persons who have been successfully treated with antimalarial drugs and yet still develop renal failure, and in persons with massive hemoglobinuria.[1, 55] Malaria-associated renal failure is rare in children. Acute renal failure in malaria is most commonly oliguric or anuric but urine output may be normal or increased.[1]

The management of acute renal failure in severe malaria patients is the same as for any cause of acute renal failure,[55] with indications for hemodialysis: hyperkalemia, unresponsive metabolic acidosis, fluid overload, or uremic signs or symptoms. A rapidly rising serum creatinine (>2.5 - 3 mg/dl/day) was one of the most sensitive indicators of the need for dialysis. With dialysis, renal function can be expected to return after a median of 4 days, although some patients may requires dialysis for 2-3 weeks.[55, 56]

Cerebral malaria

Because hypoglycemia may be the underlying cause of impaired consciousness or convulsions, blood glucose should be checked. Vital signs should be monitored along with level of consciousness, Glasgow (or Blantyre) coma score.[1] A lumbar puncture should be performed to rule out bacterial meningitis.[1, 15] Cerebral edema is not thought to be part of the primary pathology of cerebral malaria, but may develop terminally or during prolonged intensive care if there is fluid overload or gross hypoalbuminemia. Deterioration in the level of consciousness and neurologic abnormalities in the absence of hypoglycemia are indications for computerized tomography of the head to rule out intracranial bleed, cerebral edema, or cerebral/ medullary herniation. Patients may need assisted ventilation in the event of central respiratory failure.[1] Most patients who survive cerebral malaria regain consciousness within 2-3 days, though it may occasionally take more than a week.[57]

Seizures

Generalized seizures occur in less than 20% of adults but more than 80% of infants with cerebral malaria.[15, 58] Seizures frequently mark the onset of coma or are followed by neurological deterioration.[1] Seizures may be focal and may be quite subtle in the unconscious patient.[15, 59, 60] Hyperpyrexia (fever >39 C) and hypoglycemia should be ruled out as a cause of seizures.[1] Seizures should initially be managed with diazepam (0.2 mg/kg at 5 mg/minute, which can be repeated in 5 minutes if needed) or lorazepam (0.1 mg/kg infused at 2 mg/min). Because of their short duration of action, these benzodiazepines should be followed by use of phenytoin (15-20 mg/kg at a maximum rate of 50 mg/minute). If the additional dose of phenytoin does not successfully control seizures, additional doses of 5 mg/kg may be administered up to a total cumulative dose of 30 mg/kg. For cases that do not respond to benzodiazepines and phenytoin, phenobarbital should be given at a maximum rate of 100 mg/min until seizures are controlled or till a maximum dose of 20 mg/kg is reached. Inhalational anesthesia and neuromuscular blockage may be needed in a small percentage of refractory cases; urgent neurological consultation should be obtained.[51, 61]

The use of prophylactic anticonvulsants has been considered for prevention of seizures in patients with cerebral malaria. Use of a single dose of phenobarbitone administered to children or adults prior to the onset of seizures has been suggested to prevent seizures from occurring.[62] However, given that a recent study found an increased mortality among children treated preventively with phenobarbitone,[63] the role of prophylactic anticonvulsants is unclear at this time.[64]

Hypoglycemia

Hypoglycemia occurs in approximately 8% of adults[65] and one-third of children[13, 66] with severe malaria. Pregnant women and children are especially susceptible to hypoglycemia. After rehydration, 5% or 10% dextrose should be administered by intravenous infusion and blood glucose should be monitored frequently. Further complicating blood glucose levels is the fact that quinidine can cause hyperinsulinemic hypoglycemia, usually commencing at least 24 hours after initiation of treatment.[15]

Fever

Although there is some evidence that fever may inhibit parasite growth,[67, 68] there are clearly negative effects of fever, such as febrile seizures in young children and increased metabolic demands, and

currently there are insufficient data to recommend a change in the practice of fever management during malarial illness.[69] Hyperpyrexia should be treated with antipyretic drugs,[69] especially if rectal temperature is greater than 39 C.[1] Acetaminophen can be administered; however, non-steroidal anti-inflammatory agents are not recommended given that thrombocytopenia is common and coagulation abnormalities may occur.

Anemia and bleeding disorders

Anemia can develop rapidly secondary to severe hemolysis, increased RBC destruction (phagocytosis of RBCs, hypersplenism), and decreased RBC production.[70] There is no specific hemoglobin or hematocrit level below which a transfusion should be administered and the indications for red cell transfusion include evidence of impaired tissue oxygenation or ongoing coronary or cerebrovascular ischemia in patients with an adequate blood volume. In addition, correction of hemoglobin < 7 g/dL in patients with a history of active coronary artery disease, cerebrovascular insufficiency, or significant cardiac dysfunction is recommended.[51] Severe anemia may be best treated with exchange transfusion in patients with circulatory overload. Repeated transfusion may be required to offset abnormally rapid hemolysis of transfused red blood cells.[1]

Thrombocytopenia is often present. Laboratory evidence of activated coagulation is more commonly seen than is disseminated intravascular coagulation (DIC) with bleeding.[71, 72] However, DIC has been reported in series of patients in both endemic and non-endemic areas and is associated with other manifestations of severe illness such as renal, pulmonary, or cerebral end organ complications.[1, 73, 74] For this reason, drugs which increase the risk of bleeding (aspirin, corticosteroids, NSAIDs, heparin) should be avoided in patients with severe malaria.

Hemoglobinuria/ Blackwater fever

Hemoglobinuria or blackwater fever may develop in patients with severe malaria. Historically it was attributed to sensitization of RBCs to quinine after the intermittent use of this drug as a prophylactic. Hemoglobinuria in patients with malaria is seen under 3 scenarios: (a) in persons with G6PD deficiency who have received oxidant drugs or foodstuffs; (b) in persons with G6PD deficiency who have acute malaria and have received treatment with antimalarial drugs (hemolysis may either be due to the infection or the drugs); or (c) in persons with normal concentrations of G6PD but who have acute, often severe, malaria.[1] Despite the hypothetical relationship between antimalarial drugs and hemolysis, antimalarial drugs should be continued until parasitemia is resolved.[1]

Because quinidine is the only parenteral antimalarial drug available in the United States, the decision of when the patient can be changed to a second drug will need to be individualized and based on the patient's clinical condition.

PROGNOSIS

Death from malaria is preventable provided there is prompt attention given to the following 3 events--medical attention must be sought; an accurate diagnosis must be made; and efficacious treatment must be initiated. Unfortunately, there are too often delays in one or more of these components.

Several parameters have been examined for prognostic value in severe malaria. The following clinical features are associated with a poor prognosis in patients with severe malaria: impaired consciousness; repeated seizures (>3 in 24 hours); respiratory distress; substantial bleeding; and shock. Laboratory features associated with a poor prognosis are: serum creatinine >3 mg/dl; acidosis (plasma bicarbonate <15mmol/l); jaundice (serum total bilirubin >2.5mg/dl); hyperlactatemia (venous lactate > 45mg/dl); hypoglycemia (blood glucose<40 mg/dl); elevated aminotransferase levels (>3 times normal); parasitemia >500,000 parasites/mm³ or >10,000 mature trophozoites and schizonts / mm³; and 5% or greater neutrophils containing malaria pigment. [15]

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