

Severe Malaria

Current concepts and practical overview - what every intensivist should know!

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Take home message

Severe malaria is a life-threatening multi-organ disease and serious global healthcare problem. This review provides the most current concepts, contemporary issues and recent developments in the understanding and management of this potentially fatal disease and offers practical direction for all involved in the care of such patients. What every intensivist should know!

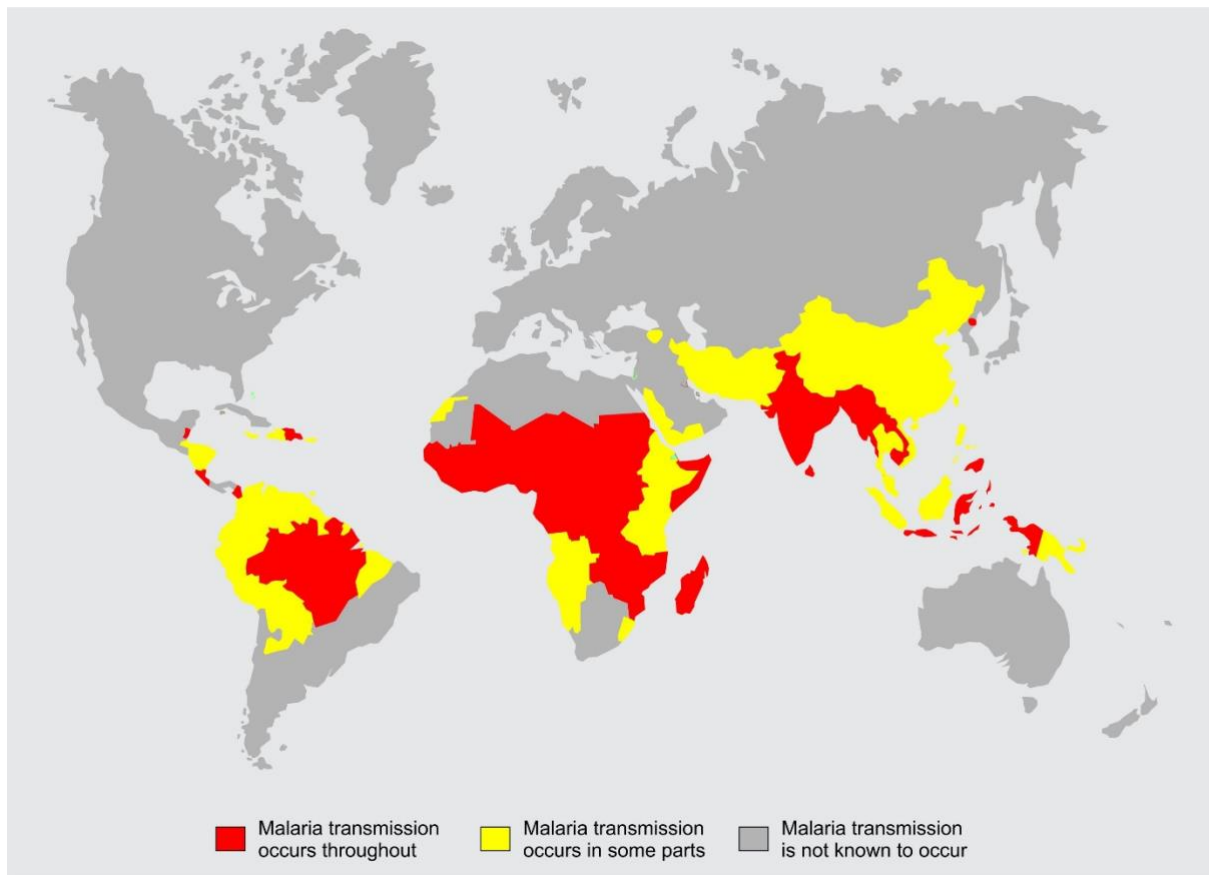
Introduction and history

Malaria is a life-threatening disease and serious global healthcare problem. It has plagued humans throughout history and has been referred to as the “King of Diseases” [1,2]. Malarial DNA going back 4000 years has been identified in Egyptian mummy tissue as well as in amber dating back more than 100 million years. Ancient works from China, India and Sumeria have also been linked with the disease and Hippocrates is credited with providing one of the first descriptions of malaria around 350-450 BC.

Epidemiology and global distribution

Malaria is a leading cause of death and disease in malaria-endemic regions such as sub-Saharan Africa, South-East Asia, the Eastern Mediterranean, Western Pacific, and South and Central America [3-5] (see Figure 1 and Table 1), as well as being an increasingly important cause of significant imported infection in non-endemic areas amongst returning travellers who have visited endemic regions [6-9]. The disease is caused by parasites of the genus *Plasmodium* that are transmitted to humans via the bite of infected female *Anopheles* mosquito vectors [1,5]. If the disease is not treated timeously, progression to severe disease with organ dysfunction and death may occur, depending on the infecting *Plasmodium* species and immune status of the patient [1,3,5,10-12]. Six *Plasmodium* species can cause malaria in humans – *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, the sympatric species *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri*, and zoonotic *Plasmodium knowlesi* (monkey malaria) [1,3]. Severe malaria is predominantly caused by *P. falciparum* but may also occur with *P. vivax* and *P. knowlesi* infections [1,3,10]. Approximately 1% of *P. falciparum* infections result in severe malaria which may rapidly progress to death if left untreated in non-immune individuals [1,3,11]. This pathogen accounts for 99% of malaria deaths, the vast majority of which occur in sub-Saharan Africa [1,3,5]. Criteria and definitions for severe malaria in both endemic and non-endemic settings have been defined by the World Health Organization (WHO) [1,3,4,11,12] (see Table 2). In 2017 there were 87 countries and regions with ongoing malaria transmission, and malaria resulted in an estimated 219 million cases and 435 000 deaths [3]. This represented an increase of 2 million cases as compared to 2016 with a similar number of deaths [3] (see Table 1).

Figure 1: Global Malaria Distribution* [3,13,14-16]



* Primary source of figure: Centers for Disease Control (CDC) and Prevention 2018 [15]

Table 1: Malaria cases and mortalities per geographic region [3]

| WHO Region | Malaria Cases | Malaria Deaths |
|-----------------------|---------------|----------------|
| Africa | 200 million | 403 000 |
| Americas | 976 000 | 630 |
| Eastern Mediterranean | 4.4 million | 8300 |
| South-East Asia | 11.3 million | 19 700 |
| Western Pacific | 1.9 million | 3620 |
| World | 219 million | 435 000 |

Risks and outcomes

Approximately half the world's population is at risk of malaria. Particularly vulnerable populations at high risk of contracting malaria and developing severe malaria include infants, children under the age of 5 years, pregnant women, patients with HIV/AIDS, as well as non-immune travellers, mobile populations and migrants [1,3,11,16]. Partial immunity is acquired following years of exposure in endemic areas. Although this does not provide complete protection, it does importantly, reduce the risk of severe disease. Consequently, children under the age of 5 years in high transmission settings are at heightened risk of severe infection and death. In 2017, an estimated 266 000 children died from malaria prior to their fifth birthday, accounting for 61% of all malaria deaths worldwide [3]. Partial immunity is lost after residing in a non-endemic area for a few years [3].

Case fatality in severe malaria varies between 5% and 50% depending on the extent of organ involvement at presentation, the availability of optimal antimalarial therapy (parenteral artesunate), and the institution of appropriate supportive measures [1,3,4,9-12,17]. Death usually supervenes within the first few days of admission. Survivors generally have limited or no sequelae.

Table 2. World Health Organization definition of Severe Malaria: one or more of the following conditions, in the absence of an identified alternative cause, and in the presence of *Plasmodium* species asexual parasitaemia [12].

| | Adults | Children |
|--|---|---|
| Severe Malaria (predominantly caused by <i>Plasmodium falciparum</i> ; may also occur with <i>P. vivax</i> and <i>P. knowlesi</i> infections) | | |
| *Impaired consciousness | Glasgow Coma Scale <11 | Blantyre Coma Score <3 |
| Prostration | generalized weakness so that the person is unable to sit, stand or walk without assistance | |
| Multiple convulsions | more than two episodes within 24 hours | |
| *Acidosis | a base deficit >8 mmol/L, or, if not available, a plasma bicarbonate level <15 mmol/L or a venous lactate ≥5 mmol/L | |
| Hypoglycaemia | blood or plasma glucose <2.2 mmol/L (<40 mg/dL) | |
| Severe malarial anaemia | haemoglobin concentration <7 g/dL or a haematocrit <20% | haemoglobin concentration <5 g/dL or a haematocrit <15% |
| *Renal impairment | plasma or serum creatinine >265 µmol/L (>3 mg/dL) [#] or blood urea >20 mmol/L | |
| Jaundice | plasma or serum bilirubin >50 µmol/L (>3 mg/dL) with a parasite count >100,000/µL | |
| Pulmonary oedema | radiologically confirmed or oxygen saturation <92% on room air and a respiratory rate >30/min, often with chest wall indrawing and crackles on auscultation | |
| Significant bleeding | recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena | |
| Shock | compensated shock: capillary refill time ≥3 sec or temperature gradient on leg (mid to proximal limb), but no hypotension | |
| | decompensated shock: systolic blood pressure <80 mmHg with evidence of impaired perfusion (cool peripheries or prolonged capillary refill time) | decompensated shock: systolic blood pressure <70 mmHg with evidence of impaired perfusion (cool peripheries or prolonged capillary refill time) |
| Hyperparasitaemia | parasitaemia >10% | |
| Severe <i>Plasmodium knowlesi</i> Malaria (two differences) | | |
| Jaundice | plasma or serum bilirubin >50 µmol/L (>3 mg/dL) with a parasite count >20,000/µL | |
| Hyperparasitaemia | parasite density >100,000/µL | |
| Severe <i>Plasmodium vivax</i> Malaria (one difference) | | |
| Hyperparasitaemia | no parasite threshold included | |

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119 *Factors associated with strong prognostic significance - have been shown to be independent
120 predictors of mortality [5,17-20,30,48]

121 [#] The World Health Organization definition does not provide an adapted threshold for creatinine for
122 paediatric populations

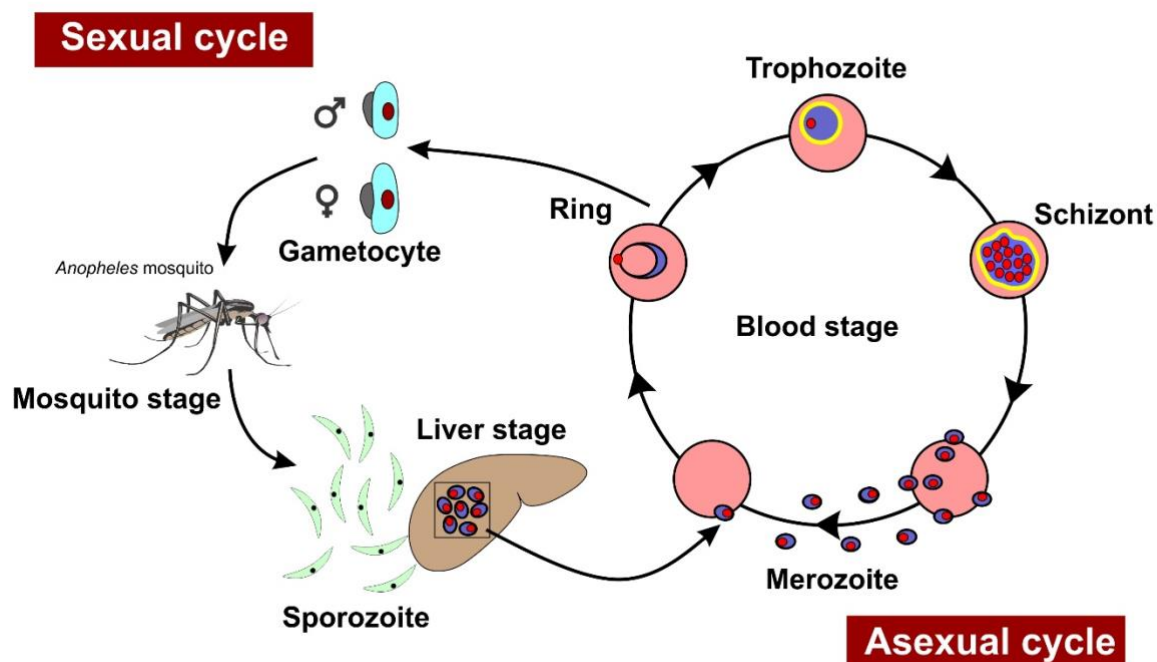
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124 **Malaria lifecycle, parasitological elements and pathophysiology**

125 **Malaria lifecycle and parasitological elements (see Figure 2)**

During a blood feed on the human host, the infected mosquito inoculates motile sporozoites into the dermis which then travel to the liver where they multiply in hepatocytes. Subsequently, the liver schizonts burst and release 1000s of daughter merozoites which invade red blood cells where they start an asexual cycle exponentially increasing their numbers [1]. Depending on immunity, clinical symptoms develop when the number of circulating parasites reach a threshold of approximately 100 million (approximately 50 parasites/ μL blood). In contrast to *Plasmodium falciparum* and *Plasmodium knowlesi* merozoites, merozoites of *Plasmodium vivax* selectively invade reticulocytes and young erythrocytes explaining why parasitaemia in severe malaria due to *Plasmodium vivax* is typically low (<1%) [1].

Figure 2: Schematic representation of malaria lifecycle*



*Figure adapted and compiled from [1,21,22]

Pathophysiology

The development of severe malaria results from a combination of parasite-specific factors together with host inflammatory responses [23-25]. The main pathophysiological hallmark of severe malaria (as typified by *P. falciparum* malaria), is the cytoadherence and sequestration of parasitized erythrocytes to capillary and postcapillary venular endothelium of vital organs, especially in the brain, kidneys, intestines and lung [1,5,23-30]. These processes result in microvascular obstruction, impaired tissue oxygenation and metabolism, and consequent organ dysfunction [1,5,23-30]. Markers of the extent of the microvascular obstruction include plasma lactate and base deficit which are closely correlated with disease severity and prognosis [1,17-20]. Lactic acidosis results mainly from anaerobic glycolysis secondary to microcirculatory hypoperfusion. Other contributory factors to the lactic acidosis include impairment of hepatic and renal clearance [1,23,30]. It has also been suggested that translocation of intestinal bacteria following cytoadherence and microcirculatory disturbance may be associated with organ dysfunction [31]. Increased susceptibility to bacterial

infections, particularly in children, has been postulated to occur as a result of granulocytic phagocytosis of parasitic digestive vacuoles causing functional exhaustion, with resultant blunting of the microbiocidal activity of immune cells [32-34].

Clinical Features and Presentation

Malaria is an important cause of fever, particularly in tropical regions. The initial symptoms of the disease are non-specific and include lassitude, fatigue, headache, abdominal discomfort and muscle aches followed by irregular fever, chills and rigors [1,11]. Nausea, vomiting and orthostatic hypotension are frequent manifestations. Because the symptoms are not distinctive, severe malaria should be distinguished from other acute febrile disorders including bacterial sepsis, meningitis, viral encephalitides, viral haemorrhagic fevers such as dengue, severe influenza, leptospirosis, typhoid fever, rickettsial disorders such as typhus, viral hepatitis, intoxications and other non-infected causes of coma [1,4,11].

In non-immune persons pyrexia may approach or exceed 40°C and be associated with tachycardia and occasionally delirium. In addition to the fever, signs of anaemia and palpable splenomegaly are often the only findings on initial physical examination. Hepatomegaly may occur, especially in young children, and jaundice is frequently noted in adults. Generalized seizures are characteristically associated with falciparum malaria and may be followed by the development of diffuse encephalopathy and coma (cerebral malaria) [1,4,11,12,35]. Several additional neurological signs may be present with cerebral malaria, the most common of which are dysconjugate gaze, abnormal posturing and malaria specific retinal changes [1,4,20].

Various clinical features may be useful in helping to differentiate malaria from other disorders. Although headaches in malaria may be severe, they are not associated with neck stiffness or photophobia as characteristically is the case with bacterial meningitis. Myalgia is a frequent complaint in malaria but tends to be milder than that encountered in dengue, and muscle tenderness is less than may be elicited in leptospirosis or typhus. Malaria is not associated with a rash which may help to differentiate it from meningococcaemia, rickettsial infections, typhoid fever, viral exanthems and drug reactions. Cutaneous and mucous membrane petechial haemorrhages are not common in severe malaria and may be a useful clinical parameter that assists in differentiating the disorder from viral haemorrhagic fevers and leptospirosis, where such findings are more typical.

The time during which uncomplicated malaria progresses to severe malaria is variable with one study reporting the mean duration from onset of symptoms to intensive care unit admission as 5.5 days [35].

The presentation of severe malaria varies with age and the background level of acquired protective immunity [1,17,36,37] (see Table 3). Severe anaemia, hypoglycaemia, seizures and concomitant bacterial infection are more common in children, whereas in adults, acute kidney injury, non-cardiogenic pulmonary oedema (ARDS) (particularly in pregnant women) [38], and jaundice are more frequently encountered. Coma (cerebral malaria) and metabolic/lactic acidosis occur in all age groups and have strong predictive value for fatal outcome [5,17,18,20,30].

The major manifestations and complications of severe malaria are discussed further under management.

Table 3

Clinical Features and Presentation of Severe Malaria

| Clinical feature/complication | Adult | Children | Pregnant Women |
|----------------------------------|-------|----------|----------------|
| Anaemia | + | +++ | ++ |
| Seizures | + | +++ | + |
| Acute kidney injury | +++ | - | +++ |
| Non-cardiogenic pulmonary oedema | ++ | + | +++ |
| Jaundice | +++ | + | +++ |
| Hypoglycaemia | + | +++ | +++ |

Adapted and compiled from [1,7,36-38]

Key: - seldom + occasionally ++ common +++ very common

Diagnosis, diagnostic work-up and considerations (see Table 4)

Prompt and accurate diagnosis is critical to the effective management of malaria. Malaria must be excluded in any patient with a severe febrile illness acquired in a malaria endemic region and should always be a consideration in returning visitors from such regions who present with an acute febrile illness. A travel history is mandatory and an important clue to the diagnosis [6-9]. Clinical findings should always be confirmed by a diagnostic test for malaria [11-12]. Diagnostic tools include microscopy, rapid diagnostic tests (RDTs) and molecular techniques.

The World Health Organization (WHO) currently recommends prompt malaria diagnosis either by microscopy or RDT [2,11,12,39].

Microscopy

Microscopy, widely regarded as the reference standard for diagnosis, involves identification of asexual forms of the parasite in suitably stained peripheral blood smears. Both thin and thick blood smears should be examined [1,2,11,12]. Microscopy allows for species identification and quantification of parasitaemia. A single negative blood smear does not exclude malaria and repeat smears should be evaluated if there is a high degree of suspicion of malaria [4,11,12]. In non-immune patients, smear microscopy may underestimate the parasite biomass as most red blood cells are sequestered in the microcirculation. As a consequence, low peripheral parasite counts can still have a high total body parasite burden with a significant disease severity [1,2,11,12].

Rapid Diagnostic Tests

These tests are simple, sensitive and quick, and detect circulating parasite-associated proteins and enzymes such as *P. falciparum*-specific Histidine-Rich Protein 2 (PfHRP2), lactate dehydrogenase or aldolase antigens with a drop of blood e.g. from a finger prick blood sample [1,11,12]. Some of the RDTs carry an additional antibody that serves to distinguish *P. falciparum* from other plasmodium species [12]. PfHRP2-based tests may remain positive for several weeks after acute infection which has been postulated to limit their usefulness in endemic areas where infections are frequent. They may however be useful in severe malaria patients who have taken antimalarial agents and cleared peripheral parasitaemia, yielding a negative malaria slide - but in whom the PfHRP2 test remains

positive. These tests are being increasingly employed because of their ease of use, rapidity of results and similar sensitivity to microscopy [1,2,4,11,12]. They do not however quantify peripheral blood parasitaemia.

Molecular techniques

Molecular diagnosis by polymerase chain reaction (PCR) amplification of parasite nucleic acid is more sensitive than microscopy or RDTs for detecting low-density parasitaemia and is more accurate in speciation, but is largely used for research purposes and not universally available [2,11,12,40].

Loop-mediated isothermal amplification is a low technology PCR variant that has been adapted for resource-limited settings but which currently has not been deployed on a large scale. [12,40-42]

Serology involving malaria antibody measurements has no role in the diagnosis of acute malaria.

Additional Tests

In addition to the malaria specific diagnostic tests, various additional tests form part of the initial workup and include a full blood count, blood biochemistry, standard coagulation tests, repeated glucose measurements, lactate levels and blood gas analysis. These additional tests assist in determining whether the patient has manifestations of severe malaria, including severe anaemia, hypoglycaemia, renal failure, hyperbilirubinemia and acid-base disturbances.

Mild to severe anaemia as well as thrombocytopenia are almost universal findings [1,40]. Both anomalies are so common in severe malaria that their absence should stimulate consideration of alternative diagnoses. Hypoglycaemia is a frequent complication in malaria patients with particularly high rates among children, pregnant women, and those treated with quinine which is an insulin secretagogue [1, 4, 30, 44-46]. Metabolic acidosis and elevated blood lactate levels are both associated with heightened disease severity and an increased risk of death [19,20,47,48]. Low plasma albumin levels are commonly noted and have been reported to have prognostic significance in severe malaria [11,12,49]. Other biomarkers have been evaluated as indicators of severity and include plasma PfHRP2 and sTREM-1 (soluble triggering receptor expressed on myeloid cells 1) but these are currently not widely available or routinely recommended [49]. Blood cultures should be performed early in patients with severe malaria to exclude bacterial bloodstream co-infection. In addition, all patients with suspected malaria should where appropriate, be checked for HIV and women of childbearing age should undergo a pregnancy test, as both conditions are associated with an increased risk of organ dysfunction and death from malaria [1,4].

Imaging studies usually reveal few abnormalities in patients with severe malaria and should be performed to answer specific diagnostic issues [1,11,12]. Cranial computer tomography may reveal cerebral oedema in patients with cerebral malaria and deep coma. Chest radiographs and lung ultrasonography may be useful adjuncts to help diagnose concomitant pneumonia or non-cardiogenic pulmonary oedema (ARDS), and abdominal imaging may reveal splenomegaly and hepatomegaly.

Table 4: Malaria Diagnosis

| Component | Comments |
|------------------|--|
| Clinical aspects | Malaria is a frequent cause of fever in tropical regions |

| | |
|---|---|
| | <p>History of travel to an endemic area and presentation with an acute febrile illness is an important clue to the diagnosis.</p> <p>Good clinical acumen can be helpful to assist in differentiating malaria from a variety of other tropical and important diseases and disorders.</p> <p>Clinical findings should always be confirmed by a diagnostic test for malaria</p> |
| <p>Microscopy</p> <p>Blood smears peripheral blood</p> <p>-Thin and thick films</p> | <p>Microscopic examination gold standard</p> <p>Allows species identification and quantification of parasitaemia and parasite asexual stage</p> <p>Thick films have a higher sensitivity for diagnosis</p> <p>Thin films allow more accurate speciation and quantification of parasitaemia</p> |
| Rapid diagnostic tests (RDTs) | <p>Detect circulating parasite-associated antigens</p> <p>Allow for the diagnosis of malaria without a trained microscopist</p> <p>Similar sensitivity to microscopy (require the presence of 100 parasites/μL of blood to give a positive result; blood smears require 50 parasites/μL)</p> <p>Do not quantify parasitaemia</p> <p>Do not usually provide speciation although the PfHRP2 (Plasmodium falciparum-specific Histidine-Rich Protein2) test identifies <i>P. falciparum</i></p> |
| Molecular techniques | <p>Remain largely a research tool</p> <p>Occasionally may be useful when doubt exists in infecting species to help with differentiation</p> |
| <p>Other clinically relevant investigations</p> <p>-Blood (full blood count, biochemistry profile, coagulation profile, glucose, blood gas analysis, lactate, blood cultures)</p> <p>-Imaging</p> | <p>Assist in determining severity, identifying organ dysfunction and help to guide subsequent management</p> <p>Largely used to address specific diagnostic issues and directed by patient's clinical condition</p> |

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268 **Management of severe malaria**

269 **Antimalarial drug treatment**

Prompt initiation of treatment with an effective parenteral antimalarial drug is pivotal in order to save lives in severe malaria. Large randomized trials have established that intravenous or intramuscular artesunate is the preferred antimalarial drug when compared to parenteral quinine for reducing mortality in both children and adults with severe *falciparum* malaria [48, 50-53]. It has also been shown to be associated with faster parasite clearance and reduced duration of intensive care and hospital stays [54,55]. Furthermore, artesunate is not associated with an increase in neurological sequelae in patients surviving cerebral malaria [50,51]. Artesunate is a remarkably safe drug, but an important adverse effect is so-called post-artesunate delayed haemolysis (PADH), which can cause a significant drop in haemoglobin levels one to several weeks following artesunate treatment and which occurs most commonly in non-immune travellers presenting with high parasitaemia counts [56-58]. PADH is much less common in paediatric severe malaria in moderate to high transmission areas [58]. Parenteral artesunate is now the recommended first-line treatment for severe malaria in all patient groups, including pregnant women and returning travellers [5,11,12]. It is also recommended for the treatment of severe *P. vivax* or *P. knowlesi* malaria [5,11,12]. If artesunate for injection is not available, intramuscular artemether is the second drug of choice, and intravenous or intramuscular quinine a third option [11,12,59,60]. Dosing regimens are listed in Table 5. As soon as the patient is sufficiently recovered to take oral medication, parenteral treatment can be stopped, and antimalarial treatment should be completed with a full course of any artemisinin combination therapy (ACT) [1,11,12]. ACT with artesunate-mefloquine is not recommended and should be avoided as it is associated with post-malaria neurological syndrome [61]. In patients with severe *P. vivax* malaria, a two-week course of primaquine given in a dose of 0.25 mg/kg (or 0.5 mg/kg in parts of the Asian pacific region) daily orally is advocated to address persistent liver forms and prevent relapses (antimalarials that are active against the erythrocytic forms of the parasite do not act on the liver forms). Prior testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency is recommended in these patients in view of the oxidative haemolytic potency of the drug [4,11,12].

Adjunctive treatments

No adjunctive treatments are currently routinely recommended in the management of severe malaria. An exception might be paracetamol which has renoprotective properties, and has been shown in adult patients to ameliorate the oxidative effects of plasma cell-free haemoglobin, which is always elevated in severe malaria [63]. Corticosteroids are not recommended, but the evidence is based on older small trials [64]. Mannitol therapy is not beneficial in cerebral malaria and prolongs coma duration in adult patients [65]. There are no randomized trials on exchange transfusion in patients with hyperparasitaemia, but current evidence suggests no benefit [66-68]. Exchange transfusion can only clear the circulating ring stage parasitized red blood cells, whereas the more pathogenic mature stages are sequestered in the microcirculation. Artesunate confers an almost equally very rapid clearance of peripheral blood parasitaemia [67,68].

Treatment of concomitant diseases

Invasive concomitant bacterial infection has been well documented in children with severe *P. falciparum* malaria [69] but is much less frequent in adult patients [70]. Addition of broad-spectrum parenteral antibiotic treatment is recommended for the treatment of paediatric severe malaria. In adult patients this is currently recommended only when there is a high index suspicion of bacterial co-infection such as in the presence of hypotensive shock or a neutrophilic leucocytosis.

Supportive treatment

Severe malaria is a sepsis syndrome, and its management largely follows the recommendations of the “Surviving Sepsis Campaign” guidelines (see Table 6). Not all the interventions discussed may be readily available in resource-limited regions and for some of the suggestions, there is a paucity of evidence. Where this is the case, recommendations based on current best clinical practice or expert opinion are provided. However, because of its unique pathophysiology, there are some important management principle differences. In particular, fluid management should be more restricted in patients with hyperlactatemia in the absence of hypotensive shock. Fluid bolus therapy in children with severe malaria and compensated shock has been shown to be detrimental, significantly increasing mortality [71]. In the absence of hypotensive shock, a maintenance crystalloid fluid therapy of 1 to 3 ml/kg/hour during the first day depending on the level of dehydration, is usually sufficient [5,72,73]. In cerebral malaria patients, plasma glucose should always be checked without delay, and hypoglycaemia treated immediately with continued glucose monitoring as rebound and recurrent hypoglycaemia is well documented [44-46]. In comatose patients requiring mechanical ventilation immediate airway control and controlled mechanical ventilation should be instituted. Rapid sequence intubation has been advocated by various authorities as a means to limit both aspiration and further brain swelling of the engorged brain [74-76]. This is also the rationale why permissive hypercapnia as a ventilation strategy is not recommended.

Table 5

| |
|---|
| Antimalarial treatment of severe malaria |
| <p>Adults, pregnant women and children</p> <p>First-line initial therapy</p> <ul style="list-style-type: none"> ▪ Artesunate intravenously 2.4 mg/kg per dose at hour 0, 12, and 24, then every 24 hours <ul style="list-style-type: none"> - If <20 kg: artesunate intravenous 3.0 mg/kg per dose - No dose adjustment required in renal failure <p>Alternative initial therapy</p> <ul style="list-style-type: none"> ▪ Quinine dihydrochloride intravenous infusion 20mg salt/kg loading dose (over 4 hours) then maintenance dose 10mg salt/kg (over 2 hours) every 8 hours <ul style="list-style-type: none"> - Administer in 5% dextrose water with careful cardiac and glucose monitoring - Reduce maintenance dose by one third in patients with renal failure ▪ Artemether intramuscular injection 3.2 mg/kg loading dose, then 1.6 mg/kg every 24 hours <p>After 24 hours and able to eat and drink</p> <ul style="list-style-type: none"> ▪ Artemisinin-based combination therapy orally for 3 days (avoid mefloquine) <p>Travel history to countries with artemisinin resistance* (Cambodia, South Vietnam, North-eastern Thailand [11,12])</p> <ul style="list-style-type: none"> ▪ Intravenous artesunate PLUS intravenous quinine (expert opinion, no evidence) |

* artemisinin resistance has been linked to single point mutations in the “propeller” region of the *P. falciparum* kelch protein gene on chromosome 13 (kelch 13) with resultant delayed parasite clearance [62]

Table 6: Treatment and pathophysiological explanation of manifestations and complications of severe malaria

| Manifestations and complications | Pathophysiology | Treatment |
|--|--|--|
| Coma (Glasgow Coma Score <11; Blantyre Coma Score <3 in preverbal children and convulsions) | Sequestration of parasitized red blood cells in the cerebral microcirculation and other factors | Hypoglycemia and other causes of meningo/encephalitis should be excluded Good general intensive nursing care, including close observation of breathing, eye care Place nasogastric tube and urinary catheter If feasible: intubation to protect airway Frequent monitoring of blood glucose; Treat convulsions |
| Anaemia (Haematocrit <20%, in presence of parasitaemia >100 000/ μ L) | Loss of parasitized red blood cells, increased splenic clearance of uninfected red blood cells (decreased red cell deformability, possible immunologic factors), dyserythropoiesis | General recommendation: transfusion if in distress (severe tachycardia, respiratory distress metabolic acidosis, active bleeding, other severity symptoms), or Haematocrit <20% (adults), or Haemoglobin <5 g/dL in children |
| Hyperparasitaemia (>10% infected red blood cells) | Host immunologic factors and parasite virulence factors (multiplication rate, red cell selectivity) | Start parenteral antimalarial drugs promptly in effective doses (artesunate; if quinine: give loading dose) Exchange transfusion controversial - done in some centres (no clear benefit appears to exist when treating with i.v. artesunate) [66-68] |
| Hypoglycaemia (blood glucose <54 mg/dL); <3 mmol/L) | Increased use, possible decreased production Quinine-related hyperinsulinism | Glucose 10%, 4 mg/kg bodyweight administered immediately. Check glucose thereafter and ongoing glucose monitoring essential [44-46] |
| Acute renal failure (plasma creatinine >3 mg/dl ; >265 μ mol/l), or elevation 1.5 x baseline within 7 days | Acute tubular necrosis Pre-renal component (dehydration) | Record input/output (Foley catheter); Check biochemistry (BUN, electrolytes), start or transfer for renal replacement therapy (haemofiltration or haemodialysis preferred over peritoneal dialysis – better outcomes reported [77]) |
| Severe jaundice (bilirubin >3.0 mg/dL or 50 μ mol/L, with parasitaemia >100 000/ μ L) | Mainly in adults; multifactorial – haemolysis, hepatocyte injury, cholestasis | No specific treatment; Monitor blood glucose; patients may remain jaundiced if ongoing renal dysfunction |
| Fluid/electrolyte imbalances, metabolic acidosis (venous plasma bicarbonate <15 mmol/L or lactate >4 mmol/L) | Dehydration, possible SIADH; Only minor increase in capillary permeability, compromised microcirculation by sequestration and other factors causing anaerobic glycolysis | Careful fluid resuscitation Bicarbonate administration only if pH <7.15 Dialysis as treatment for severe acidosis has been advocated |
| Respiratory distress and pulmonary edema | Acidosis-related deep breathing Pulmonary oedema (ARDS) mainly in adults and pregnant women | See also acidosis ARDS: do not overfill, positive pressure lung protective mechanical |

| | | |
|--|--|--|
| | Aetiology unknown; possibly cytokine mediated with increased pulmonary permeability. Typically occurs several days after initiation of antimalarial treatment and parasite clearance [38] | ventilation with PEEP, appropriate driving pressures, tidal volumes etc. Do not allow 'permissive hypercapnia' (brain swelling) Distinguish from pneumonia |
| Blackwater fever | Related to severe malaria, quinine use and G6PD deficiency. Haemolysis with haemoglobinuria [78] | Transfusion if needed Consider bicarbonate administration Consider paracetamol as renoprotective therapy |
| Circulatory shock (systolic BP <90 mmHg [80 mmHg in children] with cold extremities) | Uncommon in severe malaria may (may be related to nitric oxide binding by free haemoglobin) Consider concurrent bacteraemia | Fluids, inotropic drugs (adrenaline [epinephrine] may potentially worsen lactic acidosis), antibiotics |
| Abnormal bleeding | Diffuse intravascular coagulation: consider concomitant sepsis Isolated thrombocytopenia (very common) - splenic sequestration, dysfibrinogenemia, perhaps endothelial binding and lysis [1,40] | No specific treatment. Correction of coagulation factors and platelet transfusion in severe bleeding. Packed red cell transfusion if indicated |
| Postartesunate delayed-onset hemolysis (PADH) | Delayed haemolysis of once infected ("pitted") erythrocytes, related to the parasite clearance mechanism after artesunate treatment in non-immune patients | Follow up of haemoglobin level up to 1 month after artesunate treatment in non-immune patients, in particular those presenting with high ring stage parasitaemia [56-58] |

Preventive Measures

Prevention of malaria focuses on three main strategies that include vaccination, vector control and chemoprophylaxis. Currently, vaccines against malaria show acceptable safety but only moderate efficacy, with 30% protection being demonstrated against malaria in infants during the 12 months following the last dose [79]. Key elements of vector control include mosquito nets (particularly pyrethroid-insecticide-treated nets), use of appropriate clothing (i.e. wearing of long sleeves and long trousers, particularly between dusk and dawn, as the *Anopheles* mosquito vector tends to bite at night), insect repellents, and indoor residual spraying with insecticides¹. Avoiding and addressing stagnant pools of water also ameliorates the presence of mosquitoes which thrive in these situations. Chemoprophylaxis is recommended for travellers with potential exposure to malaria. It is important to remember that no chemoprophylaxis is completely reliable, and that malaria should always also be considered in febrile patients who have travelled to malaria endemic regions even if they have taken chemoprophylaxis [1,4,9].

Conclusion

It is incumbent on all health care workers involved in acute and critical care, irrespective of geographic location, to have a working knowledge and current understanding of the contemporary concepts, principles, and management aspects pertaining to this highly relevant, potentially devastating and impactful disease. A malaria memoir is provided in Table 7.

Table 7

Malaria memoir – 10 pivotal principles and practical pointers

- Malaria is a serious global healthcare problem, with approximately half the world's population living in areas at risk of malaria transmission
- The most vulnerable individuals are those with little or no immunity against the disease and include young children, pregnant women, travellers and migrants from areas with low or no malaria transmission
- Severe malaria is a medical emergency characterized by multi-organ disease
- A diagnosis of severe malaria should be considered in all patients with severe febrile illness, illness acquired in a malaria endemic area, or in those with a history of travel. A travel history should always be obtained from patients presenting with febrile illness.
- Severe malaria and malaria mortality is mainly caused by *Plasmodium falciparum*, but both *P. vivax* and *P. knowlesi* can also cause severe disease
- Microcirculatory impairment caused by sequestration of parasite-infected erythrocytes, red cell rigidity and red cell clumping, differentiates severe malaria pathophysiologically from bacterial sepsis
- Early diagnosis (confirmed by microscopy or rapid diagnostic testing) and treatment is essential to prevent disease progression and limit mortality in severe malaria
- Parenteral artesunate is the drug of choice to treat severe malaria in all patient groups, including children, pregnant women and travellers
- Presenting manifestations with the strongest prognostic significance are coma (cerebral malaria), metabolic (lactic) acidosis and renal dysfunction.
- The most common pitfalls to avoid in the management of severe malaria include delay of initiation of antimalarial treatment, failure to recognize hypoglycaemia, and overly zealous fluid administration in patients without hypotension (cautious and judicious fluid administration is advised in these patients to prevent potentially lethal pulmonary oedema)

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657 **Compliance with ethical standards**

658 **Conflict of interest statement**

659 None of the authors has a conflict of interest with any of the details shared in the manuscript.

660 All authors contributed to the manuscript.

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