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Intensive care in severe malaria: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine

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ABSTRACT

Severe malaria is common in tropical countries in Africa, Asia, Oceania and South and Central America. It may also occur in travelers returning from endemic areas. Plasmodium falciparum accounts for most cases, although P vivax is increasingly found to cause severe malaria in Asia. Cerebral malaria is common in children in Africa, manifests as coma and seizures, and has a high morbidity and mortality. In other regions, adults may also develop cerebral malaria but neurological sequelae in survivors are rare. Acute kidney injury, liver dysfunction, thrombocytopenia, disseminated intravascular coagulopathy (DIC) and acute respiratory distress syndrome (ARDS) are also common in severe malaria. Metabolic abnormalities include hypoglycemia, hyponatremia and lactic acidosis. Bacterial infection may coexist in patients presenting with shock or ARDS and this along with a high parasite load has a high mortality. Intravenous artesunate has replaced quinine as the antimalarial agent of choice. Critical care management as per severe sepsis is also applicable to severe malaria. Aggressive fluid boluses may not be appropriate in children. Blood transfusions may be required and treatment of seizures and raised intracranial pressure is important in cerebral malaria in children. Mortality in severe disease ranges from 8 to 30% despite treatment.

Contents

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1. Introduction

Malaria is a protozoal infection transmitted by the bite of the female Anopheles mosquito and is endemic in tropical regions of Africa, Asia, Oceania and South and Central America [1]. Five species of Plasmodia can cause infections in humans however *Plasmodium falciparum* is responsible for 60% and Plasmodium vivax for most of the remainder [1]. *Plasmodium ovale*, *P malariae* and *P knowlesi* (monkey malaria) account for <1% of malarial infections [1]. This article focuses mainly on P falciparum and P vivax malaria which are responsible for almost all cases of severe, life-threatening malaria. As per WHO estimates, there were 212 million new cases of malaria worldwide in 2015 of which 90% were in the African Region, 7% in South-East Asia and 2% in the Eastern Mediterranean region, with about 429,000 deaths [2]. Between 2010 and 2015, malaria incidence rates dropped by 21% globally, and mortality rates similarly fell by 29% [2]. Almost 92% of malarial deaths occur in Sub Saharan Africa and 70% of deaths worldwide occur in children <5 years of age.

Approximately 1% of P falciparum infections result in severe malaria characterized by organ dysfunction, metabolic changes and anemia which may rapidly progress to death if untreated [3]. Most publications on severe malaria are from Sub-Saharan Africa which is classified as hyper-endemic by the WHO. In this region >50% of children aged 2 to 9 years will have had at least one episode of malaria and the frequency of malarial inoculation by bites of mosquitos harboring the parasite is >10 per person/year [1,4]. As such in Sub-Saharan Africa, clinical infections, including severe malaria are seen predominantly in children below the age of 5 years [1-4]. By the age of 6 these children develop natural immunity due to frequent infections and severe malaria is rare in adolescents or adults [1,3,4]. In other endemic areas of Asia, the Mediterranean region, and South and Central America, malaria transmission is highly seasonal, and the inoculation rate is often <1/year [1,4]. The acquisition of natural immunity is low and adults and children are equally predisposed to acute or severe malaria [1-4]. Consequently, almost all reports of severe malaria from Africa are of infections in children with predominantly cerebral involvement, or involve travelers to the region, while reports from other parts of the world deal with infections in adults with more involvement of other organ systems [1,4-6]. These differences in clinical patterns are important in interpreting findings of studies from different parts of the world.

2. Parasitology

The infected mosquito inoculates sporozoites into the host during a bite. These invade the liver and develop into hepatic merozoites over the next 5 to 8 days [1,4]. Mature merozoites are released into the circulation initiating the asexual intra-erythrocytic cycle which takes 48 h for both P falciparum and P vivax, and during which the parasites form ring-like schizonts [4]. After 48 h, the infected erythrocytes rupture and release 6–30 daughter merozoites, each of which can infect new erythrocytes, propagating the infection and producing the clinical manifestations [4]. The incubation period usually lasts 7 to 14 days; it may however be longer in patients who have received macrolides, trimethoprim –sulfamethoxazole, quinolones or tetracyclines. A few schizonts develop into gametocytes, which when ingested by a mosquito, can propagate the sexual phase of the life cycle in the mosquito, ultimately leading to the formation of sporozoites that can infect humans [4]. The infected erythrocytes in falciparum malaria adhere to endothelial cells in capillaries and arterioles at a particular phase of the asexual lifecycle, causing microcirculatory occlusion, endothelial damage and also intravascular hemolysis. In patients with high levels of parasitemia (where >10% of erythrocytes are infected) cerebral or other organ dysfunction occurs leading to severe or complicated malaria [1,4]. Although malaria tends to be more severe with increasing levels of parasitemia, severe malaria may also occur with lesser degrees of parasitemia, as parasitized red cells adhere to the endothelial surface and are not seen in peripheral blood [1,3,7]. In plasmodium vivax infection the degree of parasitemia is much less (usually <1%) and microcirculatory occlusion is rare [4]. As a result severe vivax malaria is still rare, but is being increasingly reported in Asia and South America [8,9].

Repeated clinical or subclinical infections in residents of endemic areas confer partial protective immunity which prevents severe or clinically apparent falciparum malaria [1-4]. However, this partial immunity is lost after residing in a non-endemic area for a few years. Severe falciparum malaria is therefore commonly seen in nonimmune residents or visitors to endemic areas. Pregnancy too is an important predisposing factor for severe falciparum malaria [1,3].

3. Clinical features and diagnosis of severe malaria

Uncomplicated falciparum malaria is characterized by high spiking fever usually accompanied by chills and rigors [4]. The fever is intermittent and lasts for a few hours, after which it subsides with profuse sweating. Patients may get multiple spikes of fever per day for the first few days. Other symptoms at this time include headache and febrile delirium. If untreated, the illness may progress to severe malaria of which cerebral

Table 1
WHO Criteria (2015) for diagnosis of severe malaria [1].

Feature	Definition
Impaired consciousness	Glasgow coma score < 11 or Blantyre coma score < 3 in children
Prostration	Generalized weakness – person unable to sit, stand or walk without assistance
Multiple convulsions	>2 episodes in 24 h
Acidosis	Base deficit of >8 mEq/L, serum bicarbonate <15 mmol/L or plasma lactate ≥5 mmol/L
Hypoglycemia	Blood or plasma glucose <2.2 mmol/L or <40 mg/dL
Anemia	Hemoglobin ≤5 g/dL or hematocrit ≤15% in children and Hemoglobin <7 g/dL or hematocrit <20% in adults
Renal impairment	Serum creatinine >265 μmol/L or >3 mg/dL or blood urea >20 mmol/L
Jaundice	Serum bilirubin >50 μmol/L or >3 mg/dL with parasite count (number of infected RBCs) > 100,000/μL
Pulmonary edema	Radiological features, hypoxemia, tachypnea and crackles
Bleeding	Spontaneous bleeding or coagulopathy
Shock	Systolic blood pressure < 70 mmHg in children and <80 mmHg in adults, cool peripheries, prolonged capillary refill
Hyperparasitemia	P falciparum parasitemia >10%

Note: Any one of these criteria in the presence of P falciparum infection is required to make the diagnosis.

malaria is the most dreaded form [3]. Severe malaria is characterized by altered consciousness, seizures, organ dysfunction, metabolic changes, hypoglycemia, hemolysis and severe thrombocytopenia [1-6]. The WHO criteria (Table 1) are commonly used to define severe malaria [1].

The gold standard for diagnosis of P falciparum is the demonstration of parasitized red cells on microscopic examination of a peripheral blood smear by a trained microscopist [1,3,4]. It permits the identification of asexual intra-erythrocytic forms of the parasite, it differentiates between falciparum and vivax malaria, it identifies mixed infections with both P falciparum and P vivax, it allows an estimate of the extent of parasitemia (percent of red cells harboring the parasite) and identifies gametocytes. However, it is time consuming and is now being replaced by rapid diagnostic tests that use immunochromatography to identify parasite antigens [1]. The Pf-HRP2 test detects the P falciparum histidine-rich protein in a drop of blood and is very specific for falciparum infection [1]. The other commonly used test detects parasite lactate dehydrogenase and gives a positive result with any plasmodial infection. It can also differentiate between P falciparum infection and infection from other plasmodial species [1]. These tests require the presence of 100 parasites/μL of blood to give a positive result while a blood smear requires 50 parasites/μL [1]. A negative blood film does not exclude malaria and may yield a positive result if repeated after 8 to 12 h [1,3].

In residents of endemic areas, severe malaria should be differentiated from severe bacterial sepsis, meningitis or encephalitis and other tropical diseases with overlapping clinical features such as dengue, leptospirosis, rickettsial typhus and enteric fever [1,10]. With increasing international travel, severe malaria is increasingly common in visitors returning from endemic areas if preventative measures and prophylaxis have been neglected. Fever usually develops 4–28 days after returning home and a history of travel is the most important clue to the diagnosis [11].

4. Management of severe malaria

4.1. Choice of antimalarial drugs

Quinine was the drug of choice for severe malaria till 2005 [3,10]. A large randomized controlled trial (RCT) (the SEAQUAMAT study) compared outcomes in 730 South East Asian patients with severe falciparum malaria treated with intravenous artesunate with 731 patients treated with intravenous quinine [13]. The mortality in the former (14.7%) was significantly lower than that in the latter (22.4%) [13]. Another RCT in African children (AQUAMAT study) showed similar results and intravenous artesunate is now the recommended agent for severe malaria [14]. The dose of artesunate in adults is 2.4 mg/kg body weight administered at 0, 12 and 24 h and then once daily for 7 days; a higher dose is required in children [1,13]. No dose adjustment is required for patients with hepatic or renal impairment [1]. After the initial 3 intravenous doses, patients who can tolerate enteral medications should be given a combination of the fixed-dose combination of artemether and lumefantrine (dose 80 mg and 480 mg respectively for adults) twice daily by the enteral route for 3 days [1].

4.2. Critical care Management

The basic principles of management are similar to those of severe sepsis of any cause. This discussion will only highlight those aspects of care that are specifically applicable to severe plasmodial infections.

4.3. Fluid management and shock

Judicious intravenous fluid therapy in newly admitted patients is useful [1,12]. Initial fluid resuscitation in children with severe malaria is however more controversial [12]. In a RCT (FEAST Study), African children with severe infection and impaired perfusion were randomized to 3 groups; 20-40 ml/kg of normal saline over 1 h, 20-40 ml/kg of 5% albumin over 1 h, or intravenous maintenance fluids (2.5 to 4.0 ml/kg/h) without the initial fluid bolus. The mortality at 48 h was significantly lower in the group that did not receive a bolus dose (7.3% versus 10.5% in the albumin bolus group and 10.6% in the saline bolus group) [15,16]. Fifty six percent of children in this study had malaria and subgroup analysis showed that the mortality in this subgroup was similar to that of the overall cohort [15,16]. Consequently, the WHO malaria guidelines from 2015 advise against rapid fluid boluses of colloids or crystalloids in children [1]. In adults, hemodynamic monitoring is essential as excessive fluid may increase the risk of pulmonary edema due to leaky pulmonary capillaries while inadequate volume replacement may lead to acute kidney injury and worsening metabolic acidosis [4].

Shock occurs in about 10% of patients with severe malaria [5,6,12]. The role of coexistent bacterial infections in these patients has been highlighted in many publications [4,10,12,17]. Blood cultures should be sent on admission and antibiotics started early and de-escalated or discontinued later if bacterial infection is ruled out. The use of vasopressor agents should be as per the guidelines for septic shock, but adrenaline should be avoided as it may increase lactate production [18].

5. Metabolic changes

Lactic acidosis is common and is a marker of a poor prognosis [4,19]. It results mainly from anaerobic glycolysis in under-perfused tissues due to microcirculatory obstruction by parasitized erythrocytes. Other factors include lactate production by the parasites and impairment of hepatic and renal lactate clearance [19]. Other metabolic changes that have adverse prognostic implications are hyponatremia and hypoglycemia [1,3,20]. Hypoglycemia is common in children and pregnant women with malaria and in patients treated with intravenous quinine [3]. Hypoglycemia may lead to coma and seizures and this must be detected and treated before ascribing these features to cerebral malaria [3,5,10].

6. Cerebral malaria

Cerebral malaria is the commonest form of severe malaria seen in children [1,3] and most are reported from Africa [1-4]. Stupor, coma, seizures, decerebrate posturing and raised intracranial pressure are common [3,4]. Raised intracranial pressure is less often encountered in adults however [4,21]. Hypoglycemia is common in these patients and blood glucose should be frequently monitored and hypoglycemia promptly treated by glucose infusions [1,3,4]. Besides cerebral edema, neuroimaging may reveal typical changes in the basal ganglia and thalamus and rarely in the cerebellum [21,22]. At autopsy, petechial hemorrhagic foci are seen all over the cerebral hemispheres [3,22]. While neurological outcomes are better in adult survivors, up to 15% of children that survive cerebral malaria have sequelae including hemiplegia, spasticity, blindness and impaired learning [4]. Residual deficits are associated with hypoglycemia, severe anemia and refractory seizures [4]. The role of prophylactic anticonvulsants is controversial and is not routinely recommended [1,3]. One study in Indian adults showed worse outcomes in patients treated with intravenous mannitol (1.5 g/kg followed by 0.5 g/kg every 8 h) [23] however measures to reduce fever, elevation of the head of the bed, effective treatment of seizures and osmotic therapy and hyperventilation specifically targeted to transient surges in intracranial pressure may be useful [21]. High dose dexamethasone is deleterious and may prolong duration of coma [24].

7. Thrombocytopenia and hematological manifestations

Thrombocytopenia is almost universal in severe malaria [1,3], and is often severe; in one series, 43% of patients had platelet counts <50,000/μL [5]. However, spontaneous bleeding is not common. Patients will also have some degree of anemia, which is hemolytic in etiology, as all infected RBCs as well as some non-infected RBCs are hemolyzed at some stage of the 48 h asexual erythrocytic lifecycle of the plasmodia [1,3,4]. The greater the percentage of infected RBCs, the greater the extent of

hemolysis. In a large Indian series of severe falciparum malaria, 76% of patients required blood transfusions [5]. The recommended threshold for transfusion in adults is 7 g/dL, as for other critically ill patients [1,4], although a lower level of 4–6 g'dL has been suggested for children in resource-limited settings [25]. Most patients with malaria will have normal leucocyte counts, which helps differentiate it from other bacterial infections that may mimic malaria. Deranged coagulation with DIC is seen in <10% of patients with severe malaria, and occurs late in the course of the disease along with multiple organ system failure and has a grave prognosis [5,6,12]. Exchange transfusion has been reported as a salvage therapy in patients with severe malaria with high parasite index. The rationale is to physically remove infected cells and in so doing rapidly reduce parasitemia and also remove cells that would otherwise undergo hemolysis, replacing them with healthy, more deformable RBCs cells to improve the microcirculation [1,3]. However, evidence to support this therapy is limited.

8. Renal failure

This may occur due to volume depletion, shock, microcirculatory obstruction along with hemoglobinuria from intravascular hemolysis [1,3,4] in patients with a high parasite index. Early hemodialysis or continuous renal replacement therapy is required in up to 35% of patients with acute kidney injury in malaria [5,12].

9. Hepatic involvement

Hyperbilirubinemia may occur due to hemolysis, cholestasis and hepatocyte dysfunction [3,4]. Bilirubin may be moderately elevated, but transaminases are not very high. In one study from India, hyperbilirubinemia >6 mg/dL was seen in 26%, but a > 3-fold transaminase elevation was seen in less than half of these patients [5]. Almost 60% of patients with elevated transaminases had hypoglycemia and also had a significantly higher mortality [5].

10. Pulmonary involvement

Acute pulmonary edema is usually a late manifestation of organ dysfunction in malaria and manifests as ARDS [5,7,12,26]. It is often seen a few days after starting antimalarial treatment and its pathogenesis is unclear [5]. Leaky capillaries due to parasite- erythrocyte-capillary interactions, cytokine mediated damage and possibly bacterial co-infection are suspected to play a role [5,7,26]. The same strategies used to treat ARDS due to other causes are also applicable in severe malaria [26]. Since underlying bacterial infections may play a role in the pathogenesis of ARDS in malaria, the threshold for starting antibacterial agents should be low [5,7,26]. Most patients with ARDS will also have thrombocytopenia, renal failure and hemodynamic disturbances [5]. Malarial ARDS carries a high mortality [5,7,12,26].

11. Therapies that have failed to show benefit

Therapies that have been studied in small RCTs that have not shown benefit include intravenous heparin, intravenous dexamethasone in cerebral malaria, desferrioxamine, pentoxyfylline, aspirin, anti-TNF antibody, cyclosporine A and prostacyclin [1].

12. Severe vivax malaria

Although P vivax infection is generally considered to be a benign condition, it can cause all the complications that are seen in falciparum malaria including cerebral malaria, severe thrombocytopenia, shock, renal failure, hemoglobinuria and jaundice [1,8,9]. Most cases of severe vivax malaria have been reported from Indonesia, Papua New Guinea, India, and the Amazon region [4,8,9]. The proportion of patients with vivax malaria among all patients with severe malaria admitted to the ICU in India is changing. While in 1996–1999, only one of 334 patients with severe malaria admitted to a tertiary care hospital in Mumbai, India had P vivax infection [5], this had increased to 448 of 711 patients by 2012 [27]. Various reasons have been ascribed to this change and these include the presence of comorbidities, antimalarial resistance in P vivax and the emergence of more virulent strains [1,4,28]. Occasionally, falciparum and vivax co-infection may be seen in severe malaria; these patients usually have more severe disease and a worse outcome. The antimalarial therapy is as for P falciparum malaria [1,4], but unlike *P falciparum*, the liver forms (hypnozoites) of *P vivax* may persist for up to 10 years and cause relapses of blood stream infection in the first 1 or 2 years [1]. Antimalarial drugs active against the erythrocytic forms of the parasite do not act on the hyponzoites. Primaquine is the only drug active against these liver forms and should be administered only after testing for G6PD deficiency [1]. The usual dose of primaquine is 15 mg daily orally for 14 days [1].

13. Severe knowlesi infection

P knowlesi infection is common in long-tailed macaque monkeys in the forests of South East Asia [1,4]. Human cases have been reported from Myanmar, Thailand, Vietnam, the Philippines, Singapore, Malaysia and Indonesia [1,29]. In a large published series from Malaysia, 56 patients had PCR-confirmed P knowlesi infection of which 22 (39%) had severe malaria with 6 (27%) deaths [29]. This parasite has an asexual erythrocytic lifecycle of 24 h and therefore multiplies more rapidly, resulting in sudden onset of severe organ dysfunction and death [1,29]. The treatment is as for severe falciparum infection [1].

14. Conclusions

Severe malaria is most commonly due to P falciparum infection. However, P vivax and P knowlesi may also cause life-threatening complications [1,4]. Prompt diagnosis and treatment with artesunate has reduced mortality over the last decade [2]. Diagnosing severe malaria in travelers can be a challenge if the history of recent travel to an endemic area is missed [11]. Intensive care management is crucial as multiple organ failure is common [4]. Neurological complications and residual deficits may be seen in children with cerebral malaria [1,4]. Mortality of severe disease in various series has ranged from 10 to 32% [1,12]. Factors associated with poor outcome include shock, ARDS, bacterial coinfection, delay in starting antimalarial treatment and lack of adequate intensive care facilities. Chemoprophylaxis in travelers to endemic areas is essential to prevent malaria [1,4]. The role of a malaria vaccine in preventing severe malaria in African children is being investigated [4].

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