# 24 Falciparum Malaria

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## 24.1 Introduction

Malaria is one of the most common infectious diseases in the world today, being the most important parasitic infection, and *Plasmodium falciparum* is the organism responsible for most of the mortality [1]. It has been estimated that approximately 300–500 million people contract malaria every year, with approximately 1–2 million deaths, most of these occurring in children [1–5]. *Plasmodium falciparum, Mycobacterium tuberculosis* and measles currently compete for the title of the single most important pathogen causing human morbidity and mortality [2, 3]. Infection with *Plasmodium falciparum* has a wide variety of potential clinical consequences [4, 6, 7].

Factors that may influence presentation include the age of the patient, their degree of immunity to the parasite and the duration of infection [7]. In holo- or hyperendemic areas, most adults and older children are partially immune and the disease burden is mainly in children in the first few years of life [7, 8]. The greatest mortality is between the ages of 1 and 3 years [7]. Parasitization may be almost universal in this age group and effects range from an asymptomatic infection, to a febrile illness, or even life-threatening disease [8]. In areas of low endemicity, severe malaria occurs in both adults and children and non-immune travelers and migrant workers are also vulnerable [7]. In adults infected with falciparum malaria for the first time, the range of clinical syndromes is wide and may include specific and multi-organ failure [8].

## 24.2 The Organism

Malaria is a protozoal disease caused by several species of *Plasmodium* which are spread by mosquitoes of the genus *Anopheles* [4]. *Plasmodium falciparum* is one of the four species of *Plasmodium* causing human infection. The period from inoculation to the appearance of parasitemia (prepatent period) is usually 9–13 days for *P. falciparum*, but may be longer, particularly in those who have been on ineffective prophylaxis [4]. During feeding the female mosquito injects saliva, within which malaria sporozoites are carried, into the skin. Within minutes the sporozoites penetrate into hepatocytes and produce tissue schizonts (also known as meronts). After 5–7 days, each tissue schizont has produced 30,000 daughter merozoites that enter the circulation, invade erythrocytes and form ring trophozoites [4]. Using hemoglobin as energy, development occurs after 48 h into late trophozoites (larger and lacier in appearance), early blood schizonts (division begins) and then mature schizonts [4]. The erythrocytes then lyse and merozoites are released into the circulation to invade other red blood cells [4]. In non-immune individuals, the process is amplified 20-fold with each cycle. When parasitemia reaches 10–15 trophozoites per microliter, it is detectable on thick blood films, ending the prepatent period [4]. After several cycles, some trophozoites differentiate into sex cells or gametocytes, which are infectious to the mosquito. The gametocyte of *P. falciparum* is characteristically banana-shaped. If male and female gametocytes are taken up by the mosquito, they mate, migrate through the midgut wall and form an oocyst which eventually leads to the release of about 1,000 sporozoites after 5–8 days [4]. These invade the salivary glands of the mosquito to complete the cycle at the next blood meal [4].

The time from first inoculation to first symptoms is the incubation period [4]. Its length depends on the patient's immune status and is usually 1–2 days longer than the prepatent period. In non-immune patients, symptoms may occur even before parasitemia is present. The other extreme is premunition where partial immunity is associated with asymptomatic parasitemia [4].

## 24.3 Epidemiology

Malaria persists in those parts of the world where the population of anopheline mosquitoes as well as the infected human population remain above the critical density required for sustained transmission. Approxi-

mately 40% of the world's population is at risk of acquiring malaria, resulting in those 300–500 million cases annually [4]. In Africa alone approximately 200 million cases occur every year, with a mortality of about one million. In rural Africa one in 20 children die from malaria before the age of 5 years [4]. Compounding the problem of malaria control in the developing world is the presence of drug resistance, and resistance of mosquitoes to insecticides [4].

Malaria also afflicts individuals in Southeast Asia, Latin America and South America. In 1992 approximately 75% of malarial infections were acquired in Africa, 17% in Asia, 4% in Central America and the Caribbean and 1% each in South America, North America, and Oceania [4]. In developed countries such as the United States, malaria largely occurs as a result of importation from other countries in the blood of immigrants, visitors, military personnel and occasionally also from importation of infected mosquitoes [4].

Recently there has been renewed interest in epidemiological aspects of falciparum malaria [9]. It is recognized that there are clear-cut distinctions between severe and non-severe disease and between the different forms of severe disease [10]. An important question is why *Plasmodium falciparum* causes severe infection in some, but not all, patients. This relates partly to the age of the patient, history of prior exposure to the parasite and various aspects of the hosts' immune response [7–11]. Most interestingly, it is now recognized that many of the differences in response may relate to diversity or polymorphisms in both the host and the parasite, which may impact on disease pathogenesis and be the major determinants of the outcome of a malarial infection [8–10, 12–16]. For example, in the host, possession of hemoglobin AS genotype influences the risk of both cerebral malaria and severe anemia [9], whereas possession of certain HLA genotypes (e.g., HLA-B53) may be linked to resistance to these two complications [12, 13]. Susceptibility to both these complications is linked to polymorphism in the promoter sequence for the tumor necrosis factor (TNF) gene [15, 16], whereas susceptibility to each of these complications individually is influenced by mutations at other sites [9]. Also, different strains of *P. falciparum* have been shown to vary in their ability to induce production of host TNF, and this may determine the clinical severity of the infection [14]. In addition, clonal phenotypic variation with antigenic switching is linked to, and may alter, adhesive properties of the parasite and this may be an important mechanism of immune evasion [8]. Finally, specific adhesive and linked antigenic types may be associated with severe infection [1, 8]. One of the best studied genetic markers associated with *P. falciparum* virulence is the erythrocyte membrane-protein-1 family that is responsible for antigenic variation and cytoadherence of parasitized erythrocytes to endothelial and placental syncytiotrophoblast cells. Parasites causing severe malaria express a small subset of these proteins that differ from those expressed by parasites causing uncomplicated infection [1].

## 24.4
## Severe Malaria

The salient manifestations of severe *P. falciparum* infection are shown in Table 24.1 [5]. There has been some debate in the literature about the definition of both severe malaria and cerebral malaria. A definition of cerebral malaria proposed by the World Health Organization (WHO) reads as follows "A clinical syndrome characterized by coma (inability to localize a painful stimulus) at least one hour after termination of a seizure or correction of hypoglycemia, detection of asexual forms of *P. falciparum* malaria parasites on peripheral blood smears, and exclusion of other causes of encephalopathy" [17, 18]. More recently, severe malaria has been recognized to be a complex multi-system disorder and to have many of the features in common with severe sepsis or a severe inflammatory response syndrome [19, 20]. Studies of outcome of patients with falciparum malaria in the intensive care unit (ICU) commonly report that markers of severity of illness (such as the SAPS or APACHE II score), shock, acidosis, coma, pulmonary edema and coagulation disorders are indicators of poor outcome [21]. The level of parasitemia has not consistently been shown to be a good predictor of outcome. Metabolic acidosis has long been recognized as a major predictor of, as well as a significant contributor to, death [6, 20]. Whereas lactate has been considered to be the major contributor to the acidosis, unidentified anions other than lactate have been shown, more recently, to be even more important [22]. Attempts to assess severity of infection objectively have included other markers, such as the procalcitonin level, which has shown some promise [23].

One other consideration with regard to severe infection, at least in certain areas of the world, is the potential interaction between malaria and human immunodeficiency virus (HIV) infection in those patients who

**Table 24.1.** Manifestations of severe *Plasmodium falciparum* infection

| |
|---|
| Cerebral malaria |
| Severe anemia |
| Acute renal failure |
| Pulmonary edema |
| Metabolic acidosis |
| Coagulation disturbances |
| Hypoglycemia |
| Hypotension |
| High severity of illness score (e.g., APACHE II, SAPS) |

are co-infected [24–26]. On the one hand it has been suggested that this may be associated with increased HIV viral replication, viral genotypic heterogeneity and CD4 T-lymphocyte loss leading to accelerated decline in immune function, reduced survival and increased HIV transmission [25]. On the other hand studies have suggested that HIV infection may be significantly associated with the development of severe and complicated malaria [24], being associated with a high parasite burden with the associated risk that this may potentially lead to poor malaria control and a greater chance for the development of resistance to anti-malarial agents [26].

## 24.5
## Pathogenesis of Severe Disease and Cerebral Malaria

The adhesive properties that the parasite confers on the host's erythrocytes appear to play a central role in malaria pathogenicity [27–29]. As the parasite grows in the red blood cells it induces the expression of surface ligands, as well as various endothelial receptors, that mediate adhesion to the endothelium of post-capillary venules, which results in sequestration of the parasite within the peripheral circulation [27, 28]. In addition, some isolates induce expression of receptors on non-infected red cells, leading to rosette formation, and still others induce expression of adhesion molecules on other parasitized cells causing auto-agglutination [27]. These phenomena can lead to reduced microcirculatory flow or even obstruction to local blood flow and/or cause local metabolic disturbances, such as the production of lactic acid, which may manifest as organ-specific dysfunction [27–30]. Multiple endothelial receptors have been recognized (reviewed elsewhere [30, 31]), and it has now been demonstrated that endothelial activation and leukocyte sequestration in the brain appear to be a feature of fatal malaria [27, 32].

A number of theories have been forwarded to more fully explain the mechanisms of cerebral malaria [3, 27–29, 33–40]. Initially it was assumed that it was simply a mechanical effect related to sludging of parasitized red blood cells within the vasculature, causing decreased cerebral perfusion with hypoxia [28]. Other theories have included altered microvascular permeability, secondary to malarial "toxins" or mediators such as kinins, causing cerebral edema, but this has largely been discounted [35]. Immunological mechanisms were considered following the detection of immune complexes and complement in affected brains [7, 34] and still others have investigated the possibility that disseminated intravascular coagulation (DIC) [34] or endotoxemia [36] may be involved.

Clarke and co-workers proposed the cytokine theory of human cerebral malaria [38–40].

They recognized that cytokines such as TNF and interleukin (IL)-l when overproduced could themselves cause clinical syndromes such as those seen in human malaria [38–40].

Many of these may simply be manifestations of a severe systemic inflammatory response syndrome. Products of schizogony have been shown to trigger release of TNF and IL-l and serum levels of these cytokines correlate with the severity of malaria infection, including the presence of cerebral symptoms [38–40]. The cytokine theory is also consistent with the concept of sequestration of parasites in the cerebral circulation in that schizogony could cause higher local levels of cytokines and their products [40].

Sequestration, however, may not be essential to the development of cerebral dysfunction according to the cytokine theory [40]. Cytokines themselves may alter cerebral function through the local generation of nitric oxide (NO), which may act as a vasodilator to increase intracranial pressure and which may also function as a false neurotransmitter [39, 40]. Cytokines, especially IFNγ, TNF, and lymphotoxins, and chemokine receptors are also said to be responsible for both blood-brain barrier alterations and biochemical changes that may also lead to parenchymal brain lesions [41]. It is also important to consider that septic encephalopathy may be a feature of any severe critical illness and may be indistinguishable clinically from cerebral malaria [42].

## 24.6
## Laboratory Diagnosis of Malaria

For the laboratory diagnosis of malaria, thick and thin blood smears should be made according to standard procedures [4, 43]. Thick smears are 20–40 times more sensitive and should be used for screening. Thin smears fixed with methanol, to preserve erythrocyte morphology, and Giemsa stained allow speciation as well as determination of the level of parasitemia [4, 43]. Various clues to distinguish falciparum malaria on thin smear include the finding of small tight rings, appliqué forms and banana-shaped gametocytes.

Parasitemia should be quantified and counted on thin smears as parasites per 1,000 red blood cells corrected to percentage [4, 43]. After initiation of treatment, parasitemia should be followed regularly until resolution to confirm therapeutic efficacy. The time from initiation of treatment until thick smears are repeatedly negative is called the parasite clearance time. A number of newer techniques have been developed for the diagnosis of malaria including quantitative buffy coat methods, antigen detection, enzyme linked immunosorbent assay, polymerase chain reaction (PCR), including real time PCR, and indirect fluorescent antibody tests [4, 43–46].

## 24.7
## Treatment of Severe and Complicated Malaria

If possible, patients with severe or cerebral malaria should be treated in an intensive care Unit (ICU) [6]. Treatment should be initiated as rapidly as possible, and should not necessarily await parasitological confirmation of the diagnosis if this is likely to be delayed [6]. Patients should be weighed in order to determine drug dosages accurately [6]. Careful fluid management is essential and may be aided by the placement of a central venous catheter and a urinary catheter. The importance of hypovolemia in severe malaria is well recognized, particularly in children, and early recognition and treatment may be associated with an improved outcome [47, 48]. However, care should be taken to avoid fluid overload with the possibility of precipitating pulmonary edema. In patients with severe hemodynamic instability, non-invasive cardiac output monitoring may be of value. A recent meta-analysis of exchange transfusion as adjunctive management of severe malaria concluded that there was no evidence of an increase in survival with its use [49]. However, the authors indicated that there were substantial problems with the comparability of the two treatment groups and suggested that only a randomized controlled trial would give definitive answers. Hyperpyrexia >38.5°C should be treated with tepid sponging, fanning and a cooling blanket [6].

The drug treatment of severe or complicated malaria is shown in Table 24.2 [1, 4–7, 50, 51].

Chloroquine is only used in areas where the infection is definitively known to be sensitive to this agent. Parenteral antimalarial drugs are recommended initially in most cases, at least until there is clear evidence of clinical improvement and oral medication is able to be tolerated [4, 6, 7, 51].

Parenteral quinine is the drug of choice in most of the tropical world. In some countries, such as in the United States, quinidine may be the drug of choice. An intravenous loading dose of either agent is recommended to achieve therapeutic levels rapidly since most deaths occur within the first 48 h [4, 6, 7, 50–52]. A total of 7 days medication is required, which may be completed with oral quinine or quinidine.

Artemisinin and its derivatives, although not yet licensed in many areas, appear to be exciting new agents for the treatment of severe and multidrug-resistant malaria [53–71]. This group of drugs is being used more commonly and it has been suggested that these agents may be the drugs of choice for severe malaria because of their efficacy and safety [53–71]. Artesunate is water soluble and may be given intravenously or intramuscularly, while artemeter is oil-based and is given intramuscularly [61]. Both preparations come in suppository form and may be given rectally, which has also been shown to be effective in the treatment even of severe malaria [59–62]. However, there is growing concern about the development of resistance to these agents, which is already beginning to emerge [72–74]. This, together with the fact that these agents have a short half-life, has led to the recommendation that they always be

**Table 24.2.** The parenteral treatment of severe and complicated falciparum malaria

| Drug | Regimen |
|---|---|
| **Chloroquine**[a] | Chloroquine 10 mg base/kg by constant infusion over 8 h followed by 15 mg base/kg over 24 h |
| **Quinine** (intravenous) | Quinine dihydrochloride salt 20 mg/kg intravenously in 200 ml 5% dextrose and/or saline over 4 h (loading dose) followed by quinine dihydrochloride salt 10 mg/kg infusion over 4 h every 8 h (maintenance dose) beginning 8 h after start of the loading dose, until patient can take oral medication |
| | ALTERNATIVE[b]<br>Quinine dihydrochloride salt 7 mg/kg intravenously over 30 min (loading dose) followed immediately by 10 mg/kg infusion over 4 h repeated 8 hourly (maintenance dose) until patient can take oral medication |
| **Quinidine** (intravenous) | Quinidine base 15 mg/kg intravenously over 4 h (loading dose) followed by quinidine base 7.5 mg/kg over 4 h (maintenance dose) every 8 h beginning 8 h after start of loading dose, until patient can take oral medication |
| | ALTERNATIVE[b]<br>Quinidine base 10 mg/kg intravenously over 1–2 h (loading dose) followed immediately by 0.02 mg/kg/min by infusion (maintenance dose) for 72 h or until patient can take oral medication[c] |
| **Artemesinin derivatives**<br>Artesunate | 2.4 mg/kg IVI or IM bolus initially followed by 1.2 mg/kg at 12 h and 24 h then 1.2 mg/kg daily for 5–7 days<br>OR |
| Artemether | 3.2 mg/kg IM initially followed by 1.6 mg/kg IM daily for 5–7 days |

[a] For the parenteral treatment of severe malaria in cases of drug-sensitive infections; if any doubt treat as for resistant infections
[b] Alternative regimens suggested particularly in the ICU setting
[c] The same dosing regimen has also been reported for the quinidine salt [5]

given with another agent such as mefloquine, doxycycline or clindamycin, which may be associated not only with a better and/or more rapid cure of the infection, but also limit the development of resistance [5, 53, 63, 75].

Combination therapy with various drugs with different modes of action is increasingly being recommended for the treatment of malaria and a number of new combinations are at different stages of development [1, 75]. Additional drugs that are sometimes recommended as combination therapy with quinine include antibiotics such as the macrolides (e.g., azithromycin), doxycycline or clindamycin, which should be added particularly in areas of intense quinine resistance or where prolonged treatment with quinine would otherwise be necessary [50, 75]. Tetracyclines are contraindicated in pregnancy and childhood. Where initial response to therapy is poor, halofantrine or mefloquine have been recommended [6, 7]. Other agents that have been used in treatment of malaria, but which are now no longer recommended, include dexamethasone, mannitol, heparin and dextran [3, 6, 76, 77].

## 24.8
## Cerebral Malaria

In many parts of the world cerebral malaria is said to be the most common clinical presentation of severe malaria in man, with a mortality in the region of 20%, or greater, and accounting for 80% of deaths [6, 7]. However, in some parts of Africa, anemia is a more common severe manifestation particularly in children. Patients fulfilling the criteria for cerebral malaria [3, 6, 17, 18] manifest features of a diffuse symmetrical encephalopathy.

In adults cerebral malaria tends to develop after several days of fever and other non-specific symptoms [3, 7]. In children it tends to be more acute in onset, usually after less than 2 days [3, 7]. It may start dramatically with a generalized convulsion followed by persistent unconsciousness. Post-ictal coma should resolve within 30 min, but coma due to cerebral malaria usually persists more than 24–72 h. The most common neurological picture of cerebral malaria is that of a bilateral symmetrical upper motor neuron lesion with increased muscle tone and reflexes [7].

Various forms of posturing may be observed, including decerebrate and decorticate rigidity [6, 7]. These may occur in hypoglycemic and normoglycemic patients. While neck rigidity and photophobia do not tend to occur, mild neck stiffness is not uncommon [3, 6, 7]. Neck retraction and opisthotonus may, however, occur in both adults and children [7]. Corneal and eyelash reflexes and papillary responses are usually nor-

mal in adults, but disorders of conjugate gaze are common [6, 7]. The gag reflex is usually maintained but abdominal reflexes are invariably absent. This latter may be a valuable clinical sign [6, 7]. Papilledema is not a feature of cerebral malaria, probably reflecting the fact that raised intracranial pressure is not found in the majority of patients early in the course of the illness [6, 7, 78]. Forcible jaw closure and bruxism are common [6, 7].

Studies in children recovering from cerebral malaria have shown neurological sequelae in approximately 10% or more of cases and these occur especially with infections that were complicated by hypoglycemia [3, 7]. Hemiplegia, cortical blindness, behavior disturbances, cranial nerve lesions, extrapyramidal tremor, polyneuropathy, mononeuritis multiplex, Guillain-Barre syndrome, and prolonged coma have all been described as neurological sequelae of patients with cerebral malaria [3, 7].

The APACHE II severity of illness scoring index has been used to predict the mortality of patients with cerebral malaria. In one study, a cut-off of 24 stratified patient mortality with an accuracy of >95%. In that study, high APACHE II score, deep unconsciousness, acute renal failure and acidemia were identified as poor prognostic factors [79].

## 24.9
## Convulsions

Convulsions may occur in as many as 50% of cases of cerebral malaria and are more common in children [6]. In children it may be difficult to differentiate febrile convulsions from those due to cerebral malaria and the possibility that they may be related to hypoglycemia should also always be considered [6]. Convulsions are usually generalized, but other types, including focal seizures, may occur [6]. Generalized convulsions appear to impact negatively on the outcome.

The role of prophylactic anticonvulsants in patients with cerebral malaria is under investigation. Once seizures occur they should be managed in the usual way [6, 80]. Treatment is initially with lorazepam 0.1 mg/kg or midazolam 0.2 mg/kg intravenously, together with maintenance of the airway and appropriate cooling of the patient [6, 80]. Studies of generalized convulsive status epilepticus have suggested that 0.1 mg/kg lorazepam, or 15 mg/kg phenobarbital, or diazepam 0.15 mg/kg followed by 18 mg/kg phenytoin, are all acceptable initial treatment regimens; however most people would treat status with lorazepam initially followed by midazolam (0.2 mg/kg then infusion at 0.1 mg/kg/h) or propofol (5 mg/kg then infusion at 30 μg/kg/min) if not successful [80].

## 24.10
## Severe Anemia

The occurrence of anemia is invariable in patients with severe falciparum malaria [6, 7].

It is due to hemolysis of parasitized red blood cells, shortened survival of unparasitized cells and bone marrow dysfunction [6]. Certain red cell enzyme defects, such as G6PD deficiency, may increase susceptibility to antimalarial induced oxidant-mediated hemolysis. Coombs positive hemolytic anemia and microangiopathic hemolytic anemia also occur [6]. It is recommended that patients should be transfused if the hematocrit falls below 20 % [6]. Specific clotting factors should be administered as needed [6]. Transfusions should be carefully monitored to prevent fluid overload with its associated complications and in some patients low dose loop diuretics (e.g., furosemide 20 mg) may be administered during the transfusion to prevent its occurrence [6].

## 24.11
## Blackwater Fever

This was previously described as the occurrence of unusually severe intravascular hemolysis with other severe manifestations of falciparum malaria, including renal failure, hypotension and coma, despite relatively low levels of parasitemia [6, 7]. The condition was attributed to some form of immunological response to quinine or one of the other anti-malarial agents, but it is also possible that it may have represented unrecognized G6PD deficiency [6, 7]. No special treatment of hemoglobinuria is currently recommended, although alkalinization of the urine may be desirable [6].

## 24.12
## Renal Failure

Some degree of renal dysfunction, as manifested by a raised serum creatinine, is common in patients with severe falciparum malaria [81, 82]. This may be related to hypovolemia and blackwater fever, but more commonly occurs in association with severe malaria in which the mechanism is said to be a reduction in renal capillary blood flow [6].

A variety of glomerular lesions have been described; however the clinical course of all three forms of renal failure is usually that of acute tubular necrosis [6, 7, 82]. The management is similar to that of renal failure in other critical care settings [83, 84]. Attention should be given to fluid status, electrolytes and acid-base balance. If there is anuria or oliguria after fluid replacement, increasing intravenous doses of furosemide should be given in an attempt to increase urine output [6]. Whereas the absolute indications for dialysis are similar to those of other situations and include severe hyperkalemia, fluid overload, metabolic acidosis and uremia, continuous dialysis should be initiated early, prior to the development of fluid overload, and not be dictated by an arbitrary metabolic parameter such as creatinine [6, 83, 84].

It has been recommended that the doses of antimalarials should be reduced in patients with renal failure [6]. This was based on the observation of high plasma concentrations of quinine in patients with renal failure. However, this was probably due to impaired hepatic clearance as a consequence of severe infection, rather than impaired renal clearance, which has not been documented to occur even in patients with moderately elevated serum creatinine levels [6]. A suggested dosing regimen is as follows: initial dose 20 mg/kg of intravenous quinine dihydrochloride (salt) over 4 h followed by 10 mg/kg every 8 h [6]. The infusion volume may be reduced to 50 – 100 ml of 5 % dextrose. After the second day the dose should be reduced to 5 mg/kg eight hourly [6].

Hemodialysis removes quinine and in this situation the dose should remain 10 mg/kg every 8 h [6]. There does not appear to be a need to alter the dose of chloroquine in patients in renal failure, even in those on hemodialysis [6].

## 24.13
## Pulmonary Edema

This is a particularly serious consequence of severe falciparum malaria and is often fatal [6, 7]. It is similar in most respects to the acute respiratory distress syndrome (ARDS), and hyperparasitemia (>10 %) and pregnancy are important predisposing factors [6]. The pathogenesis is not entirely clear, but as it is associated with a normal/low pulmonary capillary wedge pressure it is most likely due to an increase in pulmonary capillary permeability, as occurs with ARDS [6, 7]. The first indication of the onset of this condition is an increase in the respiratory rate, which precedes the development of any of the other chest signs [6, 7]. Careful fluid management is the cornerstone of the prevention and management [6]. Hemodynamic monitoring by means of a central venous catheter or a non-invasive cardiac output monitor may aid in management of fluid status.

## 24.14
## Metabolic Acidosis

Metabolic acidosis is common in patients with pulmonary edema, although it may also occur in its absence [6]. The mechanism is not entirely certain and it may

occur even in the absence of significant hypoxia or hypoperfusion [6]. It appears to be due to tissue hypoxia as a consequence of stagnant flow of parasitized red blood cells through capillary beds [6]. Other factors may include impaired hepatic blood flow (a site of lactate disposal) and high cytokine levels (TNF leads to lactate production) [6]. In addition, the malaria parasite itself produces large amounts of lactate as a by-product of glycolysis. The possible important role of unidentified anions other than lactate has been described above [22]. The acidosis of severe bacterial sepsis appears to involve peroxynitrite induced mitochondrial dysfunction and it is possible that a similar mechanism is involved with severe malaria [85]. Therapy should include correction of hypotension and hypoxemia, if present [6]. Whether correction of an acidosis improves outcome is not known. It should only be corrected if the pH falls below 7.15, if at all, since infusion may worsen pulmonary edema due to the large sodium load [6]. The prognosis of patients with severe lactic acidosis is poor [6].

## 24.15
## Hyperthermia

Progressively increasing body temperature may be associated with convulsions, delirium and coma [6]. High fever increases metabolic demand, which may further compromise tissues damaged by stagnant capillary blood flow [6]. Heat stroke may be associated with permanent neurological sequelae [6]. Patients with cerebral malaria often improve with a decrease in the temperature, which may be achieved by tepid sponging, fanning and cooling blankets [6].

## 24.16
## Coagulation Disturbances

While thrombocytopenia is very common in severe falciparum malaria, in most cases it does not appear to be an indicator of disseminated intravascular coagulation as it usually occurs in the setting of normal coagulation and without evidence of bleeding [6, 7]. It appears that the previous concerns of an important pathogenic role for DIC in severe falciparum malaria were exaggerated and that full blown DIC with bleeding probably only occurs in 5 % or less of patients with severe malaria [6, 7].

## 24.17
## Hyperparasitemia

Patients with a blood parasitemia of > 10 % were previously said to be at increased risk for the complications of severe malaria, which was said to be proportionate to the degree of parasitemia [6]. It was further recommended that patients with hyperparasitemia should have an exchange blood transfusion [6, 86]. This recommendation was not based on large prospective randomized studies, but followed individual case reports and is confounded in some cases by patients with malaria with higher levels of parasitemia who recover without transfusion and in others by the fact that total parasite burden may not be reflected in the peripheral smear [4, 6, 86]. In addition, as described above, a recent meta-analysis of exchange transfusion in the literature, while acknowledging problems with the studies reviewed, concluded that there was no evidence, in general, of its benefit [49]. It has also been noted that facilities for full exchange transfusions (6–8 units of blood) are often not widely available, although in these situations it was previously suggested that partial exchange transfusion (e.g., 4 units) could be undertaken [3, 6].

## 24.18
## Hepatic Dysfunction

While abnormalities in "liver function tests" are quite common in patients with severe malaria, true hepatic dysfunction is uncommon and if present is mild [6]. Raised bilirubin levels are often noted and are mostly due to hemolysis [6]. Raised serum levels of aspartate aminotransaminase may also be associated with hemolysis. Occasional patients with severe falciparum malaria do, however, have marked jaundice with raised serum levels of both aspartate and alanine aminotransferases in addition to prolonged prothrombin time [6]. These patients may have true hepatic dysfunction contributed to by hemolysis and DIC [6].

## 24.19
## Hypoglycemia

Hypoglycemia is a commonly reported complication in severe malaria [6, 7]. It occurs in two situations in particular [6, 7, 87]. Firstly it may occur in pregnant women, where in addition to neurological sequelae it may also cause fetal distress [6, 7]. Unless it has been prolonged and very severe it is associated with a good prognosis and responds well to glucose administration. Secondly, hypoglycemia may occur in severely ill patients and be associated with severe anemia, jaundice, hyperparasitemia, lactic acidosis and coma [6, 7]. Quinine-induced stimulation of insulin release may be an important mechanism, but other factors, including glucose consumption by the parasite, may be contributory [6, 7, 87]. Other mechanisms that have been considered as possible causes of hypoglycemia include depleted hepatic glycogen stores and inhibition of hepatic gluco-

neogenesis [7]. Many of the usual clinical features of hypoglycemia are absent, or are masked by, or interpreted as the symptoms of malaria, but whenever the level of consciousness deteriorates in patients with malaria, hypoglycemia should be suspected [6, 7, 87]. Glucose requirements may be high and infusions of 50 % glucose followed by 10–20 % glucose, preferably through a central venous catheter, may be required to maintain adequate blood levels [6].

## 24.20
## Bacteremia/Septicemia

Gram-negative microorganisms are frequently cultured from the blood of patients with severe malaria [6, 7]. While there is often no apparent source for these organisms it is possible that they may arise via translocation through ischemic bowel. In addition these patients often have central venous and urinary catheters in place [6, 7]. The manifestations of bacteremia vary from asymptomatic to severe sepsis with shock [6]. One study has shown a high incidence of bacterial infection in patients with falciparum malaria presenting in shock [88]. The previously described "algid malaria" is very reminiscent of Gram-negative sepsis and it has been suggested that they may represent one and the same condition [6, 7]. Many authorities recommend both conventional antibiotics and antimalarial agents in the initial therapy of patients with severe malaria [6].

## 24.21
## Gastrointestinal Bleeding

This complication has been noted particularly in patients who have been given high-dose corticosteroids, and is thought to be due to gastric erosion [3, 6, 76]. It should be treated in the usual way together with the infusion of fresh blood [6].

## 24.22
## Aspiration Pneumonia

This complication may occur in any patient with a decreased level of consciousness and is particularly common in severe malaria since these patients often vomit [6]. The latter may be associated with convulsions or be due to anti-malarial agents. Antiemetics may be given but their efficacy has not been consistently demonstrated [6].

## 24.23
## Special Considerations in Pregnancy

Falciparum malaria is a particularly dangerous disease in pregnancy, especially during the second and third trimester [6]. The mortality of cerebral malaria is approximately 40 % in pregnant women and both mother and fetus may die despite aggressive treatment [4, 6]. Pregnant women are at particular risk of hypoglycemia and pulmonary edema [4, 6]. The exact mechanism by which pregnancy enhances the susceptibility to, and the risk of, complicated disease is not certain. However, red cells containing mature forms of the asexual parasites are found in the placenta, being a key feature of maternal infection with *P. falciparum*, and are associated with significant compromise of placental function [6, 89]. Placental parasites express different surface ligands that facilitate immune evasion and their adhesion to specific placental molecules [89]. Treatment should start immediately and the potential teratogenic or abortifacient properties of quinine and chloroquine in this severe situation should be ignored and in any case are considered by many authorities to have been largely exaggerated [4, 6, 7, 90]. Blood glucose levels should be measured frequently and, where possible, fetal monitoring should be undertaken [6]. Some clinicians favor cesarian section or induction of labor if the fetus is viable [6].

## 24.24
## Special Considerations in Children

Children tend to have a shorter disease course and progress much more rapidly than adults to severe malaria [4]. Hypoglycemia, seizures, severe anemia and sudden death are more common, whereas renal failure, pulmonary edema and jaundice are less likely than in adults [4, 6, 7]. Although respiratory distress does not appear in the original WHO definition of severe malaria, it is recognized by clinicians treating children with malaria as an important sign which is not usually due to pulmonary edema or ARDS [91–93]. It has also been termed the malaria hyperpneic syndrome [91]. Possible causes include cardiac failure, coexistent pneumonia, direct sequestration of parasites in the lungs, or a sign of cerebral malaria [93]. It is important to remember that the clinical features of pneumonia and malaria, both common causes of childhood morbidity and mortality in the developing world, overlap considerably and many children fulfilling the WHO criteria for pneumonia may actually have malaria [9, 94]. The majority of cases of respiratory distress in children are associated with lactic acidosis and this is well documented as a poor prognostic factor [93, 95]. After cerebral malaria, 9–26 % of children may have neurologic sequelae of

which half will resolve completely [3, 4, 96]. Hypoglycemic children are at greater risk of neurologic sequelae and/or death [4]. It is important to remember in the treatment of children with malaria that drug dosages need to be modified [4].

## 24.25
## Conclusions

The enormous cost in lives, as well as the cost of treatment, makes malaria a considerable socioeconomic burden. Control of the disease through control of parasite and insect vectors has become largely ineffective due to mosquito and parasite mutation with subsequent development of resistance, together with a change in the social behavior of the host [97]. The need for effective control measures has never been greater [97–99]. Measures to achieve this should include prevention, such as insecticide impregnated bednets and mosquito repellents as well as targeted chemoprophylaxis, and provision of easy access to early treatment once infection occurs [97, 98, 100].

Measures for the future include the possibility of a vaccine which could be anti-parasite or even anti-disease, a variety of which are currently being tested [101–109]. However, a recent Cochrane meta-analysis [110] of some of the studies of currently available vaccine candidates suggested that they were not yet optimal. The possible substantial socioeconomic savings that would occur with effective vaccine use underlies the need for emphasis on immunoprophylaxis.

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