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# Treatment of childhood *Plasmodium falciparum* malaria: current challenges

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**Malaria continues to be a major cause of mortality and morbidity in tropical countries. Infection with *Plasmodium falciparum* may be asymptomatic, cause an uncomplicated febrile illness or give rise to severe disease complicated by coma, acidosis or severe anemia. Treatment of the febrile illness with two drugs – preferably in the form of an artemisinin-containing combination therapy – is now widely recommended, both for greater efficacy and in order to delay the evolution of drug resistance. The clinical picture of severe malaria differs according to the age and immune status of the individual; treatment requires a range of supportive measures, as well as an efficacious antimalarial drug. Insecticide-treated bednets and presumptive treatment programs are increasingly deployed in malaria control programs, while vaccines are showing promise.**

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CONTENTS



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Malaria is the most important of all the parasitic diseases and is responsible for huge morbidity and mortality in most countries in the tropical regions. Malaria parasites are transmitted to humans by the female *Anopheles* mosquito, which inoculates the parasites with its saliva at the time of biting. The disease is due to infection with one of four species of the *Plasmodium* genus, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. The geographical distribution of these species varies; *P. vivax* infection is rare in Africa but common in Asia [1]. It is estimated, that in 2001, there were 1.21 million deaths due to malaria, most of which were in Africa and in young children [2]. Malaria is also responsible for a huge amount of illness and absence from school [3]. In all parts of the world, it is *P. falciparum* that is responsible for the vast majority of deaths and morbidity. In this review, we will focus on the treatment of *P. falciparum* malaria in children living in endemic areas and not on malaria in returning travellers. Readers should look to other sources for reviews on the so-called benign malarias. This is not a list of all available antimalarials, their pharmacology, mechanisms of action and indications for use. Instead, there will be a discussion of some of the broader issues and challenges relating to the treatment of malaria in endemic countries.

## Background

The consequences of infection with *P. falciparum* malaria can be broadly classified into three groups: asymptomatic infection, uncomplicated malaria and severe malaria. Asymptomatic infection occurs when an individual is able to tolerate the presence of parasitemia without having any symptoms of the infection. As a result of repeated malaria infections, malaria-specific partial immunity gradually develops. In high-transmission areas, for example much of sub-Saharan Africa, immunity is built up during early childhood [4]. In such areas, much of the malarial morbidity and nearly all of the mortality affect young children [5]. Symptomatic malaria is less common in older children and adults, and malaria infections are often cleared by the body's own defences without treatment being sought. In countries with low-intensity or sporadic transmission, there is little acquired immunity and malaria infection results in symptomatic disease in all age groups.


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The symptoms of malaria are related to the asexual (blood-borne) stage of the parasite. Uncomplicated or nonsevere malaria accounts for more than 90% of all disease events and consists of fever, malaise, headache, myalgia and minor gastrointestinal symptoms. This nonspecific 'fever illness' is mediated by host cytokine responses to toxins that are released when erythrocytes containing mature parasites (schizonts) rupture and release their contents. Infected erythrocytes circulate in the peripheral blood and, as they mature, adhere to the endothelial walls of small vessels in the brain, gut and other organs. This process, known as cytoadherence, leads to the sequestration of large numbers of parasitized erythrocytes in microvascular beds and is unique to *P. falciparum* malaria [6]. There is strong (but not conclusive) evidence that this process of sequestration leads to some of the life-threatening complications that characterize severe malaria, including coma and acidosis.

### Malaria diagnosis & access to treatment

The diagnosis of malaria is usually made by examining a peripheral blood slide for the presence of parasites. This process requires some laboratory training and equipment and is time consuming. In skilled hands, this is still the most sensitive means of detecting infection. Rapid diagnostic tests (RDTs), by which parasite antigens are detected in a drop of blood applied to a test-strip, have become more widely available in recent years, but their cost remains prohibitive in many countries [101]. The currently available RDTs detect one or more of the parasite antigens, histidine-rich protein 2 (HRP2), lactate dehydrogenase and aldose and are usually specific for *P. falciparum* infections or mixed infections containing *P. falciparum* [7]. In most sub-Saharan African countries, there are insufficient staff or resources available to perform blood tests – whether by microscopy or by RDTs – on every patient with suspected malaria.

Interpreting the results of a RDT or blood film is, in some circumstances, fraught with difficulty. In much of the world where malaria is endemic, asymptomatic infection is common and the presence of parasites in the blood does not equate to disease [8]. A child with a fever and a cough with a positive blood film or RDT may in fact have pneumonia and not be ill from the malaria infection. This leads to overdiagnosis and overtreatment of malaria, and often to a failure to identify and treat the true cause of the illness. In low-transmission countries, asymptomatic carriage is not seen and a positive blood test is indicative of disease. The sensitivity of the commercially available RDTs is usually reported as greater than 90% with sensitivities approaching 100%. Sensitivity is reduced at low parasitemias and the tests may be falsely positive for several weeks after the parasite infection has been treated owing to the persistence in the blood of the parasite antigens, particularly HRP2 [7,9].

To add to the difficulty, a single negative blood film does not rule out malaria; infected red blood cells sequester in the tissues in the later stages of the parasite's life-cycle and may not be detectable in the blood at the time of the test [10]. Even if parasites are circulating, a nonimmune person may become sick when the parasite density in the peripheral blood is too low to detect by microscopy or RDT. As a consequence of these difficulties in interpreting the slide result and owing to the often poor quality of the diagnostic laboratory, many clinicians will choose to treat a patient for malaria on clinical grounds, despite a negative blood test.

In light of these difficulties, many countries have a policy of presumptive diagnosis of malaria [11]. A child presenting with clinical features consistent with malaria, and in whom no other cause is apparent, is treated for malaria without any blood tests being performed. In most sub-Saharan African countries, the majority of malaria treatments are bought over-the-counter by parents who think that their child has malaria, without the child having accessed any healthcare facility or undergone any tests. The Integrated Management of Child Illnesses (IMCI) guidelines of the WHO contain within them this principle of presumptive diagnosis [102]. The clinician attending a sick child will follow a diagnostic algorithm based upon relatively simple symptoms and signs leading to the diagnosis. The IMCI guidelines are amended to cover the diseases common to children of each country and to follow national treatment policies. Common conditions covered include acute respiratory infections, diarrheal diseases, meningitis, sepsis, malaria, measles, ear infection, malnutrition and anemia. A policy of treatment based on presumptive diagnosis is a pragmatic answer to the problems outlined above and is usually affordable. In the coming era of more expensive treatment regimes, such as artemisinin combination therapy (ACT), this policy is coming under increasing scrutiny. Presumptive diagnosis may lead to the overtreatment of malaria and undertreatment of other conditions misdiagnosed as malaria. One study from Tanzania demonstrated that only 46% of patients (adults and children) admitted to hospital and treated for severe malaria were blood film positive. In addition, there was a higher mortality in those patients treated for malaria who were blood film negative, which may have been due to the undertreatment of bacterial infections [12].

### Uncomplicated malaria

#### *Objectives of treatment*

The aims of treatment of uncomplicated malaria are to prevent disease progression to more severe disease or even death, and to minimize morbidity so that the child can return to normal activities. In the past, the aim of treatment in high-transmission areas has not necessarily been to render the child parasite free. When antimalarial drugs are compared in clinical trials, two endpoints are often measured: the parasitological cure rate (percentage of children cleared of parasites after treatment) and the clinical cure rate (percentage of children symptomatically better after treatment, but in whom there may still be parasites) [103]. The parasitological cure rate is recommended by the WHO as the gold standard when drugs are compared but, at a public health level, it is arguably the clinical cure rate that matters – which treatment makes most children feel better and prevents progression of disease. The best therapy for a national program is the one that has the greatest impact on the case fatality rate, anemia, malaria in pregnancy and other morbidity, and keeps

the child or adult at school or work. We do not yet have a way of predicting this from standard *in vivo* or *in vitro* measures of drug efficacy.

### *Treatments for* Plasmodium falciparum

The ideal treatment for uncomplicated malaria would be a cheap single-dose regime with no side effects and against which parasites would not develop resistance. Unfortunately, none of the therapies available to date have satisfied all of these criteria. For many decades, chloroquine (CQ) and then sulfadoxine–pyrimethamine (SP) were the mainstay of therapy for uncomplicated malaria. Both drugs are cheap and serious side effects are rare. A treatment course with CQ is 3 days and SP is a single dose. Resistance to CQ began to appear in southeast Asia in the 1950s and in Africa by the 1970s [13]. Resistance to SP arose soon after its introduction as a first-line therapy in national programs [14]. Despite high levels of resistance and low cure rates, many countries in Africa have persisted with CQ or SP or a combination of the two, but this situation is rapidly changing. Parasite resistance to CQ is now found throughout most malarial regions of the world and with the exception of a few countries in Central America, CQ should not be used to treat *P. falciparum* malaria.

Quinine is most commonly used as a parenteral therapy for severe disease, but it is sometimes used as a second-line therapy for uncomplicated malaria when the first treatment has failed. Quinine requires frequent dosing over a long period (5–7 days) and has unpleasant adverse effects (commonly tinnitus, dizziness and nausea) in most people at normal doses. For these reasons, compliance with a course of oral quinine is likely to be very poor when used outside of the context of a supervised environment. Quinine is still the most widely used antimalarial in the UK for both severe and uncomplicated *P. falciparum* infections, although artemether–lumefantrine (Coartem® – see below) is increasingly being used. Mefloquine can be used as a treatment or prophylaxis but is slow to clear parasites and has frequent side effects, such as nausea, vomiting and, rarely, neuropsychiatric effects. In addition, at a cost of more than US$3 per treatment, it is not a realistic treatment option for uncomplicated malaria in Africa. In southeast Asia, resistance rapidly developed when mefloquine was used on its own to treat malaria [15]. Halofantrine is also an effective treatment for multidrug-resistant malaria but is rarely used owing to its cardiac side effects (prolongation of the QTc interval, which may induce fatal arrhythmias [16]).

Amodiaquine (AQ), a 4-amino-quinoline like CQ, was first marketed for both the treatment and prevention of malaria. In the mid-1980s severe adverse reactions in the form of agranulocytosis and hepatitis were described in travellers taking AQ as a prophylaxis at frequencies of one in 2100 and one in 15,650, respectively [17]. The adverse effects are thought to be immunological, with susceptible individuals developing antibodies to a metabolite of the parent drug after repeated exposure [18]. As a result, AQ was withdrawn but, in the late 1990s, in the face of high levels of resistance to CQ, mefloquine and SP and since there were few alternatives, AQ returned as a treatment for malaria. Atovaquone–proguanil (Malarone®) is effective against multidrug-resistant malaria but is very expensive (US$30 per treatment) and only likely to be used in richer countries. Chlorproguanil-dapsone (CD; Lapdap®), like SP, inhibits parasite folic acid synthesis. It is effective against SP-resistant parasites in Africa but not in Asia where the parasites carry an additional genetic mutation [19]. This mutation has been detected sporadically in some African countries but so far has not become established in parasite populations [20].

#### *Selection of resistance*

Resistance is thought to develop by the spontaneous development of *de novo* mutations within the parasite genome, which confer a survival advantage in the presence of the drug. Once such a mutation has arisen, its spread within a population is influenced by the half-life of the drug against which it confers an advantage. Drugs with long terminal-elimination phases favor this selection process [21]. As the drug concentration falls, parasites are exposed to subtherapeutic drug concentrations and recrudescent or newly infecting parasites carrying resistance-associated genetic mutations are preferentially selected. This is especially important in areas of moderate-to-high transmission where the likelihood of a reinfection occurring during the period of drug elimination is high. CQ, sulfadoxine, pyrimethamine, mefloquine and AQ all have long elimination phases.

#### *Potential benefits of combination therapy*

Combination therapy is the standard of care for the treatment of HIV and tuberculosis, and the WHO now recommends the use of combination therapy for malaria, with the aim of trying to slow or even prevent, the development of resistance [104]. Using two drugs together, A and B, with different sites and mechanisms of action, the chance of resistance developing to both is equal to the chance of resistance developing to drug A multiplied by the chance of resistance developing to drug B. Ideally, the two drugs in the combination should both be highly efficacious on their own with little or no resistance and the pharmacokinetics (PKs) of the drugs, in particular, the elimination half-lifes, should be similar. If one drug has a short half-life and the other drug a longer half-life, the second drug will remain in the blood as a monotherapy after the first drug is gone and will be unprotected. In areas of low transmission, the likelihood of a new infection occurring during this time is small but, in higher transmission areas, this is an important consideration. Although combinations of two drugs, SP and chlorproguanil–dapsone are not considered as combination therapies since the component drugs of each act on the same target, the parasite folate synthesis pathway, and their actions are synergistic and not independent.

#### *Artemisinin drugs*

The WHO currently recommends five combination therapies for uncomplicated malaria, four of which contain an artemisinin [104]. The artemisinins are active against malaria parasites

at all stages of their life cycle, from circulating ring forms to sequestered schizonts and cause the most rapid drop in circulating parasite numbers of all the antimalarial drugs [22]. There is no documented *in vivo* resistance to artemisinins, although a few case reports have suggested it [23]. At the present time, this is not a major public health concern. Artemisinins have very short elimination half-lifes (1–4 h) and a monotherapy must be taken for 5–7 days for a cure. In practice, most patients would not complete this course and the WHO is urging drug companies to stop producing artemisinins in single-drug formulations. When an artemisinin is combined with another antimalarial as an ACT, the treatment need be taken for only 3 days.

### *Artemisinin combination therapy & drug resistance*

Treatment with an artemisinin causes a rapid fall in the initial parasite biomass and, in theory, this reduces the risk of *de novo* resistance emerging. Owing to the short half-life of artemisinin drugs, there is little selective pressure for the spread of resistance mutations through the parasite population. In Thailand, the combination of artesunate with mefloquine was introduced in 1994 after successive failures with CQ, SP and mefloquine as monotherapies. Since then, there has been a sustained high efficacy rate, a reversal of *in vitro* mefloquine resistance and a decline in malaria transmission rates [24]. This decline in malaria transmission is thought to be due, in part, to the gametocytocidal activity of the artemisinins, by which the number and viability of circulating sexual-stage parasites and, therefore, the individual's infectivity to mosquitoes, are reduced [25]. Whether the same beneficial effect on transmission will result from the widespread use of ACTs in high transmission regions remains to be seen. In these areas, malaria-specific partial immunity is common and many people have asymptomatic parasitemia. This reservoir of infected blood in asymptomatic individuals continues to drive transmission and is not touched by any drug therapy [26].

There are many reasons to hope that the widespread deployment of ACTs in national malaria control programs will prevent the evolution of antimalarial drug resistance that has characterized previous policies based on monotherapies. However, it remains to be seen whether the high cure rates currently achieved in all parts of the world by ACTs will be sustained in the high-transmission areas of Africa, as they have been in southeast Asia. The reason for this uncertainty relates to the PKs of the drugs. All four of the ACTs recommended by the WHO combine an artemisinin drug (eliminated from circulation within ~15 h of last dose) with a partner drug that has a long elimination half-life, so that low levels of the partner drug persist in circulation for a longer period after therapy – amodiaquine (5–10 weeks), mefloquine (~10 weeks), lumefantrine (~3 weeks) and SP (4–6 weeks). Combined with a rapidly eliminated artemisinin, these partner drugs are left unprotected as their concentrations fall below the therapeutic range. As outlined above, this is known to drive the selection of subpopulations of parasites carrying resistance mutations. These parasites may be recrudescent, not cleared from the primary infection or parasites from a new infection occurring in the days or weeks after the primary infection, a common occurrence in high transmission areas. There is already evidence in Africa that this could happen with the ACT artemether–lumefantrine. A study in Zanzibar demonstrated a significant increase in parasites carrying the *Pfmdr1* 86N allele after treatment with artemether–lumefantrine [27]. The observed selection occurred mainly in new infections between 20 and 30 days after treatment. This allele has been reported to be associated with *in vitro* lumefantrine resistance [28], although, *in vivo*, it may only be a minor determinant [29]. The significance of this observation remains to be seen. If the nonartemisinin drug is rendered ineffective, patients treated with the ACT will receive, in effect, 3 days of artemether monotherapy, a schedule that is known to be inadequate. Many patients will fail treatment and this may potentially drive the selection of artemisinin resistance.

### *Deployment of ACTs*

At the present time, there are two ACTs available as fixed-ratio tablets, with both drugs coformulated as a single tablet, artemether–lumefantrine and piperaquine–dihydroartemisinin. Artemether–lumefantrine (Coartem®) has been adopted by many African countries as first-line therapy for uncomplicated malaria; although, so far, only a few have been able to implement this policy owing to a shortage of artemisinin. This shortage has now been rectified, and sufficient quantities of artemether–lumefantrine are available, but there remain difficulties and delays in actually getting the drugs into the countries that need it. Even provided at cost price, the therapy will cost national programs US$1 per adult treatment course. When compared with the cost of a treatment course of CQ (US$0.05) or SP (US$0.05) and typical health expenditure per capita in many African countries of around US$40 per annum, this is a big increase. The Global Fund has been set up to enable poorer countries to buy effective drugs rather than cheap ineffective drugs [105]. High efficacy rates (day 28 parasitological cure rates > 95%) have been reported with artemether–lumefantrine in Tanzania and Uganda, and adherence to the six doses over a 3-day regime appears to be good [30,31]. Piperaquine plus dihydroartemisinin (Artekin) is increasingly being used in southeast Asia and also costs approximately US$1 per adult treatment. One study from Rwanda showed it to be efficacious, with a day 28 parasitological cure rate of 95.2% [32]. Further studies are underway in Africa and regulatory approval is being sought for its use there. Other fixed ratio ACTs in the pipeline include chlorproguanil–dapsone plus artesunate (CDA), which is about to start Phase III trials, amodiaquine plus artesunate; and mefloquine plus artesunate. A theoretical advantage of CDA in Africa is that both the CD and artesunate have short (and matching) half-lifes, which may lead to a longer therapeutic lifespan for the drug.

AQ plus SP is the only nonartemisinin combination therapy that is currently recommended by WHO and this combination is only to be used as an interim measure if ACTs are not

available [104]. A meta-analysis of data from clinical trials in Africa using this combination concluded that the AQ plus SP was inferior to artemether–lumefantrine but comparable with AQ plus artesunate [33]. In most parts of Africa, the efficacy of SP is poor and its use in a combination therapy cannot be recommended. Where ACTs are not available or where SP and AQ both have high efficacy, the combination may prove effective, cheap and have a long therapeutic life, as both drugs have matched elimination half-lifes.

The issue of cost of treatment is important in a setting where malaria diagnosis is presumptive, treatment is available over the counter at the village shop and asymptomatic carriage is common. As countries throughout the world switch their treatment policies to provide ACTs as first-line therapy for malaria, many issues will require continuing and careful attention. These include the long-term availability and quality of the drugs, the continuing place of presumptive diagnosis, risks and consequences of noncompliance and mechanisms to identify and cope with the emergence of drug resistance. Counterfeit artesunate, containing little or no active drug, is widely available in southeast Asia and is likely to move into Africa as the demand for ACTs increases [34].

#### *Pediatric formulations of antimalarial drugs*

During the development of a new drug, dose-finding studies are, in the vast majority of cases, undertaken in healthy adult volunteers. Later in the development process, PK studies are repeated in patients with disease to see what effect the disease has on the drug disposition. Owing to the obvious practical and ethical difficulties of taking multiple blood samples from sick young children, few, if any, of the antimalarials currently in use have their pediatric dosing schedules derived from studies in children with malaria. In most cases, the pediatric schedule is derived from the results of PK studies in adults. Drug disposition may be different in children; there is evidence that young children treated with SP according to current guidelines are failing to achieve drug concentrations equivalent to those in adults [35]. Doses for children are usually determined according to the child's weight or, in settings where accurate determination of weight is not practical, according to the child's age. Estimating weight according to age is problematic where malnutrition and chronic infections, such as HIV, are common. Syrup formulations, which are more expensive, are only currently available for CQ and AQ and not for any of the artemisinins, piperaquine, lumefantrine, mefloquine or SP. For small children, the dose to be administered may involve fractions of whole tablets, which may lead to inaccurate dosing. A pediatric tablet formulation of artemether–lumefantrine is under development.

#### *Intermittent presumptive therapy for infants & children*

Intermittent presumptive therapy (IPT) is a measure now being considered to attempt to protect children living in high or seasonally high malaria transmission areas. Children are administered a full treatment dose of an antimalarial, at set times throughout the year or during the transmission season, irrespective of whether they are known to be infected at that time. In Tanzania, a dose of SP, given to healthy infants at 2, 3 and 9 months of age at the time of their routine vaccinations, reduced episodes of clinical malaria by 59% and episodes of anemia by 50% during the first year of life compared with a placebo group [36]. The children in this study were followed up to the age of 2 years and there was no evidence of a rebound in the incidence of malaria after the last SP dose at 9 months [37]. IPT is not currently a WHO recommended policy.

### Severe malaria

Malaria is prominent as a world health problem owing to the capacity of *P. falciparum* infections to progress to severe and life-threatening disease in some infected individuals. Severe malaria is characterized by the development of one or more organ or tissue complications, the presence and severity of which affect the prognosis of the illness. For research purposes, *P. falciparum* malaria is defined as severe (or complicated) when parasitemia is accompanied by any of the following and when there is no other identifiable explanation for the illness: altered consciousness (Blantyre coma score < 3), convulsions, severe anemia (hemoglobin [Hb] < 5g/dl), hypoglycemia, metabolic acidosis, acute renal failure, pulmonary edema, acute respiratory distress syndrome (ARDS), shock, abnormal bleeding, jaundice, hemoglobinuria [38]. Other features of malaria indicate a clinical emergency, although they do not meet the above research definition (e.g., confusional state, drowsiness and extreme weakness [prostration, or inability to sit, stand or suck when normally able to do so]).

#### *Determinants of severe disease*

For the local population, the likelihood of a *P. falciparum* infection leading to severe disease falls with increasing transmission intensity and, in high-transmission areas, with increasing age of the individual. These observations suggest that specific acquired immunity plays an important part in moderating the consequences of a *P. falciparum* infection. Previously unexposed travellers to an endemic area remain susceptible to a greater risk of severe disease than local adults, while local children are at risk and suffer the greatest burden of disease in the population.

The risk of progression to severe disease is reduced by antimalarial drug prophylaxis and by the promptness of therapy for the earliest signs and symptoms of the infection. The efficacy of the drugs used for prophylaxis and treatment also contributes to the size of this protective effect.

Some host genetic factors influence the risk that a *P. falciparum* infection will lead to severe disease. The best documented of these are the protection afforded against severe malaria by the heterozygous state for HbS (the sickle cell trait) [39] and by the $\alpha^+$ thalassemias [40,41]. Many other genetic polymorphisms have been shown to affect risk of severe malaria to a lesser degree, some of these effects being inconsistent between regions [42]. Current multicenter studies are in progress to improve our understanding of host genetic factors that may affect malaria disease risk.

HIV and malaria coexist at high intensity in many countries. Available evidence suggests that immunosuppression due to HIV conveys an increased risk of malarial infection [43] and is associated with higher circulating parasite densities [44]. However, evidence remains equivocal as to whether HIV-infected individuals are at greater risk than others of developing severe disease when infected with *P. falciparum* [45].

Parasite genetic factors appear to affect the 'virulence' of parasite clones, and several studies have suggested that some *P. falciparum* variants are significantly associated with severe disease [46]. A family of *P. falciparum* genes code for proteins (PfEMP1) expressed on the surface of the parasitized erythrocyte and several studies indicate that virulence of parasite clones is associated with the expression of some of these rather than others [47]. Parasite diversity is enormous and it is likely that many determinants of parasite virulence have yet to be properly elucidated.

### *Patterns of severe disease*

In children in high-transmission areas, syndromes that characterize severe malaria are predominantly severe anemia, altered consciousness and convulsions, acidosis and hypoglycemia [48,49]. One or several of these may be present in one subject – the prognosis worsens with the number of complications. In areas with the most intense transmission, severe anemia is the most common complication, predominantly affecting infants and toddlers. Where transmission is less intense, several studies have suggested that cerebral malaria, characterized by coma, commonly accompanied by convulsions, becomes a more common complication and that it predominantly affects slightly older children (mean age 3–4 years). Intravascular hemolysis with hemoglobinuria occurs occasionally in children with malaria; it is usually short lived and is not associated with a poor prognosis. Renal failure, ARDS and disseminated intravascular coagulation (DIC) are rare in children as complications of malaria.

Nonimmune adults, including travelers from nonmalarious areas, differ from children in endemic areas in the pattern of malarial complications. The complications listed for children may all occur, but acute renal failure, ARDS and DIC are all more commonly encountered in adults than in children. Jaundice, usually with a combination of hemolytic and hepatocellular components, affects a small minority of children with severe malaria, although it is a much more common feature in adults.

Individuals who recover from complicated *P. falciparum* infections usually have no residual disease. When acute renal failure occurs, its pathology suggests acute tubular necrosis, and recovery may be complete. Most children suffering coma and/or convulsions make a full neurological recovery, but up to 20% of individuals are left with neurological sequelae detectable on clinical examination [38,50,51]. Others may be more likely to have long-term brain damage, taking the form of epilepsy or subtle motor or cognitive defects [38,51]. Further studies are in progress to assess the extent of these long-term effects.

### *Recognizing severe malaria*

The outlook for an individual who develops malarial complications is likely to be determined by how promptly the warning signs are detected and how quickly and correctly the infecting organism and the organ complications are managed. Several principles are important to remember:

- Complications may develop rapidly in an apparently uncomplicated malarial illness, even after antimalarial therapy has been started;
- An individual may present to a health facility with an established complication (e.g., acute renal failure, coma or anemia) without an obvious or available history of preceding fevers suggestive of malaria;
- The patient's temperature may be normal or low at the time of presentation with complication/s;
- Organ complications must be managed in their own right, while the infection is treated with antimalarial drugs; complications may need continued management for some time after the parasites have been successfully eliminated.

Early recognition, prompt initial treatment and appropriate referral of severe malaria can only be achieved if health workers, in the community and in primary-care facilities, are taught and regularly reminded of the danger signs.

## Management of the patient with severe malaria

Two objectives must be pursued simultaneously: to support the patient until organ or tissue dysfunctions are corrected and to eliminate parasites. The majority of deaths in hospital occur in the first few hours, before specific antimalarial therapy can be expected to have any benefit. Accurate supportive and adjunctive therapy is, therefore, of immediate importance, while appropriate antiparasitic therapy must also be administered as promptly as possible.

### *Severe anemia*

Anemia may result from a combination of red blood-cell destruction by parasites, hemolysis of unparasitized erythrocytes, bone marrow dysfunction and, sometimes, Hb loss due to bleeding or hemoglobinuria. Eliminating parasites commonly leads to the restoration of bone marrow function, with reticulocytosis and improving blood Hb concentration during the second and third weeks after the start of antimalarial therapy. The clinician must decide whether blood transfusion is needed during the early stages of management – the objective not being to restore the circulating Hb to normal immediately, but to support the patient through the acute stages of the disease. The WHO recommends that blood transfusion should be given routinely if Hb is 4 g/dl or less and that transfusion should be considered at higher Hb levels if there is associated hyperparasitemia (>10% of circulating erythrocytes parasitized), hypovolemia, altered consciousness, acidosis, bleeding or other complications [38]. The provision of blood for transfusion is problematic in many under-resourced areas and risks of transmission of viral agents must be carefully considered against

the risks of failure to transfuse. The possibility of transmitting malaria by blood transfusion is not a concern in children who are already receiving antimalarial therapy.

After children have been admitted to hospital for treatment of severe anemia, there is a considerable risk that severe anemia will recur in subsequent months, possibly as a result of new or recrudescent malaria infection. A randomized trial is currently in progress to determine whether further monthly treatment with antimalarial drugs, during the 3 months after initial hospital management for severe anemia, is beneficial in reducing the risk of recurrence of severe anemia.

#### *Altered consciousness & coma*

All degrees of altered consciousness may occur and it is a useful part of the patient's management to record the depth of coma at regular intervals using a scoring system (e.g., Glasgow coma scale for adults – Blantyre coma score for children between the ages of 9 months and 6 years [50]). Altered consciousness may be due to the underlying pathogenetic processes established or triggered by the infection, including the sequestration of mature parasitized erythrocytes in microvascular beds and the release of toxins eliciting a multiplicity of host cytokine responses. Other potentially reversible factors may cause or contribute to altered consciousness, and must be identified and treated – these include hypoglycemia, acidemia, hyperpyrexia and seizures.

#### *Seizures*

Febrile convulsions may occur in young children. These are usually simple and are followed by recovery of consciousness within a few minutes, although seizures associated with malarial fever are more likely to be complex or prolonged than in other fevers. Seizures are a usual feature of severe malarial coma (cerebral malaria), when the seizures may be generalized or may take a variety of focal forms including abnormal repetitive cries, irregular breathing, or persistent movements of a limb or face. Seizures may be revealed by electroencephalography in a patient without visible convulsive movements, or they may be indicated by subtle flickers of facial or limb muscles, or by conjugate deviation of the eyes, repetitive 'pedaling' of the legs, an abnormal cyclical cry, or irregular breathing [52].

Seizures may be a manifestation of central pathology, but may also result from secondary causes – hypoglycemia, hyponatremia, hyperpyrexia or acidemia – that must be identified and corrected. The seizure itself should be treated with the safest and most rapidly effective drug available; for example:

- Lorazepam 0.1 mg/kg intravenously or by intranasal spray
- Diazepam 0.2 mg/kg slowly intravenously or 0.5 mg/kg intrarectally
- Paraldehyde 0.2 mg/kg intramuscularly or 0.4 mg/kg intrarectally

The same treatment should be repeated after 10 min if the seizure persists. If there is still seizure activity after a further 10 min, phenytoin (loading dose 18 mg/kg in N saline intravenous over 20 min) or phenobarbitone intravenous (15 mg/kg loading dose, then 5–8 mg/kg daily) should be given (all intravenous doses can alternatively be administered by an intraosseous infusion, if intravenous access is unavailable). Children with *P. falciparum* malaria and altered consciousness should not routinely be given phenobarbitone as a measure to prevent convulsions – this approach using a dose of 20 mg/kg led to an increased case-fatality rate in one study [53].

#### *Hypovolemia & acidosis*

In the early stages of malaria, there may be vomiting, pyrexia, tachypnoea, sweating, decreased fluid intake and, sometimes, diarrhoea, all of which may contribute to underhydration or hypovolemia. Combined with anemia and parasite sequestration in tissues with potentially impaired microcirculation, tissue hypoxia may develop and contribute to systemic acidosis. This may be detected clinically by the resultant deep breathing, which may be severe enough to require the use of accessory muscles and to result in subcostal recession or indrawing of the chest wall, especially in young children (severe respiratory distress [54]). Hypovolemia may progress to shock with cold distal skin temperature, wide core-surface temperature difference and delayed nailbed capillary refill, with or without hypotension [55].

Fluid replacement is urgently required in this situation. The patient should be receiving a standard maintenance infusion according to body weight (e.g., 4 ml/kg/h for first 10 kg, plus 2 ml/kg/h for each additional kilogram of body weight up to 20 kg and 1 ml/kg/h for each kilogram of body weight over 20 kg). For the hypovolemic or shocked patient, supplementary fluid should be added: a bolus of normal saline or 4.5% human albumin solution (20 ml/kg rapid intravenous) repeated if peripheral coldness, prolonged capillary refill and hypotension continue. Fluid requirements can be monitored by careful attention to urine volumes, jugular venous pressure, lung signs, liver size and, if possible, central venous pressure.

There is currently controversy about what should be the emergency replacement fluid of choice. This is particularly problematic in the child who is also unconscious and may have cerebral edema, as fluid may be necessary to correct a volume deficit but may also increase the risk or degree of cerebral edema. Preliminary studies suggest that in such circumstances a fluid that provides volume replacement without potentially increasing cerebral edema (e.g., albumin or plasma) is safer than normal saline [56]. The superiority of albumin over saline in this situation does not seem to be due solely to its colloid properties, as the synthetic colloid Gelofusine has not shown the same beneficial effects in a clinical trial [57]. Definitive guidance on the optimal fluid therapy for different severe malaria syndromes must await the outcome of currently ongoing randomized trials. When anemia is part of the clinical picture, whole blood transfusion may be the ideal treatment for the conflicting needs of the patient.

### *Hypoglycemia*

Altered consciousness or convulsions indicate the need for urgent measurement of blood glucose concentration. Hypoglycemia may complicate malaria, especially in children, and was present in 20% of 95 children with malaria and unrousable coma in a Malawi study [49]. Hypoglycemia appears to result from a combination of impaired hepatic gluconeogenesis, reduced intake, anaerobic glycolysis and the consumption of glucose by parasites [49]. Hypoglycemia identified in a severely ill child usually precedes treatment with quinine and cannot be attributed to the drug, but the possibility of quinine-induced hypoglycemia must be borne in mind during the management of the child. Hypoglycemia should be corrected by intravenous infusion of 10–20% dextrose (5 ml/kg of 10% glucose) or, in straitened circumstances, by giving glucose or sucrose by nasogastric tube. Regular monitoring of the blood glucose concentration during further management is important in the unconscious patient.

### *Acute renal failure*

This complication is almost always due to acute tubular necrosis. It is rarely encountered in children in Africa. When it develops in a nonimmune adult, it is commonly a component of complicated malaria affecting several tissues or systems. Prompt and adequate volume replacement may prevent progression from hypovolemia to established renal failure. Once established, spontaneous recovery from renal failure is probable within days – provided that the patient can be sustained for the necessary time by standard supportive management. Peritoneal dialysis is the most accessible form of management in many settings where severe malaria occurs, but hemofiltration proved superior to peritoneal dialysis in a randomized trial in 70 Vietnamese adults with infection-related acute renal failure, of whom 48 had *P. falciparum* malaria [58].

### *Bacteremia*

A proportion of African children with severe malaria are bacteremic [59]. Nontyphi salmonellae are the most common organisms, especially in young and anemic children [60]. Findings are conflicting as to whether bacteremia affects the prognosis. Blood culture should be part of the investigation of the patient with severe malaria, where possible, and antibiotics should be given immediately (before blood culture results are known) to children who are in shock, to those under 2 years of age who are severely anemic (the group most likely to be bacteremic) and to others according to clinical judgment and local experience.

### *Specific antimalarial therapy*

For centuries, quinine has been the mainstay of antiparasitic treatment for severe malaria, and it remains the drug most frequently used in many parts of the world. Quinine may be given by intravenous, intramuscular, oral or rectal routes. Where intravenous infusions can be safely controlled, a slow intravenous infusion is preferable – quinine dihydrochloride salt 20 mg/kg (loading dose – given to achieve adequate blood levels quickly) is diluted in infusion fluid and administered over 4 h, to be followed by 10 mg/kg in similar slow infusions every 12 h. In children, 12-h doses have been shown to provide adequate blood levels. Intramuscular quinine in the same doses provides a very similar kinetic profile and has the advantage of ease of administration and control, important in some crowded, understaffed hospital wards. As soon as the patient can take oral drugs, quinine may be continued by mouth, to complete a 7-day course; alternatively, quinine can be stopped and a treatment course of an effective combination therapy can be administered.

Quinine may cause hypotension and hypoglycemia, and invariably causes (reversible) tinnitus when administered in doses adequate for malaria therapy.

Artemether administered by intramuscular injection (3.2 mg/kg, followed by 1.6 mg/kg at 12 h and then daily, until oral treatment can be administered) has proved to be as efficacious as quinine in children with severe malaria [61].

Intravenous artesunate (2.4 mg/kg at 0, 12 and 24 h, then daily) was shown to be superior to quinine for the treatment of severe malaria in 730 patients in southeast Asia, being associated with a 36% lower case-fatality rate than in a comparison group treated with quinine [62]. Only 100 of the patients receiving artesunate were children under 15 years of age (45 were under 6 years), among whom the case-fatality rate was reduced to a similar degree, although this benefit was not statistically significant in these smaller groups. Artesunate has fewer toxic effects than quinine. It is now the preferred primary therapy for complicated malaria in that region. Partial quinine resistance has long been recognized in southeast Asia but is not present in Africa, where most of the severe malaria occurs in children. Trials comparing intravenous artesunate with quinine in African children are in progress.

### *Management of suspected severe malaria at the village level*

In many endemic areas, health facilities and transport may be scarce and appropriate care may inevitably be delayed. In such circumstances, it may be possible to give both antimalarial drugs and other supportive therapy promptly and without equipment, in order to provide benefit during the period required to transfer the patient to a hospital or other health facility. Artesunate, artemether or quinine can be given by rectal infusion or suppository [63–67]. Glucose can be administered in the form of a sugary solution by nasogastric tube, convulsions can be treated by nasal lorazepam [68] or intrarectal diazepam and hyperpyrexia by rectal or nasogastric paracetamol.

## Conclusions

Malaria remains a major world health problem, with its largest impact being on children in Africa. Well-established control methods are available but the deployment of these is hampered by the widespread distributon of the infection, the remoteness of many communities and the constraints of funding, staff and infrastructure that prevail in most affected areas.

The phenomenon of asymptomatic parasitemia poses diagnostic difficulties, as the demonstration of circulating parasites is not proof that these are responsible for a current disease. Prompt treatment, based on presumptive diagnosis of uncomplicated febrile illness, is a mainstay of control, but this will become increasingly difficult and expensive as new combination therapies are deployed. Early recognition and preliminary treatment of complicated disease may reduce the case-fatality rate during the dangerous process of referral from a village health post to more sophisticated health services. Artemisinin combination therapies are likely to provide more rapid and dependable cures of uncomplicated *P. falciparum* infections and to delay or prevent the evolution of drug-resistant parasites. Improved intensive and supportive care is likely to be important for reducing the case-fatality rates of severe malaria and it should soon be known whether the use of intravenous artesunate will add further benefit in children in Africa.

While optimal and prompt treatment for both uncomplicated and severe malaria are essential for the control of disease and death due to *P. falciparum,* preventive measures must be maintained and improved. The increasing use of insecticide-impregnated bednets has the potential to reduce both infections and disease events, as does a resurgence of indoor residual spraying. Vaccines against malaria are beginning to show promise. A combination of these existing and potential control methods may soon lead to important advances in malaria control, provided that determination and funding are maintained.

### Expert commentary

The widespread deployment of ACTs is an exciting and potentially highly beneficial advance in malaria control. However, some caution needs to be maintained. There has been no proof that ACTs deployed on a national scale will indeed protect against the development and spread of drug-resistant parasites in high-transmission areas. The mismatch of terminal half-lives of the component drugs in nearly all ACTs creates the possibility of the dissemination of drug-resistant parasite mutants where infections are frequent. When ACTs are used in routine services, it is inevitable that many young women who do not know that they are pregnant will be given the drugs at a time when the fetus is at its most susceptible and anxieties remain about the early fetotoxic potential of the artemisinin drugs, although none has yet been demonstrated in humans [106]. World supplies of artemisinins have only recently become sufficient to provide for all countries, and these countries will depend on international support to pay the cost of these drugs, which is tenfold higher than former regimens. Failure to sustain this international support could have disastrous consequences.

### Key issues

- Malaria is responsible for over a million deaths, mostly in African children and due to *Plasmodium falciparum*. Infection may cause uncomplicated malaria, severe malaria or be asymptomatic, depending on the degree of malaria-specific immunity (if any) of the infected individual.
- Making the diagnosis of malaria is problematic and many countries have adopted treatment policies based on the principle of presumptive diagnosis.
- Multidrug-resistant *P. falciparum* is a major public health problem worldwide and combination therapy, using two or more antimalarials together, is recommended to try to halt the development of resistance in the future.
- Artemisinins cause the most rapid fall in parasite numbers of all the antimalarials and there is no *in vivo* resistance. In southeast Asia, artemisinin combination therapies (ACTs) have resulted in sustained high cure rates. ACTs are now being deployed in Africa as part of national treatment policies. It is hoped that this will prevent the evolution of antimalarial resistance, but there are concerns that the high rates of transmission seen in Africa may drive the development of resistance even to ACTs.
- The development of severe malaria is influenced by host immunity and genetics, parasite factors, promptness of therapy and the efficacy of the drugs used.
- For children in high-transmission areas, severe malaria is characterized by severe anemia, altered consciousness and convulsions, acidosis and hypoglycemia. The clinical presentations are different in nonimmune adults, when acute renal failure, acute respiratory distress syndrome and disseminated intravascular coagulation are more common. Most complications are reversible, but 10–20% of children are left with neurological sequelae after cerebral malaria.
- Fluid replacement is required to manage hypovolemia and acidosis, and the choice of fluid is problematic in a child who also has coma and convulsions.
- Quinine remains the mainstay of treatment for severe disease in Africa. In southeast Asia, intravenous artesunate has been demonstrated to be superior to quinine for severe disease, and comparative studies are ongoing in Africa.
- Increased use of insecticide-treated bednets will reduce infections and mortality. Careful surveillance is required to identify any impairment in the acquisition of protective malarial immunity in children that might theoretically ensue. A malaria vaccine is showing promise in clinical trials.

Widespread use of impregnated bednets is likely to make a major contribution to reducing infections and especially life-threatening disease, in areas where vectors bite mainly in the middle of the night. But it remains critically important to monitor the consequences of widespread bednet usage, as there is a theoretical possibility that bednets could reduce infections in young children to a level that impairs the acquisition of immunity, so that more children remain susceptible at a slightly older age, when cerebral forms of *P. falciparum* disease are more likely to develop. No such adverse effect has been identified in studies to date [69].

These concerns are not reasons for inactivity, but rather indicate the importance of combining improved preventive and therapeutic measures with improved surveillance, so that any adverse consequences of control efforts can be identified and managed appropriately.

### Five-year view

The next 5 years will be critical in revealing whether large-scale use of ACTs fulfils the early promise of these drugs in malaria control at the population level and whether programs using them can be sustained. Meanwhile, the increasing use of intermittent preventive therapy in infants, linked to the extended program of immunization and the possible introduction of a similar approach in older children, may add an important limb to national malaria control programs. We will discover whether distribution of rectal therapies, such as artesunate or quinine, to the village level can improve the prospects of survival of the villager with life-threatening malaria. Continuing studies will identify whether intravenous artesunate has the same superiority over quinine for the treatment of severe malaria in children in Africa as it has been shown to have in adults in southeast Asia. Measures to improve the supportive care of the patient with complicated malaria – fluids, metabolic monitoring and intensive care – are likely to lead to improvements in hospital management. An artificial substitute for blood to treat dangerous degrees of anemia would be a helpful advance, but is probably beyond a 5-year horizon. The early promise of the RTS,S malaria vaccine [70,71] has provided encouragement that a malaria vaccine could become a usable commodity within the next few years. Meanwhile other approaches to vaccination are meanwhile being explored, while studies of parasite diversity and pathogenesis are likely to provide leads towards the development of new vaccines directed against specific targets (placental malaria and cerebral malaria).

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104 WHO. Guidelines for the treatment of malaria www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

- **Contains background information on doses, side effects and pharmacokinetics of the antimalarials and on WHO policies for malaria management.**

105 The Global Fund. The Global Fund to fight AIDS, Tuberculosis and Malaria www.theglobalfund.org/en/

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