Review

Clinical review: Severe malaria

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Abstract

Malaria represents a medical emergency because it may rapidly progress to complications and death without prompt and appropriate treatment. Severe malaria is almost exclusively caused by *Plasmodium falciparum*. The incidence of imported malaria is increasing and the case fatality rate remains high despite progress in intensive care and antimalarial treatment. Clinical deterioration usually appears 3–7 days after onset of fever. Complications involve the nervous, respiratory, renal, and/or hematopoietic systems. Metabolic acidosis and hypoglycemia are common systemic complications. Intravenous quinine and quinidine are the most widely used drugs in the initial treatment of severe falciparum malaria, whereas artemisinin derivatives are currently recommended for quinine-resistant cases. As soon as the patient is clinically stable and able to swallow, oral treatment should be given. The intravascular volume should be maintained at the lowest level sufficient for adequate systemic perfusion to prevent development of acute respiratory distress syndrome. Renal replacement therapy should be initiated early. Exchange blood transfusion has been suggested for the treatment of patients with severe malaria and high parasitemia. For early diagnosis, it is paramount to consider malaria in every febrile patient with a history of travel in an area endemic for malaria.

Keywords *Plasmodium falciparum*, severe malaria, treatment

Introduction

Malaria remains a devastating global health problem. Worldwide, an estimated 300–500 million people contract malaria each year, resulting in 1.5–2.7 million deaths annually [1,2]. Because of the increase in global travel to and immigration of people from areas endemic for malaria, the incidence of imported cases of malaria in developed countries has risen. Approximately 10 000–30 000 travelers from industrialized countries are expected to contract malaria each year [3]. In addition, drug-resistant *Plasmodium falciparum* malaria continues to spread and at present involves almost all areas of the world. An increasing number of travelers are exposed to drug-resistant plasmodia.

Malaria is caused by obligate intraerythrocytic protozoa of the genus *Plasmodium*. Humans can be infected with one (or more) of the following four species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Plasmodia are primarily transmitted by the bite of an infected female *Anopheles* mosquito, but infections can also occur through exposure to infected blood products (transfusion malaria) and by congenital transmission. In industrialized countries, most cases of malaria occur among travelers, immigrants, or military personnel returning from areas endemic for malaria (imported malaria). Exceptionally, local transmission through mosquitoes occurs (indigenous malaria).

Among patients with unexplained fever or clinical deterioration who have returned from an endemic area within the past few years, malaria must be included in the differential diagnosis. The evaluation of such cases should always include taking a comprehensive travel history. Delays in recognition and appropriate treatment of malaria increase morbidity and mortality [4]. Here, the clinical manifestations, laboratory findings, diagnosis, and treatment of severe malaria are reviewed.

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; TNF = tumor necrosis factor; WHO = World Health Organization.

Characteristics of malaria

Life cycle and morphology

When the infected anopheline mosquito takes a blood meal, sporozoites are inoculated into the bloodstream. Within an hour sporozoites enter hepatocytes and begin to divide into exoerythrocytic merozoites (tissue schizogony). For *P. vivax* and *P. ovale*, dormant forms called hypnozoites typically remain quiescent in the liver until a later time; *P. falciparum* does not produce hypnozoites. Once merozoites leave the liver, they invade erythrocytes and develop into early trophozoites, which are ring shaped, vacuolated and uninucleated. Once the parasite begins to divide, the trophozoites are called schizonts, consisting of many daughter merozoites (blood schizogony). Eventually, the infected erythrocytes are lysed by the merozoites, which subsequently invade other erythrocytes, starting a new cycle of schizogony. The duration of each cycle in *P. falciparum* is about 48 hours. In nonimmune humans, the infection is amplified about 20-fold each cycle. After several cycles, some of the merozoites develop into gametocytes, the sexual stage of malaria, which cause no symptoms, but are infective for mosquitoes [5].

Pre-patent and incubation periods

In nonimmune individuals with *P. falciparum* infection, the median pre-patent period (time from sporozoite inoculation to detectable parasitemia) is 10 days (range 5–10 days), and the median incubation period (time from sporozoite inoculation to development of symptoms) is 11 days (range 6–14 days). The incubation period may be significantly prolonged by the level of immunity acquired through previous exposures, by antimalarial prophylaxis, or by prior partial treatment, which may mitigate, but not prevent the disease [6]. Most nonimmune travelers develop symptoms of falciparum malaria within 1 month of departing from a malaria-endemic area (median 10 days); there have been reports of falciparum malaria presenting up to 4 years later [7]. For nonfalciparum malaria the incubation period is usually longer (median 15–16 days), and both *P. vivax* and *P. ovale* malaria may relapse months or years after exposure due to the presence of hypnozoites in the liver. The longest reported incubation period for *P. vivax* is 30 years [7].

Signs and symptoms of malaria

The clinical symptoms of malaria are primarily due to schizont rupture and destruction of erythrocytes. Malaria can have a gradual or a fulminant course with nonspecific symptoms. The presentation of malaria often resembles those of common viral infections; this may lead to a delay in diagnosis [8]. The majority of patients experience fever (>92% of cases), chills (79%), headaches (70%), and diaphoresis (64%) [9]. Other common symptoms include dizziness, malaise, myalgia, abdominal pain, nausea, vomiting, mild diarrhea, and dry cough. Physical signs include fever, tachycardia, jaundice, pallor, orthostatic hypotension, hepatomegaly, and splenomegaly. Clinical examination in nonimmune persons may be completely unremarkable, even without fever.

Severe malaria

Almost all severe forms and deaths from malaria are caused by *P. falciparum*. Rarely, *P. vivax* or *P. ovale* produce serious complications, debilitating relapses, and even death [10]. In 1990, the World Health Organization (WHO) established criteria for severe malaria in order to assist future clinical and epidemiological studies [11]. In 2000, the WHO revised these criteria to include other clinical manifestations and laboratory values that portend a poor prognosis based on clinical experience in semi-immune patients (Table 1) [12]. The major complications of severe malaria include cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding. Acidosis and hypoglycemia are the most common metabolic complications. Any of these complications can develop rapidly and progress to death within hours or days [12]. In many patients, several of these complications exist together or evolve in rapid succession within a few hours. In clinical practice, patients must be assessed for any of these signs or symptoms that suggest an increased risk for developing complications and must be treated immediately. In various studies risk factors for severe malaria and death include age greater than 65 years, female sex (especially when associated with pregnancy), nonimmune status, coexisting medical conditions, no antimalarial prophylaxis, delay in treatment, and severity of the illness at admission (coma, acute renal failure, shock, pulmonary edema, coagulation disorders) [13–15]. In tropical countries with a high transmission of malaria (hyperendemic areas), severe malaria is predominantly a disease of young children (1 month to 5 years of age). In industrialized countries, most life-threatening complications occur in nonimmune travelers returning from endemic areas. Severe malaria accounts for approximately 5% of imported malaria cases (range 1–38%) [9]. The case fatality rate in returning travelers with falciparum malaria varies from 0.6% to 3.8%, and for severe malaria it may exceed 20%, even when managed in intensive care units (ICUs) [4].

Laboratory findings

Thrombocytopenia is the most common laboratory abnormality (60% of cases), followed by hyperbilirubinemia (40%), anemia (30%), and elevated hepatic aminotransferase levels (25%) [16]. The leukocyte count is usually normal or low, but neutrophilia with a marked increase in band forms (left shift) is present in the majority of cases. The erythrocyte sedimentation rate, C-reactive protein, and procalcitonin are almost invariably elevated. The severity of malaria corresponds to the degree of the laboratory abnormalities. In one study of travelers who returned from the tropics, thrombocytopenia and hyperbilirubinemia had a positive predictive value of 95% for malaria [17].

Diagnosis of malaria

Conventional microscopy

Light microscopy of thick and thin stained blood smears remains the standard method for diagnosing malaria [18].

Table 1

Indicators of severe malaria and poor prognosis

Manifestation	Features
Initial World Health Organization criteria from 1990 [11]	
Cerebral malaria	Unrousable coma not attributable to any other cause, with a Glasgow Coma Scale score ≤9. Coma should persist for at least 30 min after a generalized convulsion
Severe anemia	Hematocrit <15% or hemoglobin <50 g/l in the presence of parasite count >10 000/μl
Renal failure	Urine output <400 ml/24 hours in adults (<12 ml/kg/24 hours in children) and a serum creatinine >265 μmol/l (>3.0 mg/dl) despite adequate volume repletion
Pulmonary edema and acute respiratory distress syndrome	The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoxemia, and positive end-expiratory pressure [26]
Hypoglycemia	Whole blood glucose concentration <2.2 mmol/l (<40 mg/dl)
Circulatory collapse (algid malaria)	Systolic blood pressure <70 mmHg in patients >5 years of age (<50 mmHg in children aged 1–5 years), with cold clammy skin or a core-skin temperature difference >10°C
Abnormal bleeding and/or disseminated intravascular coagulation	Spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation
Repeated generalized convulsions	≥3 convulsions observed within 24 hours
Acidemia/acidosis	Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l)
Macroscopic hemoglobinuria	Hemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency
Added World Health Organization criteria from 2000 [12]	
Impaired consciousness	Rousable mental condition
Prostration or weakness	
Hyperparasitemia	>5% parasitized erythrocytes or >250 000 parasites/μl (in nonimmune individuals)
Hyperpyrexia	Core body temperature >40°C
Hyperbilirubinemia	Total bilirubin >43 μmol/l (>2.5 mg/dl)

Thick smears are 20–40 times more sensitive than thin smears for screening of *Plasmodium* parasites, with a detection limit of 10–50 trophozoites/μl. Thin smears allow one to identify malaria species (including the diagnosis of mixed infections), quantify parasitemia, and assess for the presence of schizonts, gametocytes, and malarial pigment in neutrophils and monocytes. The diagnostic accuracy relies on the quality of the blood smear and experience of laboratory personnel. Before reporting a negative result, at least 200 oil immersion visual fields at a magnification of 1000× should be examined on both thick and thin smears, which has a sensitivity of 90%. The level of parasitemia may be expressed either as a percentage of parasitized erythrocytes or as the number of parasites per microliter of blood. In nonfalciparum malaria, parasitemia rarely exceeds 2%, whereas it can be considerably higher (>50%) in falciparum malaria. In nonimmune individuals, hyperparasitemia (>5% parasitemia or >250 000 parasites/μl) is generally associated with severe disease [19].

In falciparum malaria, parasitized erythrocytes may be sequestered in tissue capillaries resulting in a falsely low parasite count in the peripheral blood ('visible' parasitemia) [7]. In such instances, the developmental stages of the parasite seen on blood smear may help to assess disease severity better than parasite count alone. The presence of more mature parasite forms (>20% of parasites as late trophozoites and schizonts) and of more than 5% of neutrophils containing malarial pigment indicates more advanced disease and a worse prognosis [20]. One negative blood smear makes the diagnosis of malaria very unlikely (especially the severe form); however, smears should be repeated every 6–12 hours for 48 hours if malaria is still suspected.

Alternative diagnostic methods

Although examination of the thick and thin blood smear is the 'gold standard' for diagnosing malaria, important advances have been made in diagnostic testing, including fluorescence microscopy of parasite nuclei stained with acridine orange, rapid dipstick immunoassay, and polymerase chain reaction assays. Sensitivity and specificity of some of these methods approach or even exceed those of the thin and thick smear [21]. Rapid dipstick immunoassays detect species-specific circulating parasite antigens targeting either the histidine-rich protein-2 of *P. falciparum* or a parasite-specific lactate dehydrogenase. Although the dipstick tests may enhance diagnostic speed, microscopic examination remains mandatory in

patients with suspected malaria, because occasionally these dipstick tests are negative in patients with high parasitemia, and their sensitivity below 100 parasites/μl is low [22]. Tests based on polymerase chain reaction for species-specific *Plasmodium* genome are more sensitive and specific than are other tests, detecting as few as 10 parasites/μl blood [23]. Antibody detection has no value in the diagnosis of acute malaria. It is mainly used for epidemiologic studies.

Complications in patients with severe malaria

Patients with severe malaria should be treated in an ICU. Should clinical deterioration to severe malaria occur, it usually develops 3–7 days after fever onset, although there have been rare reports of nonimmune patients dying within 24 hours of developing symptoms. Severe malaria may develop even after initial treatment response and complete clearance of parasitemia due to delayed cytokine release.

Neurologic complications

Cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. The onset may be dramatic with a generalized convulsion, or gradual with initial drowsiness and confusion, followed by coma lasting from several hours to several days. The strict definition of cerebral malaria requires the presence of *P. falciparum* parasitemia and the patient to be unrousable with a Glasgow Coma Scale score of 9 or less, and other causes (e.g. hypoglycemia, bacterial meningitis and viral encephalitis) ruled out [24]. From a practical standpoint, any alteration in mental status should be treated as cerebral malaria. A lumbar puncture should be performed to rule out bacterial meningitis. To distinguish cerebral malaria from transient postictal coma, unconsciousness should persist for at least 30 min after a convulsion. The deeper the coma, the worse is the prognosis. On examination, neurologic abnormalities resemble those of a diffuse symmetric encephalopathy, similar to a metabolic encephalopathy. Nuchal rigidity and focal neurologic signs are rare. Corneal and pupillary reflexes are usually intact. The plantar responses are extensor in about half of the patients. Convulsions are usually generalized, with nonspecific abnormalities on electroencephalographic examination. Computed tomography or magnetic resonance imaging often shows evidence of mild cerebral swelling; marked edema or focal lesions are unusual. Delirium, agitation, and even transient paranoid psychosis may develop as the patient recovers consciousness. Apart from cerebral malaria, other neurologic sequelae can occur, such as cranial nerve abnormalities, extrapyramidal tremor, and ataxia.

Several hypotheses have been proposed to explain the pathophysiology of cerebral malaria, but none have been completely satisfactory. The excellent neurologic recovery argues against ischemia alone being the culprit. Raised intracranial pressure, at least in nonimmune adults, appears not to play an important role in the pathogenesis of cerebral malaria. The mortality of cerebral malaria ranges from 10% to 50% with treatment. Most survivors (>97% adults and >90% children) have no neurologic abnormalities on hospital discharge [25].

Pulmonary complications

Acute lung injury usually occurs a few days into the disease course. It may develop rapidly, even after initial response to antimalarial treatment and clearance of parasitemia. The first indications of impending pulmonary edema include tachypnea and dyspnea, followed by hypoxemia and respiratory failure requiring intubation. Pulmonary edema is usually noncardiogenic and may progress to acute respiratory distress syndrome (ARDS) with an increased pulmonary capillary permeability [26]. Acute lung injury is defined as the acute onset of bilateral pulmonary infiltrates with an arterial oxygen tension/fractional inspired oxygen ratio of 300 mmHg or less, a pulmonary artery wedge pressure of 18 mmHg or less, and no evidence of left atrial hypertension. ARDS is defined as acute lung injury and an arterial oxygen tension/fractional inspired oxygen ratio of 200 mmHg or less [27]. Volume overload and hypoalbuminemia may aggravate pulmonary capillary leakage. Chest radiograph abnormalities range from confluent nodules to basilar and/or diffuse bilateral pulmonary infiltrates. Noncardiogenic pulmonary edema rarely occurs with *P. vivax* and *P. ovale* malaria.

Renal complications

Acute renal failure is usually oliguric (<400 ml/day) or anuric (<50 ml/day), rarely nonoliguric, and may require temporary dialysis [28]. Urine sediment is usually unremarkable. In severe cases, acute tubular necrosis may develop secondary to renal ischemia [29]. The term 'blackwater fever' refers to passage of dark red, brown, or black urine secondary to massive intravascular hemolysis and resulting hemoglobinuria. Usually, this condition is transient and not accompanied by renal failure.

Hypoglycemia

Hypoglycemia is a common feature in patients with severe malaria. It may be overlooked because all clinical features of hypoglycemia (anxiety, dyspnea, tachycardia, sweating, coma, abnormal posturing, generalized convulsions) are also typical of severe malaria itself. Hypoglycemia may be caused by quinine- or quinidine-induced hyperinsulinemia, but it may be found also in patients with normal insulin levels.

Hypotension and shock

Most patients with shock exhibit a low peripheral vascular resistance and elevated cardiac output. Cardiac pump function appears remarkably well preserved despite intense sequestration of parasitized erythrocytes in the microvasculature of the myocardium. Postural hypotension may be secondary to autonomic dysfunction. Severe hypotension can develop suddenly, usually with pulmonary edema, metabolic acidosis, sepsis, and/or massive hemorrhage due to splenic rupture or from the gastrointestinal tract.

Hematologic abnormalities

Severe anemia is more common in children in highly endemic areas due to repeated or chronic *Plasmodium* infections. Thrombocytopenia is common, but usually not associated with bleeding. Disseminated intravascular coagulation is reported in fewer than 10% of patients with severe malaria.

Antimalarial treatment of severe malaria

Nonimmune patients with *P. falciparum* malaria should be treated as a medical emergency and be considered for hospital admission, regardless of disease severity at presentation. All patients with severe malaria (Table 1) and those who are unable to tolerate drugs orally should initially receive parenteral treatment immediately (Table 2) and be admitted to the ICU [8]. In these patients, gastrointestinal intolerance and erratic intestinal absorption make the oral route of administration unreliable. To prevent medication errors it is important to check whether the recommended dose relates to a base or salt. Patients with severe malaria should always receive a full treatment dose, including those with breakthrough malaria and those who received some prior antimalarial medication.

Monitoring treatment response

When reliable blood smear results are not immediately available and malaria is suspected on clinical grounds, empiric treatment for falciparum malaria should be administered without delay. Treatment response should be assessed by parasite count daily until clearance of all trophozoites is achieved. Parasitemia may rise during the first 12–24 hours, because available drugs do not inhibit schizont rupture and release of merozoites. Rising parasitemia beyond 36–48 hours after the start of antimalarial treatment indicates treatment failure, usually because of high-level drug resistance [30]. Because nonimmune hosts may exhibit a high pretreatment total parasite burden (up to 10^{12} parasites), it may take up to 6 days to achieve complete elimination of *P. falciparum* trophozoites from the blood, even with fast-acting antimalarial agents (e.g. quinine, artemisinin derivatives). A rising gametocyte count does not indicate treatment failure. Persons with partial immunity can tolerate low parasitemia (<10 000 parasites/μl) without clinical symptoms [19]. Therefore, in a proportion of semi-immune individuals parasitemia may not be responsible for current signs and symptoms [6]. In 5–10% of patients with falciparum malaria, treatment failure will occur, with recurrence of symptoms usually within 1 month of treatment. A repeated blood smear examination at 7 and 28 days after completion of therapy is recommended to monitor for relapse of severe falciparum malaria [31].

Quinine and quinidine

Intravenous quinine is currently the most widely used agent in the treatment of severe falciparum malaria, usually formulated as a dihydrochloride salt. In the USA, quinidine gluconate (the dextrorotatory optical diastereoisomer of quinine) is the only available intravenous antimalarial agent, and it may be used instead of quinine [32]. Quinidine has a twofold to threefold greater antimalarial activity than does quinine, but it is also more cardiotoxic and mandates electrocardiographic monitoring [33]. Therefore, most authors prefer quinine over quinidine for the treatment of severe malaria. Both quinine and quinidine may cause cinchonism (bitter taste, dysphoria, tremor, tinnitus, reversible high-tone hearing loss, headache, nausea, vomiting, and abdominal pain) or pruritus, which should not lead to dose reduction. Both drugs have narrow therapeutic windows. Severe toxicities include cardiac arrhythmias, hypotension, blindness, deafness, and hyperinsulinemic hypoglycemia [12,34].

An initial loading dose of quinine or quinidine should be administered as soon as possible, followed by the maintenance dose. Both drugs should be given by a rate-controlled intravenous infusion (infusion pump), and never by a bolus injection, which may cause fatal hypotension or cardiac arrhythmia. Without a loading dose, it takes more than 24 hours to achieve therapeutic drug concentration. This delay may allow sequestration of trophozoites causing major organ dysfunction. The loading dose should not be administered to patients who received quinine, quinidine, halofantrine, or mefloquine within the preceding 12 hours. If intravenous treatment is continued past 48 hours, the maintenance dose should be reduced by 30–50%. In renal failure (clearance <10 ml/min) and in dialysis patients a normal loading dose should be administered, but the maintenance dose should be reduced by 30–50%. If hemodialysis is performed, quinine or quinidine should be administered after dialysis. Electrocardiographic monitoring is mandatory with quinidine infusion and with quinine infusion if the patient has acute renal failure. If the QRS complex lengthens by more than 25% beyond baseline or the QTc interval increases to more than 500 ms, the infusion should be slowed or discontinued. Monitoring of plasma quinine concentrations does not predict cardiotoxicity; electrocardiography may be a more accurate approach for monitoring cardiotoxicity [35]. Therapeutic plasma concentration for quinine ranges from 8 to 20 mg/l measuring the total (protein bound and free) drug. Free (unbound) quinine level is more reliable for therapeutic monitoring than total drug concentration and should be 1–2 mg/l. For quinidine the total therapeutic plasma concentration is between 4 to 8 mg/l [33]. Apart from lengthening of the QTc interval, common electrocardiographic abnormalities include supraventricular and ventricular ectopic beats, sinus bradycardia (<50 beats/min), and ventricular tachycardia [36].

Artemisinin derivatives

Although artemisinin derivatives clear parasites from blood about 20% faster than quinine dihydrochloride, improved survival was observed only in regions of South East Asia with recognized quinine resistance [37]. Furthermore, recovery from coma may be delayed and the incidence of seizures was higher than with quinine dihydrochloride [12,38,39]. At present, artemisinin derivatives are recommended for treat-

Table 2

Recommended regimens for initial parenteral treatment of severe falciparum malaria

Drug	Loading dose[1]	Maintenance dose	Comments
Regimen 1			
Quinine dihydrochloride salt (available outside the USA), reconstituted in 5% glucose or normal saline	7 mg salt/kg iv over 30 min followed immediately by maintenance dose OR 20 mg salt/kg over 4 hours, followed 8 hours later by maintenance dose	10 mg salt/kg diluted in 10 ml/kg isotonic fluid iv over 4 hours repeated every 8 hours[2]	If hemodialysis is performed, then quinine is administered after dialysis. Monitor blood glucose because of risk for developing hyperinsulinemic hypoglycemia
PLUS (either concurrently or immediately thereafter)			
Doxycycline[3]	Not required	1.5 mg/kg (usually 100 mg) po or iv every 12 hours for 7 days	Should not be given to pregnant or breast-feeding women or children <8 years old
Regimen 2			
Quinidine gluconate (available in the USA), reconstituted in normal saline	10 mg salt/kg (equivalent to 6.2 mg base/kg) iv infused over 1–2 hours, followed immediately by maintenance dose	0.02 mg/kg/min salt (equivalent to 0.0125 mg/kg/min base) continuous iv infusion[2]	Electrocardiographic monitoring is mandatory; slow or stop infusion if QRS lengthens >25% of baseline value or QTc interval >500 ms
PLUS (either concurrently or immediately thereafter)			
Doxycycline[3]	Not required	Same as above	
Regimen 3			
Artesunate	2.4 mg/kg iv bolus	1.2 mg/kg iv daily[4]	Artesunic acid 60 mg is dissolved in 0.6 ml 5% sodium bicarbonate, diluted to 3–5 ml 5% glucose, and given immediately by iv bolus injection
PLUS			
Mefloquine	15 mg/kg (750 mg) base po initial dose	10 mg/kg (500 mg) base po at 6–8 hours and (if >60 kg) followed by 5 mg/kg (250 mg) po at 16 hours	Total dose: 1500 mg
Regimen 4			
Artemether	3.2 mg/kg im	1.6 mg/kg im daily[4]	
PLUS			
Mefloquine	Same as above	Same as above	

[1]Loading dose should not be administered to patients who received quinine, quinidine, halofantrine, or mefloquine within the preceding 12 hours. [2]Intravenous quinine or quinidine should be given for at least 24 hours but oral antimalarial treatment should be substituted as soon as the patient is stable and can take oral therapy to complete the treatment course. If intravenous treatment is continued past 48 hours, then the maintenance dose should be reduced by 30–50%. In renal failure and in dialysis patients, the maintenance dose of quinine should be reduced by 30–50%. [3]Clindamycin 5 mg/kg (usually 300 mg) po or iv every 8 hours can be administered if the patient is unable to take doxycycline. [4]Parenteral artesunate or artemether should be given for at least 3 days but oral antimalarial treatment should be substituted as soon as the patient is stable and can take oral therapy to complete the treatment course. im = intramuscularly; iv = intravenously; po, orally.

ment of quinine-resistant *P. falciparum* infections, combined with mefloquine, doxycycline, or clindamycin to prevent recrudescence. There are four artemisinin formulations: dihydroartemisinin, artesunate (a water-soluble compound for intramuscular injection), arteether, and artemether (an oil-soluble compound for intravenous injection). Artesunate and artemether are metabolized to the biologically active metabolite dihydroartemisinin. Artemisinin derivatives are well tolerated. Side effects include nausea, vomiting, pruritus, and fever; bleeding and cardiac arrhythmias rarely occur. Despite reports of brainstem neurotoxicity with high doses in animal studies, this side effect has not been observed in humans to date.

Chloroquine

Parenteral chloroquine is the drug of choice for severe chloroquine-susceptible *P. falciparum* infections (originating from Central America north of the Panama Canal, Haiti, Dominican Republic, Argentina, Paraguay, Egypt, Syria, Turkey, Saudi Arabia, Iraq, Azerbaijan, and Mauritius) and for those rare cases of life-threatening malaria caused by

Table 3

Recommended oral treatment for severe falciparum malaria after initial parenteral therapy for at least 24 hours when clinical improvement is evident and the patient can tolerate oral medication

Drug	Dose	Comments
Artemether/lumefantrin	80 mg arthemeter/480 mg lumefantrin once daily for 3 days	Well tolerated, faster parasite clearance, but longer fever resolution time
Atovaquone/proguanil	1000 mg atovaquone/400 mg proguanil at 0, 8, 24, 36, 48 and 60 hours	Well tolerated, more effective than mefloquine in treatment of multidrug-resistant falciparum malaria
Mefloquine	15 mg/kg (750 mg) base at 0 hours, followed by 10 mg/kg (500 mg) base at 6–8 hours, and (if >60 kg) followed by 5 mg/kg (250 mg) at 16 hours	Contraindicated in persons with seizure or psychiatric disorders, or with cardiac conduction abnormalities
Quinine (sulfate salt)	10 mg salt/kg (600–650 mg) every 8 hours to complete 7 days of treatment (total duration)	Side effects include cinchonism and pruritus

P. ovale, *P. malariae*, and *P. vivax* (except for infections from Papua New Guinea, Sumatra, Irian Jaya, Myanmar, Vanuatu, India, and the Amazon region of Brazil) [40]. Chloroquine may have a more rapid effect on lowering parasitemia than either quinine or quinidine, but it also has a more profound hypotensive side effect. Chloroquine should be given by a controlled intravenous infusion with a loading dose 10 mg/kg base over 8 hours, followed immediately by a maintenance dose of 15 mg/kg base infused over 24 hours.

Oral treatment

When patients with severe falciparum malaria show significant clinical improvement (after at least 24 hours of parenteral therapy) and can tolerate tablets, they should be switched to oral medication (Table 3). The choice of oral antimalarials is guided by the susceptibility pattern of the plasmodia. Combined regimens, such as artemether–lumefantrin or atovaquone–proguanil, are associated with lower risk for development of resistance than are mefloquine or quinine. Higher blood levels are reached when oral antimalarials are given with or after food intake.

Critical care management

Basic supportive care

The intravascular volume should be maintained at the lowest level sufficient for adequate systemic perfusion. In hypotension early use of inotropic support is indicated rather than overhydration. Negative fluid balance is critical to avoid exacerbating acute lung injury, but is balanced against the risk for precipitating acute renal failure [41]. The patient may need to be intubated because of impaired consciousness or because of acute lung injury. Mechanical ventilation with lower tidal volume improves the clinical outcome [42]. A higher positive end-expiratory pressure may be needed to maintain optimal arterial oxygenation. In respiratory acidosis, the plateau pressure should be in excess of 25 cm H_2O and the ventilator rate should be increased. Surfactant therapy, inhaled nitric oxide, and corticosteroids have no effect on survival or duration of ventilation in patients with ARDS [43,44].

Comatose patients should be placed in a semirecumbent position to reduce the risk for aspiration. Serum sodium concentration, arterial carbon dioxide tension, blood glucose, and arterial lactate concentration should be monitored frequently. Seizures should be treated promptly with anticonvulsants, but their prophylactic use is still in dispute [12]. The efficacy of hypertonic mannitol in treatment of cerebral edema is not proven.

Early institution of renal replacement therapy may avoid the development of ARDS [45]. Patients with hypotension tolerate continuous renal replacement therapy better than conventional intermittent hemodialysis. In addition, a continuous regulation of body fluid avoids periods of volume overload and depletion. A meta-analysis involving 13 studies (only three of which were randomized controlled trials) in which conventional dialysis was compared with continuous hemofiltration showed overall no significant difference in mortality between groups. However, after adjusting for severity of illness these authors concluded that continuous renal replacement therapy was associated with a reduced risk for death [46]. Acidosis is usually multifactorial in origin, with causes including tissue hypoxia, liver dysfunction, and impaired renal handling of bicarbonate [47]. Blood transfusion should be considered if the hematocrit falls below 20%, but volume overload should be avoided.

Antimicrobial therapy

Bacterial infections often complicate the course of patients with severe malaria. Common infections include aspiration pneumonia and sepsis. Parasite factors stimulate the production and release of cytokines such as tumor necrosis factor (TNF)-α and interleukin-1 by macrophages, resulting in fever, chills, and hyperkinetic hemodynamic changes. The clinical and laboratory characteristics of severe malaria are similar to those of sepsis. Therefore, a bacterial infection in a patient with malaria may not be recognized initially. Repeated microbiologic sampling of appropriate body fluids such as blood, sputum, cerebrospinal fluid, and urine may help to diagnose and treat a possible infection early.

Exchange blood transfusion and red cell exchange (erythrocytapheresis)

Death in patients with malaria is related to the level of parasitemia, with significant mortality when parasitemia exceeds 5% despite appropriate parenteral antimalarial therapy. Exchange transfusion may rapidly reduce parasitemia, decrease the risk for intravascular hemolysis, improve blood flow, decrease cytokines, and improve oxygen-carrying capacity. Although there are no sufficiently powered, randomized, controlled studies, exchange blood transfusion has been suggested in patients with severe malaria, especially for those with hyperparasitemia (>5%) [12]. Some authors recommend exchange transfusion only in countries with well equipped and staffed ICUs and safe blood supplies [48]. Published data about the effectiveness of this method is controversial. A meta-analysis involving eight studies [49], in which groups of patients with severe malaria who received adjunct exchange transfusion were compared with patients who received antimalarial chemotherapy alone, found no difference in survival rates between groups. However, patients who received transfusions had higher parasitemia and were much more ill according to WHO criteria for severe malaria. Cytokines such as TNF-α and interleukin-1 probably contribute to the pathogenesis of severe malaria, and some authors have suggested that plasma exchange, plasmapheresis, and hemodialysis are effective alternatives to exchange transfusion [50].

Unproven treatments

Therapy with monoclonal antibodies against TNF-α shortens the duration of fever, but has no impact on mortality in patients with severe and complicated malaria, and may increase morbidity due to neurologic sequelae [51]. Although corticosteroids were used in the past to treat patients with cerebral malaria, a controlled trial has shown that they are harmful. Those who received dexamethasone had a longer duration of coma and worse outcome than did patients who received antimalarial chemotherapy alone [24]. Results of studies of antipyretics, pentoxifylline, hyperimmune serum, and iron chelators (deferoxamine) have shown no effect on outcome [52].

Conclusion

Malaria should be included in the differential diagnosis of every febrile illness in a person with a history of travel to a malaria-endemic area. Delays in recognition and appropriate treatment of malaria increase morbidity and mortality. The major complications of severe malaria include cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding. Any of these complications can develop rapidly and progress to death within hours or days. Light microscopy of blood smears is the standard method for diagnosing malaria, although new and promising nonmicroscopic diagnostic methods are under development. All patients with severe malaria should receive parenteral treatment immediately. Currently, intravenous quinine and quinidine are the most widely used agents, whereas artemisinin derivatives in general are recommended for treatment of quinine-resistant *P. falciparum* infections. Several Internet websites with additional and updated information on malaria are listed in the Appendix.

Competing interests

None declared.

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Appendix

Internet websites for obtaining additional information on malaria:

- Centers for Disease Control and Prevention (CDC), National Center for Infectious Diseases, USA: http://www.cdc.gov/travel
- World Health Organization: http://www.who.int/health_topics/malaria
- Health Canada, Population and Public Health Branch: www.TravelHealth.gc.ca
- Public Health Laboratory Service, Malaria Reference Laboratory at London School of Hygiene and Tropical Medicine, UK: http://www.malaria-reference.co.uk
- Swiss Tropical Institute, Switzerland: http://www.sti.ch
- Safe travel: http://www.safetravel.ch
- International Society of Travel Medicine: http://www.istm.org
- Malaria Foundation International: http://www.malaria.org